Therapeutic Class Overview
Attention Deficit/Hyperactivity Disorder (ADHD) Agents

Therapeutic Class Overview/Summary:
This review will focus on the agents used in the treatment of attention deficit/hyperactivity disorder (ADHD). These agents come from a variety of drug classes and are summarized in Table 1.[1-27] ADHD is a common psychiatric disorder often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.[28,29] The core symptoms of ADHD utilized in the diagnosis of the disorder include hyperactivity, impulsivity and inattention. There are three subtypes of ADHD, including a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype and a combined subtype in which both symptoms are displayed.[28,29] Untreated, or undertreated, ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities[29]. There are several central nervous system agents that are Food and Drug Administration (FDA)-approved for the treatment of ADHD, including the cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine (Strattera®), clonidine extended-release (Kapvay®) and guanfacine extended-release (Intuniv®).[1-27] Due to the potential for abuse, the cerebral stimulant agents are classified as Schedule II controlled substances.[1-24] Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.[25-27] Clonidine and guanfacine extended-release formulations are approved for use as both adjunctive therapy with stimulant medications and as monotherapy.[26,27]

Most ADHD agents and stimulants are currently available generically. Agents that are available only as a brand name product include: lisdexamfetamine capsules (Vyvanse®), amphetamine tablets (Evekeo®), orally disintegrating tablets (Adzenys XR-ODT®), and extended-release suspension (Dyanavel XR®), atomoxetine capsules (Strattera®), methylphenidate patch (Daytrana®), extended release chewable tablet (Quillichew®), and extended-release suspension (Quillivant XR®). Aptensio XR® (methylphenidate extended-release capsule) is also available only as a brand name product; however, other extended-release biphasic capsules are available generically.[31]

Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children.[29,30,32] Although initial therapy with atomoxetine or extended-release formulations of clonidine and guanfacine may reduce core symptoms of ADHD, there is less evidence to support their use compared to stimulants. The selection of therapy should be based on comorbid conditions, adverse event profiles, compliance issues, risk of drug diversion and patient/parent preference.[33] Stimulants, particularly methylphenidate, are recommended as first-line therapy in adult patients with ADHD.[30,34] Consensus guidelines also list theses agents as options in the treatment of narcolepsy.[35-37]

Table 1. Current Medications Available in the Therapeutic Class[1-27]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine (Adzenys XR-ODT®, Dyanavel XR®, Evekeo®)	Treatment of ADHD, narcolepsy†, exogenous obesity†	Extended-release suspension 2.5 mg/mL Tablet: 5 mg 10 mg	-
Amphetamine/dextroamphetamine salts (Adderall®*, Adderall XR®*)	Treatment of ADHD, narcolepsy‡	Capsule: 5 mg 10 mg 15 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		20 mg 25 mg 30 mg Extended-release orally disintegrating tablet: 3.1 mg 6.3 mg 9.4 mg 12.5 mg 15.7 mg 18.8 mg Tablet: 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg	
Dextroamphetamine (ProCentra®*, Dexedrine®*, Dexedrine Spansule®*, Zenzedi®*)	Treatment of ADHD, narcolepsy	Solution: 5 mg/5 mL Sustained-release capsule: 5 mg 10 mg 15 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg	✔
Lisdexamfetamine (Vyvanse®)	Treatment of ADHD, binge eating disorder§	Capsule: 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg	-
Methamphetamine (Desoxyn®*)	Treatment of ADHD, exogenous obesity	Tablet: 5 mg	✔
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Dexmethylphenidate (Focalin®*, Focalin XR®*)	Treatment of ADHD	Extended-release capsule: 5 mg 10 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		15 mg 20 mg 25 mg 30 mg 35 mg 40 mg Tablet: 2.5 mg 5 mg 10 mg	
Methylphenidate (Aptensio XR®, Concerta®*, Daytrana®, Metadate CD®*, Metadate ER®*, Methylin®*, Methylin ER®*, Quillichew ER®, Quillivant XR®, Ritalin®*, Ritalin LA®*, Ritalin SR®*)	Treatment of ADHD, narcolepsy‖	Chewable tablet: 2.5 mg 5 mg 10 mg Extended-release capsule (Aptensio XR®) 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Metadate CD®, generic): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Ritalin LA®, generic): 10 mg 20 mg 30 mg 40 mg Extended-release chewable tablet: 20 mg 30 mg 40 mg Extended-release	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		suspension: 25 mg/ 5 mL Extended-release tablet (Concerta®, generic): 18 mg 27 mg 36 mg 54 mg Extended-release tablet (Metadate ER®, generic): 10 mg 20 mg Solution: 5 mg/5 mL 10 mg/5 mL Sustained-release tablet (Ritalin SR®, generic): 20 mg Tablet: 5 mg 10 mg 20 mg Transdermal patch: 10 mg/9 hours (1.1.mg/hour) 15 mg/9 hours (1.6 mg/hour) 20 mg/9 hours (2.2 mg/hour) 30 mg/9 hours (3.3 mg/hour)	
Central α-Agonists			
Clonidine extended-release (Kapvay®*)	Treatment of ADHD	Extended-release tablet: 0.1 mg 0.2 mg	✔
Guanfacine extended-release (Intuniv®*)	Treatment of ADHD	Extended-release tablet: 1 mg 2 mg 3 mg 4 mg	✔
Central Nervous System Agents-Miscellaneous			

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Atomoxetine (Strattera®)	Treatment of ADHD	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg	-

ADHD=attention deficit hyperactivity disorder
*Generic available in at least one dosage form or strength.
†Evekeo®
‡Adderall®
§For use in moderate to severe binge eating disorder. Not indicated for weight loss or treatment of obesity.
‖Metadate ER®, Methylin®, Ritalin® and Ritalin SR®

Evidence-based Medicine

- The attention deficit/hyperactivity disorder (ADHD) agents and stimulants have demonstrated the safety and efficacy for their Food and Drug Administration (FDA)-approved indications.[39-132]
- Overall, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of ADHD. [39-132]
- Limited data exists to demonstrate the efficacy of a variety of cerebral stimulants and atomoxetine in the adult population. [44,46,52-54, 62,63,71,90,93,98,99,101,104,113,114,116]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children.[29,30,32]
  - Although initial therapy with atomoxetine or extended-release formulations of clonidine and guanfacine may reduce core symptoms of ADHD, there is less evidence to support their use compared to stimulants. The selection of therapy should be based on comorbid conditions, adverse event profiles, compliance issues, risk of drug diversion and patient/parent preference.[33]
  - Stimulants, particularly methylphenidate, are recommended as first-line therapy in adult patients with ADHD.[31,34]

- Other Key Facts:
  - At least one short-, intermediate-, and long-acting stimulant is available generically.[29]

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Therapeutic Class Overview
Alzheimer's Agents

Therapeutic Class

- **Overview/Summary:** Alzheimer's disease is a progressive neurodegenerative disorder in older adults that affects cognition, behavior and activities of daily living.[1] It is the most common form of dementia and the average life expectancy from the onset of symptoms to death is approximately 8 to 10 years.[1-3] Diagnostic features include memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1]

  The pathophysiologic mechanisms are not entirely understood; however, the disease is characterized by the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in various regions of the brain. Inflammation and free radical processes lead to neuron dysfunction and death. It is thought that memory loss is partially the result of a deficiency of cholinergic neurotransmission.[2-3] Glutamate, an excitatory neurotransmitter, may also play a role in the pathophysiology of Alzheimer's disease. Glutamate activates N-methyl-D-aspartate (NMDA) receptors and is involved in learning and memory. However, excessive amounts of glutamate in the brain may lead to excitotoxicity and cell death.[3]

  There are five agents approved for the treatment of Alzheimer's disease, including cholinesterase inhibitors (donepezil, galantamine and rivastigmine), an NMDA receptor antagonist (memantine) and a combination product (memantine extended release [ER]/donepezil).[4-13] Although none of the agents delay the progression of neurodegeneration, they do delay the progression of symptoms. The cholinesterase inhibitors enhance cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Memantine blocks NMDA receptors and inhibits their overstimulation by glutamate. Currently, memantine ER (Namenda XR®) and memantine ER/donepezil (Namzaric®) are the only products not available generically.

Table 1. Medications Included Within the Therapeutic Class Review[4-13]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Products			
Donepezil* (Aricept®*)	Mild-to-moderate dementia of the Alzheimer's type Moderate-to-severe dementia of the Alzheimer's type	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg 23 mg	✔
Galantamine (Razadyne®*, Razadyne ER®*)	Mild-to-moderate dementia of the Alzheimer's type	Extended release capsule: 8 mg 16 mg 24 mg Tablet: 4 mg 8 mg 12 mg	✔
Rivastigmine (Exelon®*, Exelon Patch®*)	Mild-to-moderate dementia of the Alzheimer's type (capsule and solution) Mild, moderate, and severe dementia of the Alzheimer's type (transdermal	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	patch) Mild-to-moderate dementia associated with Parkinson's disease	Solution: 2 mg/mL Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours 13.3 mg/24 hours	
Memantine (Namenda®*, Namenda XR®, Namenda Titration Pack®*, Namenda XR Titration Pack®)	Moderate-to-severe dementia of the Alzheimer's type	Extended release capsule: 7 mg 14 mg 21 mg 28 mg Solution: 10 mg/5 mL Tablet: 5 mg 10 mg	✔
Combination Products			
Memantine ER/donepezil (Namzaric®)	Moderate to severe dementia of the Alzheimer's type for patients stabilized on memantine and donepezil	Capsule: 14 mg/10 mg 28 mg/10 mg	-

ER=extended-release
*Generic is available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the Alzheimer's agents.[15-103]
- Overall there is limited head to head data available comparing the efficacy of the different agents used to treat Alzheimer's disease. Several different outcomes have been assessed using more than forty different instruments, including cognition, global function, behavior and quality of life. There is inconsistent evidence from well-designed trials that donepezil, galantamine, rivastigmine and memantine positively affect cognition and global function, although the improvements are modest. These findings are less consistent for other outcomes, including behavior and quality of life. In most cases, the duration of well-designed clinical trials were less than one year. There are very few studies that directly compare their various agents. Most of the trials have compared active treatment to placebo or no treatment. The published studies also differ with regards to design, patient population and treatment duration, which make it difficult to directly compare the results.

Key Points within the Medication Class

- According to Current Clinical Guidelines:[104-109]
    - Supports use of the cholinesterase inhibitors as first-line agents for mild-moderate Alzheimer's disease.
    - Memantine is effective in the treatment of moderate-to-severe Alzheimer's disease.
    - Memantine may be added to a cholinesterase inhibitor.
    - Evidence does not show clinically meaningful advantages to administering higher doses of donepezil; however, higher doses of rivastigmine patch may be associated with greater benefit.[107]
- Other Key Facts:
    - Memantine ER (Namenda XR®) and memantine ER/donepezil (Namzaric®) are the only products not available generically.

- Rivastigmine is uniquely indicated for symptoms of dementia in Parkinson's disease patients.

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Therapeutic Class Overview
Androgens (testosterone)

Therapeutic Class

- **Overview/Summary:** The topical testosterone products listed in Table 1 are approved by the Food and Drug Administration for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired) with testosterone pellets also having an indication to stimulate puberty in carefully selected males with clearly delayed puberty.[1-11] There are few differences between the topical testosterone products with the exception of formulation and site of administration. Androderm® is the only testosterone product available as a transdermal patch. AndroGel®, Fortesta®, Natesto®, Testim®, and Vogelxo® are available in gel preparations, while Axiron® is formulated as a topical solution. These products are available as metered-dose pumps or single-use packets/tubes. Natesto® is the only nasal gel available in the form of a metered dose pump. Striant® is a mucoadhesive buccal tablet system that is placed on the gum for 12 hours and applied twice a day, once in the morning and once in the evening. Testopel® is an implantable pellet that consists of crystalline testosterone. It is a cylindrically shaped pellet, 3.2mm (1/8 inch) in diameter and approximately 8-9mm in length. When implanted subcutaneously, the pellet(s) slowly release the hormone over three to six months for a long acting androgenic effect. Androderm® is applied at night, while the topical gels and solution are generally applied in the morning.[1-11] A higher incidence of skin pruritus is associated with the transdermal patch compared to the topical gels; however, the use of hydrocortisone cream, may reduce skin irritations that develop.[1] The labeling of testosterone solution and gels, excluding testosterone nasal gel, include a Black Box Warning regarding the risk of virilization of female sexual partners that has been reported with male use of topical testosterone gels and solution.[2-7] The occlusive backing film on Androderm® prevents the partner from coming in contact with the active material in the system, and therefore the warning is not included on this product.[1] Currently, only AndroGel® has an A-rated generic formulation.

  Hypogonadism refers to a defect of the reproductive system resulting in a lack of gonad function.[12-19] Hypogonadism is classified based on the level of the defect within the reproductive axis. Primary hypogonadism results from a defect of the gonads and occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) concentrations are above normal.[13] Secondary hypogonadism, known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary. This occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum LH and/or FSH concentrations are normal or reduced.[13] Combined primary and secondary hypogonadism may occur and results in below-normal testosterone concentrations and variable LH and/or FSH concentrations, depending upon which clinical condition predominates.[17] Male hypogonadism may manifest as testosterone deficiency with or without infertility. Clinical signs and symptoms depend primarily on the age at the onset of the condition. Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor concentration, and an increase in the risk of osteoporosis and fractures.[12-19]

Table 1. Current Medications Available in the Therapeutic Class[1-11]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Testosterone (Androderm®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Androderm®: 2 mg/day patch 4 mg/day patch	-
Testosterone (AndroGel®*)	Hypogonadism in males, primary (congenital or acquired) and	AndroGel® 1%: Metered-dose pump:	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	hypogonadotropic hypogonadism in males (congenital or acquired)	12.5 mg testosterone/actuation Unit-dose packet: 50 mg testosterone/packet AndroGel® 1.62%: Metered-dose pump: 20.25 mg/actuation Unit-dose packet: 20.25 mg/packet	
Testosterone (Axiron®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Axiron®: Metered-dose pump: 30 mg/actuation	-
Testosterone (Fortesta®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Fortesta®: Metered-dose pump: 10 mg/actuation	-
Testosterone (Natesto®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Natesto®: Intranasal gel metered-dose pump: 5.5 mg/actuation	-
Testosterone (Striant®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Striant®: Buccal mucoadhesive system: 30 mg	-
Testosterone (Testim®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Testim® 1%: Unit-dose tubes: 50 mg/tube	-
Testosterone (Testopel®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired); stimulate puberty in carefully selected males with clearly delayed puberty	Testopel®: Implantable pellet: 75 mg	-
Testosterone (Vogelxo®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Vogelxo®: Metered-dose pump: 12.5 mg/actuation Unit-dose packet: 50 mg/packet Unit-dose tube: 50 mg/tube	-

*A-rated generic available in at least one dosage form or strength

Evidence-based Medicine

- Topical and miscellaneous testosterone products have been evaluated in several clinical trials.[20-33]

- The efficacy of testosterone nasal gel was evaluated in an unpublished, 90-day, open-label, multicenter study of 306 hypogonadal men 18 years of age and older. Individuals were instructed to self-administer one spray of testosterone intranasally either two or three times daily. The primary endpoint assessed was the percentage of individuals with an average serum total testosterone concentration within the range of 300 to 1,050 ng/dL on Day 90. Of the 306 men in the study, results were only available for 73 hypogonadal men who had received the nasal gel three times daily. On Day 90, 90% of these individuals had an average concentration within the established normal range, 10% were below normal and no individuals were found to be above the desired range.[8]
- The safety and efficacy of Striant® (testosterone buccal tablet) was evaluated in a 12 week, open-label, multicenter, phase III clinical trial involving 98 hypogonadal men. At the conclusion of the trial, 86.6% of patients with sufficient data for full analysis had mean serum testosterone concentration values within the physiologic range. The mean (± standard deviation) serum testosterone concentration at the end of the study was 520 (±205) ng/dL compared with a mean of 149 (±99) ng/dL at baseline.[9]
- The clinical trials evaluating the safety and effectiveness that were used to obtain FDA approval of testosterone pellets are not available. However, a literature search identified a phase IV clinical trial by Kaminetsky et al. Mean testosterone significantly increased and luteinizing hormone (LH) levels significantly decreased from pre-implantation values at week one, week four and week 12 visits, and had returned to pre-implantation levels by week 24 ($P<0.001$ for mean testosterone and LH levels at week one, week four and week 12 visits; $P=0.58$ and $P=0.87$ for mean testosterone and LH at week 24 respectively). Prostate-specific antigen levels remained unchanged for the duration of the study.[19]
- Several clinical studies have shown that the transdermal patch and gels all restore serum testosterone concentrations to within normal limits and maintain sexual characteristics, sexual behavior, mood, and muscle development, and improve bone mineral density in hypogonadal men. The results of these head-to-head trials favored the use of the gel over the patch.[21-24]
- In an open-label study, Axiron® topical solution applied to the axilla provided a serum testosterone level in the normal range for 84.1% of patients after 120 days of treatment.[17] Results from a second open-label study reported that 76.2% of men achieved a mean serum testosterone level within the normal physiologic range following 35 days of treatment with Fortesta®.[26]
- In an open label extension study Kaufman et al evaluated efficacy of testosterone 1.62% gel up to one year of therapy.[30] Results from the study show that testosterone 1.62% is effective in replacement therapy with 78% (95% CI, 70.0% to 84.6%) and 87.0% (95% CI, 66.4% to 97.2%) of the different dosing regimens reaching therapeutic levels of testosterone.[31]
- Blick et al evaluated the use of testosterone replacement therapy in human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS). In this prospective cohort study the effects of replacement therapy with testosterone 1% (Testim®) were evaluated in HIV/AIDS patients. During the twelve month study, but non-HIV/AIDS patients and HIV/AIDS cohorts had significant increases in total testosterone and free testosterone to within normal limits along with increased sexual function and improved and decreased antidepressant use. Body composition profiles improved significantly in men without HIV/AIDS ($P\leq0.05$) and remained stable in men with HIV/AIDS during the twelve months of follow-up. [32]
- A meta-analysis of 16 studies evaluating testosterone supplementation for the diagnosis or erectile dysfunction was conducted by Jain et al. The overall response rate was 57% ± 2.3% (203 of 356 cases). Among the studies with stratified results, 75 of 117 (64% ± 4%) men with a primary etiology responded and 53 of 120 (44% ± 2.9%) men with a secondary etiology responded, which was determined to be statistically significant ($P<0.001$). [33]

Key Points within the Medication Class

- According to Current Clinical Guidelines[14-17]:
    - Intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients.
    - The oral alkylated androgens are not recommended due to poor androgen effects, adverse lipid changes, and hepatic side effects, but may be considered when other agents are not suitable.

- The selection of testosterone replacement therapy should be a joint decision between the patient and physician and should be made after consideration of patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden and cost.
- The short-acting preparations may be preferred over long-acting depot preparations when initiating treatment in patients with late-onset hypogonadism due to the potential development of an adverse event that may require rapid discontinuation of testosterone replacement therapy. Treatment guidelines do not recommend one topical preparation over another.

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Therapeutic Class Overview
Anticonvulsants

Therapeutic Class

Overview/Summary: The anticonvulsants class encompasses over 20 different chemical entities including barbiturates, benzodiazepines, hydantoins, succinimides, and miscellaneous anticonvulsants. These agents are Food and Drug Administration (FDA)-approved for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. The goals of epilepsy management are to control seizures, avoid treatment side effects and maintain or restore patients' quality of life. Anticonvulsants work by various mechanisms of action to achieve these treatment goals, often by stabilizing neuronal membranes in the brain to reduce seizure activity and to elevate the seizure threshold. Some anticonvulsants are also FDA-approved for the prevention of migraines and the management of bipolar disorder, fibromyalgia, neuropathic pain, along with other non-seizure conditions.[1,2] The specific FDA-approved indications for each of these agents are outlined in Table 1.[3-49] Seizure disorders can be organized into three major categories: generalized seizures, focal seizures, and unknown. Generalized seizures are subdivided into tonic-clonic (in any combination), absence, myoclonic, clonic, tonic, and atonic seizures types. Absence seizures are further divided into typical, atypical, and absence with special features (myoclonic absence, eyelid myoclonia) while myoclonic seizures are further divided into myoclonic, myoclonic atonic, and mycolonic. Epileptic spasms fall into the unknown seizure category. However, based on FDA-approved labeling, seizures are more commonly referred to as partial (or focal) seizures and generalized tonic-clinical seizures.[50]

Pharmacologic management of epilepsy should be individualized, and focused on controlling seizures, avoiding treatment-related adverse events and maintaining or restoring quality of life. Prior to 1990, six major antiepileptic drugs were available for the treatment of various forms of epilepsy, including carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone (metabolized to phenobarbital) and valproic acid. Over the past two decades, many new chemical entities or formulations have become available in the United States. Some advantages of the newer antiepileptic drugs include more favorable adverse event profile, drug interaction profiles and ability to treat without the requirement of serum concentration monitoring.[51-53] Anticonvulsants are primarily used for their FDA-approved indications; however, in instances of severe and refractory seizure disorders, anticonvulsants may be used off-label for seizure types that are non-FDA approved. Currently there are several generic anticonvulsants available, and at least one generic agent is available within each anticonvulsant subclass.[1] Many anticonvulsants contained within this class review, such as pregabalin and lacosamide, are controlled substances. Anticonvulsants are available in a varity of formulations, which include: immediate release, delayed-release, and extended-release capsules or tablets; sprinkle capsules; chewable tablets; orally disintegrating tablets; solutions or suspensions; and injections.[3-49]

Table 1. Current Medications Available in Therapeutic Class[1-49]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Barbiturates			
Phenobarbital	Anticonvulsant (tablet), emergency control of certain acute convulsive episodes (injection), long term anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures (injection), treatment of generalized and partial seizures (elixir), hypnotic, for short term treatment of insomnia (injection), preanesthetic (injection), sedative	Elixir: 20 mg/5 mL Injection: 65 mg/mL 130 mg/mL Tablet: 15 mg 16.2 mg 30 mg 32.4 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		60 mg 64.8 mg 97.2 mg 100 mg	
Primidone (Mysoline®*)	Control of grand mal, psychomotor, and focal epileptic seizures, used alone or concomitantly with other anticonvulsants	Tablet: 50 mg 250 mg	√
Benzodiazepines			
Clobazam (Onfi®)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients two years of age or older	Tablet: 5 mg 10 mg 20 mg	-
Clonazepam (Klonopin®*)	Treatment of Lennox-Gastaut Syndrome (petit mal variant), akinetic, and myoclonic seizures, alone or as adjunct therapy, treatment of panic disorder, with or without agoraphobia	Orally disintegrating tablet: 0.125 mg 0.25 mg 0.5 mg 1 mg 2 mg Tablet: 0.5 mg 1 mg 2 mg	√
Diazepam (Diastat®*)	Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity	Rectal gel: 2.5 mg 10 mg 20 mg	√
Hydantoins			
Ethotoin (Peganone®)	Control of generalized tonic-clonic and complex partial seizures	Tablet: 250 mg	-
Phenytoin (Phenytek®*, Dilantin®*)	Control of status epilepticus of the grand mal type (injection), control of generalized tonic-clonic and complex partial seizures (chewable tablet, extended-release capsule, suspension), prevention and treatment of seizures occurring during or following neurosurgery	Chewable tablet: 50 mg Extended-release capsule: 30 mg 100 mg 200 mg 300 mg Injection: 50 mg/mL Suspension: 125 mg/5 mL	√
Succinimides			
Ethosuximide	Control of absence epilepsy	Capsule:	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Zarontin®*)		250 mg Syrup: 250 mg/5 mL	
Methsuximide (Celontin®)	Control of absence seizures that are refractory to other drugs	Capsule: 300 mg	-
Anticonvulsants, Miscellaneous			
Brivaracetam (Briviact®)	Adjunctive therapy in the treatment of partial seizures	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg Oral solution: 10 mg/mL Injection: 50 mg/5 mL	-
Carbamazepine (Carbatrol®*, Epitol®*, Equetro®, Tegretol®*, Tegretol XR®*)	Generalized tonic-clonic seizures, mixed seizure patterns, partial seizures with complex symptomatology, acute treatment of manic or mixed episodes associated with bipolar disorder (Equetro®), trigeminal neuralgia	Chewable tablet: 100 mg Extended-release capsule: 100 mg 200 mg 300 mg Extended-release tablet: 100 mg 200 mg 400 mg Suspension: 100 mg/5 mL Tablet: 200 mg	√
Divalproex (Depakote®*, Depakote ER®*)	Adjunctive therapy in patients with multiple seizure types, that include absence seizures (extended-release, delayed-release), monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), acute treatment of manic or mixed episodes associated with bipolar disorder (extended-release), prophylaxis of migraine headaches (extended-release, delayed-release)	Capsule (sprinkle): 125 mg Delayed-release tablet: 125 mg 250 mg 500 mg Extended-release tablet:	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		250 mg 500 mg	
Eslicarbazepine (Aptiom®)	Adjunctive treatment of partial-onset seizures	Tablet: 200 mg 400 mg 600 mg 800 mg	-
Ezogabine (Potiga®)	Adjunctive therapy in the treatment of partial onset seizures	Tablet: 50 mg 200 mg 300 mg 400 mg	-
Felbamate (Felbatol®*)	Patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use	Suspension: 600 mg/5 mL Tablet: 400 mg 600 mg	√
Gabapentin (Neurontin®*)	Adjunctive therapy in the treatment of partial seizures, postherpetic neuralgia	Capsule: 100 mg 300 mg 400 mg Solution: 250 mg/5 mL Tablet: 600 mg 800 mg	√
Lacosamide (Vimpat®)	Adjunctive therapy in the treatment of partial seizures	Injection: 200 mg/20 mL Solution: 10 mg/mL Tablet: 50 mg 100 mg 150 mg 200 mg	-
Lamotrigine (Lamictal®*, Lamictal CD®*, Lamictal ODT® Lamictal XR®*)	Adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome (chewable and orally disintegrating tablets), monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single antiepileptic drugs, maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients	Chewable tablet: 2 mg 5 mg 25 mg Extended-release tablet: 25 mg 50 mg 100 mg 200 mg 250 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	treated for acute mood episodes with standard therapy (chewable and orally disintegrating tablets)	300 mg Orally disintegrating tablet: 25 mg 50 mg 100 mg 200 mg Tablet: 25 mg 50 mg 100 mg 150 mg 200 mg 250 mg	
Levetiracetam (Elepsia XR®, Keppra®*, Keppra XR®*)	Adjunctive therapy in the treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy (injection, tablets), adjunctive therapy in the treatment of partial seizures, adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (injection, tablets),	Extended-release tablet: 500 mg 750 mg Extended-release tablet (Elepsia XR®): 1,000 mg 1,500 mg Injection: 500 mg/5 mL Solution: 100 mg/mL Tablet: 250 mg 500 mg 750 mg 1,000 mg	√
Oxcarbazepine (Oxtellar XR®, Trileptal®*)	Monotherapy and adjunctive therapy in the treatment of partial seizures	Extended-release tablet: 150 mg 300 mg 600 mg Suspension: 300 mg/5 mL Tablet: 150 mg 300 mg 600 mg	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Perampanel (Fycompa®)	Adjunctive therapy in the treatment of partial onset seizures†	Tablet: 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	-
Pregabalin (Lyrica®)	Adjunctive therapy in the treatment of partial seizures, fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy, neuropathic pain associated with spinal cord injury, postherpetic neuralgia	Capsule: 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg 300 mg Solution: 20 mg/mL	-
Rufinamide (Banzel®)	Adjunctive therapy for seizures associated with Lennox–Gastaut syndrome	Suspension: 40 mg/mL Tablet: 200 mg 400 mg	-
Tiagabine (Gabitril®*)	Adjunctive therapy in the treatment of partial seizures	Tablet: 2 mg 4 mg 12 mg 16 mg	√
Topiramate (Qudexy XR®, Topamax®*, Trokendi XR®)	Adjunctive therapy in patients with partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for seizures associated with Lennox–Gastaut syndrome, monotherapy (initial) in patients with partial onset or primary generalized tonic-clonic seizures, prophylaxis of migraine headaches	Capsule (sprinkle): 15 mg 25 mg Tablet: 25 mg 50 mg 100 mg 200 mg Extended-release capsule: 25 mg 50 mg 100 mg 150 mg 200 mg	√
Valproic acid (Depakene®* Stavzor®)	Adjunctive therapy in patients with multiple seizure types, that include absence seizures, monotherapy and adjunctive therapy of complex partial seizures and simple and	Capsule: 250 mg Delayed-	√

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	complex absence seizures, acute treatment of the manic episodes associated with bipolar disorder (delayed-release), prophylaxis of migraine headaches (delayed-release)	release capsule: 125 mg 250 mg 500 mg Solution: 250 mg/5 mL	
Vigabatrin (Sabril®)	Adjunctive therapy for adult patients with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss (tablet), monotherapy for pediatric patients (one month to two years of age) with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss (solution)	Solution (powder): 500 mg Tablet: 500 mg	-
Zonisamide (Zonegran®*)	Adjunctive therapy in the treatment of partial seizures	Capsule: 25 mg 50 mg 100 mg	√

*Generic available in at least one dosage form or strength.
†With or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Evidence-based Medicine

- The safety and efficacy of anticonvulsants, as monotherapy and as adjunct therapy, have been evaluated in numerous clinical trials for their respective FDA-approved indications. Selected trials have evaluated the use of anticonvulsants for the treatment of various seizures disorders as well as non-seizure disorders.[54-198]
- The safety and efficacy of Elepsia XR® (levetiracetam extended-release tablets) was established based on the clinical trials used to approve Keppra ER® (levetiracetam extended-release tablets).[20,49]
- Hancock et al conducted a meta-analysis of 14 randomized controlled trials which included infants and children with infantile spasms. Treatment with vigabatrin was associated with a complete cessation of spasms in 7/20 (35%) patients compared to 2/20 (10%) patients treated with placebo. A >70% reduction in the number of spasms was reported in 40% of patients treated with vigabatrin compared to 15% of patients treated with placebo.[55]
- Another meta-analysis by Hancock et al included trials that evaluated the safety and efficacy of felbamate, lamotrigine, rufinamide and topiramate in the treatment of Lennox-Gastaut Syndrome (LGS). While all of these agents demonstrated some efficacy, the optimum treatment of LGS remained uncertain as no single drug was highly efficacious. Felbamate, lamotrigine, rufinamide and topiramate may be helpful as add-on therapy.[145]
- The results of a study by Ng et al demonstrated that the mean percent reduction in weekly drop seizures was 41.2% with clobazam 0.25 mg/kg/day (P=0.0120), 49.4% with clobazam 0.5 mg/kg/day (P=0.0015) and 68.3% with clobazam 1.0 mg/kg/day (P<0.0001) compared to 12.1% for placebo.[125]
- In a study by Porter et al, treatment with ezogabine 600, 900 and 1,200 mg reduced the total monthly seizure frequency from baseline by 23, 29 and 35% compared to 13% with placebo (P<0.001 for all).[55] In a second study of patients with drug-resistant partial epilepsy, ezogabine 1,200 mg daily reduced the total monthly seizure frequency from baseline by 44.3% compared to 17.5% with placebo (P<0.001).[70]
- Perampanel is approved as adjunctive therapy in patients with partial onset seizures. In one study perampanel 8 or 12 mg significantly reduced seizure frequency compared to placebo (P=0.0261 and P=0.0158 for 8 and 12 mg, respectively); however, there was no significant difference in the

proportion of patients who achieved a seizure reduction >50% from baseline compared to the placebo group.[87] Similar results were reported in a second study (P<0.001 and P=0.011 for 8 and 12 mg, respectively); however, more patients treated with perampanel 8 or 12 mg had a reduced seizure frequency >50% from baseline compared to placebo (P=0.002 and P<0.001 for 8 and 12 mg, respectively).[88] In a third study, treatment with perampanel 4 or 8 mg significantly reduced seizure frequency compared to placebo (P=0.003 and P<0.001 for 4 mg and 8 mg, respectively). Moreover, a greater proportion of patients treated with perampanel 4 or 8 mg achieved a reduction in seizure frequency >50% from baseline compared to placebo (P=0.013 and P<0.001 for 4 and 8 mg, respectively).[89]

- Eslicarbazepine was evaluated in three double-blind, multi-center, randomized, placebo-controlled trials. Each of these trials compared adjunctive treatment with eslicarbazepine to placebo in patients who were currently receiving one to three anti-epileptic drugs. In the first and second published trials, the investigators compared eslicarbazepine at a dose of 400, 800 and 1,200 mg once daily to placebo for 12 weeks.[64,65] In a pooled analysis of the three studies (third trial has not been published), the primary endpoint of seizure frequency per four weeks was 7.7 in the placebo group (N=406) compared to 7.3 with eslicarbazepine 400 mg (N=185; P=0.8136), 6.1 with 800 mg (N=375; P=0.0001) and 5.7 with 1,200 mg (N=352; P<0.0001). The proportion of patients who achieved a seizure reduction of at least 50% from baseline was 20.9% in the placebo group compared to 22.2% with eslicarbazepine 400 mg, 32.3% with 800 mg and 40.9% with 1,200 mg.[64-66] A fourth double-blind, multi-center, randomized, placebo-controlled trial compared adjunctive treatment with eslicarbazepine to placebo in patients who were currently receiving one to two anti-epileptic drugs. Investigators compared eslicarbazepine at a dose of 800 and 1,200 mg once daily to placebo for 12 weeks. The primary endpoint of seizure frequency per four weeks was 7.3 in the placebo group (N=88) compared to 5.7 with eslicarbazepine 800 mg (N=85; P=0.048) and 5.5 with 1,200 mg (N=80; P=0.021). The proportion of patients who achieved a seizure reduction of at least 50% from baseline was 22.6% in the placebo group compared to 34.5% with eslicarbazepine 800 mg (P=0.106) and 37.7% with 1,200 mg (P=0.020).[67]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The 2012 National Institute for Clinical Excellence guideline recommends carbamazepine and lamotrigine as first-line treatment of children, young people, and adults with newly diagnosed focal seizures (partial seizures). Levetiracetam, oxcarbazepine or sodium valproate should be offered if first-line therapies prove inadequate, and adjunctive therapy should be considered if a second well-tolerated antiepileptic also proves inadequate. Sodium valproate is recommended first-line for the treatment of children, young people, and adults with newly diagnosed generalized tonic-clonic focal seizures. Lamotrigine should be offered if sodium valproate proves inadequate, and carbamazepine and oxcarbazepine should be considered. Adjunctive therapy with clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate should be offered to all patients if first-line therapies are inadequate.[199]
    - Vigabatrin (oral solution) is Food and Drug Administration (FDA)-approved for the management of infantile spasm. According to the 2012 American Academy of Neurology medical management of infantile spasms guideline, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone and vigabatrin. Evidence suggests that adrenocorticotropic hormone may be preferred over vigabatrin for short-term management.[200]
    - Clobazam, clonazepam, lamotrigine, rufinamide and topiramate are FDA-approved for the management of Lennox Gastaut Syndrome. Sodium valproate is recognized as first-line, with lamotrigine recommended as adjunctive therapy if needed.[199]
    - Treatment guidelines recommend valproate and carbamazepine as potential beneficial options for the management of adults with a manic or mixed bipolar episode. Lamotrigine, topiramate, or gabapentin are unlikely beneficial in this clinical situation and oxcarbazepine may be considered for treatment. With regard to bipolar depression in adults, lamotrigine should be considered as a potential first-line option, and patients who do not respond to initial monotherapy should receive combination therapy with lithium.[201-205]

  - Divalproex, topiramate and valproic acid are FDA-approved for the prophylaxis of migraine headaches, and all should be offered for migraine prevention according to the 2012 guidelines from the American Academy of Neurology/American Headache Society. Furthermore, carbamazepine may be considered for migraine prevention as it is a possibly effective treatment, and lamotrigine is ineffective.[206]
  - According to the American Academy of Neurology, anticonvulsants, antidepressants, opioids and other pharmacologic agents (capsaicin, isosorbide dinitrate spray, and lidocaine patch) are potential treatment options for painful diabetic neuropathy. If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment.[207]
  - According to the American Academy of Neurology, first-line therapies for the management of postherpetic neuralgia include tricyclic antidepressants, gabapentin, pregabalin, opioids, and topical lidocaine. At this time the use of these therapies for long-term management remains uncertain.[208]
  - The use of anticonvulsants in the management of fibromyalgia is not addressed in the European League Against Rheumatism guidelines.[209]
- Other Key Facts:
  - The majority of anticonvulsants are available in a generic formulation, and there is at least one generic agent available within each pharmacologic class.
  - Clobazam was approved by the FDA in 2011; however, this agent has been available internationally for several years for the treatment of anxiety and epilepsy.
  - Ezogabine has a unique mechanism of action in that it may act as an anticonvulsant by reducing excitability through the stabilization of neuronal potassium channels in an “open” position.[35]
  - Perampanel is a first-in-class anticonvulsant that works as a highly selective, non-competitive AMPA-type glutamate receptor antagonist.[210]
  - The most recently FDA-approved anticonvulsant, eslicarbazepine, provides for another treatment option for patients with partial-onset seizures.

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Therapeutic Class Review
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Therapeutic Class

- **Overview/Summary:** A significant advancement in the management of type 2 diabetes has been the development of incretin-based therapies. This novel therapeutic approach is important as type 2 diabetics have been shown to have an impaired incretin response.[1] Currently, there are two classes of incretin-based therapies available: the dipeptidyl pepetidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 receptor agonists, or incretin mimetics. The DPP-4 inhibitors include alogliptin, linagliptin, saxagliptin, and sitagliptin, which are all available as single-entity agents (alogliptin [Nesina®], linagliptin [Tradjenta®], saxagliptin [Onglyza®], and sitagliptin [Januvia®]) or in fixed-dose combination products (alogliptin/metformin [Kazano®], alogliptin/pioglitazone [Oseni®], linagliptin/empagliflozin [Glyxambi®], linagliptin/metformin [Jentadueto®], saxagliptin/metformin [Kombiglyze ER®], and sitagliptin/metformin [Janumet®, Janumet XR®]).[2-12] The DPP-4 inhibitors are Food and Drug Administration (FDA)-approved as adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. Single-entity and combination agents containing alogliptin are available for use either as monotherapy or in combination with other antidiabetic agents. The fixed-dose combination products are available for use when treatment with both drug components is appropriate.[2-12]

  The DPP-4 inhibitors reversibly block the DPP-4 enzyme, which is responsible for the rapid degradation of endogenous incretin hormones. These hormones are produced by the gastrointestinal tract in response to meals and are involved in the regulation of insulin. The antidiabetic actions of endogenous incretin hormones include the enhancement of meal-stimulated insulin secretion, decreased glucagon secretion, improvements in β cell function, and slowing of gastric emptying. Through their effect on these hormones, the DPP-4 inhibitors primarily target post-prandial glucose and have also been shown to decrease fasting plasma glucose.[13,14] In general, the DPP-4 inhibitors are associated with a favorable side effect profile and also have a weight neutral effect compared to other antidiabetic agents commonly used in the management of type 2 diabetes. Compared to sulfonylureas, the risk of hypoglycemia associated with the DPP-4 inhibitors is low due to the glucose-dependent nature of incretin hormone activity. In addition, the DPP-4 inhibitors have not been associated with the same increased risk of cardiovascular disease that has been observed with the use of thiazolidinediones (TZDs). The DPP-4 inhibitors improve the function of β cells and although TZDs and metformin treat insulin resistance, these agents do not address the progressive decline in β cell function that is observed in patients with type 2 diabetes.[13-15]

  The DPP-4 inhibitors are available as fixed-dose combination products with metformin. Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization.[6-10] Additionally, alogliptin is available in a fixed-dose combination with pioglitazone. Pioglitazone is a TZD, an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ).[11] PPAR receptors are found in adipose, skeletal muscle, and liver tissue and activation of these receptors modulates transcription of insulin response genes that control glucose and lipid metabolism, providing an overall effect of increasing insulin sensitivity in muscle and adipose tissue while inhibiting hepatic gluconeogenesis.[2,11] Linagliptin is available as a fixed-dose combination with empagliflozin (Glyxambi®).[12] Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and improves glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion.[12] The net effect is an increase excretion of glucose from the body and normalization of plasma glucose levels.[12] Overall, the DPP-4 inhibitors are significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and post-prandial glucose, with no major effect on body weight. Combination therapy with a DPP-4 inhibitor and metformin consistently demonstrates improved benefits in glycemic control over monotherapy with either a DPP-4 inhibitor or metformin; limited within class head-to-head trials have been conducted.[16-63,65-68,76,77]

Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[37,61] However, a recent clinical trial suggested an increased risk of heart-failure with saxagliptin compared to placebo.[38] In April 2016, the FDA added heart failure warnings to the labeling of medications containing saxagliptin and alogliptin.[65]

With regards to the specific DPP-4 inhibitor agents, all single-entity agents are available for once-daily dosing.[2-5] Three fixed-dose combination products contain metformin immediate-release (alogliptin/metformin [Kazano®], linagliptin/metformin [Jentadueto®] and sitagliptin/metformin [Janumet®]) which are available for twice-daily dosing.[6,7,9] One fixed-dose combination product (alogliptin/pioglitazone [Oseni®]) contains pioglitazone and is dosed once daily.[11] Two fixed-dose combination products contain metformin extended-release (ER) (saxagliptin/metformin ER [Kombiglyze XR®] and sitagliptin/metformin ER [Janumet XR®]), and because of the metformin ER component, these products are available for once-daily dosing.[8,10] The fixed-dose combination product containing linagliptin and empagliflozin (Glyxambi®) is also available for once-daily dosing.[12] Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing.[3] The fixed-dose combination of alogliptin/pioglitazone [Oseni®] carries a boxed warning regarding the risk of use in patients with congestive heart failure as the TZD component may cause or exacerbate congestive heart failure in some patients.[11] Furthermore, because of the metformin component in certain fixed-dose combination products, caution is recommended with both renal and hepatic dysfunction.[6-10] In addition, these products all have a boxed warning regarding the risk of lactic acidosis due to metformin accumulation.[6-10] Currently, alogliptin, alogliptin/metformin, and alogliptin/pioglitazone are available generically.[2,6,11]

Table 1. Medications Included Within the Therapeutic Class Review[2-12]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alogliptin (Nesina®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 6.25 mg 12.5 mg 25 mg	✔
Linagliptin (Tradjenta®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg	-
Saxagliptin (Onglyza®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 2.5 mg 5 mg	-
Sitagliptin (Januvia®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 25 mg 50 mg 100 mg	-
Combination Products			
Alogliptin/ metformin (Kazano®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet (alogliptin/ metformin): 12.5/500 mg 12.5/1,000 mg	✔
Alogliptin/ pioglitazone (Oseni®)	Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2	Tablet (alogliptin/ pioglitazone): 12.5/15 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	diabetes	12.5/30 mg 12.5/45 mg 25/15 mg 25/30 mg 25/45 mg	
Linagliptin/ empagliflozin (Glyxambi®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet (linagliptin/ empagliflozin): 5/10 mg 5/25 mg	-
Linagliptin/ metformin (Jentadueto®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet (linagliptin/ metformin): 2.5/500 mg 2.5/850 mg 2.5/1,000 mg	-
Saxagliptin/ metformin (Kombiglyze XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡	Tablet (saxagliptin/ metformin ER): 5/500 mg 2.5/1,000 mg 5/1,000 mg	-
Sitagliptin/ metformin (Janumet®, Janumet XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes§	Tablet (sitagliptin/ metformin): 50/500 mg 50/1,000 mg Tablet (sitagliptin/ metformin ER): 50/500 mg 50/1,000 mg 100/1,000 mg	-

*When treatment with both linagliptin and empagliflozin is appropriate.
†When treatment with both linagliptin and metformin is appropriate.
‡When treatment with both saxagliptin and metformin extended-release is appropriate.
§When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.
ER=extended-release, XR=extended-release

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitors in the management of type 2 diabetes.[16-63,65-68,76,77] Of note, there have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.[6-12] Available trials evaluating the fixed-dose combination of sitagliptin/metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.[57]
- In studies, alogliptin was associated with significant decreases in HbA_{1c} from baseline as monotherapy compared to placebo. In addition, in studies with metformin or pioglitazone combination therapy with alogliptin, significant decreases in HbA_{1c} were observed and more patients reached specific HbA_{1c} goals compared to the monotherapy comparator. As an add-on therapy in patients already being treated with metformin, pioglitazone, metformin/pioglitazone, glipizide or insulin therapy, the additions of alogliptin demonstrated significant improvements in HbA_{1c} from baseline compared to placebo.[16-23]
- Overall, linagliptin is more effective compared to placebo in decreasing HbA_{1c} and fasting plasma glucose (FPG) as monotherapy or as add-on therapy to other antidiabetic agents in type 2 diabetics

not achieving glycemic goals. In addition, more patients achieved glycemic goals (HbA_{1c} <7.0%) with linagliptin compared to placebo.[24-27] Combination therapy with linagliptin and pioglitazone has been shown to be more efficacious in terms of reducing HbA_{1c} compared to pioglitazone monotherapy.[53]
- Similar results were achieved with saxagliptin when compared to placebo.[29-36] In addition, combination therapy with saxagliptin and metformin was "superior" to monotherapy with either agent in observed reductions in HbA_{1c}, FPG, and post-prandial glucose (PPG), and a significantly greater proportion of patients achieved glycemic goals with combination therapy.[55,56]
- Similar to the results of clinical trials evaluating other DPP-4 inhibitors, sitagliptin is consistently more efficacious in improving glycemic control compared to placebo, and combination therapy with sitagliptin and metformin is more efficacious than monotherapy with either agent.[40-51]
- In a single head-to-head trial, saxagliptin demonstrated non-inferiority to sitagliptin in reducing HbA_{1c}. However, a significantly greater proportion of patients achieved an HbA_{1c} ≤6.5% and achieved significant reductions in FPG with sitagliptin compared to saxagliptin.[52] While the beneficial effects of the DPP-4 inhibitors in improving HbA_{1c}, FPG, and PPG compared to placebo are well established, observed improvements in body weight and β cell function with these agents are not consistent.[16-63,64]
- In general, meta-analyses and systematic reviews evaluating incretin-based therapies, including the DPP-4 inhibitors, support the results observed in randomized-controlled trials evaluating these agents.[37,54,62-64,65-68] Two meta-analyses revealed that DPP-4 inhibitors are not associated with an increased risk of cardiovascular events or cancer compared to placebo or other antidiabetic agents, respectively.[37,61]

Key Points within the Medication Class
- According to Current Clinical Guidelines for the management of type 2 diabetes:[69-73,78-80]
    - Metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals.
    - At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
    - The DPP-4 inhibitors are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.
    - Clinical guidelines note a lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin as advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents.
    - Patients who are not appropriate for initial therapy with metformin may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one DPP-4 inhibitor over another is not stated.
- Other Key Facts:
    - All single-entity agents are available for once-daily dosing.[2-5]
    - Single-entity linagliptin is the only agent within the class that does not require renal and hepatic dosing.[3]
    - The metformin component in certain fixed-dose combination products requires caution in patients with renal and hepatic dysfunction.[6-10]
    - The DPP-4 inhibitors are associated with low risk of hypoglycemia and is weight neutral when used as monotherapy.[2-12]
    - DPP-4 inhibitors improve the function of β cells in the pancreas.[1-13-15]

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Therapeutic Class Overview
Incretin Mimetics

Therapeutic Class

- **Overview/Summary:** The glucagon-like peptide-1 (GLP-1) receptor agonists, or incretin mimetics, are one of two incretin-based therapies currently available for the management of type 2 diabetes. Specifically, albiglutide (Tanzeum®), dulaglutide (Trulicity®), exenatide (Bydureon®, Byetta®), and liraglutide (Victoza®) are Food and Drug Administration-approved as an adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-5] This medication class was developed to mimic the effects of endogenous GLP-1, a hormone that maintains glucose homeostasis through several different mechanisms. The incretin mimetics work by stimulating insulin secretion, inhibiting glucagon secretion, improving β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. In addition, these agents increase insulin secretion from pancreatic β cells in the presence of elevated glucose concentrations. Therefore, due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia compared to other antidiabetic agents.[6] The incretin mimetics are most commonly associated with gastrointestinal-related adverse events and all agents are associated with the risk of developing pancreatitis. Only albiglutide, dulaglutide, exenatide extended-release, and liraglutide have boxed warnings regarding the risk of thyroid C-cell tumors. The incretin mimetics are available as subcutaneous injections. Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals), exenatide IR is administered twice-daily (60 minutes before meals) and liraglutide is administered once-daily (independent of meals).[1-5] There are currently no generic incretin mimetics available.

Table 1. Current Medications Available in Therapeutic Class[1-5]

Generic (Trade Name)	Food and Drug Administration Approved Indications*	Dosage Form/Strength	Generic Availability
Albiglutide (Tanzeum®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Pre-filled pen powder (solution) for Injection: 30 mg 50 mg	-
Dulaglutide (Trulicity®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Solution for injection (pen or syringe): 0.75 mg/0.5 mL 1.5 mg/0.5 mL	-
Exenatide (Bydureon®, Byetta®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Extended-release powder (suspension) for injection (Bydureon®; pen or dual chamber pen): 2 mg Solution for injection (Byetta®; pen): 250 µg/mL	-
Liraglutide (Victoza®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Solution for Injection (pen): 6 mg/mL	-

* Consider reducing the dosage of concomitantly administered insulin secretagogues (e.g., sulfonylureas) and/or insulin to reduce the risk of hypoglycemia.

Evidence-based Medicine

- In general, the incretin mimetics have been evaluated in clinical trials as add-on therapy to treatment regimens of established antidiabetic agents. Data consistently demonstrate that incretin mimetics are

associated with positive effects on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), post-prandial glucose (PPG), and body weight. In addition, glycemic goals were consistently achieved when an incretin mimetic was added to existing treatment regimens.[7-59]

- When compared to other antidiabetic agents (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, insulin therapy), efficacy data are not consistent, with the incretin mimetics achieving superiority or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents.[7-59]
- Safety and efficacy of dulaglutide has been evaluated in an extensive clinical trials program including monotherapy trials, add-on therapy to metformin, metformin and sulfonylurea, pioglitazone and insulin (with or without metformin).[7-12]
    - The 52-week double-blind AWARD-3 study of patients inadequately treated with diet and exercise, or with diet and exercise and one anti-diabetic agent used at submaximal dose (N=807). At week 26, noninferiority in reduction of hemoglobin A1c (HbA_{1c}) was demonstrated between dulaglutide and metformin for both the 0.75 mg weekly and 1.5 mg weekly doses (-0.7% and -0.8% vs. -0.6%, respectively).[7]
    - AWARD-1 was a 52-week placebo-controlled study that evaluated dulaglutide safety and efficacy as an add-on to maximally tolerated doses of metformin (≥1500 mg per day) and pioglitazone (up to 45 mg per day) (N=976). At 26 weeks, treatment with dulaglutide 0.75 mg and 1.5 mg once weekly resulted in a statistically significant reduction in HbA_{1c} compared to placebo (-0.8% and -1.1 placebo corrected difference, respectively; P<0.001 for both comparisons) and compared to exenatide (-0.3% and -0.5 exenatide-corrected difference, respectively; P<0.001 for both comparisons).[12]
- Albiglutide was compared in a non-inferiority trial with liraglutide. Albiglutide effectively reduced HbA_{1c}; however, based upon the prespecified non-inferiority parameters, the criteria for non-inferiority of albiglutide were not met. The HbA_{1c} treatment goal of <7.0% was achieved by 42% of albiglutide-treated patients and 52% of liraglutide-treated patients (P=0.0023), while the goal of HbA_{1c} lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009).[14]
- Few head-to-head clinical trials within the class have been conducted. Compared to exenatide, exenatide extended-release significantly decreased HbA_{1c}, and achieved similar decreases in body weight.[30,37] In a single trial, liraglutide significantly decreased HbA_{1c} compared to exenatide. Furthermore, liraglutide significantly decreased FPG while exenatide significantly decreased PPG.[45]
- In a 26-week open-label trial, there was a significantly greater reduction from baseline in HbA_{1c} at 26 weeks for patients treated with liraglutide compared to exenatide extended-release (-0.21%; 95% confidence interval [CI], -0.08 to -0.33). In addition, significantly more patients receiving liraglutide achieved an HbA_{1c} <7.0% compared to patients treated with exenatide extended-release (60 vs 53%; P=0.0011). Reductions in bodyweight also favored treatment with liraglutide (-0.90 kg; 95% CI, -0.39 to -1.40).[38]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Type 2 diabetes: [60-66]
        - Metformin remains the cornerstone to most antidiabetic treatment regimens.
        - Patients with high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals.
        - The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.
            - A lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss are noted as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents. [60-66]

- No one incretin mimetic is recommended or preferred over another. [52-57]

- Other Key Facts:
  - Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals).[1-3]
  - Exenatide IR is administered twice-daily (60 minutes before meals).[4]
  - Liraglutide is administered once-daily (independent of meals).[5]
  - No generic incretin mimetics are available.

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Therapeutic Class Overview
Insulins

Therapeutic Class

- **Overview/Summary:** This review will focus on the antidiabetic insulins, including human insulin products and synthetic insulin analogs.[1-18] Insulin products are Food and Drug Administration (FDA)-approved improve glycemic control in patients with diabetes mellitus (DM) type 1 and type 2. DM is a group of metabolic disorders with types 1 and 2 being the broadest categories. All categories of DM ultimately results in hyperglycemia, but the etiologies for each are distinct and may include reduced insulin secretion, decreased glucose utilization, or increased glucose production. Due to the metabolic dysregulation of DM, secondary pathophysiologic changes in multiple organ systems occur. Examples of severe complications that may occur include end-stage renal disease (ESRD), nontraumatic lower extremity amputation, and adult blindness. Additionally, it also predisposes the patient to cardiovascular disease.[19] Overall, there are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. Available insulin products are summarized in Table 1. Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection.[1-18,20] Additionally, regular insulin is also formulated as an inhalation.[4] At least one formulation of all insulin products are supplied in multidose vials, with the exception of insulin degludec.[1-18] Inhaled insulin powder is formulated in disposable, single-use cartridges, known as Technosphere® which provided a more efficient inhalation device than what has been used in the past.[4] Another inhaled formulation of regular insulin, Exubera®, was previously FDA-approved; however, this agent was removed from the market in 2007 due to low patient and provider acceptance.[21] All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Several agents are also formulated with a higher concentration, regular insulin as 500 units/mL (U-500; Humulin® R U-500), and insulin glargine as 300 units/mL (U-300; Toujeo® SoloSTAR) and insulin degludec (Tresiba®) and insulin lispro (Humalog U-200®).[1-18]

Table 1. Current Medications Available in the Therapeutic Class[1-18]

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Products			
Insulin aspart (NovoLog®, NovoLog® FlexPen, NovoLog® PenFill)	To improve glycemic control in diabetes mellitus*	Cartridge: 100 units/mL Pen: 100 units/mL Vial: 100 units/mL	-
Insulin degludec (Tresiba®)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL 200 units/mL	-
Insulin detemir (Levemir®, Levemir® FlexTouch)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin glargine (Lantus®, Lantus® SoloSTAR, Toujeo® SoloSTAR)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL (Lantus® SoloSTAR) 300 units/mL	-

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
		(Toujeo® SoloSTAR) Vial: 100 units/mL	
Insulin glulisine (Apidra®, Apidra® SoloSTAR)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin lispro (Humalog®, Humalog® KwikPen, Humalog® U-200 KwikPen)	To improve glycemic control in diabetes mellitus*	Cartridge: 100 units/mL Pen: 100 units/mL 200 units/mL Vial: 100 units/mL	-
Insulin NPH (isophane), (Humulin® N, Humulin® N KwikPen, Novolin® N, Novolin® N ReliOn)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin regular (Afrezza®, Humulin® R, Humulin® R U-500, Humulin® R U-500 KwikPen, Novolin® R)	To improve glycemic control in diabetes mellitus* Treatment of diabetic patients with marked insulin resistance*,†	Inhalation powder (Afrezza®): 4 units/cartridge Inhalation powder pack (Afrezza®): 4 units-8 units 8 units-12 units Vial: 100 U/mL 500 U/mL (Humulin® R U-500, Humulin® R U-500 KwikPen)	-
Combination Products			
Insulin aspart/insulin aspart protamine (NovoLog® Mix 70/30, NovoLog® 70/30 Flex Pen)	To improve glycemic control in diabetes mellitus*	Pen: 70/30 units/mL Vial: 70/30 units/mL	-
Insulin lispro/insulin lispro protamine (Humalog® Mix 50/50, Humalog® Mix 75/25, Humalog® Mix 50/50 KwikPen, Humalog® Mix 75/25 KwikPen)	To improve glycemic control in diabetes mellitus*	Pen: 50/50 units/mL 75/25 units/mL Vial: 50/50 units/mL 75/25 units/mL	-
Insulin, regular/insulin, NPH (Humulin® 70/30, Humulin®	To improve glycemic control in diabetes mellitus*	Pen: 70/30 units/mL	-

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
70/30 KwikPen, Humulin® 70/30 Pen, Novolin® 70/30, Novolin® 70/30 ReliOn)		Vial: 70/30 units/mL	

FDA=Food and Drug Administration
*Includes diabetes mellitus type 1 and type 2. Generally, these agents have not been studied for the treatment of type 2 diabetes in pediatric patients. Additionally, some agents may carry an indication for use in pediatric patients, but have never been studied in that population.
†Humulin® R U-500 only

Evidence-based Medicine

- There are numerous clinical trials demonstrating the safety and efficacy of insulin products in the management of diabetes type 1 and 2.[22-157] Of note, only head-to-head or active-comparator trials have been included as insulin is a well-established treatment.
- The efficacy and safety of insulin degludec was evaluated in the BEGIN clinical trial program. This included multiple 26-week and 52-week clinical trials with several trials being extended to 78 or 104 weeks in order to gather additional long-term safety and efficacy data. Insulin degludec once-daily injection was evaluated in both insulin-naïve and insulin-experienced adults with type 1 and 2 diabetes who had inadequate blood sugar control at trial entry.[13,47-49,75-81]
    - Hemoglobin A1c (HbA1c) reduction was in line with reductions achieved with insulin glargine and insulin detemir (-0.3 to -0.6% decrease from baseline in type 1 DM and -1.0% to -1.5% decrease from baseline in type 2 DM).[13,47-49,75-81]
    - In addition, the agent was associated with a lower risk of hypoglycemia compared to insulin glargine.[13,47-49,75-81]
    - A meta-analysis of four of these trails demonstrated a lower rate of overall and nocturnal hypoglycemia in type 1 and 2 DM.[82]
    - A concentrated formulation of insulin degludec (200 units/mL) was compared to the standard formulation of insulin glargine with similar results.[83]
- The safety and efficacy of inhaled regular insulin (Afrezza®) in both diabetes type 1 and type 2. Clinical trials were 24 weeks each.[4,156,157]
    - For type 1 diabetes, inhaled regular insulin was non-inferior to insulin aspart for mean reduction in HbA_{1c}. However, it provided less HbA_{1c} reduction than insulin aspart (-0.4% vs -0.21%). On the other hand, there was a reduction in the rate of hypoglycemia (9.8 vs 14.0 events per subject month; P<0.0001) and less weight gain (−0.39 kg vs 0.93 kg; P=0.0102) with inhaled regular insulin.
    - For type 2 diabetes, mean reduction in HbA_{1c} was significantly greater in the insulin group compared to the placebo group (-0.82% vs -0.42%; 95% confidence interval [CI]: −0.57 to −0.23; P<0.0001).
- The safety and efficacy of insulin glargine U-300 (Toujeo®) was evaluated in four clinical trials. Each study compared insulin glargine U-300 to insulin glargine U-100 in an open label design over 26 weeks of therapy.
    - In all studies, insulin glargine U-300 was shown to be non-inferior to insulin glargine U-100. Additionally, the dose of basal glargine insulin required was higher in all studies for U-300 (requiring 11% to 17.5% more units). Generally, both U-100 and U-300 had similar rates of adverse events, including hypoglycemia and all three studies showed similar changes in weight.[12,84-86]
- Differences in safety and efficacy of insulin preparations are modest with slightly better improvement in in HbA_{1c} with the rapid-acting analogues compared to regular insulin.[45,46]
- Long-acting insulin analogs have been shown to be at least as effective as NPH insulin in HbA_{1c} reduction, with some studies showing a significant improvement associated with the long-acting insulin analogs compared with NPH insulin with similar rates of side effects.[68,115,116,118]

- When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in type 2 diabetics.[50,51,88-90]
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Key Points within the Medication Class

- According to Current Clinical Guidelines:[158-168]
    - The goal of treatment for both type 1 and type 2 DM is to control hyperglycemia and reduce the risk of long-term complications.
    - For patients with type 1 DM, insulin therapy is required due to pathogenesis of the disease. The standard approach to therapy is a regimen that includes long-acting basal insulin and rapid-acting prandial insulin tailored to the individual.
    - For type 2 DM, there are many more options for therapy, including the insulin products, oral antidiabetic agents, and other injectable antidiabetic agents.
        - Metformin remains the cornerstone of most antidiabetic treatment regimens.
        - Patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals.
        - At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
    - For both conditions, the trend in treatment is toward a patient-centered approach focusing on patient needs, preferences and tolerances, individualized treatment, and flexibility in the choice of drugs, the over-riding goal being to improve glycemic control while minimizing adverse effects.
- Other Key Facts:[1-18]
    - Insulin therapy is usually administered by subcutaneous injection. Regular insulin is also formulated as an inhalation. At least one formulation of all insulin products are supplied in multidose vials with only regular insulin not being formulated in a prefilled pen or syringe.[1-18]
    - All insulin products have at least one formulation with a concentration of 100 units/mL.[1-18]
    - A Risk Evaluation and Mitigation Strategy (REMS) is required for this inhaled regular insulin and includes requirements for patient evaluation and testing prior to initiating therapy in order to ensure appropriate patient selection (e.g., avoiding this agent in patients with underlying chronic lung disease).
    - There are currently no generic formulations of insulin; however, there are several products available over-the-counter.

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Therapeutic Class Overview
Meglitinides

Therapeutic Class

- **Overview/Summary:** The meglitinides and the sulfonylureas are two classes of oral antidiabetic medications utilized in the management of type 2 diabetes mellitus that work by stimulating the release of insulin from pancreatic β-cells. While the meglitinide and sulfonylurea agents differ in chemical structure and act on different receptors, both medication classes act by regulating potassium channels in pancreatic β-cells, thereby increasing insulin secretion.[1] The available meglitinides, nateglinide (Starlix®) and repaglinide (Prandin®), are Food and Drug Administration (FDA)-approved as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Nateglinide and repaglinide are both available as single-entity agents, and repaglinide is also available as a fixed-dose combination product with metformin (PrandiMet®). Metformin, a biguanide, improves glucose tolerance in type 2 diabetics by lowering both basal and postprandial plasma glucose. Specifically, the actions of metformin result in decreased hepatic glucose production, decreased intestinal absorption of glucose, and improvement in insulin sensitivity via increased peripheral glucose uptake and utilization. The repaglinide/metformin combination product is FDA-approved for patients already treated with a meglitinide and metformin or for patients who have inadequate glycemic control on a meglitinide or metformin alone. Due to their mechanism of action and pharmacokinetic profiles, the meglitinides are dosed three times daily with meals.[2-4] Currently, nateglinide, repaglinide, and the repaglinide/metformin combination are all available generically.

Table 1. Current Medications Available in the Class[2-4]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Nateglinide (Starlix®*)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Tablet: 60 mg 120 mg	✔
Repaglinide (Prandin®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Tablet: 0.5 mg 1 mg 2 mg	✔
Combination Products			
Repaglinide/ metformin (PrandiMet®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone	Tablet: 1/500 mg 2/500 mg	✔

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Available evidence suggests that the sulfonylureas may be associated with poorer outcomes following myocardial infarction in patients with diabetes.[1] Specifically, an increased mortality from cardiovascular disease in patients taking tolbutamine with diabetes was noted in the University Group Diabetes Study.[5] There are no long-term trials evaluating cardiovascular outcomes or mortality in patients receiving meglitinide therapy, and whether these agents are associated with adverse outcomes following a myocardial infarction is not known at this time.[1]
- Overall, meglitinides are effective in decreasing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, and postprandial glucose in patients with type 2 diabetes mellitus.
- Data from limited head-to-head clinical trials, suggest that repaglinide results in greater reductions in HbA_{1c} and fasting plasma glucose levels compared to nateglinide.[6-28]

Key Points within the Medication Class

- According to current clinical guidelines:
  - Metformin remains the cornerstone of most antidiabetic treatment regimens.
  - Patients with a high HbA_{1c} will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
  - The meglitinides are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.
  - Patients for whom initial therapy with metformin is not appropriate may be initiated on another oral antidiabetic agent, such as a sulfonylurea/meglitinide, pioglitazone, or a dipeptidyl peptidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful.
  - In addition, guidelines recognize the potential use of meglitinides when postprandial hyperglycemia is present.
  - Among all current clinical guidelines, preference of one meglitinide over another is not stated.[29-34]
- Other Key Facts:
  - Nateglinide is the only meglitinide that is available generically.

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Therapeutic Class Overview
Sodium-glucose co-transporter 2 (SGLT2) Inhibitors

Therapeutic Class

- **Overview/Summary:** Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of oral antidiabetic agents approved by the Food and Drug Association (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-7] The kidneys play a pivotal role in controlling plasma glucose concentration; reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is done in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2] SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, such as weight loss observed during clinical trials and small decreases in systolic and diastolic blood pressure.[1,2]

Table 1. Current Medications Available in Therapeutic Class[3-9]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Agent Products			
Canagliflozin (Invokana®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 100 mg 300 mg	-
Dapagliflozin (Farxiga®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg 10 mg	-
Empagliflozin (Jardiance®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 10 mg 25 mg	-
Combination Products			
Canagliflozin/ metformin (Invokamet®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg	-
Dapagliflozin/ metformin ER (Xigduo XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg	-
Empagliflozin/ linagliptin (Glyxambi®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡	Tablet: 10 mg/5 mg 25 mg/5 mg:	-

Empagliflozin/metformin (Synjardy®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes§	Tablet: 5/500 mg 5/1000 mg 12.5/500 mg 12.5/1000 mg	-

ER=extended-release
*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.
†When treatment with both dapagliflozin and metformin is appropriate.
‡When treatment with both empagliflozin and linagliptin is appropriate.
§When treatment with both empagliflozin and metformin is appropriate.

Evidence-based Medicine

- Each agent has been studied as monotherapy and dual and triple therapy compared to placebo and active controls and combinations of placebo and active controls.
- As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in FPG and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo (P values not reported).[10]
- As monotherapy in treatment-naïve patients, dapagliflozin was evaluated in two placebo-controlled trials. The first trial included 274 patients randomized to treatment with 2.5, 5 and 10 mg or placebo. At week 24, treatment with dapagliflozin 5 and 10 mg resulted in significant improvements in HbA_{1c} compared to placebo (-0.6, -0.8, -0.9 vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg groups compared to placebo (P<0.05 for both comparisons).[12]
- There have been no clinical efficacy studies conducted with Xigduo XR® (dapagliflozin/metformin) combination tablets. FDA-approval of dapagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[7] Combination therapy with metformin extended-release in patients who were treatment-naïve led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin or metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In the second study, treatment with 10 mg strength (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.[14]
- The safety and efficacy of empagliflozin monotherapy was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM (N=986). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo.[15]
- There have been no clinical efficacy studies conducted with empagliflozin/metformin combination tablets. FDA-approval of empagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[9] The safety and efficacy of empagliflozin added to metformin was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM inadequately controlled on at least 1,500 mg of metformin per day (N=637). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-20 mg/dL and -22 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo.[24] In addition, the safety and efficacy of empagliflozin was evaluated in an active-control study versus glimepiride (in combination with metformin). The study was a double-blind, active-controlled, non-inferiority design of patients with type 2 DM inadequately controlled on metformin monotherapy (N=1,545). At week 52, empagliflozin 25 mg daily meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs. -0.7%). There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride;

however the significance was not reported (-19 mg/dL vs. -9 mg/dL and -3.9 kg vs. 2 kg; P values not reported).[25]

- The safety and efficacy of empagliflozin added to linagliptin was evaluated in a 52 week double-blind, active-control, randomized trial. Change from baseline in HbA_{1c} at week 24 was significantly improved in the combination groups compared with the individual component groups (P<0.001).[32] When started as initial therapy, empagliflozin/linagliptin reduced HbA_{1c} from baseline significantly greater when compared with individual linagliptin and empagliflozin 10 mg. Empagliflozin 25 mg/linagliptin 5 mg, however, did not show a statistically significant difference compared with empagliflozin alone (P=0.179).[33]
- Similar results were observed when comparing sodium glucose co-transport 2 agents in combination for the treatment of diabetes mellitus.[17-31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[34-41]
    - Metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
        - Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
        - The role of sodium-glucose co-transporter 2 (SGLT2) inhibitors are addressed in several available treatment guidelines and are recommended as a potential alternative to metformin in patients who cannot receive that agent or as a part of two- or three-drug regimens in combination with other antidiabetic agents in patients not achieving glycemic goals.[35,38-39]

- Other Key Facts:
    - Canagliflozin is formulated with metformin in a single tablet (Invokamet®). Empagliflozin is formulated with linagliptin in a single tablet (Glyxambi®) and with metformin in a single tablet (Synjardy®). Dapagliflozin is formulated with metformin as a single extended-release tablet (Xigduo XR®).[6-9]
    - All products are dosed once daily, with the exception of canagliflozin/metformin and empagliflozin/metformin, which are dosed twice dialy.[3-9]
    - Other effects observed in trials include weight loss and small decreases in systolic and diastolic blood pressure.
    - Common adverse side effects associated with SGLT2 inhibitor use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.

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Therapeutic Class Overview
Oral Atypical (Second-Generation) Antipsychotics

Therapeutic Class Overview/Summary:
This overview will focus on the atypical antipsychotics, which are also known as second-generation antipsychotics (SGAs).[1-16] While several atypical antipsychotics are formulated as long-acting injections, these formulations will not be covered in this review. Antipsychotic medications have been used for over fifty years to treat schizophrenia and a variety of other psychiatric disorders.[17] Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine D_2 in the mesolimbic and/or mesocortical regions of the brain. Antipsychotic medications exert their effect in part by blocking D_2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with the disorder.[18]

In addition to blocking D_2 receptors in the mesolimbic pathway, FGAs also block D_2 receptors in the mesocortical, tuberoinfundibular, and nigrostriatal pathways.[18] D_2 blockade in these other pathways is thought to be responsible for the hyperprolactinemia and extrapyramidal symptoms (EPS) associated with this class.[19] FGAs may be characterized according to their affinity for the D_2 receptor. Low potency antipsychotics, such as chlorpromazine and thioridazine, are more sedating and associated with a higher incidence of anticholinergic side effects. Fluphenazine, haloperidol, pimozide, thiothixene, and trifluoperazine are high potency antipsychotics that are less sedating but associated with a higher incidence of EPS. The medium potency antipsychotics (loxapine, molindone, and perphenazine) possess a moderate risk of EPS and anticholinergic side effects.[20] With the exception of pimozide, all FGAs are indicated for use in the treatment of schizophrenia. FGAs are effective in the treatment of positive symptoms of schizophrenia, which include agitation, aggression, delusions, and hallucinations. Negative symptoms of schizophrenia which include avolition, anhedonia, alogia, affective flattening, and social withdrawal, do not respond as well to this antipsychotic class.[19] Pimozide is indicated only for the suppression of motor and phonic tics in patients with Tourette's disorder.

The term "atypical antipsychotic" was introduced in 1989 when clozapine was approved for use by the Food and Drug Administration (FDA). Originally, this term referred to an antipsychotic with a low risk of EPS.[18] As a class, SGAs or atypical antipsychotics are more selective in targeting the mesolimbic D_2 pathway. They also block or partially block serotonin $(5\text{-HT})_{2A}$ and 5-HT_{1A} receptors and have a greater affinity for 5-HT_2 receptors than D_2 receptors.[18,20] These differences in neuropharmacologic activity are associated with a lower risk of EPS and tardive dyskinesia; the risks vary with the specificity of each agent for D_2 and serotonin receptors.[18,20] Atypical antipsychotics have a more favorable outcome in the treatment of the negative symptoms of schizophrenia.[18] The SGAs are comprised of nine separate chemical entities, each with a unique neuropharmacologic and adverse event profile, mechanism of action, and chemical structure. The SGAs are aripiprazole, asenapine, brexpiprazole clozapine, cariprazine, iloperidone, lurasidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone and ziprasidone.

Although in some respects the SGAs are safer and better tolerated than the FGAs, they are still associated with a number of serious risks and side effects. For this reason, the FDA has required various warnings to be inserted in the manufacturers' product information for these agents. All agents have a black box waring regarding an increased risk of death when used in the treatment of psychosis and behavioral problems in elderly patients with dementia. Most of the deaths that prompted the addition of the warning were due to cardiac-related events (e.g., heart failure or sudden death) or infection.[21] Of note, atypical antipsychotics are not FDA-approved for this indication. With the exception of pimavanserin, all atypical antipsychotics bear a warning that alerts prescribers and patients to the risk of hyperglycemia and other metabolic changes.[1-16] Aripiprazole, brexpiprazole, lurasidone and quetiapine carry a black box warning regarding suicidality and antidepressant drugs.[1,3,9,13,14] Ziprasidone also has a warning concerning QTc interval prolongation; however, all of the SGAs can increase the QTc interval to some degree.[16]

Due to the potential side-effect risks associated with these medications, any off-label use deserves close attention. Data published in peer-reviewed journals and in national and international guidelines support the use of SGAs as a treatment option for certain off-label uses. In many of these scenarios, SGAs are reserved for patients who are refractory to other first-line treatment modalities, including both pharmacotherapy and psychotherapy, and used in adjunction to mainstream therapies, as part of a multimodal approach.

Over the past 20 years, antipsychotic use in children and adolescents has grown. In the United States, the frequency of prescribing an antipsychotic agent increased from 8.6 per 1000 children in 1996 to 39.4 per 1000 children in 2002. According to a survey of national trends in the outpatient use of antipsychotics in children and adolescents, only 14.2% of antipsychotic prescriptions in children were for patients diagnosed with psychotic disorders.[24] Indications commonly associated with antipsychotic prescribing in pediatric patients include psychosis, schizophrenia, bipolar disorder, aggressive and disruptive behavior, and tic disorders. Off-label indications with limited available evidence for the use of atypical antipsychotics in children and adolescents include autistic spectrum disorders, major depressive disorder, anxiety disorders, and eating disorders. At this time, risperidone and aripiprazole are FDA-approved for the management of children and adolescents with autism (aged 5 to 16 and 6 to 17 years, respectively). Moreover, the following agents are indicated for the treatment of schizophrenia in adolescents: aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone. Aripiprazole, asenapine, olanzapine, quetiapine and risperidone are FDA-approved for the treatment of manic or mixed bipolar I disorder in children and adolescents. None of the other available atypical antipsychotic agents are currently indicated for use in pediatric patients.[1-16]

Concerns have also been raised about the risks of combination therapy with the antipsychotics, which can multiply the risks of dangerous adverse events. The practice of polypharmacy is not supported by well-designed clinical trials published in the peer-reviewed literature. However, national and international consensus guidelines consider this approach in patients with treatment-refractory illness.

Table 1. Current Medications Available in Therapeutic Class[1-16]

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Aripiprazole (Abilify®*, Abilify Discmelt®*)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years; adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in adults and in pediatric patients aged 10 to 17 years; maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of agitation associated with bipolar I disorder, manic or mixed in adults; acute and maintenance treatment of schizophrenia in adults; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; treatment of schizophrenia in adults; adjunctive treatment to antidepressants for major depressive disorder in adults; irritability associated with autistic disorder in children and adolescents aged six to 17 years	Injection: 7.5 mg/mL Orally disintegrating tablet: 10 mg 15 mg Oral solution: 1 mg/mL Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg	✔

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Asenapine (Saphris®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults or adolescents (10 to 17 years of age); adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder; acute and maintenance treatment of schizophrenia in adults	Sublingual tablet: 2.5 mg 5 mg 10 mg	-
Brexpiprazole (Rexulti®)	Adjunctive treatment to antidepressants for major depressive disorder in adults; treatment of schizophrenia in adults	Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	-
Cariprazine (Vraylar®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of schizophrenia	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Capsule, dose-pack: 1.5/3 mg	-
Clozapine (Fazaclo ODT®*, Clozaril®*, Versacloz®)	Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults; treatment-resistant schizophrenia in adults	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg 150 mg 200 mg Tablet: 25 mg 50 mg 100 mg Suspension: 50 mg/mL	✔
Iloperidone (Fanapt®)	Treatment of schizophrenia in adults	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg Dose Pack: 1/2/4/6 mg	-
Lurasidone	Treatment of schizophrenia in adults, treatment	Tablet:	-

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Latuda®)	of depressive episodes associated with bipolar disorder in adults	20 mg 40 mg 80 mg 60 mg 120 mg	
Olanzapine (Zyprexa®*, Zyprexa Zydis®*)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years; adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder; maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of agitation associated with bipolar I disorder, manic or mixed in adults; treatment of agitation associated with bipolar I mania in adults; treatment of depressive episodes associated with bipolar disorder in adults; acute and maintenance treatment of schizophrenia in adults; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; adjunctive treatment to antidepressants for major depressive disorder in adults	Injection: 10 mg vials Orally disintegrating tablet: 5 mg 10 mg 15 mg 20 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg	✔
Paliperidone (Invega®*)	Acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 12 to 17; treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants in adults	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg	✔
Pimavanserin (Nuplazid®)	Hallucinations and delusions associated with Parkinson's disease psychosis	Tablet: 17 mg	-
Quetiapine (Seroquel®*, Seroquel XR®)	Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex in adults; treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in children and adolescents aged 10 to 17 years; treatment of manic or mixed episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; treatment of depressive episodes associated with bipolar disorder in adults; acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; treatment of schizophrenia in adults; adjunctive treatment to antidepressants for major	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Tablet: 25 mg 50 mg 100 mg 200 mg 300 mg 400 mg	✔

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	depressive disorder in adults		
Risperidone (Risperdal®*, Risperdal M-Tab®*)	Adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder; maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults and in children and adolescents aged 10 to 17 years; short-term treatment of acute mixed or manic episodes associated with bipolar I disorder in combination with lithium or valproate in adults; acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; irritability associated with autistic disorder in children and adolescents aged five to 16 years	Orally disintegrating tablet: 0.25 0.5 mg 1 mg 2 mg 3 mg 4 mg Oral solution: 1 mg/mL Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	✔
Ziprasidone (Geodon®*)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; treatment of acute manic or mixed episodes associated with bipolar disorder; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adults	Capsule: 20 mg 40 mg 60 mg 80 mg Injection: 20 mg/mL	✔

*Generic available in at least one dosage form and/or strength.

Evidence-based Medicine

- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of second generation antipsychotics (SGAs) compared to first generation antipsychotics (FGAs) in patients with chronic schizophrenia.[48-50] Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out as robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation.
    - Due to relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The role of the SGAs has been clearly established in the treatment of bipolar disorder and schizophrenia (and, in the case of aripiprazole, quetiapine extended-release and olanzapine/fluoxetine combination therapy, as adjunctive treatment of major depressive disorder).
- Meta-analyses evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo.[51-63,75-79] The trends for respective efficacy suggest that clozapine is the most effective agent in the class, followed by olanzapine and risperidone. Aripiprazole tended to exhibit lower efficacy than the other agents.[51-63,75-79]

- A meta-analysis in adult patients with bipolar disorder found risperidone to be the most effective treatment option (taking into account both efficacy and tolerability).[75] The next best treatment options, in order of decreased efficacy, were olanzapine, haloperidol, quetiapine, carbamazepine, aripiprazole, valproate, lithium, and ziprasidone. Lamotrigine, topiramate and gabapentin were found to be less effective than placebo.
- In the management of major depressive disorder, aripiprazole, quetiapine, and risperidone augmentation therapies were associated with improved outcomes.[84]
- The efficacy and safety of brexpiprazole in the treatment of schizophrenia was demonstrated by two pivotal multicenter, randomized, double-blind, placebo controlled six week trials, VECTOR and BEACON.[29,30] Positive and Negative Syndrome Scale (PANSS) scores were significantly improved with brexpiprazole when compared to placebo. Treatment differences were -8.72 (P<0.0001), -7.64 (P=0.0006) and -6.47 (P=0.0022) for brexpiprazole 2 mg, 4 mg, and 4 mg respectively.[29,30]
- The efficacy of cariprazine for the treatment of schizophrenia was established in three, 6-week, randomized, double-blind, placebo-controlled trials in patients with a diagnosis of schizophrenia. In each study, the primary endpoint was change from baseline in PANSS total score at the end of week six.[4,35,36] There was a significant improvement in PANSS when each fixed-dose or flexable-dose range cariprazine group was compared to placebo (P value varies; all significant when reported).[4,35,36]
- The efficacy of cariprazine in the acute treatment of bipolar mania was established in three, three-week placebo-controlled trials in patients with a diagnosis of bipolar I disorder with manic or mixed episodes with or without psychotic features. In each study, the primary endpoint was decrease from baseline in Young Mania Rating Scale (YMRS) total score at the end of week three.[4,69,70] In the first study, there was a demonstrated improvement with cariprazine dose groups (3 to 6 mg/day or 6 to 12 mg/day) compared to placebo on the YMRS total score (-P<0.05 for both comparisons). However, the 6 to 12 mg/day dose group showed no additional advantage.[4,69] In the second study, there was a demonstrated improvement with cariprazine (3 to 12 mg/day) compared to placebo on the YMRS total score (15.0 vs. -8.9, respectively; P<0.05).[4] In the third study, cariprazine (3 to 12 mg/day) was superior to placebo on the YMRS total score (19.6 vs. -15.3, respectively; P<0.05).[4,70]
- The efficacy of asenapine in the treatment of schizophrenia in adults has been evaluated in four, published, randomized, double-blind, placebo-controlled, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from six weeks to one year[31-34]. The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in five placebo-controlled, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features.[64-68]
    - In a direct-comparison study, asenapine was less effective than olanzapine in terms of changes from baseline in PANSS and Clinical Global Impression-Severity of Illness (CGI-S) scores.[34] Study discontinuation due to inadequate efficacy was noted in 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine.[34] In another study, clinically significant weight gain was noted in 17% of patients receiving risperidone and 9% of patients in the asenapine group.[31]
    - In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in Young Mania Rating Scale (YMRS) scores at week-52 of therapy.[68]
    - A meta-analysis of various antimanic therapy options, found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference, -0.30; -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 0.08 to 0.37).[75]
- Iloperidone has been studied as monotherapy for the treatment of adult patients with an acute or subacute exacerbation of schizophrenia.
    - Three six-week, randomized, double-blind, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo.[39]

  - One four-week, placebo- and active- comparator (ziprasidone)-controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo.[38]
- Lurasidone has been investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in two six-week, placebo-controlled studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily.[44-47]
  - Lurasidone and ziprasidone were comparable in terms of reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores and several cognition scales.[41-42] In addition, both drugs were comparable in terms of rates of discontinuation for any reason rate and discontinuation due to adverse events.[45,46] Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant ECG abnormality.
  - Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (*P*=0.046).[46]
- The safety and efficacy of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis was established in a single, six-week, double-blind, placebo-controlled trial in 185 patients. Patients in the pimavanserin group experienced a greater decrease in Parkinson's Disease-Adapted Scale for Assessment of Positive Symptoms Scores compared to placebo (-5.79 and -2.73, respectively, 95% CI, -4.91 to -1.20; P=0.001). Pimavanserin was well tolerated, with no worsening of motor function or significant safety concerns.[12,291]
- Available evidence suggests that, except for clozapine, olanzapine is associated with greater weight gain compared to all other atypical antipsychotic agents. In contrast, ziprasidone is associated with a low incidence of weight gain.[221]
- Data from the Food and Drug Administration Adverse Reporting System (AERS) indicates that the risk of experiencing a diabetes-related adverse event is greatest with olanzapine, followed by risperidone, and least with ziprasidone and aripiprazole, across all age groups.[250]
- Risperidone is associated with the greatest risk of prolactin elevation-related adverse events.[51-63,75-79,267]
- Risperidone, aripiprazole and ziprasidone are associated with a high incidence of extrapyramidal adverse events.[229] Quetiapine is associated with the least risk of extrapyramidal adverse events.[229]
- The incidence of sexual dysfunction was noted to be higher with the use of olanzapine, risperidone, and clozapine than with quetiapine, ziprasidone or aripiprazole.[233]
- The Agency of Healthcare Research and Quality (AHRQ) is the lead federal agency for research on healthcare quality, costs, outcomes and patient safety. In 2011, AHRQ had issued an update to a prior 2007 review of scientific evidence on the safety and effectiveness of atypical antipsychotics for off-labeled use.[85,196]
  - Indications associated with moderate/high strength of evidence for the use of atypical antipsychotics included general anxiety disorder (quetiapine), dementia (aripiprazole, olanzapine, risperidone), depression (aripiprazole, quetiapine, risperidone), augmentation of selective serotonin reuptake inhibitors for obsessive compulsive disorder [OCD] (risperidone), and post-traumatic stress disorder [PTSD] (risperidone).[96] Refer to Appendices IIa and IIb for additional details.
- The AHRQ had conducted a systematic review of literature on the safety and efficacy of antipsychotics in children and adolescents.[102,103] For details, refer to Appendices IIIa and IIIB.
  - Indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome.
  - No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons.
  - The risks of weight gain (weight gain: 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain.

  - Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data).
  - Extrapyramidal adverse events were significantly more common with risperidone and aripiprazole compared to placebo.
- According to a systematic review by Safer et al, weight gain secondary to atypical antipsychotics is greater in children and adolescents than in adults.[264]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Antipsychotics are a mainstay in therapy for schizophrenia.[314-316]
  - Lithium, valproate and/or antipsychotics are recommended as initial therapy of bipolar disorder.[301-304]
  - The American Psychiatric Association guideline recommends the use of antipsychotics for the management of psychosis or agitation in patients with dementia.[305]
  - For the treatment of anxiety disorders, sertraline is recommended as a first-line pharmacotherapeutic agent.[299,300] Second-line treatment options include serotonin norepinephrine reuptake inhibitors (SNRIs) or switching to alternative selective serotonin reuptake inhibitors (SSRIs). Augmentation therapy with antipsychotics is an option in treatment-refractory patients but the guidelines recommend that initiation of combination therapy be limited to specialists.
  - In major depressive disorder, first-line treatment options include SSRIs, SNRIs, bupropion or mirtazapine.[308-310] Antipsychotic augmentation therapy is an option for patients who have failed antidepressant monotherapy.
  - In obsessive compulsive disorder, SSRIs and cognitive behavioral therapy are recommended as first-line treatment options.[311] Patients who have failed an SSRI trial may be offered augmentation therapy with an antipsychotic or cognitive behavioral therapy. Similarly, SSRIs and SNRIs are considered to be first-line treatment options for the treatment of post-traumatic stress disorder (PTSD).[312,313]
  - Atypical antipsychotics may be used as adjunctive therapy for the management of treatment-refractory PTSD.[312]
  - For the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP), guidelines recommend the use of atypical antipsychotics, specifically clozapine or quetiapine, which have the most clinical data to support use. Both clinical guidelines recommend against the use of olanzapine for PDP due limited efficacy.[317-318]
  - The European Society for the Study of Tourette Syndrome guideline recommends risperidone as a first-line agent for the treatment of tics.[329] Aripiprazole has a role in treatment-refractory patients.
  - The American Academy of Child and Adolescent Psychiatry (AACAP) guideline acknowledges that atypical antipsychotics are the most commonly prescribed class of drugs for the treatment of maladaptive aggression, regardless of diagnosis; yet emphasize that pharmacotherapy should not be used as the only intervention in children with oppositional defiant disorder.[325]
  - Although the antipsychotics are not addressed in national and international insomnia treatment guidelines, the National Institute of Health (NIH) Consensus and State-of-the-Science Statement on Manifestations and Management of Chronic Insomnia in Adults state that due to the lack of evidence supporting the short and long term efficacy of antipsychotics, in addition to their significant risks, their use in the treatment of chronic insomnia cannot be recommended.[331]
  - In a practice guideline on the use of atypical antipsychotics in children and adolescents, issued by the AACAP in 2011, the panel recommends that prior to initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment, evaluation for comorbid medical conditions and concomitant medications.[329] Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion of the risks and benefits of psychotropic medication.

- Of the atypical antipsychotics, risperidone is recognized as an agent with the most substantial amount of methodologically stringent evidence for use in pediatric patients.[329]
- There is almost no data to support the use of atypical antipsychotics in pre-school aged children.[329] The guideline recommends a marked amount of caution before using these agents in pre-schoolers.
- Given the risk of metabolic side-effects, pediatric patients receiving atypical antipsychotic therapy should be closely monitored for changes in weight, blood pressure, fasting plasma glucose and lipid profile.[329]

Table 2. Evidence for the Use of Atypical Antipsychotics in Pediatrics (2011 AACAP guideline)[318]

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasi-done	Aripiprazole
Schizophrenia/ Psychosis	+++	+++*	++++*	++++*	+	++++*
Bipolar Disorder	++	+++*	+++*	++++*	+++	+++*
Disruptive behavior disorders/ Aggression	++	+++	+++	++	+	+
Autism/ PDD irritability	+	++++*	+++	+	+	++++*
Tourette's/tics		++++	+		+++	
PTSD	+					
Eating Disorder			+			
Long-term safety studies		+		+		

PDD=pervasive developmental disorder; PTSD=post-traumatic stress disorder
++++ Multiple randomized controlled studies
+++ One randomized controlled study
++ Uncontrolled study
+ Case studies
* FDA approved in children and/or adolescents

- Other Key Facts:
  - Paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug.
  - The use of clozapine is limited due to a risk of agranulocytosis.
  - Aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone are available generically.
  - Pimavanserin has a unique indication among atypical antipsychotics, the treatment of hallucinations and delusions associated with PDP.[12]

Appendix I: Summary of the Strength of Evidence for Off-Label Efficacy Outcomes (adopted from 2011 AHRQ systematic review)[196]

Indication	Strength of Evidence	Findings	Conclusions
Dementia	**High**	The 2011 meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small"	Aripiprazole, olanzapine, and risperidone **have efficacy** as treatment for behavioral symptoms of dementia.

Indication	Strength of Evidence	Findings	Conclusions
		in magnitude. Psychosis –risperidone was superior to placebo, as measured by thepsychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – Aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Three head to head trials compared atypicals; none was found superior.	
Depression			
Augmentation of SSRI/SNRI	**Moderate** (risperidone, aripiprazole, quetiapine) **Low** (olanzapine, ziprasidone)	The meta-analysis used "response" to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone was included in two trials. These reported the drug superior to placebo. The relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. In one available ziprasidone trial, the drug was superior to placebo in terms of MADRS scores. One trial compared ziprasidone at differing levels augmenting	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also have efficacy.**

Indication	Strength of Evidence	Findings	Conclusions
		sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	
Monotherapy	**Moderate**	Olanzapine alone was no better than placebo in improving symptoms at six or 12 weeks in three trials. Outcomes were too heterogeneous to allow pooling. In five PCTs, quetiapine was superior according to relative risk of both responding and remitted as measured by MADRS.	Olanzapine **does not have efficacy** as monotherapy for major depressive disorder. Quetiapine **has efficacy** as monotherapy for major depressive disorder er
Obsessive Compulsive Disorder (OCD)			
Augmentation of SSRIs	**Moderate** (risperidone) **Low** (olanzapine)	The 2006 meta-analysis pooled results of nine trials of risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Atypical antipsychotics had a clinically important benefit, (measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS), when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone. The updated 2011 meta-analysis found risperidone superior to placebo, as measured by changes in the Y-BOCS. There were too few studies (two) of olanzapine augmentation to permit separate pooling of this drug. Both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found	Risperidone **has efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine **may have efficacy.** Quetiapine is more **efficacious** than ziprasidone and clomipramine. e.

Indication	Strength of Evidence	Findings	Conclusions
		quetiapine more effective than ziprasidone as SSRI augmentation. In one new trial, quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	
Augmentation of citalopram	**Low** (quetiapine) **Very low** (risperidone)	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 vs 85 days). Two trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone **may be efficacious** as augmentation to citalopram in OCD patients.
Post-Traumatic Stress Disorder	**Moderate** (risperidone) **Low** (Olanzapine) **Very Low** (Quetiapine)	Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy. One trial found a three-fold decline in PTSD Scale (CAPS) scores in patients treated with quetiapine monotherapy compared to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A meta-analysis of risperidone, using CAPS scores as outcome, found risperidone to be superior to placebo. In a meta-analysis by condition, atypical antipsychotics were	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.

Indication	Strength of Evidence	Findings	Conclusions
		efficacious for combat-related PTSD but not PTSD in abused women.	
Personality Disorders			
Borderline	**Low** (aripiprazole) **Very low** (quetiapine, olanzapine)	Four trials provide evidence that olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Two trials of olanzapine found no difference from placebo in any outcomes compared to placebo. Aripiprazole was superior to placebo in one small trial. Another trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. A trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared to placebo at 12 weeks. One trial found quetiapine to be superior to placebo on BPRS and PANSS scales. Due to heterogeneity of outcomes, a meta-analysis could not be performed.	Olanzapine had **mixed results** in seven trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.
Schizotypal	**Low**	Risperidone was superior to placebo in one small trial. In another trial risperidone was found to be no different from placebo on a cognitive assessment battery.	Risperidone had **mixed results** when used to treat schizotypal personality disorder in two small trials.
Tourette's Syndrome	**Low**	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for eight to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared to placebo.	Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome.
Anxiety	**Moderate**	Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder.

Indication	Strength of Evidence	Findings	Conclusions
		risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.	
Attention Deficit/Hyperactivity Disorder			
No comorbidity	**Low**	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale–Parent version (CAS-P).	Risperidone **may be efficacious** in treating children with ADHD with no serious co-occurring disorders.
Mental retardation	**Low**	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone **may be superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.
Bipolar	**Low**	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Eating Disorders	**Moderate** (olanzapine) **Low** (quetiapine)	In a pooled analysis of three trials, there was no difference in change in BMI at either one or three months with olanzapine compared to placebo. One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.	Olanzapine and quetiapine **have no efficacy** in increasing body mass in eating disorder patients.
Insomnia	**Very Low**	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be **inefficacious** in treating insomnia.
Substance Abuse			
Alcohol	**Moderate** (aripiprazole) **Low** (quetiapine)	Two trials of aripiprazole and one of quetiapine reported percentage of patients completely abstinent during follow-up. In a pooled analysis, the effect vs placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse/ dependence. Quetiapine may also be **inefficacious.**
Cocaine	**Low**	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy vs placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse /dependence. Risperidone may also be

Indication	Strength of Evidence	Findings	Conclusions
			inefficacious.
Meth-amphetamine	**Low**	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse/ dependence.
Methadone	**Low**	One trial of methadone-treated patients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an **inefficacious** adjunct to methadone maintenance

ADHD=attention-deficit hyperactivity disorder; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Scale; BPRS=Brief Psychiatric Rating Scale; CGI-BPD=Clinical Global Impression Scale for Borderline Personality Disorder; CGI-I=Clinical Global Impression Improvement; CGI-S=Clinical Global Impression-Severity; CMAI =Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; NPI=Neuropsychiatric Inventory; OCD=obsessive-compulsive disorder; PANSS=Positive and Negative Syndrome Scale; PCT=placebo-controlled trial; PTSD=post-traumatic stress disorder; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitors; ZAN-BPD=Zanarini Rating Scale for Borderline Personality Disorder

Appendix II: Summary of Adverse Events of Atypical Antipsychotics for Off-Label Use (adopted from 2011 AHRQ systematic review)[196]

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
Weight Gain			
Elderly	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively, compared to a monthly weight loss of 0.9 lbs for placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	According to the meta-analysis, more common in patients taking olanzapine and risperidone than placebo.
Adults	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one	According to the meta-analysis, more common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
		trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	
Children/Adolescents	No head to head studies	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality-in the elderly	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population.
Endocrine			
Elderly	No evidence reported	No evidence reported	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
Adults	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
			Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study.
Cerebrovascular Accident (CVA)	No evidence reported	Hospitalization for CVA was increased in the first week after initiation of typical antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In a meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
Extrapyramidal Symptoms (EPS)			
Elderly	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported	More common in patients taking risperidone, according to the meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
Adults	No evidence reported	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to the meta-analysis.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
		antipsychotics in one trial each.	
Sedation			
Elderly	More common in elderly patients taking olanzapine or quetiapine than risperidone according to the meta-analysis, but not statistically significant.	No difference in one trial of olanzapine vs benzodiazepines. No difference in three trials of olanzapine and three of risperidone vs conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to the meta-analysis.
Adults	More common in patients taking quetiapine than risperidone in two trials. No difference in one trial of risperidone vs olanzapine.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. More common in olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in the pooled analysis of three trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in the meta-analysis.
Children/Adolescents	No head-to-head trials	No difference in one small trial of clonidine vs risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

BMI=body mass index; CATIE-AD=Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CVA=cerebrovascular accident; EPS=extrapyramidal symptoms; PCT=placebo-controlled trial; SSRI=serotonin selective reuptake inhibitor

Appendix III: Summary of the Strength of Evidence for Efficacy Outcomes in Children and Adolescents (adopted from the 2012 AHRQ systematic review)[103]

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
Pervasive developmental disorder			
Autistic symptoms	FGA vs SGA (2 RCTs)	Low	No significant difference
	SGA vs placebo (7	Low	Significant effect in favor of SGA on ABC (MD, 218.3; 95% CI, 227.1 to 29.5; I2, 79.6%);

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	RCTs)		CARS (MD, 24.9; 95% CI, 28.5 to 21.4; I2, 64%).
CGI	SGA vs placebo (3 RCTs)	Low	No significant difference
OC symptoms	SGA vs placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD, 21.7; 95% CI, 23.2 to 20.3; I2, 49%).
Medication adherence	SGA vs placebo (2 RCTs)	Low	No significant difference
Disruptive behavior disorder			
Aggression	SGA vs placebo (5 RCTs)	Low	No significant difference
Anxiety	SGA vs placebo (4 RCTs)	Low	No significant difference
Behavior symptoms	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for ABC (MD, 221.0; 95% CI, 231.1 to 210.8; I2, 62%); BPI (MD, 23.8; 95% CI, 26.2 to 21.4; I2, 0%); NCBRF (MD, 26.9; 95% CI, 210.4 to 23.5; I2, 62%).
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for CGI–I (MD, 21.0; 95% CI, 21.7 to 20.3; I2, 45%); CGI–S (MD, 21.3; 95% CI, 22.2 to 20.5; I2, 78%).
Medication adherence	SGA vs placebo (5 RCTs)	Low	No significant difference
Bipolar Disorder			
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.7; 95% CI, 20.8 to 20.5; I2, 36%).
Depression	SGA vs placebo (7 RCTs)	Low	No significant difference
Manic Symptoms	SGA vs placebo (7 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity).
Medication adherence	SGA vs placebo (7 RCTs)	Low	Significant effect in favor of placebo (RR, 2.0; 95% CI, 1.0 to 4.0; I2, 0%).
Suicide-related behavior	SGA vs placebo (7 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.
Schizophrenia			
CGI	FGA vs SGA (3 RCTs)	Low	Significant effect in favor of SGA (MD, 20.8; 95% CI, 21.3 to 20.3; I2, 0%).

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	Clozapine vs olanzapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (3 RCTs)	Low	No significant difference
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.5; 95% CI, 20.7 to 20.3; I2, 28%).
Positive and negative symptoms	FGA vs SGA (3 RCTs)	Low	No significant difference
	Clozapine vs olanzapine (2 RCTs, 1 PCS)	Low	No significant difference
	Olanzapine vs risperidone (3 RCTs, 1 PCS)	Low	No significant difference
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 28.7; 95% CI, 211.8 to 25.6; I2, 38%).
Medication adherence	FGA vs SGA (2 RCTs, 1 PCS)	Low	No significant difference
	Clozapine vs quetiapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (4 RCTs, 1 PCS)	Low	No significant difference
	SGA vs placebo (2 RCTs)	Low	No significant difference
Suicide-related behaviors	SGA vs placebo (5 RCTs)	Low	No significant difference
Tourette syndrome			
Tics	SGA vs placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD, 27.0; 95% CI, 210.3 to 23.6; I2, 0%)
Behavioral symptoms			
Autistic symptoms	Risperidone vs placebo (2RCTs)	Low	Significant effect in favor of risperidone in one study; NR in second study.

ABC=Aberrant Behavior Checklist, BPI=Behavior Problem Inventory, CARS=Childhood Autism Rating Scale, CGI–I=Clinical Global Impressions–Improvement, CGI–S=Clinical Global Impressions–Severity, NCBRF=Nisonger Child Behavior Rating Scale, NR=not reported, OC=obsessive-compulsive, PCS=prospective cohort study, RR=relative risk

Appendix IIIb: Summary of Evidence for Adverse Events in Children and Adolescents (adopted from 2012 AHRQ systematic review)[103]

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
Dyslipidemia	Low	Aripiprazole was significantly favored over olanzapine (RR, 0.25; 95% CI, 0.08 to 0.8)[a] and 95% CI, 271.3 to 27.4).[a] No significant differences were observed for clozapine vs olanzapine, olanzapine vs quetiapine and quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.5; 95% CI, 1.4, 4.4)[a], olanzapine (RR, 2.4; 95% CI, 1.2 to 4.9; I^2, 45%), and quetiapine (RR, 2.4; 95% CI, 1.1 to 5.4; I2, 0%).
	Moderate	Significant effect in favor of risperidone compared with olanzapine for cholesterol (MD, 10.2 mg/dL; 95% CI, 3.1 to 17.2; I^2, 0%) and triglycerides (MD, 17.3 mg/dL; 95% CI, 3.5 to 31.1; I2, 0%).	NA
EPS	Low	No significant difference for clozapine vs olanzapine, clozapine vs risperidone, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	No significant differences for placebo compared to olanzapine or quetiapine.
	Moderate	NA	Significant effect in favor of placebo over aripiprazole (RR, 4.2; 95% CI, 2.4 to 7.2; I^2, 0%) and risperidone (RR, 2.7; 95% CI, 1.4 to 4.9; I^2, 0%).
Insulin Resistance	Low	No significant difference for olanzapine vs quetiapine, olanzapine vs risperidone or quetiapine vs risperidone.	No significant difference between aripiprazole and placebo or olanzapine and placebo.
Prolactin-related sexual side effects	Low	Significant effect in favor of clozapine over olanzapine (MD, 210.8 ng/dL; 95% CI, 216.7 to 24.8; I^2, 21%). No significant difference for quetiapine vs risperidone.	Significant effect in favor of placebo over risperidone in seven or eight studies (not pooled due to heterogeneity). No significant difference for quetiapine compared to placebo.
	Moderate	Significant effect in favor of olanzapine over risperidone (RR, 0.4; 95% CI, 0.2 to 0.6; I^2, 0%).	Significant effect in favor of aripiprazole over placebo (MD, 24.1 ng/mL; 95% CI, 26.3 to

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
			21.8; I2, 0%). Significant effect in favor of placebo over olanzapine (MD, 11.5 ng/mL; 95% CI, 8.8 to 14.1; I2, 0%).
Sedation	Low	No significant differences for clozapine vs olanzapine, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.7; 95% CI, 1.1 to 6.5; I2, 76%). No significant difference in placebo comparisons with olanzapine and quetiapine.
	Moderate	NA	Significant effect in favor of placebo over risperidone (RR, 2.9; 95% CI, 1.5 to 5.5; I^2, 32%) and ziprasidone (RR, 3.0; 95% CI, 1.7 to 5.2; I^2, 0%).
Weight gain	Low	Significant effect in favor of aripiprazole over olanzapine (MD, 24.1 kg; 95% CI, 25.5 to 22.7),a quetiapine (MD, 21.6 kg; 95% CI, 23.0 to 20.3)[a] and risperidone (MD, 22.3 kg; 95% CI, 23.9 to 20.7).a No significant difference for clozapine vs olanzapine, clozapine vs risperidone, and quetiapine vs risperidone.	No significant difference for ziprasidone compared to placebo.
	Moderate	Significant effect in favor of quetiapine over olanzapine (RR, 1.5; 95% CI, 1.1 to 2.0; I^2, 0%) and risperidone over olanzapine (MD, 2.4 kg; 95% CI, 1.5 to 3.3; I^2, 72%).	Significant effect in favor of placebo over aripiprazole (MD, 0.8 kg; 95% CI, 0.4 to 1.2; I^2, 13%), olanzapine (MD, 4.6 kg; 95% CI, 3.1 to 6.1; I2, 70%), quetiapine (MD, 1.8 kg; 95% CI, 1.1 to 2.5; I^2, 49%), and risperidone (MD, 1.8 kg; 95% CI, 1.5 to 2.1; I^2, 0%).

AE=adverse event; EPS=extrapyramidal symptom; RR=relative risk.
a=Only 1 study contributed to this estimate; therefore, an I^2 value could not be calculated.

References

Please refer to the full therapeutic class review on atypical antipsychotics for a list of references.

Therapeutic Class Overview
Respiratory Corticosteroid/Long-Acting β-Agonists Combinations

Therapeutic Class Overview/Summary: The combination inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) products include Advair® (fluticasone propionate/salmeterol), Breo Ellipta® (fluticasone furoate/vilanterol), Dulera® (mometasone/formoterol) and Symbicort® (budesonide/formoterol), with fluticasone furoate/vilanterol being the most recent agent to be approved by the Food and Drug Administration (FDA). Fluticasone propionate/salmeterol, mometasone/formoterol, budesonide/formoterol and fluticasone furoate/vilanterol are approved for the treatment of asthma; however, only fluticasone propionate/salmeterol, fluticasone furoate/vilanterol and budesonide/formoterol have been approved for the treatment of chronic obstructive pulmonary disease (COPD). The ICSs exert their anti-inflammatory effect by binding to the glucocorticoid receptors with a subsequent activation of genes involved in anti-inflammatory processes, as well as via the inhibition of pro-inflammatory genes involved in the asthmatic response. The LABAs have selective action on β_2 receptors which stimulate adenyl cyclase, thereby increasing intracellular cyclic adenosine monophosphate level, and subsequently relaxing bronchial smooth muscles. The LABA medications also inhibit the release of mediators that are involved in immediate hypersensitivity. All of the combination products are associated with similar adverse events, precautions and contraindications.[1-5] Moreover, the labeling for all of the combination products has been revised to reflect the results of an analysis which reported an increased risk of asthma exacerbations and hospitalizations in pediatric and adult patients, as well as death in some patients treated with LABA-containing medications.[6] The combination ICS/LABA products appear to be equally efficacious for their respective indications, with the products differing in available dosage forms, dosing frequency (one vs two inhalations twice daily), pharmacokinetic profiles and ages for their FDA-approved indications.[1-5]

Table 1. Current Medications Available in the Therapeutic Class[1-5]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Budesonide/ formoterol (Symbicort® HFA)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema* and treatment of asthma in patients 12 years of age and older	Meter dose aerosol inhaler (HFA): 80/4.5 µg 160/4.5 µg	-
Fluticasone propionate/ salmeterol (Advair Diskus®, Advair HFA®)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema (Advair Diskus®)†, treatment of asthma in patients four years of age and older (Advair Diskus®) and treatment of asthma in patients 12 years of age and older (Advair HFA®)	Dry powder inhaler: 100/50 µg 250/50 µg 500/50 µg Meter dose aerosol inhaler (HFA): 45/21 µg 115/21 µg 230/21 µg	-
Fluticasone furoate/ vilanterol (Breo Ellipta®)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease and treatment of asthma in patients 18 years of age and older	Dry Powder Inhaler: 100 µg/25 µg 200 µg/25 µg	-
Mometasone/ formoterol (Dulera®)	Treatment of asthma in patients 12 years of age and older	Meter dose aerosol inhaler (HFA): 100/5 µg 200/5 µg	-

HFA=hydrofluoroalkane
* Symbicort® 160/4.5 µg is the only strength Food and Drug Administration (FDA) approved for this indication.
† Advair Diskus® 250/50 µg is the only strength FDA approved for this indication.

Evidence-based Medicine

- Fluticasone propionate/salmeterol, fluticasone furoate/vilanterol, mometasone/formoterol and budesonide/formoterol have been studied for the treatment of asthma and COPD.[7-49]
- The safety and efficacy of mometasone/formoterol were established in two randomized, double-blind, parallel-group, multicenter trials of 12 and 26 week duration (N=1,509).
    - After 26 weeks of treatment, mometasone/formoterol was more effective than monotherapy with the individual components in controlling asthma and reducing the risk of asthma deteriorations in patients with persistent asthma uncontrolled on medium-dose inhaled corticosteroids (ICSs).[7]
    - After 12 weeks of treatment, mometasone/formoterol was more effective than mometasone monotherapy in improving asthma control and reducing nocturnal awakenings.
        - Patients poorly controlled on high-dose ICSs experienced significant improvements in asthma control, lung function and symptoms when treated with mometasone/formoterol compared to mometasone monotherapy.[8]
    - A long term safety trial demonstrated that treatment with mometasone/formoterol for up to one year is well tolerated.[9]
- A single prospective head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated noninferiority of mometasone/formoterol in regard to the forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours. Mometasone/formoterol treatment was also associated with a significantly quicker onset of action and increase in FEV_1 five minutes post dose compared to fluticasone propionate/salmeterol.[10]
- Numerous trials have evaluated the combination ICS/LABA products to their respective individual components as monotherapy, and results have generally demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and achieving control of asthma symptoms. Moreover, there is similar efficacy between the administration of the combination ICS/LABA products to their individual components used in combination.[11-36]
- Head-to-head trials comparing budesonide/formoterol and fluticasone propionate/salmeterol have been conducted but failed to consistently demonstrate "superiority" of one product over the other.[37-46]
- Two studies comparing fluticasone propionate/salmeterol and fluticasone furoate/vilanterol did not demonstrate significant differences in improvement of 0 to 24 hour FEV_1.[47,48]
- A meta-analysis of 33 studies that compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol and budesonide/formoterol found that treatment with fluticasone furoate/vilanterol was noninferior to fluticasone propionate/salmeterol and budesonide/formoterol treatments.[49]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[50-53]
    - ICSs and β_2-agonists are well established treatment options in the management of both asthma and COPD.
    - The addition of a LABA is the preferred treatment option in asthma patients who fail to achieve adequate control with a low to medium dose ICS.
    - β_2-agonists are among the principal bronchodilators used in the treatment of COPD, and LABAs are more effective and convenient than short-acting bronchodilators.
    - ICSs are recommended as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤60% predicted and repeated exacerbations.
    - ICS/LABA products are more effective than either component alone in reducing exacerbations or improving lung function in COPD patients.
    - No one ICS/LABA product is preferred over another for the treatment of asthma or COPD.

- Other Key Facts:
    - All LABA-containing medications carry a Black Box Warning regarding an increased risk of asthma-related deaths associated with their use.

- Budesonide/formoterol and fluticasone furoate/vilanterol have quicker onsets of action (15 and 16 minutes) compared to fluticasone propionate/salmeterol (30 to 60 minutes). The onset of action of mometasone/formoterol has not been reported.[1-5]
- All ICS/LABA products are available for twice-daily dosing, except fluticasone furoate/vilanterol which is administered once daily.[1-5]
- For the treatment of asthma, Advair® HFA (fluticasone propionate/salmeterol), Dulera® (mometasone/formoterol), Symbicort® (budesonide/formoterol) are approved for use in patients 12 years of age and older, whereas Advair Diskus® (fluticasone propionate/salmeterol) is approved for use in patients four years of age and older. Breo Ellipta® (fluticasone furoate/vilanterol) was recently approved for the treatment of asthma in patients 18 years of age and older.
- No generic products are available in this therapeutic class.

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Therapeutic Class Overview
Benign Prostatic Hyperplasia (BPH) Treatments

Therapeutic Class

- **Overview/Summary:** The agents approved for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) will be the focus of this review. The α-adrenergic blockers including, alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin, reduce smooth-muscle tone in the prostate and bladder neck decreasing lower urinary tract symptoms (LUTS) secondary to BPH. Alfuzosin, silodosin and tamsulosin are selective to the α-adrenergic receptors located in the prostate and therefore are only Food and Drug Administration (FDA) approved for BPH, whereas doxazosin and terazosin also inhibit α-adrenergic receptors found in the vascular smooth muscle and are additionally indicated for hypertension.[1-6] The 5-α reductase inhibitors, dutasteride and finasteride, act by blocking the conversion of testosterone to dihydrotestosterone and in turn suppress the growth of the prostate. making them appropriate treatment options for LUTS associated with overall prostatic enlargement.[7,8] Jalyn® (dutasteride/tamsulosin) is a combination of both an α-adrenergic blocker and a 5-α reductase inhibitors.[9] The final drug approved for use in BPH is the phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.[10] Note that even though doxazosin and terazosin are FDA-approved for use in the treatment of hypertension, tadalafil is FDA-approved for use in the treatment of erectile dysfunction and pulmonary arterial hypertension, and finasteride is FDA-approved for alopecia, they are not included in this review. Jalyn® (dutasteride/tamsulosin) is a combination of both an α-adrenergic blocker and a 5-α reductase inhibitors.[9] Another drug approved for use in BPH is the phosphodiesterase-5 inhibitor, tadalafil. The exact mechanism for reducing BPH symptoms is unknown.[10] Although doxazosin and terazosin are FDA-approved for use in the treatment of hypertension, tadalafil is FDA-approved for use in the treatment of erectile dysfunction and pulmonary arterial hypertension, and finasteride is FDA-approved for alopecia, they are not included in this review.

  Clinical manifestations of BPH include LUTS (frequency of urination, nocturia, hesitancy, urgency, and weak urinary stream). The appearance and progression of symptoms is usually slow, over a couple of years, with a poor correlation between symptoms and the presence of an enlarged prostate on rectal exam.[11] Disease prevalence and the occurrence of symptoms are age dependent, with an initial onset of disease occurring patients greater than 50 years of age.[11] Current treatment guidelines acknowledge that not all men with histological evidence of BPH will develop bothersome LUTS and not all patients with BPH and LUTS actually have prostate enlargement, one of the main features of symptomatic disease. Additionally, prostate enlargement may exist in the absence of LUTS.[12-13]

Table 1. Current Medications Available in the Therapeutic Class[1-10,14]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Alfuzosin hydrochloride (Uroxatral®)	Treatment of signs and symptoms of benign prostatic hyperplasia	Tablet, extended release: 10 mg	✔
Doxazosin mesylate (Cardura®,¶, Cardura XL®)	Treatment of signs and symptoms of benign prostatic hyperplasia#; treatment of hypertension*	Tablet, extended release: 4 mg 8 mg Tablet: 1 mg 2 mg 4 mg 8 mg	✔

Dutasteride (Avodart®)	Treatment of signs and symptoms of benign prostatic hyperplasia†,‡	Capsule: 0.5 mg	✔
Finasteride (Proscar®)	Treatment of signs and symptoms of benign prostatic hyperplasia†,§	Tablet: 5 mg	✔
Silodosin (Rapaflo®)	Treatment of signs and symptoms of benign prostatic hyperplasia	Capsule: 4 mg 8 mg	-
Tadalafil (Cialis®, Adcirca®)	Treatment of signs and symptoms of benign prostatic hyperplasia, treatment of erectile dysfunction**	Tablet: 2.5 5 10¶ 20¶	-
Tamsulosin hydrochloride (Flomax®)	Treatment of signs and symptoms of benign prostatic hyperplasia†	Capsule: 0.4 mg	✔
Terazosin hydrochloride	Treatment of signs and symptoms of benign prostatic hyperplasia,	Capsule: 1 mg 2 mg 5 mg 10 mg	✔
Combination Products			
Dutasteride/tamsulosin hydrochloride (Jalyn®)	Treatment of signs and symptoms of benign prostatic hyperplasia†, treatment of hypertension††	Capsule: 0.5 mg/0.4 mg	✔

*Immediate-release formulation only.
†In men with an enlarged prostate, to improve symptoms, reduce the risk of acute urinary retention and reduce the risk of the need for BPH-related surgery.
‡To treat symptomatic BPH in men with an enlarged prostate in combination with tamsulosin.
§To reduce the risk of symptomatic progression of BPH in combination with doxazosin.
#Doxazosin indicated for both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH.
¶Generic available in at least one dosage form or strength.
**** When used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks.
†† In men with an enlarged prostate.

Evidence-based Medicine[15-67]

- FDA-approval of silodosin was based on two clinical trials where it was compared to placebo and demonstrated its efficacy in decreasing the International Prostate Symptom Score (IPSS) and improving general quality of life scores. In a pooled analysis of these two clinical trials, the mean change in total IPSS at baseline was -6.40 (±6.63) and -3.50 (±5.84) for the silodosin and placebo groups, respectively with an adjusted mean difference reported as -2.8 (P<0.0001). The maximum urinary flow rate (Q_{max}) at endpoint was 2.6 mL/second (standard deviation [SD]±4.43) in the silodosin group and 1.5 mL/ second (SD±4.36) in the placebo group; corresponding to an adjusted mean group difference of 1.0 mL/ second (P=0.0007).[16]
- The safety and efficacy of tadalafil for BPH has been evaluated in multiple studies. These studies. Tadalafil consistently showed significantly better improvement in IPSS compared to placebo.[18-25] One study evaluated men with BPH who had comorbid erectile dysfunction. Tadalafil was associated with statistically significant improvements in both internation index of erectile function (IIEF) scores and total IPSS (P<0.001 for both).[25]
- Studies comparing the α-adrenergic blocking agents to each. Although some trials have suggested superiority one agent over another, most studies, have tended toward non-inferiority within the α-blockers related to reducing IPSS.[26-46]
    - A Cochrane review has evaluated tamsulosin in comparison to other α-adrenergic blocking agents. It was concluded that tamsulosin was as effective as other α-adrenergic blockers in improving LUTS and urinary flow rates. Dizziness, rhinitis and abnormal ejaculation occurred

significantly more frequently than placebo and withdrawal was reported more often with higher doses of tamsulosin. Additionally, terazosin use was associated with a higher rate of discontinuation than low dose tamsulosin.[37]
    - A second Cochrane review evaluated terazosin to other α blockers, finasteride alone or in combination with terazosin and placebo. Terazosin was comparable to tamsulosin in improving IPSS (40% vs 43%), and more effective than finasteride (38% vs 20%) or placebo (38% vs 17%) in improving American Urological Association Symptom Score (AUA-SS). Peak urinary flow rates were similar among α blockers and higher with terazosin (22%) over finasteride (15%) and placebo (11%).[38]
    - A meta-analysis by Djavan et al of α-adrenergic blocking agents (alfuzosin, doxazosin, tamsulosin, and terazosin) in men with LUTS suggestive of benign prostatic obstruction did not identify any difference among agents in improving total urinary symptom scores or Q_{max}. However, alfuzosin and tamsulosin were better tolerated than doxazosin and terazosin.[39]
- Similar to the α-blocking agents, the 5-α reductase inhibitors have been compared to one another in a number of clinical trials, with mixed results. Dutasteride was shown to be non-inferior to finasteride for reducing prostate volume, post-void volume, and American Urological Association Symptom Score (AUA-SS).[47-50]
- Head-to-head trials between 5-α reductase inhibitors and α blockers have also been conducted.[51-62]
    - When compared to finasteride, tamsulosin showed comparable effect on urinary symptom scores at study end point (24 weeks and 1 year)[51,52], however a benefit was found with tamsulosin at earlier assessment (4 weeks) in both IPSS and Q_{max}.[51]
    - Tamsulosin in combination with dutasteride has been found to be associated with a greater benefit in IPSS and Q_{max} than each agent alone. As expected tamsulosin use resulted in a much lower decrease in prostate volume as compared to combination therapy (0.00%±0.84% and 26.90%±0.62%, respectively; P<0.001).[53,]
    - Four large, long-term trials comparing doxazosin, finasteride, each agent alone and in combination, and placebo.[58-61] Rates of nocturia were significantly reduced with monotherapy and combination treatment compared to placebo.[59]
    - Men with moderate to enlarged prostate glands benefited most from combination therapy (P<0.05), however doxazosin therapy alone was as effective as combination therapy for decreasing the risk of progression in men without an enlarged prostate.[60]
    - Doxazosin monotherapy and in combination with finasteride was associated with significantly greater improvements in Q_{max} and IPSS. Differences between finasteride alone and placebo did not reach statistical significane.[61]
    - Terazosin use alone and in combination with finasteride was associated with significantly greater reductions in symptom scores and greater increases in Q_{max} compared to finasteride monotherapy or placebo. Differences among combination therapy and terazosin monotherapy did not reach statistical significance, nor did difference between finasteride and placebo.[62]
- Studies have been conducted evaluating the safety and efficacy of combination therapy with two agents from different classes.[63-66]
    - A retrospective analysis showed that combination therapy with finasteride and an α-blocking agent significantly improved IPSS in patients with severe BPH symptoms, but was not statistically different from monotherapy in the same population.[63]
    - A meta-analysis conducted by Gacci et al found that a phosphodiesterase-5 inhibitor and α blocker combination therapy significantly improved IPSS, IIEF score and Q_{max} compared to a blockers alone (P<0.05, P<0.0001 and P<0.0001, respectively).[64]
    - Tadalafil 5 mg once daily coadministered with finasteride 5 mg for 12 weeks resulted in an IPSS total score improvement that was significantly better than finasteride/placebo (P=0.001).[66]
- A systematic review of alfuzosin studies showed a greater improvement in the primary outcome (IPSS) over placebo (weighted mean difference, -1.8 points; 95% confidence interval [CI], -2.49 to -1.11); however, when compared to other α-blockers (doxazosin, tamsulosin), doxazosin use was associated with the most favorable change from baseline IPSS. Alfuzosin alone and in combination with finasteride showed a greater improvement in LUTS compared to finasteride alone.

Key Points within the Medication Class

- According to Current Clinical Guidelines:[12,13]
  - Watchful waiting is recommended for mild symptoms of BPH (AUA symptom score <8) and patients with moderate or severe symptoms (AUA symptom score ≥8) who are not bothered by their symptoms.[12,13]
  - α blockers are considered first line; their rapid onset of action, good efficacy, and low rate and severity of adverse events, followed by a 5- α reductase inhibitor
    - The older, less costly, generic α-blockers remain reasonable treatment choices.
  - PDE-5 inhibitors reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction.[13].
  - Combination therapy is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, prostate specific antigen level as a proxy for volume, and/or enlargement on digital rectal exam.[12]
- Other Key Facts:
  - Alfuzosin, doxazosin immediate-release, tamsulosin, terazosin, dutasteride, and finasteride are available generically in standard formulations. The doxazosin sustained-release tablet (Cardura XL®), silodosin (Rapaflo®), and tadalafil (Cialis®) are not currently available generically.
  - Finasteride (Propecia®) is also available as a 1 mg tablet for the treatment of alopecia. Tadalafil (Adcirca®) is available as a 20 mg tablet for the treatment of pulmonary hypertension.[14]
  - 5-α reductase inhibitors are pregnancy category X; women who are pregnant or who could be pregnant should avoid handling dutasteride and dutasteride/tamsulosin capsules along with crushed finasteride tablets.[1-10]
  - Administration considerations:[1-5,7-10]
    - Alfuzosin, doxazosin extended-release, dutasteride, tamsulosin and dutasteride/ tamsulosin should all be swallowed whole and not crushed, chewed, or cut.
    - Doxazosin immediate-release, finasteride, and tadalafil tablets may be crushed.
    - Silodosin capsules can be opened and the powder sprinkled on applesauce.

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Therapeutic Class Overview
Calcium-Channel Blocking Agents (Dihydropyridines)

Therapeutic Class Overview/Summary:
Calcium-channel blockers (CCBs) have multiple roles in treating cardiovascular disease. The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.[1-2] Calcium-channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked, which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance.[3,4] In addition, CCBs decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload.[5] There are two classes of CCBs dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally miscellaneous group.

Dihydropyridines are more potent vasodilators than non-dihydropyridines due to greater selectivity for vascular smooth muscle. They have a lesser effect, or even no effect, upon cardiac muscle contractility or conduction.[1-6-26] One of the non-dihydropyridines, diltiazem is a potent coronary vasodilator, but is only a mild arterial vasodilator. Although it decreases atrioventricular (AV) node conduction, diltiazem does not have negative inotropic properties.[27-32] The other non-dihydropyridine, verapamil, dilates coronary and peripheral arteries. It also slows conduction through the AV node, and has negative inotropic and chronotropic effects.[33-37] A complete list of indications for the calcium channel blockers and combination products can be found in Table 1a and 1b.[6-38]

Table 1a. Current Medications Available in the Therapeutic Class (Dihydropyridines)[6-26]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Amlodipine (Norvasc®*)	Chronic stable angina; variant (vasospastic) angina; hypertension; to reduce the risk of hospitalization for angina and coronary revascularization procedures in patients with CAD;	Tablet: 2.5 mg 5 mg 10 mg	✔
Clevidipine (Cleviprex®)	Hypertension	IV Emulsion: 0.5 mg/mL	-
Felodipine ER*	Hypertension	ER Tablet (SR 24-hour): 2.5 mg 5 mg 10 mg	✔
Isradipine*	Hypertension	Capsule: 2.5 mg 5 mg	✔
Nicardipine* (Cardene IV®)	Hypertension	Capsule: 20 mg 30 mg IV Solution: 2.5 mg/mL 5 mg/mL* 10 mg/mL*	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Nifedipine* (Procardia®*)	Chronic stable angina (capsule); hypertension	Capsule: 10 mg 20 mg	✔
Nifedipine ER (Adalat CC®*, Afeditab CR®†, Nifediac CC®†, Nifedical XL®†, Procardia XL®*)	chronic stable angina without evidence of vasospasm; hypertension	ER Tablet (SR-24 hour): 30 mg 60 mg 90 mg Osmotic Release capsule (SR-24 hour): 30 mg 60 mg 90 mg	✔
Nimodipine* (Nymalize®)	Subarachnoid hemorrhage, from ruptured intracranial berry aneurysms (Hunt and Hess Grades I-V)	Capsule: 30 mg Oral Solution: 60 mg/20 mL	✔
Nisoldipine* (Sular®*)	Hypertension	ER Tablet (SR-24 hour): 8.5 mg 17 mg 20 mg 25.5 mg 30 mg 34 mg 40 mg	✔
Two Agent Combination Products			
Amlodipine/atorvastatin (Caduet®*)	Hyperlipidemia, hypertension	Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg	✔
Amlodipine/benazepril (Lotrel®*)	Hypertension	Capsule: 2.5/10 mg 5/10 mg 5/40 mg 10/20 mg 10/40 mg	✔
Amlodipine/perindopril (Prestalia®)	Hypertension	Tablet: 2.5/3.5 mg 5/7 mg 10/14 mg	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Amlodipine/olmesartan (Azor®)	Hypertension	Tablet: 5/20 mg 5/40 mg 10/20 mg 10/40 mg	-
Amlodipine/valsartan (Exforge®*)	Hypertension	Tablet: 5/160 mg 5/320 mg 10/160 mg 10/320 mg	✔
Amlodipine/telmisartan (Twynsta®*)	Hypertension	Tablet: 5/40 mg 5/80 mg 10/40 mg 10/80 mg	✔
Three Agent Combination Products			
Amlodipine/olmesartan/ hydrochlorothiazide (Tribenzor®)	Hypertension	Tablet: 5/20/12.5 mg 5/40/12.5 mg 5/40/25 mg 10/40/12.5 mg 10/40/25 mg	-
Amlodipine/valsartan/ hydrochlorothiazide (Exforge HCT®*)	Hypertension	Tablet: 5/160/12.5 mg 5/160/25 mg 10/160/12.5 mg 10/160/25 mg 10/320/12.5 mg 10/320/25 mg	✔

*Generic available in at least one dosage form or strength.
†Branded-generic

Table 1b. Current Medications Available in the Therapeutic Class (Non-Dihydropyridines)[27-38]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Diltiazem* (Cardizem®*)	Angina due to coronary artery spasm (tablet); chronic stable angina (tablet); rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias (injection); temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation (injection)	IV solution: 25 mg/5 mL 50 mg/10 mL 125 mg/25 mL 125 mg/125 mL* Tablet: 30 mg 60 mg 90 mg 120 mg	✔
Diltiazem ER* (Cardizem CD®*, Cardizem LA®*, Cartia XT®†, Dilt-XR®†, Matzim LA®†, Tiazac®*, Taztia XT®†)	Angina due to coronary artery spasm; chronic stable angina	ER bead capsule (SR 24-hour): 120 mg 180 mg 240 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		300 mg 360 mg 420 mg ER bead tablet (SR 24-hour): 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg ER capsule (SR 12-hour): 60 mg 90 mg 120 mg ER capsule (SR 24-hour): 120 mg 180 mg 240 mg	
Verapamil* (Calan®*)	Chronic stable angina (tablet), unstable angina (tablet), vasospastic angina (tablet), ventricular rate control in chronic atrial fibrillation and/or atrial flutter in association with digitalis; prophylaxis of repetitive paroxysmal supraventricular tachycardia; temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation (injection); hypertension	IV solution: 2.5 mg/mL Tablet: 40 mg 80 mg 120 mg	✔
Verapamil ER* (Calan SR®*, Verelan®*, Verelan PM®)	Hypertension	CR Tablet: 120 mg 180 mg 240 mg ER capsule (SR 24-hour): 100 mg 120 mg 180 mg 200 mg 240 mg 300 mg 360 mg	✔
Two Agent Combination Products			
Verapamil/trandolapril ER	Hypertension	CR tablet:	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
(Tarka®*)		180/2 mg 240/1 mg 240/2 mg 240/4 mg	

*Generic available in at least one dosage form or strength.
†Branded-generic

Evidence-based Medicine

- Safety and efficacy has been established for a number of agents for various indications.
- Both dihydropyridines and non-dihydropyridines have been evaluated in and approved by the FDA for: angina, cardiovascular outcomes, hypertension and other miscellaneous diagnoses.[39-160]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - In general the calcium channel blockers have been extensively studied in clinical trials for their FDA-approved diagnose.[39-160]
    - For angina, guidelines recommend long-acting CCBs as first line, or in some cases after failure with a β-blocker. In Vasospastic angina, β-blockers should be avoided and CCBs are among first-line recommended agents.[161-167]
    - CCBs are generally not offered to reduce cardiovascular risk after a myocardial infarction.[168]
    - When used in patients with heart failure, nondihydropyridine calcium channel blockers may be harmful in patients with low left ventricular ejection fraction (LVEF). Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF may consider a dihydropyridine calcium channel blocker or other antihypertensive medication if blood pressure remains >1308/80 mmHg. CCBs can be used in heart failure patients who have preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension.[169-171]
    - For the treatment of hypertension, CCBs are considered first line along with many other antihypertensive classes. Addition of a CCB to other antihypertensives may be needed to achieve therapeutic blood pressure levels.[172-175]
- Other Key Facts:
    - There are a number of generic calcium channel blockers currently marketed. Amlodipine, felodipine extended release (ER), isradipine, nicardipine, nifedipine, nifedipine ER, nimodipine, nisoldipine, diltiazem and verapamil are all available as a generic product in at least one dosage form or strength. In addition, generic combination products include amlodipine/atorvastatin, amlodipine/benazepril, amlodipine/valsartan, amlodipine/telmisartan, amlodipine/valsartan/hydrochlorothiazide and verapamil/trandolapril ER.

References

Refer to the therapeutic class review for a complete list of references.

Therapeutic Class Overview
Fibric Acid Derivatives

Therapeutic Class

- **Overview/Summary:** The fibric acid derivatives are agonists of the peroxisome proliferator activated receptor α (PPARα). Activation of PPARα increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. The resulting decrease in triglycerides (TG) produces an alteration in the size and composition of low-density lipoprotein cholesterol (LDL-C) from small, dense particles to large buoyant particles. There is also an increase in the synthesis of high-density lipoprotein cholesterol (HDL-C), as well as apoprotein AI and AII.[1-10] The major action of this class of medications is to reduce TG. The fibric acid derivatives can decrease TG by 20 to 50% and increase HDL-C by 10 to 35%. They also lower LDL-C by 5 to 20%; however, in patients with hypertriglyceridemia, LDL-C may increase with the use of fibric acid derivatives.[11]

  Several fenofibrate products are currently available, including micronized and non-micronized formulations. The different fenofibrate formulations are not equivalent on a milligram-to-milligram basis. Micronized fenofibrate is more readily absorbed than non-micronized formulations, which allows for a lower daily dose. Fenofibrate (micronized and non-micronized formulations), fenofibric acid, and gemfibrozil are available generically in at least one dosage form and/or strength.[12] Fenofibrate and fenofibric acid are Food and Drug Administration (FDA)-approved for the adjunctive treatment of primary hypercholesterolemia or mixed dyslipidemias, as well as an adjunctive treatment for hypertriglyceridemia. Gemfibrozil is FDA-approved for the treatment of hypertriglyceridemia and to reduce the risk of developing coronary heart disease (CHD) in select patients.[13] Gemfibrozil has demonstrated a reduction in the risk of fatal and nonfatal myocardial infarction (MI) for primary prevention, as well as a reduction in CHD death and nonfatal MI and stroke for secondary prevention. Clinical trial results demonstrating that the fibric acid derivatives, as a class, reduce CHD incidence is less robust than that with statin therapy.[11]

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/ Strength	Generic Availability
Fenofibrate (Antara®*, Fenoglide®, Lipofen®, Lofibra®*, Tricor®*, Triglide®)	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia. Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Capsule: 50 mg (Lipofen®) 150 mg (Lipofen®) Capsule, Micronized: 30 mg (Antara®) 43 mg (Antara®) 67 mg (Lofibra®) 90 mg (Antara®) 130 mg (Antara®) 134 mg (Lofibra®) 200 mg (Lofibra®) Tablet: 40 mg (Fenoglide®) 48 mg (Tricor®) 50 mg (Triglide®) 54 (Lofibra®) 120 mg (Fenoglide®) 145 mg (Tricor®) 160 mg (Lofibra®, Triglide®)	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/ Strength	Generic Availability
Fenofibric acid (Fibricor®*, Trilipix®†)	Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fibricor®).‡ Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG and apolipoprotein B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.	Delayed-release capsule: 45 mg (Trilipix®) 135 mg (Trilipix®) Tablet: 35 mg (Fibricor®) 105 mg (Fibricor®)	✔
Gemfibrozil (Lopid®*)	Treatment of adult patients with very high elevations of serum TG levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Reducing the risk of developing CHD only in Type IIb patients without history of or symptoms of existing CHD who have had an adequate response to weight loss, dietary therapy, exercise and other pharmacologic agents and who have the following triad of lipid abnormalities: low HDL-C levels in addition to elevated LDL-C and elevated TG.	Tablet: 600 mg	✔

CHD=coronary heart disease, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TG=triglycerides
*Generic is available in at least one dosage form and/or strength.
†Choline fenofibrate.
‡Indicated for therapy in patients with triglycerides ≥500 mg/dL.

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- In general, the fibric acid derivatives consistently demonstrate greater efficacy compared to placebo in the management of hypercholesterolemia and hypertriglyceridemia.[14-18]
- The addition of fibric acid derivatives to other well established lipid lowering agents has been shown to be safe and resulted in additional improvements in lipid profile compared to each drug given as monotherapy.[16-28]
- The five year, placebo-controlled FIELD trial (N=9,975) demonstrated that fenofibrate did not significantly reduce the risk of the combined primary outcome of coronary events (CHD), death or nonfatal myocardial infarction (MI) in patients with type 2 diabetes. When individual endpoints were analyzed, fenofibrate significantly reduced nonfatal MI by 24% (hazard ratio [HR], 0.76; P=0.010), but a nonsignificant increase in CHD mortality (HR, 1.19; P=0.22) was observed.[29] Similar results were observed in the ACCORD trial (N=5,518) which evaluated the efficacy of fenofibrate on reducing the risk of major cardiovascular events in high risk type 2 diabetics.[30]
- In the five year, Helsiniki Heart Study (N=4,081), a primary prevention trial, gemfibrozil demonstrated a significant 34% (P<0.02) reduction in the incidence of cardiac events but demonstrated no effect on all-cause mortality.[31] After 8.5 years of follow up, all-cause mortality was numerically higher with gemfibrozil, but the increase did not meet significance.[32] In a secondary prevention component of the Helsinki Heart Study, there was no difference between gemfibrozil and placebo in the incidence of fatal and nonfatal MI and cardiac death.[33]
- A meta-analysis of 10 randomized controlled trials (N=36,489) evaluated fibric acid derivatives for the primary and secondary prevention of cardiovascular events and demonstrated that treatment tended to increase all-cause mortality (odds ratio [OR], 1.07; P=0.08) and was associated with a significant increase in noncardiovascular mortality (OR, 1.16; P=0.004). No effect of fibric acid derivatives was observed for cardiovascular mortality (OR, 0.98; P=0.68). When the individual fibric acid derivatives were analyzed, the odds of cardiovascular mortality were significantly lower with gemfibrozil (OR, 0.77; P=0.05).[34]

- A second meta-analysis of 18 randomized controlled trials (N=45,058) demonstrated no effect on all-cause mortality (relative risk [RR], 1.00; P=0.918), cardiovascular mortality (RR, 0.97; P=0.582) or sudden death (RR, 0.89; P=0.190). An increased risk of noncardiovascular mortality was noted; however, this finding did not reach significance (RR, 1.10; P=0.063).[35]
- Fenofibric acid was added to rosuvastatin in patients with chronic kidney disease and it was shown that there was a significantly greater decrease in median percent TGs compared to rosuvastatin alone after eight weeks (P<0.001) and 16 weeks (P<0.001) along with an increase in HDL-C over the same time periods (P<0.001).[36]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Therapeutic lifestyle changes remain an essential modality in the management of patients with hypercholesterolemia.[37-46]
    - In general, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are considered first line therapy for decreasing low density lipoprotein cholesterol (LDL-C) levels.
    - Due to increased muscle side effects including rhabdomyolysis, gemfibrozil is not recommended to be used in a combination with statins.[43]
    - Fibric acid derivatives are typically reserved for the treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low high density lipoprotein cholesterol.[37,40]
    - Fibric acid derivatives can be considered in patients with coronary heart disease who have low levels of LDL-C and atherogenic dyslipidemia, or in combination with a statin in patients who have elevated LDL-C and atherogenic dyslipidemia.[37] Since the publication of these guidelines, the FD) requested the discontinuation of the marketing of Trilipix® indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD (coronary heart disease) or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal. This decisions was based on the FDA's conclusion that the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in TG and/or increase in HDL-C levels in statin-treated patients results in a reduction in the risk of cardiovascular events.[47]
    - The National Institute for Health and Clinical Excellence (NICE) guidelines recommend non-routine use of fibrates if intolerant to statins as monotherapy and recommend against the use of niacin, bile acid sequestrants, and omega-3 fatty acids or any combination of a stains plus either a fibrate, niacin, bile acid sequestrants, or omega-3 fatty acids for primary or secondary prevention of coronary vascular disease due to lack of evidence.[44]

- Other Key Facts:
    - Gemfibrozil (Lopid®) is the only fibric acid derivative approved for reducing the risk of developing coronary heart disease in select patients.[10]
    - Currently, all fibric acid derivatives are available generically in at least one dosage form and/or strength.[12]

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Therapeutic Class Overview
Agents for Gout

Therapeutic Class Overview/Summary:
Gout is a complex inflammatory disease that occurs in response to the presence of monosodium urate monohydrate crystals in the joints, bones and soft tissues.[1,2] The disease consists of four clinical phases.[3] The first phase is asymptomatic hyperuricemia. Although hyperuricemia is a necessary predisposing factor, the presence of high serum urate levels alone does not automatically lead to gout.[1,3] One study reported that 78% of the men in the trial with serum urate levels greater than 9 mg/dL did not develop gout over a five year period.[4] Hyperuricemia can be caused by impaired renal excretion or overproduction of serum urate and/or overconsumption of purine-rich foods that are metabolized to urate.[1] Humans, lack the enzyme uricase and therefore cannot convert urate to the soluble allantoin as the end product of purine metabolism.[2] The deposition of monosodium urate monohydrate crystals into the joints and other areas of the body begin when serum urate levels are greater than 6.8 mg/dL. This concentration is the saturation point of urate in biological fluids and it is at this concentration where monosodium urate monohydrate crystals begin to precipitate. As mentioned previously the presence of hyperuricemia does not automatically lead to gout. Other factors, when combined with hyperuricemia that contribute to monosodium urate monohydrate deposition and the development of gout include trauma or irritation of joins, lower temperatures which favor crystal deposition and previously diseased joints.[4]

The second phase is characterized by intermittent acute gout attacks.[3] These attacks are due to the abrupt release of monosodium urate monohydrate crystals into the joint space where they initiate an acute inflammatory reaction characterized by painful inflammatory arthritis.[4] These attacks typically resolve spontaneously over a period of seven to 10 days.[2] The time interval separating these acute attacks is the third phase of the disease and is known as the intercritical gout period.[5] The time period separating acute gout attacks during this period vary widely between a few days to several years. Overtime, if the disease is left untreated it evolves into chronic tophaceous gout. This phase of the disease is characterized by the deposition of solid monosodium urate monohydrate crystal aggregates known as tophi in a variety of locations including joints, bursae and tendons.[5] In addition deposits of monosodium urate monohydrate crystals in the renal tubules can also lead to renal calculi and nephropathy.[3]

Treatment of gout consists of rapid relief of pain and disability caused by acute gout attacks and the reduction of serum urate levels. This reduction prevents further acute attacks and the progression of the disease to tophaceous gout.[2] Although acute attacks can be treated with anti-inflammatory medications, the underlying cause of the disease can only be treated by lowering serum urate levels.[4]

In addition to the treatment of gout the agents included in this review are also indicated for a number of other indications. These include hyperuricemia due to chemotherapy, Familial Mediterranean Fever, increasing of penicillin levels, and treatment of calcium oxalate calculi. These indications will not be discussed in detail as they are outside the scope of this review.[6-12] These agents also have different mechanisms of actions by which they exert their effects. Colchicine is believed to exert a positive effect in gout by preventing the activation, degranulation and migration of neutrophils, implicated in the pathogenesis of gout symptoms. The mechanism by which colchicine acts in patients with Familial Mediterranean Fever has not been fully established; however, there is evidence suggesting that colchicine interferes with the assembly of the inflammasome complex found in neutrophils and monocytes that medicate the activation of interleukin-1β.[7,8] Allopurinol and febuxostat are both xanthine oxidase inhibitors. These agents causes a decrease in urate levels through the inhibition of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and then finally to uric acid.[6,9] A major difference between these two agents is that allopurinol is a purine analogue where febuxostat is not.[13] Another major difference is that febuxostat is mainly metabolized in the liver and thus does not require renal dosing in mild-moderate renally impaired patients.[6,9] Pegloticase is a recombinant uricase, a uric acid-specific enzyme, which catalyzes the oxidation of uric acid to allantoin, thereby lowering serum uric

acid. Allantoin is an inert and water soluble purine metabolite which is readily eliminated, primarily via renal excretion.[10] Probenecid is a uricosuric agent that exerts its effects on serum urate by inhibiting the reabsorption of uric acid at the proximal tubule which leads to uric acid excretion and a decrease in overall serum urate levels.[11,14] Probenecid is also available with colchicine as a combination product.[12]

The majority of these agents, with the expectation of febuxostat and pegloticase, have been available in the United States for a number of years with probenecid being available since the 1950s and allopurinol and colchicine/ probenecid being available since the 1960s. Colcrys® is the branded version of colchicine. In 2006, the Food and Drug Administration (FDA) launched the Unapproved Drugs Initiative. This initiative targeted drugs that had never formally received FDA-approval.[15] The initiative required manufacturers of the non-approved versions of colchicine to either apply for approval through the current FDA approval methods or cease manufacturing the agent. On September 30, 2010, the FDA informed manufacturers of these non-approved products that they were expected to stop manufacturing single-ingredient oral colchicine by October 14, 2010 and must stop shipping the product by December 30, 2010. Colchicine (Colcrys®), was approved by the FDA on July 30, 2009.[16] More recently, both a new capsule formulation as well as a generic version have been approved by the FDA. Other generic products currently available include allopurinol, probenecid and probenecid/colchicine.

Table 1. Current Medications Available in the Therapeutic Class[6-12]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agent			
Allopurinol (Zyloprim®*)	Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy); management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels; management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients	Tablet: 100 mg 300 mg	✔
Colchicine (Colcrys®*, Mitigare®*)	Prophylaxis of gout flares; treatment of gout flares; treatment of Familial Mediterranean Fever	Capsule: 0.6 mg Tablet: 0.6 mg	✔
Febuxostat (Uloric®)	Chronic management of hyperuricemia in patients with gout	Tablet: 40 mg 80 mg	-
Pegloticase (Krystexxa®)	Treatment of chronic gout in adult patients refractory to conventional therapy	Vial 8 mg/mL Must be administered in a health care facility.	-
Probenecid*	Treatment of hyperuricemia associated with gout and gouty	Tablet: 500 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	arthritis; adjuvant therapy with penicillin or with ampicillin, methicillin, oxacillin, cloxacillin, or nafcillin, for elevation and prolongation of plasma levels by whatever route the antibiotic is given		
Combination Products			
Colchicine/probenecid*	Treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout	Tablet: 0.5 mg/0.5 g	✔

*Generic available in at least one dosage form or strength.

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- Regarding Familial Mediterranean Fever, studies that have examined the use of colchicine for this disease state are limited. It should be noted, that approval of brand colchicine for Familial Mediterranean Fever treatment was not based on new clinical studies but rather on previously published literature. These studies as well as others confirmed that the agent is efficacious in both reducing the number of attacks and in aborting acute attacks.[7,23,24,50]
- Efficacy of colchicine for the treatment and prevention of gout and increased uric acid levels is well documented.[25-29]
- The efficacy and safety of pegloticase was evaluated in two identical randomized placebo-controlled studies. The studies were six months in duration and included adult patients with symptomatic gout and at least three gout flares in the previous 18 months or the presence of at least one gout tophus or gouty arthritis. Moreover, patients were included if they had a self-reported contraindication to allopurinol or a medical history of failure to normalize uric acid with at least three months of allopurinol treatment. Patients in both studies were treated with either pegloticase 8 mg every two weeks, every four weeks or placebo. The primary endpoint in both studies was the proportion of patients who achieved plasma uric acid (PUA) levels less than 6 mg/dL for at least 80% of the time during months 3 and 6. In the first study, 47% and 20% of patients in the 8 mg every two and four weeks respectively achieved PUA<6 mg/dL for ≥80% of the time. There was a significant difference in both groups when compared to placebo (0%, P<0.001 and P=0.044, respectively). In the second study, 38% and 49% of patients in the 8 mg every 2 and 4 weeks respectively achieved PUA<6 mg/dL for ≥80% of the time. There was a significant difference in both groups when compared to placebo (0%, P<0.001 for both pegloticase groups).[9,30]
- Regarding febuxostat, the three major trials that were the basis for approval were the FACT, APEX, and CONFIRMS trials. These studies were all randomized, double-blind, controlled trials that compared the treatment of febuxostat, in doses ranging from 40 to 240 mg/day, to allopurinol or placebo in patients with gout. The FACT and APEX studies demonstrated that a significantly greater number of patients treated with febuxostat 80, 120 and 240 mg were able to reach a serum urate goal of less than six mg/dL. In the CONFIRMS trial patients in the 80 mg group had similar outcomes to the FACT and APEX studies; however the CONFIRMS trial also evaluated a 40 mg dose where the proportion of patients with serum urate level <6 mg/dL was not found to be significantly different between the febuxostat 40 mg and the allopurinol groups. These studies also reported that febuxostat was more efficacious than allopurinol in patients with mild to moderate renal impairment. However, in all three studies there were no differences between any of the groups for the number of patients who required treatment for acute gout flares. Regarding adverse events, there were generally no significant differences in the incidence of adverse events between the febuxostat and allopurinol groups and they were generally mild to moderate in severity. There was also no statistically significant difference between groups in the incidence of cardiovascular events.[35-37]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Recommend a nonsteroidal anti-inflammatory drug (NSAID), colchicine, or a corticosteroid for the treatment of an acute gout attack.[17-20]
  - According to the more recent guidelines for the management of gout, initiation of urate lowering therapy is recommended in patients with an established diagnosis of gout and tophus or tophi, frequent attacks of acute gouty arthritis (≥2 attacks/year), chronic kidney disease stage 2 or worse, and past urolithiasis.[17]
  - Agents used to lower serum urate levels include allopurinol, probenecid, and febuxostat. The main difference between these agents is that allopurinol and febuxostat inhibit urate production and probenecid promotes urate excretion.[17-21]
  - The 2012 ACR guideline recommends either allopurinol or febuxostat as the first-line urate lowering therapy approach for the management of gout, with no preference stated between the two.[17]
  - In comparison, older guidelines, published prior to approval of febuxostat, recommend allopurinol first-line and note febuxostat as a second-line option when allopurinol is not effective or not appropriate.[19-21]
  - The ACR recommends probenecid as an alternative first-line urate lowering therapy option in patients with a contraindication or intolerance to either allopurinol or febuxostat.[16]
  - During initiation of urate lowering therapy the guidelines recommend concurrent prophylaxis with either colchicine or an NSAID, although generally colchicine is the preferred, to prevent acute attacks while starting therapy.[18-20]
  - Concomitant therapy is generally recommended for up to six months at which point only the urate lowering agent is continued. Treatment with the urate lowering agent has the potential to be lifelong.[18,19]
- Other Key Facts:
  - Colchicine tablets and colchicine capsules have different FDA-approved indications and ages approved.[1,2]
  - Colchicine tablets are approved for use in children ≥4 years of age for the treatment of Familial Mediterranean Fever (tablets)[1]

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Therapeutic Class Overview
Growth Hormone

Therapeutic Class

Overview/Summary: Growth hormone (GH) affects many of the metabolic processes carried out by somatic cells, most notably increasing body mass. Overall growth is stimulated by GH therapy; however, the effects are not evenly distributed among protein, lipid and carbohydrate compartments. Specifically, body protein content and bone mass increase, total body fat content decreases and there is an increase in plasma and liver lipid content due to the mobilization of free fatty acids from peripheral fat stores. Other physiological effects of GH include stimulation of cartilage growth.[1] In pediatric patients, once a diagnosis of growth hormone deficiency (GHD) is confirmed, GH therapy should be initiated immediately and continued at least until liner growth is nearly complete (e.g., decreased to 2.5 cm/year). Therapy should be initiated as soon as possible as evidence demonstrates that growth response is more robust when GH therapy is started at a younger age. Once adult height is achieved, patients should be retested to determine if GH treatment will be required during adulthood.[1] The role of GH therapy in adult patients with GHD is less clear. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential beneficial effects of GH therapy in adults are not as established, including improvement in bone mineral density, sense of well-being, muscle strength and lipid profile.[2] Included in this review are the various GH preparations. Specifically, all preparations contain somatropin; otherwise known as recombinant human GH.[3-12] The various preparations are Food and Drug Administration (FDA)-approved for use in a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease, Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene and Noonan syndrome, as well as for idiopathic short stature.[3-10] The majority of preparations are also indicated for the treatment of GHD in adults as well.[3-9] Of note, Serostim® (somatropin) is only FDA-approved for the treatment of human immunodeficiency virus-associated wasting or cachexia in adults.[11] In addition, Zorbtive® (somatropin) is the only agent indicated by the FDA to treat short bowel syndrome.[12] All of the available GH preparations are available for subcutaneous injection and there are currently no generics available within the class.[3-12] Treatment guidelines support the use of GH in FDA-approved indications and they do not distinguish among the various preparations.[13-22]

Table 1. Current Medications Available in Class[3-11]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Somatropin (Genotropin®)	Pediatric indications: growth failure associated with Prader-Willi syndrome, growth failure associated with Turner syndrome, growth failure in children born small for gestational age*, growth hormone deficiency, and idiopathic short stature‡ Adult indications: growth hormone deficiency‖	Cartridge, powder for reconstitution: 5 mg 12 mg Cartridge, powder for reconstitution (preservative-free): 0.2 mg 0.4 mg 0.6 mg 0.8 mg 1.0 mg 1.2 mg 1.4 mg 1.6 mg 1.8 mg 2.0 mg	-
Somatropin (Humatrope®)	Pediatric indications: growth failure associated with short-stature homeobox-containing gene	Cartridge, powder for reconstitution: 6 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	deficiency, growth failure associated with Turner syndrome, growth failure in children born small for gestational age[†], growth hormone deficiency, and idiopathic short stature[‡] Adult indications: growth hormone deficiency[‖]	12 mg 24 mg Vial, powder for reconstitution: 5 mg	
Somatropin (Norditropin®)	Pediatric indications: growth failure associated with Noonan syndrome, growth failure associated with Turner syndrome, growth failure in children born small for gestational age[†], and growth hormone deficiency Adult indications: growth hormone deficiency[‖]	Prefilled pen (Norditropin® FlexPro®): 5 mg/1.5 mL 10 mg/1.5 mL 15 mg/1.5 mL	-
Somatropin (Nutropin®)	Pediatric indications: growth failure associated with chronic renal insufficiency before renal transplant[§], growth failure associated with Turner syndrome[#], growth hormone deficiency[#], and idiopathic short stature[‡,#] Adult indications: growth hormone deficiency[‖]	Prefilled cartridge (Nutropin AQ NuSpin®): 5 mg/2 mL 10 mg/2 mL 20 mg/2 mL Prefilled pen cartridge (Nutropin AQ®): 10 mg/2 mL 20 mg/2 mL	-
Somatropin (Omnitrope®)	Pediatric indications: growth failure associated with Prader-Willi syndrome, growth failure associated with Turner syndrome, growth failure in children born small for gestational age, growth hormone deficiency, and idiopathic short stature[‡] Adult indications: growth hormone deficiency[‖]	Prefilled cartridge: 5 mg/1.5 mL 10 mg/1.5 mL Vial, powder for reconstitution: 5.8 mg/vial	-
Somatropin (Saizen®)	Pediatric indications: growth hormone deficiency Adult indications: growth hormone deficiency[‖]	Cartridge, powder for reconstitution: 8.8 mg Vial, powder for reconstitution: 5 mg (15 IU) 8.8 mg (26.4 IU)	-
Somatropin (Serostim®)	Adult indications: human immunodeficiency virus-associated wasting or cachexia	Vial, powder for reconstitution: 4 mg (12 IU) Vial, powder for reconstitution (preservative-free): 5 mg (15 IU) 6 mg (18 IU)	-
Somatropin (Zomacton®)	Pediatric indications: growth hormone deficiency	Vial, powder for reconstitution: 5 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		10 mg	
Somatropin (Zorbtive®)	Adult indications: treatment of short bowel syndrome in patients receiving specialized nutritional support	Vial, powder for reconstitution: 8.8 mg	-

IU=International units
*For patients that fail to manifest catch-up growth by age two years.
†For patients that fail to manifest catch-up growth by age two to four years.
‡Defined by height standard deviation score ≤-2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.
§Nutropin® should be used in conjunction with optimal management of CKD.
#Indicated for long-term treatment.
¶Zorbtive® should be used in conjunction with optimal management of Short Bowel Syndrome.
‖For patients who meet either adult-onset criteria (patients who have GH deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma) or childhood-onset criteria (Patients who were GH deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes).

Evidence-based Medicine

- The evidence demonstrating the safety and efficacy of growth hormone (GH) in Food and Drug Administration approved indications is well established. Overall, treatment with GH is consistently "superior" to no treatment and/or placebo and data suggests that not one specific dosing regimen for each indication is preferred over another. Treatment with GH should be individualized based on growth response and tolerability.
- Of note, limited head-to-head clinical trials exist; therefore, it is difficult to determine if one specific preparation of GH (i.e., somatropin) is "superior" to another.[23-153] Treatment guidelines do not distinguish among the various preparations.[12-22]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Among pediatric patients, growth hormone (GH) (somatropin) is recommended as a treatment option for children with growth failure associated with any of the following: growth hormone deficiency (GHD), Turner syndrome, Prader Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age or later and short stature homeobox-containing gene deficiency.[13,14,17-19] GH is also a treatment option for pediatric patients with Noonan syndrome.[15,16]
        - The choice of preparation should be individualized after informed discussion between the responsible clinician and the patient and/or caretaker about the advantages or disadvantages of available preparations, taking into consideration therapeutic need and likelihood of adherence to treatment. If more than one preparation is suitable, the least costly should be chosen.
    - Among adult patients, GH is recommended for the approved uses of the preparation in patients with clinical features suggestive of adult GHD and biochemically proven evidence of GHD.[21,22]
- Other Key Facts:
    - No agents in the class are currently available generically.

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Therapeutic Class Overview
Direct Acting Hepatitis C Antivirals and Combinations

Overview/Summary:
The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-9] Daklinza® (daclatasvir) is a once-daily NS5A inhibitor indicated for use with an NS5B polymerase inhibitor Sovaldi® (sofosbuvir) for 12 weeks in the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection. It is the first Food and Drug Administration (FDA)-approved all-oral regimen for the HCV genotype 3 infection that does not require co-administration of interferon or ribavirin.[1] Technivie® (ombitasvir/paritaprevir/ ritonavir) in combination with ribavirin is the first interferon-free Food and Drug Administration (FDA)-approved drug for the treatment of HCV genotype 4 infection.[7]

HCV is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood and is the most common bloodborne infection in the United States, with an estimated prevalence of 3.2 million people chronically infected. Chronic HCV develops in 70 to 85% of HCV-infected persons and is associated with significant morbidity (e.g., cirrhosis, hepatocellular carcinoma [HCC]) and is the leading cause of liver transplantation.[10-12] The average annual incidence rate of HCC in the U.S. between 2001 and 2006 was 3.0 per 100,000 people, with 48% to cases attributed to HCV.[11] These agents act via several different mechanisms of action to exert their therapeutic effect.[1-9] Daclatasvir (Daklinza) binds to the N-terminus of NS5A, a nonstructural protein encoded by HCV, and inhibits both viral ribonucleic acid (RNA) replication and virion assembly.[1] Simeprevir (Olysio®) works via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b, thus preventing replication of HCV host cells.[2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir (Technivie®), and ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®), elbasvir/grazoprevir (Zepatier®) and sofosbuvir/velpatasvir (Epclusa®). Grazoprevir and paritaprevir inhibit NS3/4A protease, dasabuvir inhibits NS5B polymerase and elbasvir, ledipasvir, ombitasvir and velpatasvir specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Technivie® and Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-8] Specific indications for each of the direct acting hepatitis C antiviral agents are listed in Table 1.

Efficacy of these agents have been established in multiple clinical trials with numerous clinical trials still underway.[13-47] Generally, therapy is determined by clinical guidelines developed by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America and International Antiviral Society (IDSA) rather than the FDA-approved labels of these agents.[48] The newer combination regimens that include direct hepatis C antivirals are preferred over older pegylated interferon-based regimens (including those containing older protease inhibitors) due to a higher sustained virologic response (SVR) rate, improved side effects profile, and reduced pill burden. However, many different regimens with direct-acting agents or combinations, which may or may not also include ribavirin or pegylated interferon, are recommended based on HCV genotype, previous treatment experience and certain special populations. Each of the direct HCV antivirals is recommended as part of at least one first-line regimen.[48-50] Currently, there are no generic direct-acting antivirals available.

Table 1. Current Medications Available in Therapeutic Class[1-8]

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Daclatasvir (Daklinza®)	Treatment of chronic HCV genotype 3 infection in adults as part of a combination antiviral regimen	Tablet: 30 mg 60 mg	-
Simeprevir (Olysio®)	Treatment of chronic HCV genotype 1,4	Capsule: 150	-

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
	infection in adults as part of a combination antiviral regimen	mg	
Sofosbuvir (Sovaldi®)	Treatment of chronic HCV genotype 1, 2, 3, and 4 infection in adults as part of a combination antiviral regimen	Tablet: 400 mg	-
Combination Products			
Elbasvir/grazoprevir (Zepatier®)	Treatment of chronic HCV genotype 1 and 4 infection in adults as part of a combination antiviral regimen	Tablet: 50/100 mg	-
Ledipasvir/sofosbuvir (Harvoni®)	Treatment of chronic HCV genotype 1, 4, 5, and 6 infection in adults as part of a combination antiviral regimen	Tablet: 90/400 mg	-
Ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®)	Treatment of chronic HCV genotype 1 infection in adults as part of a combination antiviral regimen	Tablet (dasabuvir): 250 mg Tablet (ombitasvir/ paritaprevir/ ritonavir): 12.5/75/50 mg	-
Ombitasvir/paritaprevir/ ritonavir (Technivie®)	Treatment of chronic HCV genotype 4 infection in adults as part of a combination antiviral regimen	Tablet: 12.5/75/50 mg	-
Sofosbuvir/velpatasvir (Epclusa®)	Treatment of chronic HCV genotypes 1, 2, 3, 4, 5 or 6 in adults	Tablet: 400 mg/100 mg	-

FDA=Food and drug administration, HCV=hepatitis C virus

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the direct acting hepatitis C antivirals in various genotypes and regimens.[13-47] Overall, data from clinical trials support the FDA-approved indications and dosing recommendations for these agents.
- The FDA approval of daclatasvir was based on the results of ALLY-3, an open-label study evaluating 12 week regimen of daclatasvir 60 mg plus sofosbuvir 400 mg in treatment-naive and treatment-experienced patients with chronic HCV genotype 3 infection. The primary endpoint was the SVR at post treatment week 12 (SVR12). High SVR12 rates were observed among patients without cirrhosis: 97% (73/75) and 94% (32/34) in treatment-naïve and treatment-experienced patients, respectively. In contrast, SVR12 rates in cirrhotic patients were much lower: 58% (11/19) and 69% (9/13) in treatment-naïve and treatment-experienced patients, respectively.[33]
    - An ongoing randomized phase III study is evaluating a combination of daclatasvir, sofosbuvir and ribavirin for 12 or 16 weeks to determine whether the addition of ribavirin or extending treatment duration improved SVR rates in cirrhotic patients with HCV genotype 3 infection.[34]
- The efficacy of simeprevir in patients with HCV genotype 1 infection was evaluated in several unpublished studies, including two phase III trials in treatment-naïve patients (QUEST 1 and QUEST 2), one phase III trial in patients who relapsed after prior interferon-based therapy (PROMISE).[2]
    - In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR at 12 weeks (SVR12) compared to control group (80 vs 50%; P value not reported).[2]
- The safety and efficacy of simeprevir in combination with sofosbuvir with or without ribavirin for the treatment of hepatitis C genotype 1 was evaluated in the COSMOS trial. Cohort 1 included prior null responders with METAVIR scores F0 to F2 and Cohort 2 included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.[2,27]
    - SVR at 12 weeks post therapy (SVR12) was achieved in 92% of the patients in the the intention to treat (ITT) population. SSVR12 for Cohort 1 and Cohort 2 were 90% (95% CI, 81

to 96) and 94% (95% CI, 87 to 98), respectively. The results were not significantly altered by use of ribavirin, duration of treatment, or treatment history (no P values reported). [20]

- The FDA approval of sofosbuvir was based on the results of five phase III trials (N=1,724) in HCV mono-infected patients (genotypes 1 to 6) and one unpublished phase III trial (N=223) in HCV/HIV-1 co-infected patients (HCV genotype 1, 2 or 3).[13,31,32]
    - All trials utilized SVR12 as the primary endpoint and overall, these studies showed that sofosbuvir provided a significant improvement in SVR12 compared with control in both treatment-naïve and treatment-experienced patients.[13,31,32]
    - Sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection. According to the prescribing information, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71%. This is based on the observed response rate in patients from the NEUTRINO study.[13]
- The FDA-approval of elbasvir/grazoprevir was based on two placebo-controlled trials and four uncontrolled phase II and III clinical trials in 1,401 patients with genotype HCV genotype 1, 4, or 6 chronic HCV with compensated liver disease (C-EDGE TN, C-EDGE COINFECTION, C-SURFER, C-SCAPE, C-EDGE TE, and C-SALVAGE). All clinical trials evaluated SVR12 as the primary endpoint. Elbasvir/grazoprevir was administered once daily in all trials and ribavirin, if received, was dosed by weightd.[4,14-20]
    - After 12 weeks to therapy, SVR12 rates in C-EDGE TN were 91.7% (genotype 1a), 98.5% (genotype 1b), 100% (genotype 4), and 80% (genotype 6). SVR12 was achieved in 97.1% of cirrhotic patients and 93.9% (231/246) of noncirrhotic patients.[14] After 12 weeks to therapy, SVR12 rates in C-EDGE COINFECTION (HIV-coinfection) were 96.5% (genotype 1a), 95.5% (genotype 1b), 96.4% (genotype 4), and 100% (genotype 6) with 100% of cirrhotic patients. All 35 patients with cirrhosis achieved SVR12.[15] The SVR12 rate after 12 weeks of therapy in C-SURFER (chronic kidney disease) was 99.1%.[16] The overall SVR12 rate in C-SALVAGE (genotype 1, previously failed ≥4 weeks of peginterferon alfa and ribavirin combined with a protease inhibitor [boceprevir, telaprevir, or simeprevir]) was 96.2% overall, including 91.2% in patients with baseline NS3 resistance, and 94.1% (32/34) in cirrhotic patients.[17,18] C-WORTHY (N=471) was a phase II, randomized, parallel-group, multicenter, open-label study comparing grazoprevir plus elbasvir with or without ribavirin in different patient populations (20 arms total) with chronic HCV genotype 1 infection. SVR12 rates ranged from 80% to 100%.[19,20]
- The FDA approval of combination ledipasvir/sofosbuvir was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection who had compensated liver disease. Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels.[20,21,25]
    - ION-1 evaluated treatment-naïve patients include patients with cirrhosis; ION-2 evaluated patients with or without cirrhosis who failed previous therapy with an interferon-based regimen including those containing an HCV protease inhibitor; ION-3 evaluated non-cirrhotic, treatment-naïve patients.[21,22,26]
    - All studies showed that ledipasvir/sofosbuvir significantly improved SVR12 rate compared to control. [21,22,26]
- The FDA approval of ombitasvir/paritaprevir/ritonavir and dasabuvir was based on the results of six randomized, multicenter, clinical trials (N=2,308) in HCV patients with genotype 1, including one trial exclusively in patients with cirrhosis and mild hepatic impairment (Child-Pugh A). All studies included at least one treatment arm with ribavirin, while several studies included treatment arms without ribavirin.[23-25,28,29]
    - Study populations for each of the studies include treatment-naïve, non-cirrhotic adults with HCV genotype 1 infection (SAPPHIRE-I), treatment-naïve, non-cirrhotic adults with HCV genotype 1b and HCV genotype 1a infections (PEARL-III and PEARL-IV, respectively), treatment-naïve or previously treated with peginterferon alfa and ribavirin cirrhotic adults with HCV genotype 1 infection (TURQUOISE-II), noncirrhotic adults with HCV genotype 1 infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (SAPPHIRE-II) and finally, non-cirrhotic adults with HCV genotype 1b infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (PEARL-II). [23-25,28,29]

  - Overall, SVR12 rates were high and significantly improved compared with control after 12 weeks of therapy. [23-25,28,29] Only TURQUOISE-II evaluated patients beyond 12 weeks of therapy and found there was no difference between 12 weeks of therapy compared with 24 weeks of therapy (P=0.09).[25]
- The FDA-approval of ombitasvir/paritaprevir/ritonavir in the treatment of HCV genotype 4 was based on the results of an open-label, randomized, multicenter phase IIb PEARL-I study, which evaluated ombitasvir/paritaprevir/ritonavir with or without ribavirin and no cirrhosis. Patients were either treatment-naïve or treatment experienced (prior failure of peginterferon alfa and ribavirin). In treatment-naive patients, the SVR12s were 100% (42/42) in the ribavirin-containing regimen and 90.9% (40/44) in the ribavirin-free regimen. In the treatment-naive group without ribavirin, on-treatment virologic breakthrough was reported in one patient (2%), two patients (5%) experienced post-treatment relapse, and one patient (2%) was lost to follow-up. All 49 treatment-experienced patients in the ribavirin-containing group achieved SVR12.[35]
  - AGATE-I is an ongoing phase III study evaluating ombitasvir/paritaprevir/ritonavir with ribavirin for 12, 16 or 24 weeks in cirrhotic patients with HCV genotype 4 infection, including treatment-naïve patients and those who have failed peginterferon alfa and ribavirin or sofosbuvir-containing regimens.[36]
  - TURQUOISE-CPB is another ongoing phase III study evaluating ombitasvir/paritaprevir/ritonavir with ribavirin for 24 weeks in patients with HCV genotype 4 infection and decompensated cirrhosis.[37]
  - Several other studies are planned or recruiting patients to evaluate ombitasvir/paritaprevir/ritonavir with or without ribavirin in less well studied subpopulations with HCV genotype 4 infection, including severe renal disease, children (three to 17 years old), and status post successful treatment of early stage hepatocellular carcinoma.[38-41]
- The FDA-approval of sofosbuvir/velpatasvir was based on the results of four phase III studies (ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4) in patients with HCV genotype 1 through 6.
  - ASTRAL-1 (N=706) was a phase III, randomized, double-blind, placebo-controlled study evaluating sofosbuvir/velpatasvir 400 mg/100 mg once daily for 12 weeks in adult patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection. Overall, SVR12 rate in the sofosbuvir/velpatasvir group of 99% (618/624) was higher than the prespecified benchmark rate of 85% (P<0.001). [42]
  - ASTRAL-2 (N=266) and ASTRAL-3 (N=552) were two phase III, randomized, open-label studies comparing sofosbuvir/velpatasvir 400 mg/100 mg once daily for 12 weeks to sofosbuvir 400 mg plus weight-based ribavirin for 12 weeks (ASTRAL-2) or 24 weeks (ASTRAL-3) in adult patients with chronic HCV genotype 2 and HCV genotype 3 infections, respectively. Among patients with HCV genotype 2, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 99% (133/134) as compared to 94% (124/132) in the 12-week sofosbuvir/ribavirin (P=0.02). Among patients with HCV genotype 3, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 95% (264/277) as compared to 80% (221/275) in the 24-week sofosbuvir/ribavirin group (P<0.001).[43]
  - ASTRAL-4 (N=267) was a phase III, randomized, open-label study evaluating sofosbuvir/velpatasvir 400 mg/100 mg once daily for 12 weeks (with or without ribavirin) or 24 weeks in adult patients with chronic HCV genotype 1, 2, 4, or 6 infection and decompensated cirrhosis (Child-Turcotte-Pugh class B). Overall SVR12 rates were 83% (75/90), 94% (82/87), and 86% (77/90) among patients who received sofosbuvir/velpatasvir for 12 weeks, sofosbuvir/velpatasvir and ribavirin for 12 weeks, and sofosbuvir/velpatasvir for 24 weeks, respectively.[44]
  - Other trials are ongoing and full results have not been published. Sofosbuvir/velpatasvir has been evaluated in treating HCV/HIV coinfection in patients with genotypes 1 through 4 (ASTRAL-5), in patients with genotypes 1 through 3 and previous sofosbuvir/velpatasvir failures and in patients undergoing liver transplant.[45-47]

Key Points within the Medication Class

- American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their guideline.[48]

- Old standards of therapy, including pegylated interferon alfa and ribavirin dual therapy and pegylated interferon alfa, ribavirin along with a protease inhibitor triple therapy are no longer recommended.
- Current, first-line therapies recommended in the new guidelines include all-oral combination therapies, each of which generally has at least one polymerase inhibitor and one other direct-acting agent that acts via a different mechanism of action.
- Each of the new HCV direct acting antivirals are recommended as part of a first-line regimen for at least one genotype and/or patient population.[48]
- Depending on genotype, previous treatment-experience and special populations, the recommended regimens and durations of treatment vary due to differences in efficacy provided by clinical trials.
    - For genotype 1, five regimens with similar efficacy are recommended. Duration and addition of ribavirin depend on cirrhosis status and/or previous treatment failures.
        - Daclatasvir 60 mg daily (QD) + sofosbuvir 400 mg QD ± ribavirin for 12 to 24 weeks
        - Ledipasvir/sofosbuvir 90/400 mg QD ± ribavirin for 12 to 24 weeks
        - Ombitasvir/ paritaprevir/ritonavir 25/150/100 mg QD + dasabuvir 250 mg twice-daily (BID) ± ribavirin for 12 to 24 weeks
        - Sofosbuvir 400 mg QD + simeprevir 150 mg QD for 12 to 24 weeks
        - Elbasvir/grazoprevir 50/100 mg QD ± ribavirin for 12 to 16 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD for 12 weeks
    - For genotype 2:
        - Daclatasvir 60 mg QD + sofosbuvir (400 mg) QD ± ribavirin for 12 to 24 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD ± ribavirin for 12 weeks
    - For genotype 3:
        - Daclatasvir (60 mg) and sofosbuvir (400 mg) ± ribavirin for 12 to 24 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD ± ribavirin for 12 weeks
    - For Genotype 4:
        - Ledipasvir/sofosbuvir 90/400 mg QD ± ribavirin for 12 to 24 weeks
        - Ombitasvir/ paritaprevir/ritonavir 25/150/100 mg+ ribavirin for 12 weeks
        - Elbasvir/grazoprevir 50/100 mg QD ± ribavirin for 12 to 16 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD for 12 weeks
    - Genotype 5 and 6:
        - Ledipasvir/sofosbuvir 90/400 mg QD for 12 weeks
        - Sofosbuvir/velpatasvir 400 mg/100mg QD for 12 weeks
    - In patients that fail a sofosbuvir, daclatasvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir plus dasabuvir, it is recommended to defer therapy if they have minimal liver disease; guidelines do not offer a specific regimen for recipients with extensive liver disease, but recommend resistance-testing. They recommend treatment for at least 24 weeks with ribavirin, if not contraindicated.[48]

- Other Key Facts:
    - There are also disparities between the FDA-approved indications and first-line recommendations according to the AASLD-IDSA guidelines.[1-8,48]
    - Prior to initiating therapy with simeprevir (in combination with sofosbuvir) in cirrhotic patients with genotype 1a, they should be screened for the presence of NS3 Q80K polymorphism. Alternative therapy should be considered if this polymorphism is present.[2]
    - When prescribing ombitasvir/paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir/dasabuvir, screening for drugs that should not be coadministered is recommended due to many, often severe, drug interactions.[5,6]
    - Dose of daclatasvir must be adjusted when given with strong CYP3A inhibitors (30 mg QD) and moderate CYP3A inducers (90 mg QD).[1]
    - Testing for NS5A-associated resistance is recommended prior to treatment with sofosbuvir, elbasvir/grazoprevir, ledipasvir/sofosbuvir and sofosbuvir/velpatasvir for several patient populations. [48]

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Therapeutic Class Overview
Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review will focus on oral and injectable immunomodulators. These agents are used for a variety of inflammatory and immunologic conditions which include: rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, juvenile/systemic idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, uveitis and several cryopyrin-associated periodic syndromes. Specific Food and Drug Administration (FDA)-approved indications for each agent are summarized in Table 1. Overall, these agents achieve their therapeutic effect via several different mechanisms of action. The majority of oral and injectable immunomodulators inhibit the effect of proinflammatory cytokines, specifically interleukins or tumor necrosis factor (TNF)-α. Interleukin (IL) inhibitors include anakinra (Kineret®), canakinumab (Ilaris®), ixekizumab (Taltz®), rilonacept (Arcalyst®), secukinumab (Cosentyx®), tocilizumab (Actemra®), and ustekinumab (Stelara®) while the TNF-α inhibitors are adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®, Simponi ARIA®), and infliximab (Remicade®). Abatacept (Orencia®) is a T-cell activation inhibitor, tofacitinib (Xeljanz®) is a Janus kinase inhibitor, and vedolizumab (Entyvio®) is an α4-β7 integrin receptor antagonist.[1-16]

Table 1. Current Medications Available in the Therapeutic Class[1-17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Abatacept (Orencia®, Orencia ClickJet®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥six years)	Auto-injector: 125 mg/mL Prefilled syringe: 125 mg/mL Vial: 250 mg	-
Adalimumab (Humira®, Humira Pen®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥two years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); Crohn's disease (age ≥six years); ulcerative colitis (adults only); plaque psoriasis (adults only); uveitis (adults only); hidradenitis suppurativa (adults only)	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL	-
Anakinra (Kineret®)	rheumatoid arthritis (adults); cryopyrin-associated periodic syndromes – neonatal-onset multisystem inflammatory disease (no age restriction)	Prefilled syringe: 100 mg/0.67 mL	-
Canakinumab (Ilaris®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥ four years); juvenile idiopathic arthritis (age ≥ two years)	Vial: 180 mg (150 mg/mL)	-
Certolizumab (Cimzia®)	Crohn's disease (adults only); rheumatoid arthritis (adults only); psoriatic arthritis (adults only); ankylosing spondylitis (adults only)	Prefilled syringe: 200 mg/mL Vial: 200 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Etanercept (Enbrel®, Enbrel SureClick®)	rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥2 years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); severe plaque psoriasis (adults only)	Auto-injector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial: 25 mg	-
Golimumab (Simponi®, Simponi Aria®)	rheumatoid arthritis (Simponi® and Simponi Aria® [adults only]); psoriatic arthritis (Simponi® [adults only]); ankylosing spondylitis (Simponi® [adults only]); ulcerative colitis (Simponi® [adults only])	Auto-injector (Simponi®): 50 mg/0.5 mL, 100 mg/mL Prefilled syringe (Simponi®): 50 mg/0.5 mL 100 mg/mL Vial* (Simponi Aria®): 50 mg/4 mL	-
Infliximab (Remicade®)	Crohn's disease (age ≥6 years); ulcerative colitis (age ≥6 years); rheumatoid arthritis (adults only); ankylosing spondylitis (adults only); psoriatic arthritis (adults only), plaque psoriasis (adults only)	Vial: 100 mg	-
Ixekizumab (Taltz®)	Plaque Psoriasis (adults)	Auto-injector: 80 mg/mL Prefilled Syringe: 80 mg/mL	-
Rilonacept (Arcalyst®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥12 years)	Vial: 220 mg (80 mg/mL)	-
Secukinumab (Cosentyx®, Cosentyx SensoReady Pen®)	Ankylosing Spondylitis (adults only), Juvenile idiopathic arthritis/juvenile rheumatoid arthritis, Plaque Psoriasis (adults only)	Auto-injector: 150 mg/mL Prefilled syringe: 150 mg/mL	-
Tocilizumab (Actemra®)	Polyarticular juvenile idiopathic arthritis (age ≥ 2 years) ; systemic juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥ 2 years); rheumatoid arthritis (adults only);	Prefilled syringe*: 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	-
Tofacitinib (Xeljanz®,	Rheumatoid arthritis (adults only)	Extended-release tablet	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Xeljanz XR®)		(Xeljanz XR®): 11 mg Tablet (Xeljanz®): 5 mg	
Ustekinumab (Stelara®)	Plaque psoriasis (adults only); psoriatic arthritis (adults only)	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL	-
Vedolizumab (Entyvio®)	Crohn's disease (adults only); ulcerative colitis (adults only)	Vial: 300 mg/20 mL	-

*Only indicated for use in patients with rheumatoid arthritis.

Evidence-based Medicine

- The immunomodulators have been shown to be effective for their respective Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional disease modifying antirheumatic drugs (DMARDs). Most research with these agents and FDA-approved indications (with the exception of ustekinumab) are for rheumatoid arthritis. In these trials, the immunomodulator were compared directly to placebo or traditional DMARD medications, either as monotherapy or in combination with a traditional DMARD. Consistently, immunomodulators have shown greater improvement in symptoms over the comparator.[48-151]
- The safety and efficacy of adalimumab for the treatment of non-infectious intermediate, posterior and panuveitis was established in two unpublished randomized, double-blind, placebo-controlled clinical trials.[8] The total length of each study was not reported; however, data is reported up to 18 weeks. The primary efficacy endpoint in both studies was time to treatment failure, defined as the development of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, an increase in anterior chamber (AC) cell grade or vitreous haze (VH) grade or a decrease in best corrected visual acuity (BCVA), on or after week six (study one) or week two (study two). At week 18 in study one, 60 patients (54.5%) failed adalimumab on or after week six compared with 84 patients (78.5%) who received placebo (hazard ratio [HR], 0.5; 95% CI, 0.36 to 0.70). Median time to failure was 5.6 months (95% CI, 3.9 to 9.2) for patients who received adalimumab and 3.0 months (95% CI, 2.7 to 3.7) for patients who received placebo. At week 18 in study two, 45 patients (39.1%) failed adalimumab on or after week two compared with 61 patients (55.0%) who received placebo (HR, 0.57; 95% CI, 0.39 to 0.84). Median time to failure for the adalimumab group was not estimable as fewer than half of the at-risk subjects had an event. Median time to failure for the placebo group was 8.3 months (95% CI, 4.8 to 12.0).[8]
- The safety and efficacy of Humira in the treatment of hidradenitis suppurativa was established in two clinical trials PIONEER I and PIONEER II. Both were 36-week, multicenter, randomized, double-blind clinical trials with a total of 633 adult patients with moderate to severe (Hurley Stage II and III) hidradenitis suppurativa who had an inadequate response to a trial of oral antibiotics, total abscess and inflammatory nodule count of ≥3 and lesions present in ≥2 body areas. At 12 weeks, therapy was evaluated and effectiveness was defined as improvement in abscesses and inflammatory nodules at 12 weeks using the Hidradenitis Suppurativa Clinical Response (HiSCR). In PIONEER I and PIONEER II, adalimumab achieved a statically significant improvement using the HiSCR measure when compared to placebo (P=0.003 and P<0.001, respectively).[48,49]
- The safety and efficacy of canakinumab in the treatment of systemic juvenile idiopathic arthritis was confirmed in two parallel clinical trials. At day 15 of the first trial, a total of 36 patients in the canakinumab group (84%), as compared with four in the placebo group (10%), had an adapted ACR30 response, which was sustained at day 29 (P<0.001). The second study concluded that There was a 64% relative reduction in the risk of flare for patients in the canakinumab group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75).[79]

- Secukinumab for the treatment of ankylosing spondylitis in patients 18 years of age or older was evaluated in two similar, double-blind, placebo controlled trials, MEASURE 1 and 2. The primary endpoint in both studies was the proportion of patients who had an Assessment of Spondyloarthritis International Society (ASAS) criteria improvement ≥20% (ASAS20) at week 16. In MEASURE 1, ASAS20 was significantly greater at week 16 in the secukinumab 150 mg group (61%) and 75 mg group (60%) than the placebo group (29%, P<0.001 for both vs placebo). In MEASURE 2, ASAS20 at week 16 was significantly greater in the secukinumab 150 mg group (61%) when compared to the placebo group (28%, P<0.001). There was no significant difference between the placebo group and the secukinumab 75 mg group (41%, P=0.10).[60]
- The safety and efficacy of secukinumab for the treatment of plaque psoriasis was evaluated in four multicenter, randomized, double-blind, placebo-controlled trials. The proportion of patients who achieved PASI 75 was statistically significantly greater in the secukinumab 300 mg group (81.6%, 77.1%, 75.9% and 86.7%) and secukinumab 150 mg group (71.6%, 67.0%, 69.5%, and 71.7%) compared with placebo (4.5%, 4.9%, 0%, 3.3%; P<0.001 for all secukinumab comparisons compared to placebo). In one of the trials, secukinumab 300 mg and 150 mg groups were compared to etanercept. Both secukinumab groups (77.1% and 67.0%) had a higher proportion of patients that achieved PASI 75 compared with etanercept (44%; P<0.001 for both secukinumab comparisons). Results were similar when IGA mod 2011 scores were compared.[5,89-91]
- Secukinumab for the treatment of psoriatic arthritis in patients 18 years of age or older was evaluated in two similar, double-blind, placebo controlled trials, FUTURE 1 and 2. The primary endpoint for both studies was the proportion of patients who had an American College of Rheumatology (ACR) improvement ≥20% (ACR20 response) at week 24.[100,101] In FUTURE 1, ACR20 response at week 24 was significantly greater in the secukinumab 150 mg group (50%) and 75 mg group (50.5%) than the placebo group (17.3%, P<0.001 for both vs placebo).[100] In FUTURE 2, ACR20 response at week 24 was significantly greater in the secukinumab 300 mg group (54%), the secukinumab 150 mg group (51%) and the secukinumab 75 mg group (29%), when compared to placebo (15%, P<0.001 for 300 mg and 150 mg groups vs placebo and P=0.0399 for the 75 mg group vs placebo).[101]
- The safety and efficacy of ixekizumab, for the treatment of moderate-to-severe psoriasis, was established in three multicenter, randomized, double-blind, placebo-controlled trials in patients 18 years of age or older (UNCOVER-1, UNCOVER-2 and UNCOVER-3). Patients had to have body surface area (BSA) involvement ≥10%, static Physician's Global Assessment (sPGA) ≥3 and Psoriasis Area Severity Index (PASI) ≥12. The three trials evaluated two different induction phase doses of ixekizumab: 80 mg every two weeks and 80 mg every four weeks over 12 weeks. In addition, two of the trials (UNCOVER-1 and UNCOVER-2) evaluated two different maintenance phase doses of 80 mg every four weeks and 80 mg every 12 weeks over 48 weeks. Two of the trials (UNCOVER-2 and UNCOVER-3) had etanercept as an active comparator arm during the induction phase.[82-84] In UNCOVER-1, treatment with ixekizumab, with an initial dose of 160 mg and subsequent induction period dosages of 80 mg every two weeks or 80 mg every four weeks resulted in significant improvement during the induction period. Across all efficacy end points, response rates associated with the dosage of 80 mg every two weeks were higher than those associated with the 80 mg every four weeks dose. In UNCOVER-1 and UNCOVER-2, for ixekizumab week 12 responders, efficacy was also maintained through the 60-week maintenance period.[82,83] In UNCOVER-2 and UNCOVER-3, treatment with both induction doses of ixekizumab (80 mg every two weeks and 80 mg every four weeks) demonstrated significantly greater efficacy than etanercept. Across all efficacy endpoints, response rates associated with 80 mg every two weeks was higher than those associated with 80 mg every four weeks.[82,84]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[19-36]
    - Support the use of the immunomodulators with respect to their Food and Drug Administration (FDA)-approved indications.
    - As more recent guidelines are published, the recommendations for use tumor necrosis factor-blockers earlier in therapy is becoming a more common occurance.[27,28,31] The adverse event profiles are similar across the class; however, routes of administration and dosing frequency may vary.

- In general, no one agent is preferred over another.

- Other Key Facts:
  - The recently upheld Patient Protection and Affordable Care Act provides a legal framework for regulatory approval of biosimilar drugs.[43]
  - While none of the agents in this class are available generically, a biosimilar for infliximab was recently approved (Inflectra®). Due to ongoing patent litigation, it is unknown when the product will become available.
  - Another biosimilar, adalimumab, is being considered by the FDA and was recently recommended for approval unanimously by an FDA panel 26-0. However, the manufacturer does not expect the biosimilar adalimumab to be available until sometime between 2018 and 2022 due to patent litigation issues.[152]
  - Dosing and administration varies both by drug and by dosage form.[1-16]
    - Oral: tofacitinib (tablet, extended-release tablet)
    - Intravenous Injection: abatacept, golimumab (Simponi ARIA®), infliximab, tocilizumab, and vedolizumab. Each is infused over 30 minutes, with the exception of infliximab which is infused over two hours.
    - Most injectables require infrequent dosing, ranging from one to 12 weeks. Anakinra is the only injectable immunomodulator that requires daily dosing.
    - Tofacitinib immediate release is taken twice daily while the extended-release formulation can be taken once daily.
    - The majority of these agents have not been studied in renal or hepatic dysfunction.
    - Anakinra and tofacitinib require renal dose adjustment for creatinine clearances less than 30 mL or 40 mL, respectively.
    - Tofacitinib requires a dose adjustment in patients with moderate hepatic dysfunction, however, it has not been studied in patients with severe hepatic dysfunction and no dosing recommendations are available.
  - The safety and efficacy of these agents in pediatric patients varies based on drug and indication.[1-16]
    - Anakinra, canakinumab and rilonacept are FDA-approved for the treatment of Cryopyrin-Associated Periodic Syndromes. Anakinra does not have a minimum age associated with its use while canakinumab is approved for use in children aged four or older and rilonacept is approved for use in children 12 to 17 years old.
    - Safety and efficacy in pediatric patients to treat juvenile idiopathic arthritis has been established for abatacept (age six or older), adalimumab (age two to 17 years), canakinumab, etanercept, and tocilizumab (all two or older).
    - Both adalimumab and infliximab have been FDA-approved for the treatment of pediatric Crohn's disease in pediatric patients aged six or older. Additionally, infliximab is also indicated to treat pediatric ulcerative colitis in pediatric patients six years of age or older.
  - Anakinra is the only FDA-approved agent for neonatal-onset multisystem inflammatory disease. Canakinumab and rilonacept are the only FDA-approved agents for the treatment of familial cold autoinflammatory syndrome and Muckle-Wells syndrome.

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Therapeutic Class Overview
Inhaled Anticholinergics

Therapeutic Class Overview/Summary:
The inhaled anticholinergics are a class of bronchodilators primarily used in the management of chronic obstructive pulmonary disease (COPD), a condition characterized by progressive airflow restrictions that are not fully reversible.[1-3] Symptoms associated with COPD typically include dyspnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled anticholinergics work via the inhibition of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation. Meaningful increases in lung function can be achieved with the use of inhaled anticholinergics in patients with COPD.[1-3] The available single-entity inhaled anticholinergics include aclidinium (Tudorza® Pressair), glycopyrrolate (Seebri Neohaler®), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva®, Spiriva Respimat®) and umeclidinium (Incruse Ellipta®) with the combination products including glycopyrrolate/indacaterol (Utibron Neohaler®), umeclidinium/vilanterol (Anoro Ellipta®), tiotropium/olodaterol (Stiolto Respimat®) and ipratropium/albuterol, formulated as either an inhaler (Combivent Respimat®) or nebulizer solution (DuoNeb).[4-15] Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are considered long-acting bronchodilators. Aclidinium is dosed twice daily, while glycopyrrolate, tiotropium and umeclidinium are administered once daily. Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are available as dry powder inhalers for oral inhalation, with tiotropium also formulated as an inhalation aerosol.[4-15]

Aclidinium, glycopyrrolate, ipratropium and tiotropium, are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is the only inhaled anticholinergic that is FDA-approved for reducing exacerbations associated with COPD. Additionally, tiotropium soft mist inhaler (Spiriva Respimat®) has been approved for the chronic management of asthma and updated guidelines recommend its use as add-on thereapy.[9,16] Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. Glycopyrrolate/indacaterol, umeclidinium, umeclidinium/vilanterol and tiotropium/olodaterol are FDA-approved for the maintenance treatment of airflow obstruction in patients with COPD.[4-15]

Table 1. Current Medications Available in the Therapeutic Class[4-15,17]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Aclidinium (Tudorza® Pressair)	Bronchospasm associated with COPD, maintenance treatment†	Powder for inhalation: 400 µg	-
Glycopyrrolate (Seebri Neohaler®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 15.6 µg	-
Ipratropium* (Atrovent HFA®)	Bronchospasm associated with COPD, maintenance treatment	Aerosol for oral inhalation (Atrovent HFA®): 17 µg Solution for nebulization: 500 µg (0.02%)	✔
Tiotropium (Spiriva®, Spiriva	Asthma, maintenance	Aerosol for inhalation	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Respimat®)	treatment (aerosol for inhalation); Bronchospasm associated with COPD, maintenance treatment†, reduce exacerbations in patients with COPD	(Spiriva Respimat®): 1.25 µg/actuation 2.5 µg/actuation Powder for inhalation (Spiriva HandiHaler®): 18 µg	
Umeclidinium (Incruse Ellipta®)	Airflow obstruction in patients with COPD, maintenance treatment*	Powder for inhalation: 62.5 µg	-
Combination Products			
Glycopyrrolate/indacaterol (Utibron Neohaler®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 15.6 µg/27.5 µg	-
Ipratropium/albuterol* (Combivent Respimat®)	Bronchospasm associated with COPD in patients requiring more than one bronchodilator	Inhalation spray (Combivent Respimat®): 20/100 µg‡ Solution for nebulization (DuoNeb®): 0.5/3.0 mg	✔
Tiotropium/olodaterol (Stiolto Respimat®)	Airflow obstruction in patients with COPD, maintenance treatment†	Inhalation Spray 5/5 µg	-
Umeclidinium/vilanterol (Anoro Ellipta®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 62.5/25 µg	-

*Generic available in at least one dosage form or strength.
†Long-term maintenance treatment.
‡Delivering 18 µg of ipratropium and 103 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- In general, the inhaled anticholinergics have demonstrated to improve lung function and/or exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).[18-80] Few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[20,43,44] A meta-analysis evaluating tiotropium added to combination inhaled corticosteroid (ICS)/long acting β-agonist (LABA) therapy compared to ICS/LABA alone for the treatment of asthma did not demonstrate a significant difference between the groups in the primary endpoints of exacerbations requiring oral corticosteroids, quality of life or serious adverse events.[81]
- The efficacy of glycopyrrolate is based primarily on the dose-ranging trials in 471 subjects with COPD and two placebo-controlled confirmatory trials in 867 subjects with COPD. The primary efficacy endpoint from the two placebo-controlled confirmatory trials, GEM1 and GEM2, was the change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ following the morning dose at day 85 compared with placebo. In both trials, the glycopyrrolate group demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ compared to placebo.
    - In GEM1, the change from baseline least squares (LS) mean was 0.125 L in the glycopyrrolate group compared to -0.014 L in the placebo group (Treatment difference LS Mean, 0.139 L; 95% CI, 0.095 to 0.184; P values not reported).

    - For GEM2, the change from baseline LS mean was 0.115 L in the glycopyrrolate group compared to -0.008 L in the placebo group (Treatment difference LS Mean, 0.123 L; 95% CI, 0.081 to 0.165; P values not reported).[5,77,78]
- The efficacy of indacaterol/glycopyrrolate was based primarily on the results of two 12-week efficacy studies (FLIGHT1 & 2).[12,79] Both were identical, multicenter, randomized, double-blinded, placebo- and active-controlled, and parallel-group trials in subjects with COPD. A total of 2,038 individuals were randomized to indacaterol/glycopyrrolate 27.5 µg/15.6 µg twice-daily (BID), indacaterol 27.5 µg BID, glycopyrrolate 15.6 mcg BID, or placebo BID. The primary endpoint was the change from baseline in FEV_1 AUC_{0-12h} following the morning dose at Day 85 compared with placebo, glycopyrrolate 15.6 µg BID, and indacaterol 27.5 µg BID.
    - In both trials, Utibron Neohaler® (indacaterol/glycopyrrolate) demonstrated a larger increase in mean change from baseline in FEV_1 AUC_{0-12h} compared to placebo, indacaterol 27.5 µg BID, and glycopyrrolate 15.6 µg BID (treatment difference: 103 mL and 88 mL vs indacaterol and glycopyrrolate, respectively, P<0.001). In addition, both indacaterol and glycopyrrolate monotherapies had a statistically greater response than placebo at week 12 in terms of FEV_1 AUC_{0-12h} (treatment difference: 143 mL and 158 mL, respectively, P<0.001).[79]

Key Points within the Medication Class

- According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines:[1]
    - Inhaled bronchodilators are preferred for the management of COPD. Regular use of long-acting β2-agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation.
    - The GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the use of short-acting bronchodilators.
- According to the National Institute for Clinical Excellence (NICE):[2]
    - Short-acting bronchodilators should be the initial empiric treatment for the relief of breathlessness and exercise limitation while long-acting bronchodilators should be used in patients who remain symptomatic with use of short-acting agents.
    - Once-daily, long-acting anticholinergic agents are preferred compared to four-times-daily short-acting anticholinergics in patients with stable COPD who remain symptomatic despite use of short-acting agents and in whom the decision has been made to begin regular maintenance therapy with an anticholinergic agent.
- According to the Global Initiative for Asthma (GINA), tiotropium (Spiriva Respimat®) is an option for add-on therapy in patients 12 years and older in uncontrolled asthma at both steps 4 and 5 in the treatment algorithm.[16] Other Asthma guidelines have not been updated since tiotropium has received this expanded indication.[82]
- Other Key Facts:
    - Ipratropium and ipratropium/albuterol solutions for nebulization are the only inhaled anticholinergic products that are currently available generically.

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Therapeutic Class Overview
Inhaled Corticosteroids

Therapeutic Class

- **Overview/Summary:** The inhaled corticosteroids (ICSs) are Food and Drug Administration (FDA)-approved for the maintenance treatment of asthma as prophylactic therapy with beclomethasone (QVAR®), flunisolide (Aerospan®) and fluticasone propionate (Flovent Diskus®, Flovent HFA®) also being indicated for use in asthma patients who require systemic corticosteroid therapy.[1-11] These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response. The ICSs exert their anti-inflammatory effects by binding to glucocorticoid receptors with a subsequent activation of genes involved in the anti-inflammatory processes as well as an inhibition of pro-inflammatory genes involved in the asthmatic response. Inflammation is also a component of chronic obstructive pulmonary disease (COPD) pathogenesis; however, no single-entity ICS has been FDA-approved for use in COPD.[1-10] Although ICSs exert their therapeutic effects through identical mechanisms of action, they differ in their potency, dosing schedules, and dosage form availability. Clinical trials comparing ICSs of varying potencies have shown that those of higher potencies do not demonstrate greater clinical efficacy than those of lower potencies when administered at equipotent doses and have not demonstrated any major differences in clinical efficacy between the available ICSs.[12-67] Currently, only budesonide nebulizer suspension is available generically.

Table 1. Current Medications Available in Therapeutic Class[1-10]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Beclomethasone (QVAR®)	Maintenance Treatment of Asthma as Prophylactic Therapy¶; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy¶	Inhalation aerosol (HFA inhaler, metered dose): 40 µg 80 µg	-
Budesonide (Pulmicort Flexhaler®, Pulmicort Respules®*)	Maintenance Treatment of Asthma as Prophylactic Therapy†,‡	Dry powder for inhalation (inhaler, breath activated, metered dose): 90 µg 180 µg Suspension for inhalation (nebulizer): 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL	✔
Ciclesonide (Alvesco®)	Maintenance Treatment of Asthma as Prophylactic Therapy§	Inhalation aerosol (HFA inhaler, metered dose): 80 µg 160 µg	-
Flunisolide (Aerospan®)	Maintenance Treatment of Asthma as Prophylactic Therapy#; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy#	Inhalation aerosol (HFA inhaler, metered dose): 80 µg	-
Fluticasone furoate	Maintenance Treatment of	Aerosol powder (breath	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Arnuity Ellipta®)	Asthma as Prophylactic Therapy§	activated inhaler): 100 µg 200 µg	
Fluticasone propionate (Flovent Diskus®, Flovent HFA®)	Maintenance Treatment of Asthma as Prophylactic Therapy‖; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy‖	Dry powder for inhalation (inhaler with blister pack; Flovent Diskus®): 50 µg 100 µg 250 µg Inhalation aerosol (HFA inhaler, metered dose; Flovent HFA®): 44 µg 110 µg 220 µg	-
Mometasone furoate (Asmanex HFA®, Asmanex Twisthaler®)	Maintenance Treatment of Asthma as Prophylactic Therapy#,**	Dry powder for inhalation (inhaler, metered dose; Asmanex Twisthaler®): 110 µg 220 µg Inhalation powder (HFA inhaler, metered dose, breath activated; Asmanex HFA®): 100 µg 200 µg	-

* Generic available in at least one dosage form or strength.
¶ In patients five years of age and older.
† Pulmicort Flexhaler®: In patients six years of age and older.
‡ Pulmicort Respules®: In patients 12 months to eight years of age.
§ In patients 12 years of age and older.
‖ In patients four years of age and older.
In patients six years of age and older.
Asmanex HFA®: In patients 12 years of age and older.
** Asmanex Twisthaler®: In patients four years of age and older.

Evidence-based Medicine

- Numerous placebo controlled trials have demonstrated the efficacy of inhaled corticosteroid agents in the treatment of asthma, and these agents are considered the most effective agents in the long-term management of the disease. The results of head-to-head trials directly comparing the inhaled corticosteroids products have not demonstrated one agent to be significantly more effective than another, regardless of the potency or dosage form of the inhaled corticosteroid agent used.[12-67]
- FDA-approval for fluticasone furoate was based on the results of three dose-ranging trials and four confirmatory trials which included a total of 3,611 patients aged ≥12 years with various asthma severities, FEV_1 of 40 to 90% predicted and varied (or no) previous ICS use.[13-15,19-22] Pre-dose, pre-bronchodilator FEV_1 (primary endpoint) was significantly improved upon treatment with the FDA-approved doses of fluticasone furoate when compared to placebo in each of the seven clinical trials.
    - Fluticasone furoate also significantly improved percentage of rescue-free 24-hour periods and although statistical significance could not be determined in some cases, fluticasone furoate also improved symptom-free 24-hour periods over the course of the studies.[13-15,19-22]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - ICSs are the most potent and consistently effective long-term controller medications for asthma patients of all ages. These agents are recommended as first-line therapy for long-term control of persistent asthma symptoms in all age groups. Although ICSs reduce both impairment and risk of asthma exacerbations, they do not appear to alter the progression or underlying severity of the disease. No ICS is recommended over another.[68,71]
        - The adverse effect on growth rate associated with these agents does appear to be dose dependant; however, it is not considered predictable. The effect on growth velocity appears to occur mainly in the first several months of treatment and is generally small and not progressive.[68]
    - For COPD: In patients with an FEV_1 <60% of the predicted value, regular treatment with ICS improves symptoms, lung function and quality of life as well as reduces exacerbations. However, long term therapy ICS as monotherapy is not recommended.[72]
    - ICSs should be used as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤50% predicted and repeated exacerbations.[73]
- Other Key Facts:
    - None of the inhaled corticosteroid products are indicated for the relief of acute bronchospasm[1-10]
    - Currently, budesonide suspension for nebulization is the only generic product available within the therapeutic class.

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Therapeutic Class Overview
Long-Acting Inhaled β2-Agonists (Single Entity)

Therapeutic Class

- **Overview/Summary:** Respiratory β_2-agonists are primarily used to treat reversible airway disease. The long-acting β_2-agonists (LABAs) are all Food and Drug Administration (FDA)-approved for chronic obstructive pulmonary disease with some agents also being approved for asthma maintenance therapy and exercise-induced asthma/bronchospasm.[1-7] Respiratory β_2-agonists act preferentially on the β_2-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-6] The respiratory β_2-agonists can be divided into two categories: short-acting and long-acting. Only the inhaled long-acting β_2-agonists will be covered in this review and they include: arformoterol, formoterol, indacaterol salmeterol, and the newest agent olodaterol. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-6] Guidelines do not recommend one long-acting agent over another.[8-11] In addition, head-to-head clinical trials have been inconclusive to determine "superiority" of any one agent .[12-60] There are currently no generic formulations for the LABAs.

Table 1. Current Medications Available in the Therapeutic Class[1-6]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Arformoterol (Brovana®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment	Solution for nebulization: 15 µg (2 mL)	-
Formoterol (Foradil®, Perforomist®)	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication†; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡ exercise-induced bronchospasm prophylaxis, acute†	Capsule for inhalation: 12 µg Solution for nebulization: 20 µg/2 mL	-
Indacaterol (Arcapta Neohaler®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§	Capsule for inhalation: 75 µg	-
Olodaterol (Striverdi Respimat®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§	Solution for inhalation (breath activated, metered-dose inhaler): 2.5 µg	-
Salmeterol (Serevent Diskus®)	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡;	Dry powder inhaler: 50 µg (28 or 60 inhalations)	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment		

COPD=chronic obstructive pulmonary disease
*Generic available in at least one dosage form or strength.
†Dry powder inhaler only
‡Twice-daily
§Once-daily

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy long-acting β_2-agonists in providing relief from asthma, COPD exacerbations and exercise induced asthma .[12-61]
- Salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. In a meta-analysis by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life threatening exacerbations and asthma-related deaths in adults and children alike when compared to placebo.[13]
- A systematic review concluded that in patients with COPD, there was no difference in rate of mild exacerbation between patients treated with an ICS or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (relative risk, 0.96; 95% CI, 0.89 to 1.02).[42]
- Overall, data from published clinical trials demonstrate that treatment with indacaterol consistently results in significantly higher mean trough FEV_1 after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo.[42-52]
- The safety and efficacy of olodaterol were evaluated in eight unpublished placebo- and/or active-controlled confirmatory clinical trials in patients with COPD. Results from four 48-week studies showed 5 µg olodaterol provided significant improvements in FEV_1 and FEV_1 $AUC_{0\text{-}3hr}$ at weeks 12 and 24 when compared with placebo (no P value provided). In addition, four 6-week cross-over studies showed that FEV_1 $AUC_{0\text{-}12hr}$ and FEV_1 $AUC_{12\text{-}24hr}$ was significantly improved with olodaterol when compared with placebo at the conclusion of the studies (no P value provided). No data was provided showing the results of the active comparators (formoterol and/or tiotropium) or whether the results were significantly different than olodaterol or not.[4]
- Two replicate, double-blind, placebo-controlled, multicenter, randomized studies evaluated FEV_1 $AUC_{0\text{-}3}$ and trough FEV_1 after 12 weeks of therapy after adding olodaterol (via Respimat® inhaler) to COPD patients being treated with tiotropium 18 µg via HandiHaler®. There was a significant improvement in both FEV_1 $AUC_{0\text{–}3}$ and trough FEV_1 responses without a significant increase in side effects when olodaterol was added to tiotropium. The mean difference in FEV_1 $AUC_{0\text{–}3}$ in ANHELTO 1 and 2 respectively were 0.117 L and 0.106 L ($P<0.001$ for both). Mean difference in FEV_1 responses were 0.062 L and 0.040 L ($P<0.001$ and $P=0.0029$).[57]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Short-acting β_2-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.[8,9]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis. [8,9]
  - In the chronic management of asthma, the long-acting β_2-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid. [8,9]
  - Long-acting β_2-agonists should not be used as monotherapy for the long-term control of asthma. [8,9]
  - Long-acting β_2-agonists can be used for exercise-induced bronchospasm and provide a longer period of coverage compared to short acting β_2-agonists. [8,9]

  - Long-acting β_2-agonists have a role in the treatment of chronic obstructive pulmonary disease (COPD), for patients who remain symptomatic even with current treatment with short-acting bronchodilators. [8,9]
  - Long-acting β_2-agonists can be added to other COPD treatment regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[10,11]
- Other Key Facts:
  - The role of the short- and long-acting respiratory β_2-agonists in the treatment of asthma and COPD has been well established.
  - Studies have failed to consistently demonstrate significant differences between products.
  - None of the long-acting respiratory β_2-agonists are currently available generically.

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Therapeutic Class Overview
Injectable Anticoagulants

Therapeutic Class

- **Overview/Summary:** The injectable anticoagulants include dalteparin (Fragmin®), enoxaparin (Lovenox®), and fondaparinux (Arixtra®). Dalteparin and enoxaparin are classified as low molecular weight heparins (LMWH), and fondaparinux is a selective factor Xa inhibitor. In general, the injectable anticoagulants are Food and Drug Administration (FDA)-approved for prophylaxis and/or treatment of venous thromboembolism (VTE). Certain agents in the class are also FDA-approved for the treatment of acute ST-segment elevation myocardial infarction (STEMI) or for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction. The specific FDA-approved indications for the injectable anticoagulants are outlined in Table 1.[1-3]

  The LMWH agents exert their anticoagulant effect by binding to antithrombin, an endogenous inhibitor of various activated clotting factors, including factor Xa and thrombin. A LMWH is a smaller fragment of unfractionated heparin (UFH) that is formed by enzymatic or chemical depolymerization processes. The difference in the average size of LMWH (5,000 daltons) compared to UFH (3,000 to 30,000 daltons) contributes to the pharmacologic differences between the agents. The LMWH agents primarily inhibit factor Xa, and do so with much less effect on thrombin compared to UFH. The inhibition of thrombin requires a heparin molecule to bind simultaneously to antithrombin and thrombin to form a ternary complex. The UFH molecules are large enough for this to occur while the LMWH molecules typically are not.[4,5] Fondaparinux is a synthetic factor Xa inhibitor that was developed to have an increased affinity to antithrombin. Its specific anti-factor Xa activity is higher than that of the LMWH agents. Because the LMWH agents are prepared using different methods of depolymerization, they differ somewhat in their pharmacokinetic properties and anticoagulant profiles. Therefore, these agents are not clinically interchangeable[5]

Table 1. Current Medications Available in the Therapeutic Class[1-3]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Dalteparin (Fragmin®)	Extended treatment of symptomatic venous thromboembolism (proximal deep vein thrombosis and/or pulmonary embolism) in patients with cancer*, prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction†, prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness, in patients undergoing abdominal surgery who are at risk for thromboembolic complications and in patients undergoing hip fracture surgery	Syringe: 2,500 IU/0.2 mL‡ 5,000 IU/0.2 mL‡ 7,500 IU/0.3 mL‡ 10,000 IU/1 mL§ 12,500 IU/0.5 mL‡ 15,000 IU/0.6 mL‡ 18,000 IU/0.72 mL‡ 95,000 IU/3.8 mL‖	-
Enoxaparin (Lovenox®¶)	Prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction†, prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness, in patients undergoing abdominal surgery who are at risk for thromboembolic complications, in	Syringe (100 mg/mL): 30 mg/0.3 mL‡ 40 mg/0.4 mL‡ 60 mg/0.6 mL§ 80 mg/0.8 mL§ 100 mg/1 mL§ 300 mg/3 mL‡‡	✔

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	patients undergoing hip replacement surgery[#], in patients undergoing knee replacement surgery, treatment of acute deep vein thrombosis**, treatment of acute ST-segment elevation myocardial infarction[††]	Syringe (150 mg/mL): 120 mg/0.8 mL[§] 150 mg/1 mL[§]	
Fondaparinux (Arixtra®[¶])	Prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in patients undergoing abdominal surgery who are at risk for thromboembolic complications, in patients undergoing hip fracture surgery[§§], in patients undergoing hip replacement surgery, in patients undergoing knee replacement surgery, treatment of acute deep vein thrombosis[‖‖], treatment of acute pulmonary embolism[¶¶]	Syringe: 2.5 mg/0.5 mL[‡] 5 mg/0.4 mL[‡] 7.5 mg/0.6 mL[‡] 10 mg/0.8 mL[‡]	✔

IU=international units
*In these patients therapy begins with the initial venous thromboembolism treatment and continues for six months.
†When concurrently administered with aspirin therapy.
‡Available as a single-dose prefilled syringe.
§Available as a single-dose graduated prefilled syringe.
‖Available as a multiple-dose vial. After first penetration of the rubber stopper, store the multiple-dose vials at room temperature for up to two weeks.
¶Generic available in at least one dosage form and/or strength.
#During and following hospitalization.
**Indicated for inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin, and for outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin.
††When administered concurrently with aspirin, enoxaparin has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute ST-segment elevation myocardial infarction receiving thrombolysis and being managed medically or with percutaneous coronary intervention.
‡‡Available as a multi-dose vial.
§§Including extended prophylaxis.
‖‖When administered in conjunction with warfarin.
¶¶When administered in conjunction with warfarin when initial therapy is administered in the hospital.
***With or without pulmonary embolism when administered in conjunction with warfarin.

Evidence-based Medicine

- Currently, dalteparin is the only injectable anticoagulant approved for the extended treatment of VTE in patients with cancer. In a trial comparing dalteparin to oral anticoagulation (warfarin or acenocoumarol [not available in the United States]) in patients with symptomatic VTE, the incidence of symptomatic, recurrent VTE was significantly lower with dalteparin at six months. At six months there was no difference in mortality rates between the two treatments; however, a 12 month follow-up revealed a significant benefit in mortality with dalteparin in patients without known metastases of their cancer.[22,23]
- A Cochrane Review that included 16 randomized-controlled trials of cancer patients receiving initial treatment suggest that LMWH agents may be “superior” to UFH for the initial treatment of VTE in cancer patients due to an observed nonsignificant advantage of these agents for reducing the incidence of recurrent VTE.[23]
- The evidence establishing the safety and efficacy of the injectable anticoagulants for VTE treatment and/or thromboprophylaxis is well established.[27-78]
- Several placebo-controlled trials, meta-analyses, and systematic reviews with the various injectable anticoagulants in medical patients, immobilized patients, and those undergoing an orthopedic surgery have been conducted and consistently demonstrate their efficacy.[28-31,36-42,57,67,75,77-78]
- When the injectable anticoagulants are compared to other methods of treatment and thromboprophylaxis which include heparin, UFH, and warfarin, “superiority” in terms of recurrent VTE

and safety is not always consistent, which supports recommendations from current clinical guidelines.[32,33,47-55,68-74]

- Treatment with fondaparinux appears to be associated with a lower incidence of VTE, and a comparable incidence of major bleeding compared to enoxaparin.[59-62]
- In a meta-analysis of randomized-controlled trials comparing fondaparinux to LMWH therapy (enoxaparin), the incidence of VTE was significantly less and the incidence of major bleeding was significantly greater with fondaparinux.[63]

Key Points within the Medication Class

- According to Current Clinical Guidelines: [8-16]
    - LMWH, fondaparinux, apixaban (Eliquis®), dabigatran (Pradaxa®), rivaroxaban (Xarelto®), low dose UFH, adjust-dose vitamin K antagonist (VKA) therapy, aspirin, or an intermittent pneumatic compression device is recommended in patients undergoing total hip or knee arthroplasty.
    - Use of LMWH, fondaparinux, low dose UFH, adjusted-dose VKA therapy, aspirin, or an intermittent pneumatic compression device is recommended in patients receiving hip fracture surgery. In these orthopedic surgeries thromboprophylaxis is recommended for a minimum of 10 to 14 days; however, for major orthopedic surgeries it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of the surgery.
    - For total hip or knee arthroplasty and hip fracture surgery, thromboprophylaxis with LMWH is suggested in preference to the other recommended agents.
    - For patients who decline or who are uncooperative with injections or intermittent pneumatic compression devices, apixaban or dabigatran is recommended over alternative forms of thromboprophylaxis, with rivaroxaban or adjusted-dose VKA therapy recommended if these two therapies are unavailable.
    - Non-orthopedic surgical patients (e.g., general and abdominal-pelvic surgery) at moderate to high risk for VTE, who are not at high risk for bleeding complications, should receive thromboprophylaxis with LMWH or low dose UFH, and extended (four weeks) LMWH is recommended in high risk non-orthopedic surgical patients with cancer who are not otherwise at high risk for major bleeding complications.
    - For prevention of VTE in nonsurgical patients (i.e., medical patients), thromboprophylaxis with LMWH, low dose UFH, or fondaparinux is recommended in acutely ill hospitalized patients at increased risk of thrombosis.
    - Clinical guidelines also recommend the use of LMWH, fondaparinux, UFH, or bivalirudin (a direct thrombin inhibitor) for the management of a non-ST-segment elevated acute coronary syndrome. The use of a specific agent over another is based on individual patient risk factors, as well as the timing and intensity of other planned management strategies. In addition, it appears that fondaparinux has a more favorable safety and efficacy profile compared to LMWH in certain clinical situations, including patients at high-risk for bleeding.

- Other Key Facts:
    - Currently, enoxaparin and fondaparinux are the only injectable anticoagulants that are available generically.

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Therapeutic Class Overview
Intranasal Corticosteroids

Therapeutic Class

Overview/Summary: Intranasal corticosteroids are primarily used to treat perennial and seasonal allergic rhinitis and may be useful in the treatment of some forms of nonallergic rhinitis.[1-14] Symptoms associated with allergic rhinitis include nasal congestion, rhinorrhea, sneezing and/or nasal itching. These symptoms result from a complex allergen driven mucosal inflammation caused by resident and infiltrating inflammatory cells and a number of vasoactive and proinflammatory mediators.[1-2] Intranasal corticosteroids downregulate the inflammatory response by binding to the intracellular glucocorticoid receptors of inflammatory cells and causing a conformational change, thereby controlling the rate of protein synthesis and suppressing the transcription of cytokine and chemokine genes.[1-2]

All intranasal corticosteroids are approved by the Food and Drug Administration (FDA) for the treatment of perennial and seasonal allergic rhinitis.[3-14] Mometasone (Nasonex®) carries an additional indication for the prophylaxis of seasonal allergic rhinitis.[12] Two currently available intranasal corticosteroids, beclomethasone (Beconase AQ®) and mometasone, are also FDA-approved for the management of nasal polyps.[4,12] Nasal polyposis is an inflammatory condition of the nasal and sinus mucosa and usually presents as persistent nasal obstruction.[1-2] Beclomethasone is principally used to prevent recurrence of nasal polyps following surgical removal.[1-2]

Beclomethasone and fluticasone propionate are approved for the management of nonallergic rhinitis (e.g., infectious rhinitis, hormonal rhinitis and vasomotor nonallergic rhinitis with eosinophilia syndrome).[4,11] Unlike allergic rhinitis, nonallergic rhinitis is characterized by periodic or perennial symptoms that are not a result of immunoglobulin E-dependent events.[1-2]

Budesonide, flunisolide, fluticasone propionate, mometasone and triamcinolone are currently available generically. Beclomethasone (QNASL®) and ciclesonide (Zetonna®), were approved in 2012 and are the only two intranasal corticosteroid products formulated as a “dry” nasal aerosol; all other products in within the class are formulated as aqueous suspensions.[3-14] Fluticasone furoate (Veramyst®), mometasone and triamcinolone are approved for use in children two years of age and older.[10-14]

According to the current clinical guidelines on the management of rhinitis, treatment should consist of patient education, allergen avoidance activities and pharmacological therapies. Patients should be educated on how to avoid known triggers, such as aeroallergens, dust mites, molds and irritants whenever possible. In addition to environmental control measures, pharmacological therapies may be used to control symptoms. Intranasal corticosteroids should be considered first-line therapy in patients with moderate to severe allergic rhinitis.[15-17] While differences in potencies, lipid solubility and systemic bioavailability exist between the older and newer intranasal corticosteroid products, no single agent has consistently has been demonstrated to be more effective than another.[17] Moreover, no one intranasal corticosteroid product is recommended over another as initial treatment in patients with perennial or seasonal allergic rhinitis.[15-17]

Table 1. Current Medications Available in the Therapeutic Class[3-14]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Beclomethasone (Beconase AQ®, QNASL®)	Treatment of seasonal and perennial allergic rhinitis, nonallergic rhinitis†, and nasal polyps†	Aerosol for nasal inhalation: 40 µg/actuation 80 µg/actuation (120 actuations) Suspension for nasal inhalation: 42 µg/inhalation (180	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		metered doses)	
Budesonide (Rhinocort Aqua®*)	Treatment of seasonal and perennial allergic rhinitis	Suspension for nasal inhalation: 32 µg/inhalation (120 metered doses)	✔
Ciclesonide (Omnaris®)	Treatment of seasonal and perennial allergic rhinitis	Aerosol for nasal inhalation: 37 µg/actuation (60 actuations) Suspension for nasal inhalation: 50 µg/inhalation (120 metered doses)	-
Flunisolide	Treatment of seasonal and perennial allergic rhinitis	Solution for nasal inhalation: 0.025% (200 metered doses) Suspension for nasal inhalation: 29 µg/inhalation (200 metered doses)	✔
Fluticasone furoate (Veramyst®)	Treatment of seasonal and perennial allergic rhinitis	Suspension for nasal inhalation: 27.5 µg/inhalation (120 metered doses)	-
Fluticasone propionate	Treatment of seasonal and perennial allergic rhinitis and nonallergic rhinitis	Suspension for nasal inhalation: 50 µg/inhalation (120 metered sprays)	✔
Mometasone (Nasonex®*)	Treatment of seasonal and perennial allergic rhinitis, nasal polyps and prophylaxis of seasonal allergic rhinitis	Suspension for nasal inhalation: 50 µg/inhalation (120 metered doses)	✔
Triamcinolone	Treatment of seasonal and perennial allergic rhinitis	Suspension for nasal inhalation: 55 µg/inhalation (120 metered doses)	✔

*Generic available in one dosage form or strength.
†Beconase AQ only.

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the intranasal corticosteroids for their respective Food and Drug Administration-approved indications.[18-90]
- Daily administration of intranasal corticosteroids is associated with statistically significant improvements in allergy-related total nasal symptom scores (TNSS), health related quality of life scores and minimal adverse events. Furthermore, numerous head-to-head clinical trials comparing the available intranasal corticosteroids have generally demonstrated no significant clinical differences

among the currently available intranasal corticosteroids with regard to efficacy.[48,62,64-85] Some studies have reported differences in sensory perceptions and patient preference with one agent compared to another.[49,57,64,65,,79,80,82,85] Patients administering the agents noted differences in odor, aftertaste, and severity of irritation, though these differences were not associated with differences in efficacy between the agents.

- Head-to-head trials evaluating the efficacy and safety of beclomethasone, fluticasone propionate and flunisolide demonstrate that these agents are comparable to other agents within the class. [58,60-62,64,65,68-71,77,82-84] However, additional results of these studies reinforce that all of the intranasal corticosteroids should be considered equally efficacious.
- To date, the newly approved intranasal corticosteroid aerosol formulations have been demonstrated to be significantly more effective compared to placebo. In a six-week study of patients with perennial allergic rhinitis, aerosolized beclomethasone significantly improved reflective TNSS compared to placebo (-2.46 vs -1.63; P<0.001). Furthermore, beclomethasone was associated with a statistically significant improvement in quality of life compared to placebo (P=0.001).[18] The aerosolized ciclesonide formulation has also been shown to significantly improve symptoms of allergic rhinitis compared to placebo. In a study by Ratner et al, ciclesonide administered at a daily dose of 80 µg or 160 µg reduced reflective TNSS by 15.1 and 16.0%, respectively, compared to 3.7% in the placebo group (P<0.001 for both). In addition, significant improvements were observed with both doses of ciclesonide compared to placebo with regard to ocular symptoms scores and quality of life (P<0.001 for both).[25] Similar improvements in outcomes were reported in additional studies of up to 26 weeks duration.[26-29]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[15-17]
    - According to the current clinical guidelines on the management of rhinitis, treatment should consist of patient education, allergen avoidance activities and pharmacological therapies.
    - Patients should be educated on how to avoid known triggers, such as aeroallergens, dust mites, molds and irritants whenever possible. In addition to environmental control measures, pharmacological therapies may be used to control symptoms. Intranasal corticosteroids should be considered first-line therapy in patients with moderate to severe allergic rhinitis.
    - While differences in potencies, lipid solubility and systemic bioavailability exist between the older and newer intranasal corticosteroid products, no single agent has consistently has been demonstrated to be more effective than another.
    - Moreover, no one intranasal corticosteroid product is recommended over another as initial treatment in patients with perennial or seasonal allergic rhinitis.
- Other Key Facts:
    - The role of the intranasal corticosteroids in the treatment of allergic rhinitis has been well established.
    - Budesonide, flunisolide, fluticasone propionate, mometasone and triamcinolone are currently available generically.
    - Two “dry” nasal aerosol products, beclomethasone (QNASL®) and ciclesonide (Zetonna®), were approved in 2012. All other agents within the class are aqueous suspensions.

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Therapeutic Class Overview
Neurokinin-1 (NK1) Receptor Antagonists and Combinations

Therapeutic Class Overview/Summary:
This review will focus on miscellaneous antiemetics, which includes doxylamine succinate/pyridoxine hydrochloride (Diclegis®) as well as the neurokin-1 (NK_1) receptor antagonists/combinations. NK_1 antagonists are all Food and Drug Administration (FDA)-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV).[1-5] Single-entity NK_1 antagonists include: aprepitant (Emend®), its prodrug fosaprepitant dimeglumine (Emend®), and rolapitant hydrochloride (Varubi®). There is a single NK_1 antagonist combination product currently available, netupitant/palonosetron (Akynzeo®). With this combination, netupitant, the NK_1 antagonist is co-formulated with palonosetron, a serotonin type-3 (5-HT_3) receptor antagonist. In addition to CINV, aprepitant is FDA-approved for the prevention of post-operative nausea and vomiting in adults.[1-4] Differences in anti-emetic effect for the acute and delayed phases of CINV exist between NK_1 antagonists and are summarized in Table 2. Doxylamine/pyridoxine is FDA-approved for the treatment of nausea and vomiting of pregnancy.[5]

As the pathophysiology of CINV is not completely understood, the exact mechanisms by which NK_1 antagonists exert there antiemetic effects are not known. NK_1 is a broadly distributed receptor located in both the central and peripheral nervous systems. One proposed mechanism of NK_1 antagonists is by depressing the substance P mediated response in the central nevous system by blocking activation of NK_1 in areas of the brain responsible for chemoreception. Decreased activation of NK_1 by substance P reduces the emetic reflex. A second proposed mechanism is the blockade of peripheral NK_1 receptors located on the vagal terminals of the gut. It is hypothesized that peripheral blockade may decrease the intensity of the signal transmitted to the central nervous system, thus decreasing the overall emetic reflex.[1-4,6,7] Doxylamine competes with histamine for H1-receptor sites and blocks the chemoreceptor trigger zone thereby decreasing nausea and vomiting. Antihistamine agents also work indirectly on the vestibular system by decreasing stimulation of the vomiting center. Hypotheses to explain the antiemetic effects of pyridoxine include prevention/treatment of vitamin B6 deficiency, intrinsic antinausea properties, and/or synergy with the antinausea properties of antihistamine.[5,8,9]

Table 1. Current Medications Available in the Therapeutic Class[1-5]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Aprepitant (Emend®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of CINV associated with initial and repeat courses of MEC, Prevention of PONV	Capsule: 40 mg 80 mg 125 mg Capsule, Dose Pack: 125 and 80 mg Oral Suspension: 125 mg/5 mL	-
Fosaprepitant dimeglumine (Emend®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of delayed CINV associated with initial and repeat courses of MEC	Vial: 150 mg	-
Rolapitant hydrochloride	Prevention of delayed CINV	Tablet:	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
(Varubi®)	associated with initial and repeat courses of HEC, Prevention of delayed CINV associated with initial and repeat courses of MEC and prevention of delayed CINV associated with combination of anthracycline and cyclophosphamide	90 mg	
Doxylamine succinate/pyridoxine hydrochloride (Diclegis®)	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management	Delayed-release tablet: 10 mg/10 mg	-
Netupitant/palonosetron (Akynzeo®)	Prevention of acute and delayed CINV associated with initial and repeat courses of HEC, Prevention of acute and delayed CINV associated with initial and repeat courses of cancer chemotherapy not considered highly emetogenic	Capsule: 300/0.5 mg	-

Other abbreviations: CINV=chemotherapy-induced nausea and vomiting, HEC=highly emetogenic cancer chemotherapy, MEC=moderately emetogenic cancer chemotherapy, PONV=post-operative nausea and vomiting

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- The safety and efficacy of the miscellaneous antiemetics have been evaluated in several clinical trials for their FDA-approved indications.[15-51] Aprepitant, being an older, more established agent has had more extensive review. Results of these trials are similar to those used by the FDA for approval.[19-36] There are currently no clinical trials that compare NK_1 antagonists to one-another.
- The approval of rolapitant (Varubi®) was based on the efficacy and safety in preventing CINV in patients receiving anthracycline combination therapy, MEC, or HEC with a cisplatin-based regimen in three clinical trials. The primary endpoint in both HEC studies was complete response (CR) in the delayed phase (defined as 25 to 120 hours post administration of chemotherapy) of CINV. Results of the showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group in HEC-1: (192 [73%] compared to 153 [58%]; P=0.0006). However, in HEC-2, this was statistically significant: (rolapitant [70%] compared to placebo control group [62%]; P=0.0426).[39,40] In the third trial, the antiemetic effect of rolapitant was evaluated in MEC. The primary endpoint of CR in the delayed phase of CINV showed a greater proportion of individuals treated with the rolapitant arm had a statistically significant CR compared with the placebo control group: (475 [71%] compared to 410 [62%]; P=0.0002).[39,41]
- The approval of netupitant/palonosetron (Akynzeo®) was based on the efficacy and safety in preventing CINV in patients receiving MEC or HEC. Both trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of netupitant/palonosetron given as a single oral dose 60 minutes before administration of chemotherapy in combination with dexamethasone. CR in the delayed phase was statically significant in HEC and MEC for patients who received netupitant/palonosetron (P=0.032 and P=0.01, respectively).[42,43]
- FDA-approval of doxylamine succinate/pyridoxine hydrochloride (Diclegis®) was based on a single double-blind, randomized, multi-center, placebo-controlled study that evaluated 298 pregnant adult women with nausea and vomiting in the gestational age range of 7 to 14 weeks. Patients were randomized to 14 days of placebo or doxylamine/pyridoxine (two to four tablets daily). Mean change from baseline was -4.8 points in the symptom domain (Pregnancy Unique-Quantification of Emesis) score at day 15 in the doxylamine/pyridoxine group compared to -3.9 points in the placebo group (P=0.006). For the Quality of Life domain, mean change from baseline was 2.8 points at day 15 in the

doxylamine/pyridoxine group compared to -1.8 points in the placebo group (P=0.005).[50] A second study compared a five-day course of low-dose ondansetron to low-dose doxylamine/pyridoxine. The study concluded that ondansetron provided a statistically significant reduction in the nausea and vomiting (P=0.019 and P=0.049, respectively).[51]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - It is recommended that antiemetic therapy be initiated before the administration of chemotherapy and then continued throughout the period when delayed emesis may occur. Choice of antiemetic regimen depends primarily on the emetogenic potential and the risk of delayed CINV associated with the chemotherapy agents. The period of risk for CINV may be up to three days after administration of highly emetogenic chemotherapy (HEC) and at least two days after moderately emetogenic chemotherapy (MEC).[10]
  - For the prevention of CINV post-HEC, triple therapy with a 5-HT_3 receptor antagonist, dexamethasone, and a NK_1 receptor antagonist is recommended.[10-11]
  - The updated 2015 National Comprehensive Cancer Network (NCCN) guidelines do not currently recommend one specific regimen over another.[10]
  - For the prevention of CINV post-MEC, a 5-HT_3 receptor antagonist and dexamethasone is recommended, with a NK_1 receptor antagonist being optional.[10-12]
  - Guidelines generally recommend palonosetron as the preferred 5-HT_3 receptor antagonist for the prevention CINV associated with MEC. Adjunctive therapies include with lorazepam, an H_2 receptor antagonist or a proton pump inhibitor.[10-12]
  - The Pediatric Oncology Group of Ontario in 2012 recommend aprepitant in combination with granisetron and dexamethasone in children 12 years of age or older who will be receiving HEC and in which the antineoplastics are not known to or suspected of interacting with aprepitant. Dual therapy with ondansetron or granisetron and dexamethasone is recommended if the antineoplastic agents interact with aprepitant.[13]
  - Several guidelines have not yet been updated to include netupitant/palonosetron and/or rolapitant.[11-13]
  - According to the Obstetrician-Gynecologists Clinical Management Guideline for Nausea and Vomiting of Pregnancy, more severe cases should be treated with pyridoxine monotherapy first-line. If monotherapy is inadequate, guidelines recommend pyridoxine in combination with doxylamine. If combination therapy failed, promethazine or dimenhydrinate can be substituted for doxylamine. Other third-line options include metoclopramide, ondansetron, trimethobenzamide or methylprednisolone.[14]

- Other Key Facts:
  - Doxylamine/pyridoxine is the only FDA-approved agent for the treatment of nausea and vomiting of pregnancy.
  - All NK_1 antagonists are formulated as either an oral capsule or tablet, with the exception of fosaprepitant, which is an intravenous injection. Aprepitant is also formulated as an oral suspension.[1-4]
  - For HEC, fosaprepitant, rolapitant, and netupitant/palonosetron are given only on day one as a single dose, while aprepitant is given for three days.[1-4]
  - Doxylamine/pyridoxine is initially given once daily at bedtime (two tablets) but may be increased to twice daily (one tablet in the morning and two tablets at bedtime). The maximum dose is two tablets in the morning and two tablets at bedtime (four tablets/day).[5]
  - All NK_1 antagonists are associated with drug interactions to some extent. Of particular concern are drug interactions with agents that are either substrates of CYP3A4 or inhibit/induce CYP3A4. Dose adjustments and contraindications may apply based on the concurrent agent.[1-4]
  - Aprepitant oral suspension and capsules are the only NK_1 antagonist currently approved by the FDA for use in pediatric patients.[1-4]

- Both the FDA-approved label and clinical guidelines do not recommend aprepitant for patients less than 12 years of age, however, the oral suspension has been shown to be safe and effective in patients 6 months of age and older.[1,13]
- Due to its co-formulation, netupitant/palonosetron carries the associated warnings of palonosetron, including a risk for serotonin syndrome.[4]

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Therapeutic Class Overview
Multiple Sclerosis Agents

Therapeutic Class

- **Overview/Summary:** Several biologic response modifiers are Food and Drug Administration (FDA)-approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) and include alemtuzumab (Lemtrada®), daclizumab (Zinbryta®), glatiramer acetate (Copaxone®, Glatopa®), interferon β (IFNβ)-1b (Betaseron®, Extavia®), intramuscular (IM) IFNβ-1a (Avonex®), subcutaneous (SC) IFNβ-1a (Rebif®), SC peginterferon β-1a (Plegridy®) along with the oral products dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®) and teriflunomide (Aubagio®).[1-14] Both IFNβ-1b and IM IFNβ-1a are also FDA-approved for the treatment of patients experiencing a first clinical episode with magnetic resonance imaging (MRI) evidence of multiple sclerosis (MS), which is often referred to as a clinically isolated syndrome.[7,8,10] The exact mechanisms of action of daclizumab, dimethyl fumarate, teriflunomide, the INFs and glatiramer acetate are unknown or not completely understood but are likely due to their antiproliferative and immuno-modulatory effects.[2,3,5-12]

  MS is a chronic and potentially disabling neurological disease characterized by repeated episodes of inflammation within the nervous tissue of the brain and spinal cord, resulting in injury to the myelin sheaths and subsequently the nerve cell axons.[16-17] There are four clinical subtypes of MS: RRMS, primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive (SPMS).[16-19] The most common form is RRMS, characterized by acute relapses followed by partial or full recovery.[17,19] Patients with PPMS have a continuous and gradual decline in function without evidence of acute attacks. Patients with PRMS also have a continuous decline in function while experiencing occasional attacks. Finally, SPMS begins as RRMS, but as time progresses the attack rate declines and patients experience a gradual deterioration.[19]

Table 1. Current Medications Available in the Therapeutic Class[1-12]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alemtuzumab (Lemtrada)	Relapsing-remitting multiple sclerosis*		-
Daclizumab (Zinbryta®)	Relapsing-remitting multiple sclerosis#		-
Dimethyl fumarate (Tecfidera®)	Relapsing-remitting multiple sclerosis*	Delayed-release capsule: 120 mg 240 mg	-
Fingolimod (Gilenya®)	Relapsing-remitting multiple sclerosis†	Capsule: 0.5 mg	-
Glatiramer acetate (Copaxone®**, Glatopa®††)	Relapsing-remitting multiple sclerosis‡, treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	Prefilled syringe: 20 mg	✔
Interferon β-1b (Betaseron®, Extavia®)	Relapsing-remitting multiple sclerosis§, treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	Single use vial: 0.3 mg lyophilized powder	-
Interferon β-1a (Rebif®)	Relapsing-remitting multiple sclerosis‖	Prefilled syringe: 8.8 µg 22 µg 44 µg	-
Interferon β-1a (Avonex®, Avonex	Relapsing-remitting multiple sclerosis¶, treatment of first clinical episode with	Prefilled syringe: 30 µg	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Administration Pack®)	magnetic resonance imaging features consistent with multiple sclerosis	Single use vial: 30 µg lyophilized powder	
Peginterferon β-1a (Plegridy®)	Relapsing-remitting multiple sclerosis*		
Teriflunomide (Aubagio®)	Relapsing-remitting multiple sclerosis*	Tablet: 7 mg 14 mg	-

*Treatment of patients with relapsing forms of multiple sclerosis.
†Treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.
‡Reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis.
§Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.
‖Treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.
¶ Treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.
#Treatment of patients with relapsing forms of multiple sclerosis in patients who have an inadequate response to two or more drugs indicated for the treatment of multiple sclerosis.
**Generic available in at least one dosage form or strength.
††Glatopa® is considered a biosimilar to reference product Copaxone®

Evidence-based Medicine

- The safety and efficacy of glatiramer acetate and interferon (IFNβ) products are well established. Recent clinical trials have not produced clinically different results compared to trials published previously.
- The FDA-approval of daclizumab was based on the results of two randomized double-blind studies in adults with a diagnosis of relapsing MS (RMS). Both utilized the primary endpoint of annualized relapse rate (ARR). The first study evaluated 1,841 patients over 96 to 144 weeks who were randomized to either daclizumab 150 mg every four weeks or to IFN β-1a 30 µg weekly. Both groups received a placebo matching the other treatment arm. The ARR was significantly reduced in the daclizumab arm (0.216) compared with the IFN β-1a group (0.393) representing a relative reduction of 45% (P<0.0001).[2,33] The second study, SELECT, evaluated a total of 621 patients over 52 weeks who were randomized to daclizumab 150 mg every four weeks, daclizumab 300 mg every four weeks or placebo. The ARR was significantly lower in both the daclizumab 150 mg group (0.21) and the daclizumab 300 mg group (0.23) compared to the placebo group (0.46; P<0.001 for both).[2,34]
- In two large, randomized trials with dimethyl fumarate 240 mg twice-daily or three times daily compared to placebo, there were statistically significant reductions in the annualized relapse rate (ARR) with both dimethyl fumarate regimens compared to placebo (P≤0.001 for both).[37,61] Fox et al also included an open-label glatiramer acetate comparator group. In a post-hoc analysis, there were significant improvements favoring dimethyl fumarate over glatiramer acetate with regard to ARR (three times daily group only), new or enlarging T2 hyperintense lesions and new T1 hypointense lesions (three times daily group only).[61]
- In the 24-month, placebo-controlled FREEDOMS trial, treatment with fingolimod 0.5 or 1.25 mg once daily significantly reduced ARR compared to placebo (54 and 60%, respectively; P<0.001 for both).[38]
- The FREEDOMS II trial had similar results, with fingolimod providing a lower ARR over 24 months compared to placebo.[87]
- In the 12-month TRANSFORMS trial, fingolimod 0.5 or 1.25 mg once-daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 µg intramuscularly (IM) once-weekly (P<0.001 for both).[43] In a 12-month extension of TRANSFORMS, patients initially randomized to IM IFNβ-1a were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IM IFNβ-1a.[44]

- In the TEMSO trial, treatment with teriflunomide 7 or 14 mg was associated with significantly greater relative reductions in ARR compared to placebo (31.2 and 31.5%. respectively; *P*<0.001).[56] In an unpublished extension study, ARR remained low after five years and the adverse event rates were similar to those reported in previous trials.[57,58]
- The TOWER study showed that over one year teriflunomide had a lower ARR than placebo.[88]
- The ComiRX trial, evaluated the combination of IFNβ-1a and glatiramer acetate versus IFNβ-1a alone versus glatiramer acetate alone. After three years, the ARR of the combination was not statistically significantly improved to the better of the two single-agent arms when adjusting for baseline age. Glatiramer acetate provided statistically significant greater reduction in risk of exacerbation compared to interferon by 31%, and the combination group provided statistically significant greater reduction in risk of exacerbation compared to interferon by 25% (P=0.027, P=0.022 respectively).[89]
- Two phase III clinical trials evaluated treatment outcomes with IFNβ-1a 44 µg SC three times weekly and alemtuzumab 12 mg. One trial evaluated a study population of treatment-experienced MS patients and the second study evaluated treatment outcomes in treatment-naive patients. In both trials, treatment with alemtuzumab resulted in a statistically significant reduction in the annualized relapse rate compared to treatment with IFNβ-1a. Time to onset of six-month disability progression was only significantly delayed in treatment-experience patients.[103,104]
- The safety and efficacy of peginterferon β-1a, was established in a single, randomized, double-blind, placebo controlled study. Annualized relapse rate was 0.26 in the peginterferon β-1a group compared to 0.40 with placebo (P=0.007). This represented a hazard ratio of 0.61 (95% CI, 0.47 to 0.80; P=0.0003). The proportion of patients with a relapse was also significantly lower with the peginterferon β-1a group compared to placebo (0.19 vs 0.29; P=0.003). [105]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The approach to treating MS includes: the management of symptoms, treatment of acute relapses, and utilization of disease-modifying therapies to reduce the frequency and severity of relapses, and delay disease and disability progression.[14,16,19,22]
    - IFNβ products or glatiramer acetate are recommended as first-line therapy in patients with RRMS.[18,19]
    - The Association of British Neurologists also recommend either of the oral agents as potential first-line options.[18]
    - Due to its adverse effect profile, fingolimod is sometimes recommended as a second-line option.[19,20] NICE recommends use of fingolimod only if patients have an unchanged or increased relapse rate, or ongoing severe relapses compared to the previous year despite treatment with IFNβ.[20]
    - Consensus guidelines do not recommend a change of therapy in patients positive for neutralizing antibodies who are responding to IFN therapy, noting that neutralizing antibodies disappear with continued treatment in the majority of patients.[18,23-25]
    - A change of therapy may be considered in patients experiencing a suboptimal response or intolerable adverse effects.[26,28,29]
    - Data suggests a significant reduction in relapse rate and a delay in disease and disability progression in patients switching from IFNβ to glatiramer acetate therapy or vice versa due to poor response.[26,28,29]
- Other Key Facts:
    - A biosimilar version of Copaxone® (glatiramer acetate 20 mg/mL) was recently approved by the FDA and is marked under the trade name Glatopa®. There are no other generic MS products available, including other strengths of glatiramer acetate.[1-14]
    - The safety and efficacy of retreatment with alemtuzumab after the initial standard treatment cycles remains uncertain. There is no information regarding retreatment in alemtuzumab's FDA-approved label.[1]
    - There are no head-to-head trials comparing IFNβ-1b products (Betaseron® and Extavia®) and the drugs are not interchangeable despite Extavia® being approved with the same active ingredient and registration trials as Betaseron®.[5,6]

- Alemtuzumab must be administered by a healthcare professional.
- Alemtuzumab and daclizumab are available only through restricted access programs. Both are associated with causing serious autoimmune disorders. In addition, alemtuzumab has been associated with life threatening infusion reactions as well as increased risk of malignancy.[1,2]

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Therapeutic Class Overview
Niacin Derivatives

Therapeutic Class

- **Overview/Summary:** Niacin favorably affects all lipids and lipoproteins when given in pharmacological doses; however, the mechanism of action is not completely understood.[1-5] Niacin has several effects on lipid metabolism including inhibition of hepatic production of very low-density lipoprotein cholesterol, and consequently its metabolite low-density lipoprotein cholesterol. In addition, it decreases plasma concentrations of triglycerides (20 to 50%), very low-density lipoprotein remnants, and intermediate density lipoprotein. Administration of niacin also causes a shift in low-density lipoprotein composition from small, dense particles to larger, more buoyant particles. Lastly, niacin increases high density lipoprotein cholesterol (15 to 35%) both by reducing lipid transfer of cholesterol from high density lipoprotein cholesterol to very low-density lipoprotein cholesterol, and by delaying high density lipoprotein cholesterol clearance. Niacin can decrease low-density lipoprotein cholesterol by 5 to 25%.[1-5]

  There are over-the-counter niacin products that are currently available, and these products are labeled as dietary supplements. While these supplements are "generally recognized as safe", the Food and Drug Administration (FDA) does not examine the efficacy and safety of these products or regulate the manufacturing process. The FDA has imposed statutory restrictions prohibiting manufacturers of dietary supplements from claiming that their products "treat, cure, or prevent any disease". Without FDA regulation, the content of nicotinic acid in niacin products is not guaranteed.[6]

Table 1. Medications Included Within the Therapeutic Class Review[4-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Niacin (Niacor®, Niaspan®*)	Hypertriglyceridemia, adjunctive therapy for the treatment of adult patients with severe hypertriglyceridemia who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them; Primary hypercholesterolemia and mixed dyslipidemia, adjunct to diet, alone or in combination with a bile acid binding resin, for reduction of elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia, adjunct to diet and in combination with a bile acid binding resin to reduce elevated TC and LDL-C levels in adult patients with primary hyperlipidemia and adjunct to diet to reduce elevated TC, LDL-C, apolipoprotein B, and TG levels, and to increase high-density lipoprotein cholesterol in patients with primary hyperlipidemia and mixed dyslipidemia; Secondary prevention of cardiovascular disease, adjunct to diet to reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia and adjunct to diet and in combination with a bile acid binding resin to slow progression or promote regression of atherosclerotic disease in patients with a history of coronary artery disease and hyperlipidemia	Extended-release tablet (Niaspan®):* 500 mg 750 mg 1,000 mg Tablet (Niacor®):* 500 mg	✔

*Generic is available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the niacin derivatives.[7-39]
- In a trial comparing niacin extended-release and immediate-release formulations, doses ≥1,500 mg/day of niacin extended-release decreased low-density lipoprotein cholesterol to a significantly greater extent (P<0.04 or P<0.01); however, at all doses niacin immediate-release significantly increased high-density lipoprotein cholesterol (P<0.04 or P<0.01). Reductions in triglycerides were similar between the two formulations, except for niacin immediate-release 1,000 mg/day which led to significantly greater reductions (P=0.009).[22]
- Direct comparisons of niacin with other lipid modifying agents demonstrated that no one medication class is consistently more efficacious over another in achieving significant alterations in individual lipid parameters, and results support the use of the niacin as combination therapy with other lipid modifying agents.[7-39]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[40-48]
    - In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.
    - When low-density lipoprotein cholesterol (LDL-C) lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels, and are recommended in patients with established coronary heart disease or coronary heart disease equivalents.
    - In patients with an elevated triglyceride level (≥500 mg/dL) a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis.
    - Omega-3-acid ethyl esters represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia.
- Other Key Facts:
    - Prescription niacin is approved by the Food and Drug Administration (FDA) for the treatment of hypertriglyceridemia.
    - Prescription niacin is also approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia.[4,5]
    - Niacin is available over-the-counter in immediate-release and sustained-release formulations.
    - Niacin is also available by prescription as immediate-release (Niacor®) and extended-release (Niaspan®) formulations.

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Therapeutic Class Overview
Ophthalmic Carbonic Anhydrase Inhibitors

Therapeutic Class Overview/Summary:
Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. It is the leading cause of blindness and second leading cause of vision loss in the world.[1] Four distinct types of glaucoma include primary open-angle, acute angle-closure, secondary and congenital. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated. The exact etiology of open-angle glaucoma is unknown. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma or a central corneal thickness of less than 545 micrometers.[2-3] Other possible risk factors that have been investigated include low ocular systolic perfusion pressure, low systolic blood pressure, cardiovascular disease, hypertension, diabetes mellitus and hypothyroidism.[1,3-6]

IOP is the one major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage.[1-3,7] Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage. An IOP greater than 22 mm Hg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors and disease progression.[7] The target IOP should be individualized based on their response to therapy and disease progression. There is no consensus target IOP below which further visual loss and optic nerve damage will be prevented.[2,3]

This class review consists of the ophthalmic carbonic anhydrase inhibitors, which includes brinzolamide (Azopt®), dorzolamide hydrochloride (Trusopt®), and the fixed dose combination products brinzolamide/brimonidine tartrate and dorzolamide hydrochloride/timolol maleate (Cosopt®).[9-13] Brinzolamide, dorzolamide and brinzolamide/brimonidine are Food and Drug Administration (FDA) approved for the treatment of elevated IOP in patients with ocular hypertension or open-angle glaucoma, while dorzolamide/timolol is indicated for the treatment of elevated IOP in patients with ocular hypertension or open-angle glaucoma who had insufficiently responded to beta blockers .[9-13]

Table 1. Current Medications Available in the Therapeutic Class[9-13]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Brinzolamide (Azopt®)	Treatment of Elevated Intraocular Pressure Due to Ocular Hypertension or Open-Angle Glaucoma	Ophthalmic suspension: 1%	-
Dorzolamide (Trusopt®*)	Treatment of Elevated Intraocular Pressure Due to Ocular Hypertension or Open-Angle Glaucoma	Ophthalmic solution: 2%	✔
Combination Products			
Brinzolamide/brimonidine (Simbrinza®)	Treatment of Elevated Intraocular Pressure Due to Ocular Hypertension or Open-Angle Glaucoma	Ophthalmic suspension: 1%/0.2%	-
Dorzolamide/timolol (Cosopt®*, Cosopt PF®)	Treatment of Elevated Intraocular Pressure Due to Ocular Hypertension or Open-Angle Glaucoma†	Ophthalmic solution: 22.3-6.8 mg/mL	✔

*Generic available in at least one dosage form or strength.

†Indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target intraocular pressure after multiple measurements over time).

Evidence-based Medicine

- Single agent ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, were evaluated in a prospective, multicenter, parallel group study. Reduction in IOP from baseline was statistically significant in each group (P<0.001); though, the changes in IOP from baseline were comparable between the treatment groups (P value not reported).[16] Similar reductions in IOP were also observed when the agents were used in combination with ophthalmic timolol.[18]
- Ophthalmic brimonidine was associated with a significantly greater reduction in IOP than either ophthalmic brinzolamide or ophthalmic dorzolamide (all in combination with a prostaglandin) after one and four months of therapy (P<0.001 for both groups).[20]
- The FDA-approval of brinzolamide/brimonidine was based on two randomized, double-blind, active-controlled clinical trials. Each trial patients with open-angle glaucoma or ocular hypertension for three months. Brinzolamide/brimonidine 1%/0.2% was administered three times daily and compared to individually administered 1% brinzolamide three times daily and 0.2% brimonidine tartrate three times daily. In the first study, the mean IOP of the brinzolamide/brimonidine treatment group was significantly lower than that of the brinzolamide or brimonidine groups (P<0.002, for all comparisons). Study two also found a statistically significant difference in IOP in favor of brinzolamide/brimonidine when compared to each individual component (P≤0.005 for all comparisons).[13,21,22]
- The efficacy of ophthalmic dorzolamide/timolol was compared against its individual components as well as agents in other ophthalmic classes. Ophthalmic dorzolamide/timolol demonstrated a greater decrease in IOP compared to monotherapy with ophthalmic dorzolamide or ophthalmic timolol (*P* value not reported).[31,32]
- When ophthalmic dorzolamide/timolol was compared to ophthalmic brimonidine/timolol, both therapies were associated with significant reductions in IOP from baseline and the difference between groups was not found to be significant (P value not reported).[24-28]
- Two large meta-analyses evaluated the relative efficacy of ophthalmic formulations of prostaglandin analogues, beta blockers, alpha agonists, and carbonic anhydrous inhibitors in reducing IOP.[45,47] These trials concluded that the largest reduction in IOP occurred with ophthalmic prostaglandin analogues and ophthalmic timolol maleate. Ophthalmic carbonic anhydrase inhibitors were associated with a lower relative reduction in IOP; though, the changes from baseline were statistically significant among patients receiving ophthalmic carbonic anhydrase inhibitors.

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Current guidelines by the American Academy of Ophthalmology and American Optometric Association recommend ophthalmic β adrenergic antagonists and prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP.[2]
    - Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients that experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents.[2]
- Other Key Facts:
    - Currently ophthalmic dorzolamide (Trusopt®) and dorzolamide/timolol (Cosopt®) are available generically.
    - Brinzolamide (Azopt®), brinzolamide/brimonidine (Simbrinza®) and dorzolamide/timolol preservative-free (Cosopt-PF®) are available as brand name products only.

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Therapeutic Class Overview
Ophthalmic Antihistamines

Therapeutic Class

- **Overview/Summary:**
  All of the ophthalmic antihistamines listed in Table 1 are Food and Drug Administration (FDA)-approved for the prevention or treatment of the signs and symptoms of allergic conjunctivitis.[1-10] Ketotifen (Alaway®, Zaditor®) is also indicated for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.[6,7] Allergic conjunctivitis is the most common form of ocular allergy. Itching manifests as the primary symptom; however, other common symptoms include ocular burning, chemosis, conjunctival and eyelid edema, hyperemia, photophobia and tearing.[11] Symptoms usually occur in both eyes, yet one eye may be affected more than the other.[11] Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea.[12] None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis. Following topical administration to the conjunctiva, ophthalmic antihistamines competitively bind histamine receptor sites to reduce itching and vasodilation.[1-10] The ocular antihistamines are relatively selective for the histamine type 1 (H_1-antihistamine) receptor but may also inhibit the degranulation of mast cells, thereby limiting the release of inflammatory mediators such as histamine, eosinophil and neutrophil chemotactic factors.[1-3,5-10] Emedastine (Emadine®) has only H_1-antihistamine activity.[4] Ophthalmic antihistamines have demonstrated a faster onset of action compared to oral antihistamines and ophthalmic mast-cell stabilizers and they are all approved for use in children.[1-11] The most common adverse events associated with these agents are ocular burning, stinging and headache.[1-11] In general, drug interactions are limited due to low systemic bioavailability via the ocular route. The administration schedule for these products ranges from once daily to four times daily, with only alcaftadine (Lastacaft®), olopatadine 0.2% (Pataday®) and olopatadine 0.7% (Pazeo®) are approved for once daily use.[1,9,10] Azelastine (Optivar®), epinastine (Elestat®), ketotifen and olopatadine 0.1% are available generically. Ketotifen is also available over-the-counter.

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alcaftadine (Lastacaft®)	Allergic conjunctivitis†	Ophthalmic solution: 0.25%	-
Azelastine (Optivar®*)	Allergic conjunctivitis†	Ophthalmic solution: 0.05%	✔
Bepotastine (Bepreve®)	Allergic conjunctivitis†	Ophthalmic solution: 1.5%	-
Emedastine (Emadine®)	Allergic conjunctivitis‡	Ophthalmic solution: 0.05%	-
Epinastine (Elestat®*)	Allergic conjunctivitis§	Ophthalmic solution: 0.05%	✔
Ketotifen (Alaway®*, Zaditor®*)	Allergic conjunctivitis§, ocular itching‖	Ophthalmic solution: 0.025%	✔ #
Olopatadine (Pataday®, Patanol®*, Pazeo®)	Allergic conjunctivitis (0.2%)† (0.1%)‡, ocular itching (0.7%)	Ophthalmic solution: 0.1% 0.2% 0.7%	-

* Available generically in one dosage form or strength.
† For the treatment of ocular itching associated with allergic conjunctivitis.
‡ For the treatment of signs and symptoms of allergic conjunctivitis.
§ For the prevention of ocular itching associated with allergic conjunctivitis.
‖ For the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.
Product is also available over-the-counter in at least one dosage form or strength.

Evidence-based Medicine

- The ophthalmic antihistamines are significantly more effective compared to placebo for reducing the symptoms of allergic conjunctivitis including ocular itching and conjunctival redness.[15-43]
- Using the conjunctival allergen challenge model for allergic conjunctivitis, ophthalmic bepotastine was shown to be more effective than placebo in relieving ocular itching after 15 minutes and eight hours in adults and children.[18,20]
- Using the conjunctival allergen challenge model, one dose of ophthalmic olopatadine 0.2% was comparable to two doses of ophthalmic olopatadine 0.1%, and both regimens were more effective than placebo in terms of mean itching scores.[22]
- Using the conjunctival allergen challenge model, ophthalmic emedastine and ophthalmic ketotifen significantly reduced the mean itching scores at all time points compared to placebo ($P<0.05$); however, there was no statistically significant difference between ophthalmic emedastine and ophthalmic ketotifen (P values not reported).[24]
- In a randomized controlled trial of patients with seasonal allergic conjunctivitis (N=100), no differences in efficacy were reported between ophthalmic formulations of emedastine, epinastine, ketotifen and olopatadine (P values not reported). All agents were more efficacious in preventing itching and redness compared to ophthalmic fluorometholone ($P<0.001$ for all).[32]\
- Ophthalmic naphazoline/pheniramine was more effective than ophthalmic olopatadine in relieving redness and chemosis, while ophthalmic olopatadine was more effective than ophthalmic naphazoline/pheniramine for relieving itching.[33]
- The safety and efficacy of olopatadine 0.7% (Pazeo®) was based on clinical trials of ophthalmic olopatadine 0.1% (Patanol®) and 0.2% (Pataday®).[8-10]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[13,14]
    - Ophthalmic formulations of agents from the following classes are useful in treating allergic conjunctivitis: corticosteroids, vasoconstrictor/antihistamine combinations, antihistamines, nonsteroidal anti-inflammatories (NSAIDs), mast-cell stabilizers, antihistamine/mast-cell stabilizers and immunosuppressants.[13]
    - An over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist is recommended for mild allergic conjunctivitis. No preference is given to any one OTC antihistamine/vasoconstrictor or antihistamine.[14]
    - If the condition is frequently recurrent or persistent, use mast-cell stabilizers. No single mast-cell stabilizer is preferred over another.[14]
    - Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. No one antihistamine/mast-cell stabilizer is preferred over another.[14]
    - If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used because of the potential for adverse events with their protracted use (e.g., cataract formation and elevated intraocular pressure).[13,14]
- Other Key Facts:
    - Alcaftadine and emedastine are classified as pregnancy category B while the other agents in this class have a pregnancy category C rating.
    - Alcaftadine and olopatadine (0.2%, 0.7%) are the only agents within the class that are approved for once daily use.
    - Ophthalmic formulations of azelastine, epinastine, ketotifen and olopatadine 0.1% are available generically.
    - Ketotifen is also available over-the-counter.

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Therapeutic Class Overview
Ophthalmic Fluoroquinolones

Therapeutic Class

- **Overview/Summary:** This review will focus on the ophthalmic fluoroquinolone antibiotics. These agents are used for the treatment of bacterial conjunctivitis and corneal ulcers caused by susceptible isolates.[1-8] Conjunctivitis occurs worldwide and affects all ages, social strata, and both genders. This infection rarely causes permanent visual loss or structural damage and mild cases may be self-limited, as many cases will resolve without treatment in immunocompetent individuals. The most common causative pathogens seen with bacterial conjunctivitis include *Staphylococcus* aureus, *Streptococcus pneumonia*, *Haemophilus influenza*, and *Moraxella catarrhalis*.[9] Major clinical features of bacterial conjunctivitis include redness and discharge in one eye, although it can be bilateral. Patients eye(s) will often be "stuck shut" in the morning. Purulent discharge continues throughout the day and is thick, globular and may be yellow, white or green in color, which may help distinguish between viral and allergic conjunctivitis which usually has watery discharge.[9] Fluoroquinolone antibiotics act via direct inhibition of bacterial DNA synthesis, preventing the action of DNA gyrase and topoisomerase IV, which blocks DNA replication and eventually leads to damage to bacterial DNA and cell death.[10] Currently, ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically.

  These ophthalmiac quinolones include besifloxacin, ciprofloxacin hydrochloride, gatifloxacin, levofloxacin, moxifloxacin hydrochloride, and ofloxacin. They are all indicated for the treatment of bacterial conjunctivitis.[1-8] In addition, ciprofloxacin solution and ofloxacin have the indication to treat corneal ulcers caused by susceptible isolates.[2,8] All medications are formulated as drops (either solution or suspension) with only ciprofloxacin hydrochloride being formulated as an ointment (Ciloxan®).[3] Although generally considered equally effective, differences in resistance exist, with fewer gram-positive cocci being resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones.[13] Frequency and duration of therapy varies depending on specific agents. Treatment for bacterial conjunctivitis with besifloxacin and moxifloxacin hydrochloride is usually dosed twice or three times daily, while the others are generally prescribed every two to four hours.[1-8] Most ophthalmic quinolones are indicated for use in patients one year of age or older, however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

Table 1. Current Medications Available in Therapeutic Class[1-8]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Besifloxacin ophthalmic (Besivance®)	Treatment of bacterial conjunctivitis	Ophthalmic suspension: 0.6% (5 mL)	-
Ciprofloxacin hydrochloride ophthalmic (Ciloxan®*)	Treatment of bacterial conjunctivitis; treatment of corneal ulcers (solution)	Ophthalmic ointment: 0.3% (3.5 g) Ophthalmic solution: 0.3% (2.5, 5, 10 mL)	✔
Gatifloxacin ophthalmic (Zymaxid®*)	Treatment of bacterial conjunctivitis	Ophthalmic solution: 0.5% (2.5 mL)	✔
Levofloxacin ophthalmic	Treatment of bacterial conjunctivitis; treatment of corneal ulcers	Ophthalmic solution: 0.5% (5 mL)	✔
Moxifloxacin hydrochloride ophthalmic (Moxeza®, Vigamox®)	Treatment of bacterial conjunctivitis	Ophthalmic solution: 0.5% (3 mL)	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Ofloxacin ophthalmic (Ocuflox®*)	Treatment of bacterial conjunctivitis; treatment of corneal ulcers	Ophthalmic solution: 0.3% (5, 10 mL)	✔

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated that ophthalmic fluoroquinolones are effective in treating and providing relief of conjunctivitis and corneal ulcers in pediatric and adult patients.[15-40]
- Several studies comparing ophthalmic fluoroquinolones to either placebo or vehicle have concluded that these medications resulted in significantly higher clinical resolution rates at days one through five.[15-20]
- Head-to-head trials evaluating the efficacy of ophthalmic antibiotics for the treatment of bacterial conjunctivitis have found that no one medication was inferior to another.[21-30]
- In one trial, significantly more patients in the ophthalmic moxifloxacin group had complete resolution of ocular signs and symptoms at 48 hours when compared to patients treated with ophthalmic polymyxin B sulfate/trimethoprim (P=0.001).[22] One study found levofloxacin 0.5% to have statistically greater microbial eradication in pediatric patients two to 11 years of age with bacterial conjunctivitis (P≤0.032) compared to ofloxacin 0.3% in, but not in any other pediatric age group..[26] In a seven day trial, a higher percentage of patients receiving levofloxacin had microbial eradication at the final visit compared to patients receiving ofloxacin (P=0.034);however, clinical cure rates were similar between the two treatments (P value not reported).[27] In a small meta-analysis, moxifloxacin was found to be associated with fewer drop-outs for treatment failure (P=0.002) compared to ofloxacin.[28]
- In patients with a diagnosis of corneal ulcer, ophthalmic ciprofloxacin hydrochloride was shown to be efficacious treatment options.[31,32] Specifically, in one trial of patients with a diagnosis of infectious keratitis ophthalmic ciprofloxacin had a shorter average time to healing as compared to ophthalmic cefazolin sodium fortified with gentamicin sulfate, although this was not found to be significant (P value not reported).[32]
- A number of studies consisted of patients with multiple diagnoses such as blepharitis, blepharoconjunctivitis, bacterial conjunctivitis and blepharitis, keratoconjunctivitis, or symptoms of surface ocular infections. These studies found that the ophthalmic formulations of ciprofloxacin, gentamicin sulfate, ofloxacin, tobramycin solution, and polymyxin B sulfate/trimethoprim were efficacious in resolving or curing multiple ocular infections. No significant differences were observed in any study with regard to cure rates, decline in bacterial counts, bacterial eradication or reduction of bacteria, microbial improvement or overall improvement. [34-39]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. Therapy for severe conjunctivitis disease be based on culture and sensitivity, but if that is not available or if mild disease is present, empiric therapy is considered appropriate.[9,11-13]
    - The selection of an ophthalmic antibiotics for bacterial conjunctivitis is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis.[11]
    - Although effective, ophthalmic quinolones are generally regarded as second-line agents for routine bacterial conjunctivitis because of resistance and cost concerns.[9,11,12]
    - Ophthalmic quinolones are the considered the treatment of choice for corneal ulcers and for infections caused by pseudomonas.[9,13]
    - The recommended ophthalmic antibiotics for treatment of keratitis vary depending on organism identified. Empiric therapy is often utilized and includes ophthalmic quinolones[13]
    - Fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones[13]

  - Single-drug therapy using an ophthalmic fluoroquinolone has been shown to be as effective as combination therapy with ophthalmic antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics.[13]
- Other Key Facts:
  - Ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically.
  - Only ciprofloxacin hydrochloride is formulated as an ointment.[3]
  - Moxeza® (moxifloxacin) is dosed twice daily while besifloxacin and Vigamox® (moxifloxacin) are dosed three times a day. The remaining agents are dosed every two or every four hours while awake.[1-8]
  - Most ophthalmic quinolones are indicated for use in patients one year of age or older; however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

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Therapeutic Class Overview
Ophthalmic Nonsteroidal Anti-Inflammatory Drugs

Therapeutic Class

- **Overview/Summary:** This review encompasses the ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) bromfenac sodium (Prolensa®, generic), diclofenac sodium, flurbiprofen sodium (Ocufen®), ketorolac tromethamine (Acular®, Acular LS®, Acuvail®) and nepafenac (Ilevro®, Nevanac®).[1-11] These agents are indicated for use prevention of intraoperative miosis during cataract surgery, management of postoperative inflammation, and the reduction of pain and discomfort following cataract and refractive surgery. Although not Food and Drug Administration (FDA)-approved, ophthalmic NSAIDs are also used for the prevention and treatment of cystoid macular edema following cataract surgery.[12,13] Ophthalmic NSAIDs exert their anti-inflammatory activity primarily by nonselective inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes.[1-10] Topical administration of anti-inflammatory agents for ocular conditions is preferred over systemic administration due to higher ocular drug concentrations with minimal systemic adverse events.[14-16]

  The American Academy of Ophthalmology and the American Optometric Association both recommend using ophthalmic NSAIDs for preventing and treating cystoid macular edema following cataract surgery. Neither organization recommends one ophthalmic NSAID over another.[17,18] The American Academy of Ophthalmology also recommends the use of NSAIDs in before and after several refractive surgeries.[19] Both organizations note that ophthalmic NSAIDs are effective in treating the signs and symptoms of allergic conjunctivitis.[20,21] The most common adverse events associated with ophthalmic NSAIDs include conjunctival hyperemia, burning and stinging.[15] Corneal ulceration and full-thickness corneal melts associated with the use of these agents is a serious complication. Ophthalmic NSAIDs were first reported to cause corneal melting in 1999. The majority of cases were related to the generic ophthalmic diclofenac sodium solution manufactured by Falcon Laboratories, and ultimately this product was removed from the market. There have been reports of corneal melts and keratitis associated with the use of other ophthalmic NSAIDs; however, available evidence does not alter the favorable benefit-risk ratio of the appropriate use of ophthalmic NSAIDs.[15]

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Bromfenac sodium ophthalmic* (Prolensa®)	Treatment of pain and inflammation associated with cataract surgery	Ophthalmic solution: 0.09% (1.7 mL, 2.5 mL, 5 mL) 0.07% (1.6 mL, 3 mL)	✔
Diclofenac sodium ophthalmic	Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery; treatment of postoperative inflammation in patients undergone cataract extraction	Ophthalmic solution: 0.1% (2.5 mL, 5 mL)	✔
Flurbiprofen sodium ophthalmic (Ocufen®*)	Inhibition of intraoperative miosis	Ophthalmic solution: 0.03% (2.5 mL)	✔
Ketorolac tromethamine ophthalmic (Acular®*, Acular LS®*, Acuvail®)	Reduction of ocular pain and burning/stinging following corneal refractive surgery (0.4%); temporary relief of ocular itching due to seasonal allergic conjunctivitis (0.5%); treatment of pain and inflammation associated with cataract surgery (0.45%); treatment of postoperative inflammation in patients who have undergone cataract extraction (0.5%)	Ophthalmic solution: 0.4% (5 mL) 0.45% (0.4 mL single-use vials in package of 30) 0.5% (3 mL, 5 mL, 10 mL)	✔

Nepafenac ophthalmic (Ilevro®, Nevanac®)	Treatment of pain and inflammation associated with cataract surgery	Ophthalmic suspension: 0.1% (3 mL) 0.3% (1.7 mL, 3 mL)	-

*Generic available in one dosage form or strength.

Evidence-based Medicine

- The ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be safe and effective in inhibiting intraoperative miosis, reducing postoperative inflammation and pain associated with cataract surgery, relieving pain and photophobia following corneal refractive surgery and relieving seasonal allergic conjunctivitis symptoms in placebo-controlled trials.[22-49,56-64] Although not Food and Drug Administration (FDA)-approved, there is evidence to support the use of ophthalmic NSAIDs for preventing or treating cystoid macular edema and for reducing pain associated with various other refractive surgeries.[51-54]
- The results of head-to-head trials comparing ophthalmic NSAIDs have not consistently demonstrated any one agent to be more efficacious than another for a given indication.[31,32,34,35,48,49,51,52,57,58,61]
- With regard to safety, not one agent was consistently reported to be better tolerated than another across trials, although there is some evidence that the preservative-free products may be associated with less ocular irritation.[45]
- Corneal complications have been reported to occur with all of the agents in the class and the risk does not appear to be higher with one agent vs another.
- Consensus guidelines established by the American Academy of Ophthalmology and the American Optometric Association recommend the use of topical NSAIDs for preventing and treating cystoid macular edema due to cataract surgery. Available evidence suggests that ophthalmic NSAIDs either alone or in combination with ophthalmic corticosteroids are more effective than ophthalmic corticosteroids alone. The ophthalmic NSAIDs are not associated with an increase in intraocular pressure, which may occur with the use of corticosteroids. [17,18]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) for preventing and treating cystoid macular edema due to cataract surgery is recommended.[17,18]
    - For refractive surgery, specifically surface ablation techniques and laser in situ keratomileusis, the use of ophthalmic NSAIDs is recommended. Judicious NSAID application should be done after surface ablation to reduce pain and inflammation and to delay corneal epithelialization NSAID application should be done before laser in situ keratomileusis to ameliorate postop pain. No NSAID is recommended over another.[19]
    - Both organizations note that ophthalmic NSAIDs are effective in treating the signs and symptoms of allergic conjunctivitis.[20,21]
- Other Key Facts:
    - Bromfenac 0.09%, diclofenac sodium, flurbiprofen sodium, and ketorolac tromethamine 0.5 and 0.4% are available generically.
    - Diclofenac sodium and ketorolac tromethamine 0.45% are the only ophthalmic NSAIDs that are formulated as preservative-free.[4,6]
    - Nepafenac 0.3% and two formulations of bromfenac sodium (0.09% and Prolensa®) are approved for once daily dosing.[1,2,10]
    - Ketorolac Tromethamine 0.4% is the only ophthalmic NSAID used as needed.[8]

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Therapeutic Class Overview
Ophthalmic Prostaglandin Analogues

Therapeutic Class

- **Overview/Summary:** Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. It is the leading cause of blindness and second leading cause of vision loss in the world.[1] Four distinct types of glaucoma include primary open-angle, acute angle-closure, secondary and congenital. Patients with open-angle glaucoma initially experience peripheral visual field loss, followed by central field loss, which may progress to irreversible blindness if untreated. The exact etiology of open-angle glaucoma is unknown. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma or a central corneal thickness of less than 545 micrometers.[2-3] Other possible risk factors that have been investigated include low ocular systolic perfusion pressure, low systolic blood pressure, cardiovascular disease, hypertension, diabetes mellitus and hypothyroidism.[1,3-6]

- IOP is the one major risk factor for glaucoma that is treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage.[1-3,7] Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage. An IOP greater than 22 mm Hg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors and disease progression.[7] The target IOP should be individualized based on their response to therapy and disease progression. There is no consensus target IOP below which further visual loss and optic nerve damage will be prevented.[2,3]

Table 1. Current Medications Available in the Therapeutic Class[9-14]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Bimatoprost (Lumigan®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.01% (2.5, 5, 7.5 mL) 0.03% (2.5, 5, 7.5 mL)	-
Latanoprost (Xalatan®*)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.005% (2.5 mL)	✔
Tafluprost (Zioptan®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.0015% (30 or 90 0.3 mL single-use containers)	-
Travoprost (Travatan Z®)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.004% (2.5, 5 mL)	-
Unoprostone	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Ophthalmic solution: 0.015%	-

*Available generically in one dosage form or strength.

Evidence-based Medicine

- Many clinical trials have evaluated the safety and efficacy of the ophthalmic prostaglandin analogues for the reduction of intraocular pressure (IOP) in patients with glaucoma or ocular hypertension.[18-59]
- Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between ophthalmic travoprost and ophthalmic latanoprost.[18,20,21,25,28,30,31,35,36]

- Available trials suggest that ophthalmic tafluprost may have a similar IOP-lowering effect as ophthalmic latanoprost but less than ophthalmic travoprost.[49-52]
- Results from one trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation and conjunctival hyperemia when switched from ophthalmic latanoprost to ophthalmic tafluprost as well as ophthalmic tafluprost also significantly reduced IOP compared to baseline treatment with ophthalmic latanoprost (16.4 vs 16.8 mm Hg; P=0.049).[48]
- A meta-analysis of 11 randomized control trials showed significant reductions in IOP with ophthalmic latanoprost compared to ophthalmic timolol (P<0.001).[38]
- The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to combination therapy.[33,34,39-42]
- The safety and efficacy of unoprostone isopropyl for lowering IOP in patients with glaucoma or ocular hypertension was established in six, six-month randomized controlled clinical studies. Patients had a mean baseline intraocular pressure of 23 mmHg, and unoprostone isopropyl lowered intraocular pressure by approximately 3 to 4 mmHg throughout the day. Unoprostone isopropyl appeared to lower intraocular pressure without affecting cardiovascular or pulmonary function.[14] A review of all clinical trial data suggests unoprostone may not be as efficacious as other prostanoids; however, it is effective for IOP reduction both as monotherapy and adjunctive therapy with timolol. In addition, unoprostone has decreased affinity for the prostaglandin F2α receptor, which may explain its well tolerated ocular and systemic side effect profile compared with other prostanoids.[59]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[1-3,7,8]
    - The current treatment of glaucoma focuses on decreasing IOP by one of three methods: laser therapy, surgery or medical intervention.
    - Medical intervention is generally used as initial therapy prior to laser or surgical treatment. Medical intervention includes five classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-$_2$ adrenergic agonists, β adrenergic antagonists, carbonic anhydrase inhibitors, parasympathomimetics and prostaglandin analogues.
    - These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow.
    - Current guidelines by the American Academy of Ophthalmology and American Optometric Association recommend ophthalmic β adrenergic antagonists and prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP. Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients that experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents.
    - o

- Other Key Facts:
    - Latanoprost is the only ophthalmic prostaglandin analogue that is available generically.[9]
    - Tafluprost is the only preservative-free ophthalmic prostaglandin product and is only available in single-use containers.[13]
    - Bimatoprost and latanoprost are formulated with benzalkonium chloride, an agent associated with ocular irritation/inflammation in some patients. Travoprost is formulated with sofZia, an ionic buffer containing borate, sorbitol, propylene glycol, and zinc.[9-14]

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Therapeutic Class Overview
Opioid Dependence Agents

Overview/Summary:
This review will focus on the agents used for the treatment of opioid dependence, which includes both partial opioid agonists and opioid antagonists. These agents are used alone or in combination for the treatment of opioid use disorder with several agents used for the reversal of opioid overdose.[1-10] Buprenorphine, buprenorphine/naloxone (Bunavail®, Suboxone®, Zubsolv®) and naltrexone (ReVia®, Vivitrol®) are all Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.[1-7] Naltrexone is also FDA-approved for use in alcohol dependence.[2,3] Naloxone (Evzio®, Narcan®) is used for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.[8-10] Products which contain buprenorphine are classified as Schedule III controlled substances.[11] Other formulations of buprenorphine, buccal film (Belbuca®), injectable (Buprenex®) and transdermal patch (Butrans®) are FDA-approved for use in the management of pain and will not be discussed within this review.[12-14] Buprenorphine, buprenorphine/naloxone sublingual tablets, naltrexone tablets and naloxone prefilled syringes are currently available as generic products.

Buprenorphine is a partial opioid agonist at the μ-opioid receptor (associated with analgesia and dependence) and an antagonist at the κ-opioid receptor (related to dysphoria).[1,4-7] Compared to full opioid agonists, partial agonists bind to the μ-opioid receptor at a higher degree while activating the receptor to a lesser degree. Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ-opioid receptor. Although buprenorphine is associated with significant respiratory depression when used intravenously, or by patients with concomitant benzodiazepine or alcohol abuse, it is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists.[15] During buprenorphine administration, opioid-dependent patients experience positive subjective opioid effects which are limited by ceiling effect.[4-7]

Naloxone and naltrexone are μ-opioid receptor antagonists.[2-10] Naloxone has measurable blood levels following sublingual buprenorphine/naloxone administration, however, due to naloxone's low oral bioavailability, there are no significant physiological or subjective differences when compared to the administration of buprenorphine alone. Following intramuscular or intravenous administration, buprenorphine/naloxone is associated with symptoms of opioid withdrawal and dysphoria which is caused by a stronger affinity of naloxone for the opioid receptor compared to buprenorphine.[4-7] Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.[11] Similarly, when naloxone alone is administered to a patient via intravenous, intramuscular, nasal or subcutaneous routes, reversal of opioid-related effects is expected. This includes respiratory and/or nevous system depression.[8-10]

The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients. This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[15] Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also reccomended.[15] Veterans Health Administration and American Psychiatric Association guidelines outline a similar strategy with methadone and buprenorphine first line.[16-17] Only the American Psychiatric Association guidelines recommend naltrexone use as an alternative regimen.[17] Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[16] Additionally, The Substance Abuse and Mental Health Services Administration and American Medical Association are among some of the prominent medical organizations and advocacy groups that recognize naloxone as standard care for pharmacologic treatment of opioid overdose.[18,19]

Table 1. Current Medications Available in Therapeutic Class[1-10]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Buprenorphine‖	Opioid dependence, treatment induction*,†; opioid dependence, treatment maintenance*,†	Sublingual tablet: 2 mg 8 mg	✔
Naltrexone (ReVia®‖, Vivitrol®)	Alcohol dependence; opioid dependence‡ (ReVia®); opioid dependence, prevention of relapse following opioid detoxification (Vivitrol®)	Suspension for injection, extended-release (Vivitrol®): 380 mg Tablet (ReVia®): 50 mg	✔
Naloxone (Evzio®, Narcan®)	Opioid overdose§	Auto-injector solution (Evzio®): 0.4 mg/0.4 mL Nasal Spray (Narcan®) Prefilled syringe: 0.4 mg/mL 2 mg/2 mL	✔
Combination Product			
Buprenorphine/naloxone‖ (Bunavail®, Suboxone®, Zubsolv®)	Opioid dependence, treatment induction† (Suboxone® film); opioid dependence, treatment maintenance†	Buccal film (Bunavail®): 2.1/0.3 mg 4.2/0.7 mg 6.3/1 mg Sublingual film (Suboxone®): 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg Sublingual tablet (Zubsolv®): 1.4/0.36 mg 5.7/1.4 mg	✔

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependance, but can be used for maintenance treatment in patients who cannot tolerate the presence of naloxone.
† As part of a complete treatment plan to include counseling and psychosocial support.
‡As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.
§As manifested by respiratory and/or central nervous system depression.
‖Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Buprenorphine and buprenorphine/naloxone significantly improve many different outcomes for patients with opioid dependence compared to placebo and no treatment, but are generally found to not be significantly different from one another.[22-32,43-50]
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence.[24,33-40]
- A meta-analysis of 1,158 participants in 13 randomized trials compared oral naltrexone maintenance treatment to either placebo or non-medication. No difference was seen between the active and control groups in sustained abstinence or most other primary outcomes.
    - Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (relative risk [RR], 2.93; 95% CI, 1.66 to 5.18).[60]
- The efficacy and safety of Vivitrol® (naltrexone extended-release) for opioid dependence was evaluated in a 24-week, placebo-controlled randomized control trial. The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the naltrexone extended release group from Week 5 to Week 24.[61]
- Evzio® (naloxone injection), Narcan® (naloxone nasal spray), buprenorphine buccal film (Bunavail®) and buprenorphine/naloxone tablet (Zubsolv®) were FDA-approved via the 505(b)(2) pathway, which allows a manufacturer to compare a new product to a previously-approved drug (or drugs) and utilize data from studies that were performed on the reference drug. These medications have not been specifically studied in clinical trials evaluating their efficacy. Clinical and safety data for these medications is based on previously approved reference products.[5,7,9,10,62]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients.[15]
    - This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[15]
    - Naloxone is recommended as an appropriate emergency pharmacologic intervention for instances of opioid overdose.[16]
    - Naltrexone is generally reserved as an alternative regimen after buprenorphine-containing products and methadone.[17]
- Other Key Facts:
    - Buprenorphine is available as a sublingual tablet; buprenorphine/naloxone is available as a sublingual tablet (Zubsolv®), sublingual film (Suboxone®) and buccal film (Bunavail®); naltrexone is available as a tablet (ReVia®) and extended-release suspension for injection (Vivitrol®); and naloxone is available as a prefilled syringe, nasal spray (Narcan®) and auto-injector (Evzio®)[1-10]
    - According to the Drug Addiction Treatment Act of 2000, the ability to prescribe buprenorphine or buprenorphine/naloxone for the maintenance or detoxification of opioid dependence is limited to physicians who have obtained a waiver and a unique Drug Enforcement Agency number beginning with an X.[20]
    - Naltrexone extended-release suspension for injection is injected intramuscularly in the gluteal muscle every 4 weeks by a healthcare provider.[3]

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Therapeutic Class Overview
Long-acting Opioids

Therapeutic Class

- **Overview/Summary:** As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 1.[1-19] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication.[20] Currently, long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[20] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[20] Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

  Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[21]

  Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[21] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[22]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[22]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[22,23]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[24]

According to the FDA abuse and misuse of prescription opioid products has created a serious and growing public health problem. The FDA considers the development of abuse-deterrent products a priority. As outlined in their guidance for evaluation and labeling, “abuse-deterrent properties” are defined as those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse. The FDA elected to use the term “abuse-deterrent” rather than “tamper-resistant” because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. The FDA has provided several categories for abuse-deterrent formulations. Categories include physical/chemical barriers, agonist/antagonist combinations, aversion (adding a product that has an unpleasant effect if manipulated or is used at a higher than recommended dose), delivery systems, new molecular entities/prodrugs, a combination of these methods, or a novel approach (encompasses approaches or technologies not currently captured in previous categories).[25]

Buprenorphine buccal film is formulated using bioerodible mucoadhesive (BEMA®) technology. BEMA® is a film formulation that consists of a water-soluble polymer that adheres to the buccal mucosa. The film dissolves over approximately 30 minutes into the buccal mucosa, leaving behind no residual film. Delivery into the buccal mucosa enhances the bioavailability of buprenorphine, as it bypasses gastrointestinal absorption and first-pass metabolism.[1]

Hysingla ER® (hydrocodone extended-release [ER]) tablets are resistant to crushing, breaking and dissolution using different solvents, and the tablets still retain some ER properties after tampering. Attempts to dissolve the tablets result in the formation of a viscous gel, which may cause difficulty passing through a hypodermic needle.[5] In addition, the tablets appear to be associated with less “drug liking”

based upon results reported from two unpublished clinical abuse potential studies conducted in a small number of non-dependent recreational opioid users.[26]

There are currently two formulation of oxycodone ER which are considered abuse deterrent, OxyContin® and Xtampza ER®. OxyContin® utilizes the RESISTEC® technology that employs a combination of polymer and processing that gives tablet hardness, imparts viscosity when dissolved in aqueous solutions and resists increased drug release rate when mixed with alcoholic beverages.[10] Results from trials support that, the reformulated oxycodone ER is able to resist crushing, breaking, extraction and dissolution in small volumes using a variety of tools and solvents.[28-29] Xtampza ER® utilizes DETERx technology, which is designed to provide adequate pain control while maintaining its drug release profile after being subjected to common methods of manipulation, including chewing and crushing.[30,31]

Originally approved by the FDA in 2009, Embeda® (morphine sulfate/naltrexone hydrochloride) was voluntarily recalled from the market in March 2011 due to stability issues with the manufacturing process.[32] Subsequently, in November 2013, the FDA approved a manufacturing supplement for the product after the stability concerns were addressed through the manufacturing process. The abuse deterrent formulation of Embeda® (morphine sulfate/naltrexone hydrochloride) was granted FDA approval in October 2014, making it the third ER opioid analgesic to obtain this designation and the first among the morphine ER products.[33] Embeda® (morphine sulfate/naltrexone hydrochloride) capsules contain pellets consisting of morphine sulfate with a sequestered core of naltrexone hydrochloride at a ratio of 100:4.[18] If morphine sulfate/ naltrexone hydrochloride is crushed, chewed, or dissolved up to 100% of the sequestered naltrexone is released, reversing the effects of morphine, potentially precipitating withdrawal in opioid tolerant individuals, and increasing the risk of overdose and death.[33]

Table 1. Current Medications Available in the Therapeutic Class[1-19]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Belbuca®, Butrans®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Buccal Film (Belbuca®): 75 µg 150 µg 300 µg 450 µg 600 µg 750 µg 900 µg Transdermal patch: 5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour	-
Fentanyl (Duragesic®*)	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Transdermal system‡: 12 µg/hour§ 25 µg/hour 37.5 µg/hour 50 µg/hour 62.5 µg/hour 75 µg/hour 87.5 µg/hour 100 µg/hour	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Hydrocodone (Hysingla ER®, Zohydro ER®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Capsule, extended release (Zohydro ER®): 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg‡ Tablet, extended release (Hysingla ER®): 20 mg 30 mg 40 mg 60 mg 80 mg‡ 100 mg‡ 120 mg‡	-
Hydromorphone (Exalgo®*)	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Tablet, extended release: 8 mg‡ 12 mg‡ 16 mg‡ 32 mg‡	✔
Methadone (Dolophine®*, Methadose®*)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet). For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet). For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet).	Concentrate solution, oral (sugar-free available): 10 mg/mL Solution, oral: 5 mg/5 mL 10 mg/5 mL Tablet, extended release: 5 mg 10 mg Tablet for oral suspension: 40 mg	✔
Morphine sulfate (Avinza®*, Kadian®*, MS Contin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (biphasic capsule, capsule, tablet).	Capsule, biphasic extended release: 30 mg 45 mg 60 mg 75 mg 90 mg‡ 120 mg‡	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Capsule, extended release: 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡	
Oxycodone (OxyContin®*, Xtampza ER®)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults (all formulations) and in opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent (extended release tablet).¶	Capsule, extended release (Xtampza ER®): 9 mg 13.5 mg 18 mg 27 mg 36 mg Tablet, extended release (OxyContin®): 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡	✔ #
Oxymorphone (Opana® ER*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet extended release: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	✔
Tapentadol (Nucynta ER®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	250 mg	
Combination Products			
Morphine sulfate/ naltrexone (Embeda®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.‡	Capsule, extended release: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg‡	-
Oxycodone/ Acetaminophen (Xartemis XR®)	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate	Biphasic tablet, extended release: 7.5 mg/325 mg	-

*Generic is available in at least one dosage form or strength.
†Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.
#Generic availability is sporadic and does not include all strengths.
¶ A single dose of OxyContin® or Xtampza ER® >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.

Evidence-based Medicine

- Food and Drug Administration (FDA) approval of hydrocodone ER tablets (Hysingla ER®) was evaluated in an unpublished randomized double-blind, placebo controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain. Patients received either hydrocodone ER 20 to 120 mg tablets or matching placebo in a 1:1 ratio. There was a statistically significant difference in the weekly average pain scores at week 12 between the hydrocodone ER and placebo groups with a least square mean (standard deviation [SD]) difference of -0.53 (0.180) (95% confidence interval [CI], -0.882 to -0.178; P=0.0016). There were also significant improvements in proportion of responders, and Patient's Global Impression of Change scores.[5,36]
- The efficacy and safety of buprenorphine buccal film was evaluated in three phase III clinical trials. However one of the clinical trials, which is currently not published, did not show a significant difference between buprenorphine and placebo.[1] The other two studies evaluated patients who had a diagnosis of chronic low back pain in a randomized withdrawal design. The first study evaluated opioid-naïve patients while the second study evaluated opioid-experienced patients. The double-blind treatment phase for both studies was 12 weeks.[1,38,39] In the first study, the increase in mean (standard deviation [SD]) pain intensity scores on the NRS from baseline to week 12 for buprenorphine buccal film (0.94 [1.85]) was significantly lower than that of patients who received placebo (1.59 [2.04]; P=0.0012).[38] The increase in mean (SD) pain intensity scores on the NRS from baseline to week 12 for buprenorphine buccal film was significantly less than that of placebo (0.88 [1.79] versus 1.92 [1.87], respectively; P<0.00001).[39]
- The effectiveness of fentanyl in relieving pain appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[49-51]
- A trial comparing hydrocodone ER capsules to placebo in patients with moderate to severe chronic low back pain demonstrated hydrocodone ER had a lower mean change from baseline in pain intensity scores compared to placebo at 12 weeks (P=0.008). In addition, there was a significantly

higher amount of treatment responders in the hydrocodone ER group compared to the placebo group (P<0.001) at the end of treatment, and subject global assessment of medication scores increased from baseline significantly in the hydrocodone ER group compared to placebo (P<0.0001).[52]

- In one trial, hydromorphone ER demonstrated greater efficacy in the treatment of lower back pain with regard to reducing pain intensity (P<0.001) and pain scores (P<0.01) compared to placebo.[53] In a noninferiority analysis of a hydromorphone ER compared to oxycodone ER, two agents provided similar pain relief in the management of osteoarthritic pain.[54]
- Methadone has demonstrated a greater efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[58,59]
- A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate ER) and MS Contin® (morphine sulfate ER) significantly reduced pain from baseline (P≤0.05 for both). Both treatments also reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each treatment significantly improved certain sleep parameters compared to placebo.[61] In a crossover trial, morphine sulfate (MS Contin®) was compared to fentanyl transdermal systems, and more patients preferred fentanyl transdermal systems (P<0.001), and reported on average, lower pain intensity scores than morphine sulfate phase (P<0.001).[62]
- Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[32]
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[65]
- Oxycodone ER (OxyContin®) has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.[66-68] For the treatment of cancer pain, no significant differences were observed between oxycodone ER and morphine sulfate ER in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate ER (P=0.01), and the incidence of nausea and sedation were similar between treatments.[69]
- The FDA-approval of oxycodone ER (Xtampza ER®) was based upon an enriched-enrollment, randomized-withdrawal, double-blind, placebo-controlled, parallel group, study was conducted in patients with persistent, moderate-to-severe chronic lower back pain, with inadequate pain control from their prior therapy (n=740). Following the titration phase, 389 subjects met the study randomization criteria of adequate analgesia and acceptable tolerability and entered the randomized, double-blind maintenance phase. Patients were randomized at a ratio of 1:1 into a 12-week double-blind maintenance phase with their fixed stable dose of oxycodone ER (Xtampza ER® or matching placebo. There was a significant difference in pain reduction as assessed by average pain intensity favoring the oxycodone ER group when compared to placebo from randomization baseline to week 12 (0.29 vs. 1.85 ;P<0.0001).[71]
- Oxymorphone ER has produced similar mean daily pain intensity scores compared to both morphine sulfate and oxycodone ER for the treatment of chronic cancer pain. [72,73] The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone ER from morphine sulfate or oxycodone ER. No significant changes were observed in visual analog pain scores, quality of life domains, or quality of sleep in any of the treatment groups.[72] In another trial, oxymorphone ER demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.[74]
- In a 12-week active comparator and placebo-controlled trial, significant pain relief was achieved with tapentadol ER compared to placebo (least squares mean difference, - 0.7; 95% CI, -1.04 to -0.33) at week 12. The average pain intensity rating at endpoint with oxycodone ER was reduced significantly compared to placebo for the overall maintenance period (least squares mean difference vs placebo, -0.3), but was not significantly lower at week 12 (least squares mean, -0.3; P values not reported).[76] In a, placebo-controlled and active comparator trial in adults with moderate to severe low back pain, improvements in average pain intensity scores occurred with tapentadol ER and oxycodone ER relative to placebo (P<0.001).[77] Schwartz et al evaluated tapentadol ER among adults with painful diabetic peripheral neuropathy. The least squares mean change in average pain intensity at week 12

was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol ER group, indicating no change in pain intensity, (least squares mean difference, -1.3; 95% CI, -1.70 to -0.92; P<0.001).[75]

- The combination product oxycodone/acetaminophen's efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/APAP XR and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; P<0.001). The median time to perceptible pain relief for oxycodone/APAP XR was 33.56 minutes vs 43.63 minutes for placebo (P=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/APAP XR group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (P<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/APAP XR versus 27.2% for placebo (P<0.0001).[83]
- Methadone is the only long-acting narcotic that is Food and Drug Administration-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[84]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The current clinical guidelines regarding the use of opioids recognize their established efficacy in the treatment of moderate to severe pain. None of the available agents are distinguished from the others in the class, and recommendations for treatment are made for the class as a whole.[86-98]
    - Guidelines published by Centers for Disease Control and Prevention's (CDC) opioid use in the management of chronic pain recommend physicians start with immediate-release (IR) opioids and reserve ER formulations for severe, continuous pain that IR opioids cannot treat.[86]
    - Physicians should prescribe the lowest effective dose and carefully reassess benefits and risks when considering a dose of ≥50 morphine milligram equivalents (MME) while avoiding increasing opioid doses to ≥90 MME unless justified.[86]
    - Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness. ER products are generally similar and selection should be based on clinical or patient-specific factors.[87]

- Other Key Facts:[1-19]
    - Products currently available as a generic include fentanyl patches, hydromorphone ER tablets, methadone (all formulations), morphine ER (all formulations), oxycodone ER tablets and oxymorphone ER tablets.
    - There are currently several abuse deterrent ER opioids approved by the FDA. These include buprenorphine sublingual film (Belbuca®), oxycodone ER (OxyContin®, Xtampza ER®) and hydrocodone ER (Zohydro ER®, Hysingla ER®) as well as morphine sulfate/naltrexone (Embeda®).
    - Oxymorphone ER (Opana ER®) and hydromorphone ER (Exalgo®) have also been formulated with abuse deterrent properties, however they are classified as abuse deterrent by the FDA.
    - All long-acting opioids are pregnancy category C, with the exception of oxycodone.
    - Only fentanyl transdermal system (age 2 to 17 years) and oxycodone ER tablets (age 11 and older) are approved for use in children
    - Tapentadol is contraindicated with monoamine oxidase inhibitors; although, caution should be used when used in combination with any long-acting opioid.
    - Oxymorphone is contraindicated in severe hepatic disease.

- Methadone and buprenorphine have been implicated in QT prolongation and serious arrhythmias, use caution in patients at increased risk of QT prolongation.
- Frequency of dosing varies by agent:
  - Buprenorphine patch: once every seven days
  - Fentanyl transdermal system: once every 72 hours
  - Hydromorphone ER (Exalgo®), hydrocodone ER (Hysingla ER®) and morphine ER (Avinza®): once daily
  - Morphine ER (Kadian®) and morphine/naltrexone (Embeda®): once or twice daily
  - Morphine ER (MS Contin®) and all methadone formulations: twice or three times daily
  - All remaining long-acting agents: twice daily
- Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose.
  - Avinza® (morphine): max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]
  - Xartemis XR (oxycodone/acetaminophen): max dose is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day[19]
- Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18]
  - Morphine ER capsules (Avinza®, Kadian®), morphine/naltrexone capsules (Embeda®) and oxycodone ER capsules (Xtampza ER®) can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,15,18]
  - Kadian® pellets can also be placed in water and used through a gastrostomy tube.
  - Xtampza® may be opened and administered through a gastrostomy or nasogastric tube.
  - Avinza®, Kadian®, and Embeda® pellets should not be used thorough a nasogastric tube.
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Therapeutic Class Overview
Phosphorus Depleters

Therapeutic Class

- **Overview/Summary:** Hyperphosphatemia, an important and inevitable clinical consequence of advanced stages of chronic kidney disease (CKD), requires appropriate management due to the risk for secondary hyperparathyroidism and cardiovascular disease. Persistent or chronic hyperphosphatemia, along with an elevated calcium times phosphorus (CaxP) product, is associated with an increased risk of vascular, valvular and other soft-tissue calcification in patients with CKD. The two principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and the administration of phosphorus binders (or phosphorus depleters). When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphorus binders is recommended. There are several different phosphorus binders that are currently available; however, the class can be divided into two subcategories: calcium- and non-calcium-containing products.[1-4] In general, calcium-containing phosphorus binders (Eliphos®, PhosLo®, Phoslyra®) are associated with higher serum calcium and lower serum parathyroid hormone levels compared to the non-calcium-containing products.[5-7] Increased serum calcium levels leads to hypercalcemia and also increases the risk of vascular calcification and arterial disease in CKD patients.[4] As a result, these products are typically avoided in CKD patients with hypercalcemia or severe vascular calcification.[2-4] The available non-calcium-containing phosphorus binders include sevelamer, available in two salt forms (hydrochloride [Renagel®] and carbonate [Renvela®]), lanthanum carbonate (Fosrenol®), ferric citrate (Auryxia®) and sucroferric oxyhydroxide (Velphoro®).[8-10] These products are typically reserved for use in CKD patients with hypercalcemia, or as adjunct to a regimen supplying the maximum allotted dose of elemental calcium from calcium-containing phosphorus binders.[1-4] The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a new, buffered formulation was created. The newer, sevelamer carbonate formulation will most likely be thought of as the preferred formulation of sevelamer because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products.[4]

Table 1. Current Medications Available in the Class[5-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Calcium acetate (Eliphos®*, PhosLo®*, Phoslyra®)	Control hyperphosphatemia in end stage renal failure. Reduce Phosphate with End Stage renal disease (Phoslyra®).	Capsule: 667 mg Oral solution: 667 mg/5 mL Tablet: 667 mg	✔
Ferric citrate (Auryxia®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Tablet: 210 mg	
Lanthanum carbonate (Fosrenol®)	Reduce phosphate with end stage renal disease.	Tablet, chewable: 500 mg 750 mg 1,000 mg Oral Powder: 750 mg 1,000 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Sevelamer carbonate (Renvela®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Powder for oral suspension: 0.8 g 2.4 g Tablet: 800 mg	-
Sevelamer hydrochloride (Renagel®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.†	Tablet: 400 mg 800 mg	-
Sucroferric oxyhydroxide (Velphoro®)	Control serum phosphorus in patients with chronic kidney disease on dialysis.	Tablet, chewable: 500 mg	-

*Generic available in at least one dosage form or strength.
† The safety and efficacy of sevelamer hydrochloride in chronic kidney disease patients who are not on dialysis have not been studied.

Evidence-based Medicine

- The available evidence supports the hypothesis that all of the phosphorus binders (or phosphorus depleters) are efficacious in controlling serum phosphorus levels.[13-54] In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been established, and most clinical trials evaluate surrogate endpoints. In addition, due to ethical concerns regarding a prolonged lack of appropriate treatment, most trials evaluating the newer phosphorus binders against placebo have been short term, with longer trials using calcium-containing binders as the comparator.[1]
- No prospective trials have specifically examined the benefits of targeting different phosphorus levels to determine the effect on patient-level endpoints. Epidemiological data suggests that phosphorus levels above the normal range are associated with increased morbidity and mortality.[1]
- The results of a recent Cochrane Systematic Review by Navaneethan and colleagues demonstrated that there was no statistically significant reduction in all-cause mortality when patients received sevelamer hydrochloride compared to those receiving calcium-based phosphate binders (relative risk, 0.73; 95% confidence interval, 0.46 to 1.16). No comparison of lanthanum carbonate to calcium-containing salts was made.[47]
- Two meta-analyses have been published reviewing the clinical trials of the phosphate binders.[48,49] Tonelli et al compared sevelamer products to any other therapy or placebo in patients with ESRD, on dialysis or who had had a kidney transplant. The pooled analysis showed that phosphate levels with sevelamer was similar or slightly higher than with calcium-based phosphate binders by 0.12 mmol/L (95% CI, 0.05 to 0.19). However, the overall weighted mean difference in serum calcium was significantly lower with sevelamer therapy (0.10 mmol/L; 95% CI, −0.12 to −0.07).[48] Jamal et al evaluated all-cause mortality and compared calcium-based phosphate binders to non-calcium phosphate binders in patients with chronic kidney disease. The results of this meta-analysis showed that patients randomly assigned to non-calcium-based phosphate binders had a statistically significant 22% reduction in all-cause mortality compared with those randomly assigned to calcium-based phosphate binders (RR,0.78; 95% CI, 0.61 to 0.98). When non-randomized trials were added to the pooled analysis, the reduction in all-cause mortality was 13% (RR,0.87; 0.77 to 0.97) in favor of non-calcium-based phosphate binders.[49]
- The safety and efficacy of ferric citrate was established in two clinical trials.[50,51]
    - The demonstrated reductions from baseline to week four in mean serum phosphorus were significantly greater with 6 and 8 grams/day than with 1 gram/day dose (-1.3 mg/dL and -1.5 mg/dL placebo-corrected differences, respectively; P<0.0001).[50]
    - Patients were eligible to enter a four-week, placebo-controlled withdrawal phase if they had been receiving ferric citrate during the 52-week study. During the placebo-controlled period,

the serum phosphorus concentration rose by 2.2 mg/dL in patients receiving placebo compared to patients who remained on ferric citrate (-0.24 mg/dL vs 1.79 mg/dL; P<0.001).[51]

- The safety and efficacy of sucroferric oxyhydroxide was demonstrated in two randomized clinical trials, one six-week, open label, active controlled dose-finding study and one 55-week, active controlled, parallel group, dose-titration and extension study.[12,52-54]
    - In the phase II, dose-finding study, at six weeks, sucroferric oxyhydroxide decreased serum phosphorus compared to baseline in the 5.0, 7.5, 10.0 and 12.5 grams/day arms but not the 1.25 grams/day arm (P≤0.016). A similar decrease to sevelamer hydrochloride was seen in the 5.0 and 7.5 grams/day arms.[1,52]
    - In the after the dose-titration study, serum phosphorus control was maintained with both sucroferric oxyhydroxide and sevelamer throughout the extension study and the difference between groups was not statistically significant (P=0.14).[53,54]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Currently available evidence supports the hypothesis that all of the phosphorus binders are efficacious in controlling serum phosphorus levels. Furthermore, it is generally accepted that no one product is effective and acceptable to every patient.[2,3]
    - Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on chronic kidney disease [CKD] Stage), there is currently no evidence to demonstrate that lowering phosphorus to a specific target range results in improved clinical outcomes in patients with CKD.
    - It is still reasonable to use phosphorus binders to lower phosphorus levels in CKD patients with hyperphosphatemia to prevent the development of secondary hyperparathyroidism and cardiovascular disease.[1]
    - Combination therapy, with multiple binders, may also be an option in order to control serum phosphorus levels while minimizing the side effects associated with any specific binder.[2,3]
    - Phosphorus binders should be utilized in patients with CKD Stages 3 to 5D who cannot adequately maintain serum phosphorus levels within the normal range with dietary phosphorus restriction.[1-3]
    - Choice of product should take into account the Stage of CKD, the presence of other components of CKD-Mineral and Bone Disorder, concomitant therapies and adverse event profiles.[1]
- Other Key Facts:
    - Currently, the calcium-containing products (Eliphos®, PhosLo®) are available generically in tablet and capsule formulations.
    - Calcium acetate (Phoslyra®) is available as an oral solution, and sevelamer carbonate (Renvela®) is available as oral powder for suspension.[7,10]
    - Lanthanum, and sevelamer carbonate/hydrochloride are contraindicated in patients with bowel obstruction, while calcium acetate is contraindicated in hypercalcemia[9-11]
    - Ferric citrate is contraindicated in iron overload syndromes.[8]

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Therapeutic Class Overview
Platelet Inhibitors

Therapeutic Class

- **Overview/Summary:** Platelet inhibitors play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. The agents in the class are Food and Drug Administration (FDA)-approved for a variety of indications including treatment and/or prevention of acute coronary syndromes (ACS), stroke/transient ischemic attack (TIA), and thrombocythemia. The platelet inhibitors are also indicated to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery. The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action.[1-9] One of the newest platelet inhibitors to be FDA-approved is vorapaxar (Zontivity®), which is indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD).[7] Vorapaxar (Zontivity®), is the first in a new class of antiplatelet agents called protease-activated receptor-1 (PAR-1) antagonists. It is a competitive and selective antagonist of PAR-1, the major thrombin receptor on human platelets. It works by inhibiting thrombin-induced platelet aggregation and thus blood clot formation. In addition, vorapaxar is not a prodrug and does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other agents.[7] Vorapaxar is available for once-daily dosing in combination with other antiplatelet agents (either clopidogrel and/or aspirin). Clopidogrel and prasugrel are administered once-daily, while ticagrelor is dosed twice daily.[2,4,5]

Table 1. Current Medications Available in the Therapeutic Class[1-9]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
Single-Entity Agents			
Anagrelide (Agrylin®*)	Treatment of thrombocytopenia associated with myeloproliferative disorders†	Capsule: 0.5 mg 1 mg	✔
Aspirin extended-release (Durlaza®)	Reduce the risk of death and myocardial infarction in patients with chronic coronary artery disease as well as to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or transient ischemic attack	Capsule: 162.5 mg	-
Clopidogrel (Plavix®*)	Recent myocardial infarction, recent stroke, or established peripheral arterial disease, reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome‡	Tablet: 75 mg 300 mg	✔
Dipyridamole (Persantine®*)	Prevention of postoperative thromboembolic complications of cardiac valve replacement§	Tablet: 25 mg 50 mg 75 mg	✔
Prasugrel (Effient®)	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are being managed with percutaneous coronary intervention‖	Tablet: 5 mg 10 mg	-
Ticagrelor (Brilinta®)	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome¶; reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome or a history of myocardial infarction	Tablet: 60 mg 90 mg	-
Ticlopidine	Reduce the incidence of subacute stent	Tablet:	✔

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
(Ticlid®*)	thrombosis in patients undergoing successful coronary stent implantation#, reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke	250 mg	
Vorapaxar (Zontivity®)	Reduce the risk of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease: Tablet: 2.08 mg QD in combination with other antiplatelet agents (clopidogrel and/or aspirin)	Tablet: 2.08 mg	-
Combination-Products			
Aspirin/ extended-release dipyridamole (Aggrenox®)	Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	Capsule: 25/200 mg	✔

*Generic available in at least one dosage form or strength.
†To reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events.
‡For patients with non-ST-segment elevation acute coronary syndrome, including patients who are to be managed medically and those who are to be managed with coronary revascularization, and for patients with ST-elevation myocardial infarction.
§As adjunct to coumarin anticoagulants.
‖Patients who are to be managed with percutaneous coronary intervention as follows: patients with unstable angina or non-ST-elevation myocardial infarction and patients with ST-elevation myocardial infarction when managed with primary or delayed percutaneous intervention.
¶Patients with unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction.
#As adjunct to aspirin.

Evidence-based Medicine

- Clopidogrel, Food and Drug Administration-approved in 1997, has been the principle platelet inhibitor for several years as the clinical data supporting its use is well established.[11-16]
- The RAPID Primary PCI study compared prasugrel to ticagrelor in patients who had a ST-Segment elevation myocardial infarction (STEMI) who were to undergo percutaneous coronary intervention (PCI). Prasugrel was noninferior as compared with ticagrelor in terms of residual platelet reactivity two hours after the loading dose (P=0.207).[17]
- Approval of prasugrel for use in ACS was based on the clinical evidence for safety and efficacy derived from the TRITON-TIMI 38 study (N=13,608). Within the study, prasugrel was significantly more effective compared to clopidogrel in reducing ischemic events in patients with ACS who underwent percutaneous coronary intervention. Prasugrel did not demonstrate a mortality benefit and a significantly higher rate of major, minor, life-threatening, and fatal bleeding events was observed with prasugrel.[18]
    - Of note, a benefit with prasugrel was not observed in certain patient subgroups within TRITON-TIMI 38, specifically those who were ≥75 years of age, those weighing <60 kg, and those with a past history of stroke or TIA.
- The approval of ticagrelor for use in ACS was based on the clinical evidence for safety and efficacy derived from the PLATO study. Within the trial, hospitalized patients with documented ACS, with or without ST-elevation, were randomized to either ticagrelor or clopidogrel (N=18,624). After 12 months of treatment, ticagrelor was significantly more effective compared to clopidogrel in reducing the primary composite endpoint of cardiovascular death, MI, or stroke; without increasing the risk of major bleeding. Ticagrelor demonstrated a mortality benefit compared to clopidogrel.[19]
    - There was no difference in quality of life scores between the clopidogrel group and the ticagrelor group in hospitalized patients with ACS.[20]

- Brener et al evaluated prasugrel-treated patients to clopidogrel-treated patients with STEMI. The prasugrel group had higher rates of procedural success (P=0.03), TIMI 3 flow (P=0.06), and lower corrected TIMI frame counts (P=0.008).[21]
- Approval of vorapaxar was based on the results of the TRA2ºP-TIMI 50 trial. The composite of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR) in post-MI or PAD patients without a history of stroke or TIA the vorapaxar group showed a significant 17% relative risk reduction over the three years of the study (HR, 0.83; 95%CI, 0.76 to 0.90; P<0.001).[22]
    - Patients who had a previous stoke were removed from the study after 24 month follow-up assessments. Among the patients with a history of stroke, the rate of intracranial hemorrhage in the vorapaxar group higher (P<0.001), without a history of stroke and was significantly increased as compared with the group without a prior stroke (P=0.049). [22]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Use of the platelet inhibitors, as monotherapy or combination therapy, is based on the specific clinical indication and the patient's risk for thromboembolic events.[23-43]
    - According to the 2016 guideline update from the American College of Cardiology and American Heart Association, aspirin therapy should be continued indefinitely in patients with coronary artery disease. In those treated with dual antiplatelet therapy (DAPT), the daily aspirin dose should be 81 mg (range 75 to 100 mg).[42]
        - Patients with stable ischemic heart disease treated with DAPT after bare metal stent (BMS) implantation, should be given $P2Y_{12}$ inhibitor therapy with clopidogrel for a minimum of one month and for a minimum of six months following drug-eluting stent (DES) implantation.
        - Patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation should be given therapy with a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel or ticagrelor) for at least 12 months.
        - Prasugrel should not be administered to patients with a prior history of stroke or TIA.
        - It may be reasonable to contine DAPT for longer than the above recommendations in patients who have tolerated DAPT without a bleeding complication and who are not considered at a high risk for bleeding.
    - Antiplatelet therapy (aspirin plus extended-release [ER] dipyridamole or clopidogrel >aspirin) is recommended for long-term secondary prevention in patients with an acute ischemic stroke who are not receiving thrombolysis. Combination aspirin plus dipyridamole ER is recommended over aspirin, and clopidogrel is suggested over aspirin. Dual antiplatelet therapy should be used with caution and is favored in patients who have had a recent acute MI, other ACS, or recently placed coronary stent.[24,25]
    - According to the 2012 guideline on Antithrombotic Therapy and Prevention of Thrombosis by the American College of Chest Physicians, dual therapy aspirin with clopidogrel or ticagrelor or prasugrel monotherapy is recommended in the first year following ACS in patients regardless of PCI status.[24]
        - The guideline recommends ticagrelor plus low-dose aspirin over clopidogrel plus low-dose aspirin in patients post-ACS independent of whether PCI has been conducted.[24]
    - The 2013 guidelines for managing patients with STEMI by American College of Cardiology Foundation and American Heart Association recommend clopidogrel, prasugrel or ticagrelor for one year following PCI, without recommendation for one antiplatelet drug over another.[28]
    - The 2011 and 2015 European Society of Cardiology guideline for the management of ACS in patients presenting without persisting ST-elevation recommends ticagrelor first-line in patients at moderate to high risk of ischemic events, regardless of treatment strategy and including those pretreated with clopidogrel.[27,43]
        - If coronary anatomy is known and PCI is planned, prasugrel is recommended.
        - Clopidogrel is recommended in patients who cannot receive prasugrel or ticagrelor.

- The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for percutaneous intervention recommends clopidogrel, prasugrel, and ticagrelor as treatment options.[28]
  - Treatment with all agents should be continued for at least one year.

- Other Key Facts:
  - Anagrelide, aspirin/dipyridamole, clopidogrel, dipyridamole and ticlopidine are available generically.

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Therapeutic Class Overview
Proton Pump Inhibitors

Therapeutic Class

- **Overview/Summary:** The proton-pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally considered the most potent acid suppressants available.[1] Parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to several stimuli. Within the parietal cell, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K+) for hydrogen ions (H+) resulting in a lower gastric pH. The PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. The PPIs can only inhibit proton pumps that are actively secreting acid.[1] Approximately 70 to 80% of the proton pumps will be active following a meal.[2] As a result, single doses of PPIs will not completely inhibit acid secretion and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. With regular dosing, maximal acid suppression occurs in three to four days.[1-3]

  There are currently a number of PPIs available on the market in a variety of formulations. The PPIs include dexlansoprazole (Dexilant®, Dexilant SoluTab®), esomeprazole (Nexium®, Nexium® 24HR), lansoprazole (Prevacid®, Prevacid SoluTab®, Prevacid® 24HR), omeprazole (Prilosec®, Prilosec OTC®, Zegerid®, Zegerid OTC®), pantoprazole (Protonix®) and rabeprazole (Aciphex®, Aciphex Sprinkle®), of which esomeprazole, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, pantoprazole and rabeprazole are available generically in at least one dosage strength or formulation. Esomeprazole strontium was Food and Drug Administration (FDA)-approved in August 2013 without a proprietary name; it was approved based on bioequivalence of esomeprazole strontium 24.65 mg and 49.3 mg delayed-release capsules to esomeprazole magnesium 20 and 40 mg delayed-release capsules. No other reference to esomeprazole strontium will be made in this review as all data is similar between esomeprazole magnesium and esomeprazole strontium.[4-17] In addition, lansoprazole, esomeprazole and omeprazole are available over-the-counter in a variety of formulations. All of the PPIs are substituted benzimidazole derivatives and are structurally related. Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole contains only the *S*-isomers of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer. The PPIs primarily differ in their pharmacokinetic and pharmacodynamic properties in addition to their formulations. While some differences have been reported in head-to-head studies directly comparing the PPIs, the magnitude of these differences is generally small and the clinical significance has not been established.[3] When administered in equivalent dosages the PPIs have generally demonstrated a comparable efficacy to one another. Dexlansoprazole, the enantiomer of lansoprazole, is the first PPI with a dual delayed-release formulation designed to provide two separate releases of medication. It contains two types of enteric-coated granules resulting in a concentration-time profile with two distinct peaks: the first peak occurs one to two hours after administration, followed by a second peak within four to five hours. In addition, it can be taken regardless of meals.[16] All approved indications listed in Table 1 are for the prescription products unless otherwise specified.

Table 1. Current Medications Available in the Therapeutic Class[4-17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Dexlansoprazole (Dexilant®)	Treatment of erosive esophagitis. Maintaining healing of erosive esophagitis. Treatment of symptomatic gastroesophageal reflux disease.	Delayed-release capsule: 30 mg 60 mg	-
Esomeprazole magnesium (Nexium®)	Treatment of erosive esophagitis. Maintaining healing of erosive esophagitis.†	Delayed-release capsule: 20 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	Treatment of symptomatic gastroesophageal reflux disease.† *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence.†§ Risk reduction of nonsteroidal antiinflammatory drug-associated gastric ulcer.† Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.†	40 mg Delayed-release suspension: 2.5 mg 5 mg 10 mg 20 mg 40 mg	
Esomeprazole sodium (Nexium IV®*)	Treatment of erosive esophagitis.	Powder for injection: 20 mg 40 mg	✔
Lansoprazole (Prevacid®*, Prevacid SoluTab®*)	Treatment of erosive esophagitis. Maintaining healing of erosive esophagitis. Treatment of symptomatic gastroesophageal reflux disease *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence.§ Treatment of active duodenal ulcers. Maintenance of healing duodenal ulcers. Treatment of active, benign gastric ulcer. Healing of nonsteroidal anti-inflammatory drug-associated gastric ulcer. Risk reduction of nonsteroidal antiinflammatory drug-associated gastric ulcer. Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome. Treatment of frequent heartburn for up to 14 days.¶	Delayed-release capsule: 15 mg 30 mg Delayed-release disintegrating tablet: 15 mg 30 mg	✔
Omeprazole (Prilosec®*)	Treatment of erosive esophagitis. Maintaining healing of erosive esophagitis. Treatment of symptomatic gastroesophageal reflux disease. *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence.§	Delayed-release capsule: 10 mg 20 mg 40 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	Treatment of active duodenal ulcers. Treatment of active, benign gastric ulcer. Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.		
Omeprazole magnesium (Prilosec®*)	Treatment of erosive esophagitis. Maintaining healing of erosive esophagitis. Treatment of symptomatic gastroesophageal reflux disease. *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence.§ Treatment of active duodenal ulcers. Treatment of active, benign gastric ulcer. Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome. Treatment of frequent heartburn for up to 14 days.¶	Delayed-release suspension: 2.5 mg 10 mg	✔
Omeprazole with sodium bicarbonate (Zegerid®*)	Treatment of symptomatic gastroesophageal reflux disease. Treatment of active, benign gastric ulcer. Treatment of active duodenal ulcers. Maintaining healing of erosive esophagitis. Risk reduction of upper gastrointestinal bleeding in critically ill patients.‖ Treatment of frequent heartburn for up to 14 days.¶	Capsule: 20 mg/1100 40 mg/1100 Powder for oral suspension: 20 mg/1680 40 mg/1680	✔
Pantoprazole (Protonix®*, Protonix IV®)	Treatment of erosive esophagitis. Maintaining healing of erosive esophagitis. Treatment of symptomatic gastroesophageal reflux disease.‡ Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.	Delayed-release suspension: 40 mg Delayed-release tablet: 20 mg 40 mg Powder for injection: 40 mg	✔
Rabeprazole (Aciphex®*)	Treatment of erosive esophagitis	Delayed-release tablet:	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	Maintaining healing of erosive esophagitis. Treatment of symptomatic gastroesophageal reflux disease. *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence.§ Treatment of active duodenal ulcers Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.	20 mg Delayed-release capsules: 5 mg 10 mg	

OTC=over the counter
*Generic available in at least one dosage form or strength.
†Oral formulations only.
‡Intravenous formulation indicated for treatment of gastroesophageal reflux disease associated with a history of erosive esophagitis.
§As triple therapy in combination with amoxicillin and clarithromycin (esomeprazole, lansoprazole, omeprazole and rabeprazole) or dual therapy with amoxicillin (lansoprazole) or clarithromycin (omeprazole).
‖ Zegerid® powder for oral suspension only.
¶Over-the-counter formulation only.

Evidence-based Medicine

- Clinical trials have consistently demonstrated that PPIs are highly effective in treating, providing symptomatic relief and preventing relapse in gastric acid disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease.[18-43]
- Meta-analyses and head-to-head trials have demonstrated comparable healing rates, maintenance of healing or symptomatic relief of GERD between lansoprazole, omeprazole, pantoprazole and rabeprazole.[18-23]
- The results of several meta-analyses and clinical trials show that esomeprazole may provide higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole and pantoprazole at four and eight weeks; however, the differences between treatments were generally small and the clinical significance of such differences has not been established.[18,20,24-29]
- Dexlansoprazole has been shown to significantly improve control of heartburn symptoms, nighttime heartburn symptoms, and healing of erosive esophagitis compared to placebo.[30-32] Head to head studies comparing dexlansoprazole to other PPIs are limited.
- Meta-analyses and head-to-head trials comparing PPIs for the treatment of peptic ulcer disease with *Helicobacter pylori* have shown comparable rates of eradication when paired with comparable antibiotic regimens.[33-41] One small trial reported higher eradication rates for patients treated with esomeprazole compared to pantoprazole.[42] In a recent meta-analysis by McNicholl et al, both esomeprazole- and rabeprazole-based *Helicobacter pylori* regimens were considered to be more effective with regard to eradication rate compared to traditional PPIs (lansoprazole, omeprazole and pantoprazole).[43]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Acid suppression is the mainstay of GERD therapy and PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients. Histamine H_2-receptor antagonists (H_2RAs) given in divided doses may be effective in some patients with less severe GERD; however, they are less effective compared to the PPIs.[44,45]
    - Twice-daily PPI therapy is recommended in patients with an inadequate symptom response to once-daily PPI therapy. There is no evidence of improved efficacy by adding a nocturnal dose of an H_2RA to twice-daily PPI therapy.[44,45]

- In the management of dyspepsia, treatment with a PPI for four to eight weeks as an initial therapy option is recommended in dyspeptic patients ≤55 years of age without alarm features (e.g., bleeding, dysphagia, family history of gastrointestinal cancer, weight loss) and where *Helicobacter pylori* prevalence is low (<10%).[46]
- The recommended primary therapies for *Helicobacter pylori* infection include a PPI, clarithromycin and amoxicillin or metronidazole (clarithromycin-based triple therapy) for 14 days for eradication rates of 70 to 85%. Alternatively, a regimen of a PPI or H_2RA, bismuth, metronidazole and tetracycline (bismuth-based quadruple therapy) for 10 to 14 days produces eradication rates of 75 to 90%.[47]
- The currently available PPIs perform comparably when used in the triple therapy regimens. A meta-analysis of 13 studies suggests that twice daily dosing of a PPI (lansoprazole, omeprazole, pantoprazole and rabeprazole) in clarithromycin-based triple regimens is more effective than once-daily dosing.[47]
- Attempts to eliminate esophageal acid exposure (PPIs in doses greater than once-daily, esophageal pH monitoring to titrate PPI dosing, or antireflux surgery) for the prevention of esophageal adenocarcinoma is not recommended.[48]

- Other Key Facts:
  - Currently, esomeprazole, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, pantoprazole and rabeprazole are available generically in at least one dosage strength or formulation.[4]
  - Furthermore, lansoprazole, esomeprazole, omeprazole, omeprazole magnesium and omeprazole with sodium bicarbonate are available over-the-counter in a variety of formulations.[4]
  - Dexlansoprazole was formerly known by the brand name Kapidex® but has since been changed to Dexilant®.[49]

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Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

Therapeutic Class

- **Overview/Summary:** The oral pulmonary hypertension agents are Food and Drug Administration (FDA)-approved for the treatment of patients with World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH); however, there are differences in the study populations for which their FDA-approvals were based.[1-10] Typically, PAH is characterized by an elevated pulmonary arterial pressure and an increased pulmonary vascular resistance leading to right-sided heart failure. The prevalence of PAH is estimated to be 15 cases/million adults. The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy.[11] The WHO classifies pulmonary hypertension into five groups. WHO Group I encompasses PAH, including idiopathic PAH, familial PAH, and PAH associated with connective tissue disorders, portal hypertension, human immunodeficiency virus infection, drugs and toxins and other disorders that affect the small pulmonary muscular arterioles. Patients with PAH are assessed based on the WHO and New York Heart Association (NYHA) functional classes that describe the disease severity from little (class I) to significant (class IV) impact on patient physical activity.[12] Five classes of medications are currently FDA-approved for the treatment of WHO Group I PAH: prostacyclin analogues (prostanoids), prostacyclin receptor agonists, endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators.[1-10,13] In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation.[11] The prostanoids act as vasodilators and platelet aggregation inhibitors. Iloprost (Ventavis®), treprostinil (Tyvaso®) and treprostinil diolamine (Orenitram®) are the only prostanoids currently available orally; however, other products are available for intravenous or subcutaneous administration.[1-3] Selexipag (Uptravi®) is a prostacyclin receptor agonist, which acts via the same receptor as the prostanoids, but is structurally distinct from prostacyclin.[4] Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B.[5-7,11] Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance.[5,6] The ERAs, ambrisentan (Letairis®), bosentan (Tracleer®) and macitentan (Opsumit®) competitively bind to both receptors with different affinities. Ambrisentan is highly selective for the ET_A receptor, while bosentan is slightly more selective for the ET_A receptor than the ET_B receptor. Macitentan is associated with a high affinity and sustained occupancy of both ET receptors. However, the clinical significance of receptor affinities of the ERAs has not been established.[5-7] In patients with PAH there is also an impaired release of nitric oxide by the vascular endothelium thereby reducing cyclic guanosine monophosphate (cGMP) concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP.[11] The PDE-5 inhibitors, sildenafil (Revatio®) and tadalafil (Adcirca®), increase the concentrations of cGMP resulting in relaxation of pulmonary vascular bed.[8,9] Soluble guanylate cyclase (sGC) is an enzyme present in the cardiopulmonary system and is the receptor for nitric oxide. When bound to nitric oxide, sGC catalyzes synthesis of cGMP, which plays a role in the regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Riociguat (Adempas®) stimulation of this nitric oxide-sGC-cGMP pathway leads to increased generation of cGMP and thus, vasodilation.[10]

Table 1. Current Medications Available in Therapeutic Class[1-9,12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Ambrisentan (Letairis®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.*	Tablet: 5 mg 10 mg	-
Bosentan (Tracleer®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.†	Tablet: 62.5 mg 125 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Iloprost (Ventavis®)	Treatment of PAH (WHO Group I) to improve a composite endpoint consisting of exercise tolerance symptoms (NYHA class) and lack of deterioration.‡	Ampule for inhalation: 10 µg/mL 20 µg/mL	-
Macitentan (Opsumit®)	Treatment of PAH (WHO Group I) to delay disease progression.‖#	Tablet: 10 mg	-
Riociguat (Adempas®)	Treatment of PAH (WHO Group I) to improve exercise ability, improve WHO functional class and delay clinical worsening and treatment of persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH to improve exercise capacity.‖	Tablet: 0.5 mg 1 mg 1.5 mg 2 mg 2.5 mg	-
Selexipag (Uptravi®, Uptravi Titration Pack®)	Treatment of PAH (WHO Group I) in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH and to improve exercise ability‡‡		
Sildenafil (Revatio®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.§‖	Tablet: 20 mg Vial for injection: 0.8 mg/mL Powder for oral suspension: 10 mg/mL	✔
Tadalafil (Adcirca®)	Treatment of PAH (WHO Group I) to improve exercise ability.¶	Tablet: 20 mg	-
Treprostinil (Tyvaso®)	Treatment of PAH (WHO Group I) to improve exercise ability. **	Ampule for inhalation: 0.6 mg/mL	-
Treprostinil (Orenitram®)	Treatment of PAH (WHO Group I) to improve exercise ability.††	Extended-release tablet: 0.125 mg 0.25 mg 1 mg 2.5 mg	-

CTEPH=Chronic Thromboembolic Pulmonary Hypertension, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization

*Studies establishing effectiveness included predominantly patients with World Health Organization (WHO) Functional Class II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (64%) or PAH associated with connective tissue diseases (32%).

†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

‡Studies establishing effectiveness included predominately patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%), PAH associated with connective tissue diseases (23%).

§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

‖ Approved for use in adults only.

¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

#Disease progression included death, initiation of intravenous or subcutaneous prostanoids or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).

** Studies included predominantly patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

††Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue diseases (19%).
‡‡ Studies included predominantly patients with NYHA class II or III symptoms and etiologies of idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%)

Evidence-based Medicine

- Randomized controlled trials have demonstrated the efficacy of the oral pulmonary arterial hypertension agents in increasing exercise capacity and improving World Health Organization and New York Heart Association functional class; however, no head to head trials have been conducted.[16-47]
- Only small studies evaluating the effect of combination therapy have been conducted, and statistically significant improvements have not consistently been demonstrated.[11,23,35,346,41, 43,45]
- Common adverse events in the prostanoids class are jaw pain, diarrhea, headache and flushing.[13] Endothelin receptor antagonists are associated with peripheral edema and elevated liver function tests. [13] The phosphodiesterase-5 inhibitors are generally well tolerated and common adverse effects include headache, flushing, and dyspepsia.[13] The most common adverse events associated with the soluble guanylate cyclase stimulators can be ascribed to the vasodilatory mechanism of action, including headache, dizziness, nausea and hypotension.[9]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Oral calcium-channel blockers (CCB) are recommended only for patients with positive acute vasodilator response to testing.[11,14,15]
    - Oral therapy with either a phosphodiesterase-5 inhibitor or an endothelin receptor antagonist or riociguat is recommended as first-line treatment in patients who are considered lower risk and are not candidates for CCBs.[11,14,15]
    - Use of inhaled or parenteral prostanoids should not be chosen as initial therapy for treatment naïve PAH patients with WHO functional class II symptoms or as second line agents for PAH patients with WHO functional class II symptoms who have not met their treatment goals.[14]
    - For WHO class III patients, addition of a parenteral or inhaled prostanoid to mono- or dual-oral therapy is recommended if rapid progression occurs, or there is poor clinical prognosis.[11,14]
    - Intravenous prostanoids are the preferred treatment in patients at higher risk and poor prognostic indexes.[11,14]
    - If a patient cannot or does not wish to use intravenous medications, they may use inhaled prostanoids and an endothelin receptor antagonist for higher risk or poorer prognostic indexes.[14]
    - Combining therapies with different mechanisms of action, either in sequential pattern or simultaneously at the beginning of treatment for the management of PAH is recommended.

- Other Key Facts:
    - Ambrisentan, bosentan, macitentan and riociguat are distributed through a restricted distribution program.[2,3,8,9]
    - Sildenafil tablet is the only oral pulmonary arterial hypertension agent that is available generically.
    - In August 2012, the prescribing information for sildenafil was updated to include a warning against the use of sildenafil in pediatric patients. This was due to increased mortality seen in long-term clinical trials that included pediatric patients.[6]

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Therapeutic Class Overview
Scabicides and Pediculicides

Therapeutic Class

- **Overview/Summary:** The agents indicated for the management of scabies and head lice are listed in Table 1. The skin and mucous membrane scabicides and pediculicides are approved to treat pediculosis and scabies.[1-10] Pediculosis is a transmissible infection, which is caused by three different kinds of lice depending on the location: head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*) and pubic region (*Phthirus pubis*). Pediculosis is often asymptomatic; however, itching may occur due to hypersensitivity to lice saliva.[11] Scabies is also a transmissible skin infection caused by the mite *Sarcoptes scabiei.* Mites burrow into the skin and lay eggs, which when hatched, will crawl to the skin's surface and begin to make new burrows. The most common clinical manifestation of scabies is itching, which is due to a hypersensitivity reaction to the mite or mite excrement.[12] When treating scabies and lice, the goal of therapy is to eradicate the parasite. Benzyl alcohol inhibits lice from closing their respiratory spiracles, which causes the lice to asphyxiate.[3] Crotamiton has scabicidal and antipruritic actions; however, the exact mechanism of action is unknown.[4] Lindane is a central nervous system stimulant, which causes convulsions and death of the arthropod.[1,2] Malathion is an organophosphate agent, which inhibits cholinesterase activity.[5] Permethrin disrupts the sodium channel current, which leads to delayed repolarization and paralysis of the arthropod.[1,2] Spinosad causes neuronal excitation, which leads to paralysis and death.[6] The suspension also contains an unspecified amount of benzyl alcohol. Retreatment with benzyl alcohol and permethrin is required after seven to 10 days to eradicate the infestation. The newest agent in the class ivermectin, is pediculicidal but not ovicidal and it is approved as a single application product only.[7] Lindane, malathion, permethrin, spinosad, and piperonyl butoxide and pyrethrins products are available generically, while permethrin, and piperonyl butoxide and pyrethrins products are also available over-the-counter.

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Benzyl alcohol (Ulesfia®)	Treatment of head lice	Lotion: 5% (227 g/bottle)	-
Crotamiton (Eurax®)	Treatment of scabies	Cream: 10% (2 oz/ tube) Lotion: 10% (2 oz/bottle, 16 oz/bottle)	-
Ivermectin (Sklice®)	Treatment of head lice	Lotion: 0.5% (4 oz/tube)	-
Lindane*	Treatment of head and pubic lice	Shampoo: 1% (2 oz/bottle)	✔
Malathion (Ovide®*)	Treatment of head lice	Lotion: 0.5% (2 oz/ bottle)	✔
Permethrin*† (Acticin®, Nix Complete Lice System®*†, Nix Crème Rinse®*†)	Treatment of head lice and scabies	Cream: 5% (2 oz/tube) Liquid: 1% (2 oz/bottle) Lotion: 1% (2 oz/bottle, 4	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		oz/bottle)	
Spinosad (Natroba®*)	Treatment of head lice	Topical Suspension: 0.9% (4 oz/bottle)	✔
Combination Products			
Piperonyl butoxide and pyrethrins*† (Licide Complete Lice Treatment Kit®*†, Pronto®*†, RID®*†)	Treatment of head, body and pubic lice	Gel: 4/0.33% (each kit) Shampoo: 4/0.33% (each kit) Solution: 4/0.33% (each kit)	✔

*Generic available in one dosage or strength.
†Over-the-counter product is available in at least one dosage form or strength.

Evidence-based Medicine

- In two, randomized, active-controlled trials in patients with an active head lice infestation, a greater proportion of patients were lice-free 14 days following treatment with spinosad alone compared to patients who received permethrin plus nit combing (P<0.001 for both trials).[13]
- The combined results of two identical, vehicle-controlled trials (N=765) in patients six months and older with head lice showed that significantly more patients treated with ivermectin lotion were lice-free on day two (94.9 vs 31.3%), day eight (85.2 vs 20.8%) and remained lice-free through day 15 (73.8 vs 17.6%; P<0.001 for each day) compared to the vehicle group.[14]
- In two studies comparing benzyl alcohol to its vehicle, the absolute difference in treatment success rate in study one was 71.4% in favor of benzyl alcohol (95% confidence interval [CI], 61.8 to 85.7) and 48.8% (95% CI, 31.1 to 62.0) in study two, again in favor of benzyl alcohol. Benzyl alcohol was associated with a lower risk of treatment failure in both studies (P<0.001 for both).[15]
- For the treatment of lice, permethrin has demonstrated a higher rate of treatment success compared to lindane, following a single application.[16-19] Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective at 14 days following treatment (P>0.01).[20,21] In multiple studies, malathion has been reported to be pediculicidal and ovicidal when compared to permethrin.[22,23]
- In studies comparing various topical agents for the treatment of scabies, a higher cure rate has been demonstrated with permethrin compared to crotamiton and lindane.[24-29] In the largest study completed (N=467), Schultz et al reported that there was a trend towards a higher cure rate with permethrin treatment compared to lindane; however, the difference was not statistically significant.[25]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Permethrin and pyrethrin products are recommended for treatment of scabies and lice, despite increasing resistance in the United States. These agents are available over-the-counter without a prescription.[29,30]
  - Malathion 0.5% can be used in people who are ≥24 months of age when resistance to permethrin or pyrethrins is documented or when treatment with these products fails despite their correct use. Due to the high alcohol concentration of the product it is highly flammable.[29,30]
  - Permethrin is the most studied pediculicide and is the least toxic to humans. Permethrin is less allergenic than pyrethrins and does not cause allergic reactions in individuals with plant allergies.[30]
  - Lindane has low ovicidal activity (30 to 50% of eggs are not killed), and resistance has been reported worldwide for many years. For these reasons, it should be used cautiously. The Food

and Drug Administration (FDA) has warned that incorrect use of lindane can be neurotoxic and its use should be restricted to patients for whom prior treatments have failed or in those patients who cannot tolerate safer medications. [29,30]
    - Lindane should not be used to treat premature infants, persons with the human immunodeficiency virus, seizure disorders, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh <110 pounds. [29,30]
    - Permethrin is the drug of choice for the treatment of scabies. Two (or more) applications may be necessary to eliminate all mites, particularly when treating crusted (Norwegian) scabies.
    - Crotamiton is approved for the treatment of scabies in adults but is frequently associated with treatment failure.[31]
    - Lindane is not recommended as a first-line therapy for the treatment of scabies due to its potential for toxicity with frequent or incorrect use. Lindane should be restricted to patients who have failed recommended therapies or who cannot tolerate recommended treatments.[31]
- Other Key Facts:
    - Several first-line therapies are available generically in at least one strength or formulation.[1]
    - According to the manufacturer, spinosad is the first FDA-approved head lice treatment that does not require nit combing following treatment.[33]
    - Ivermectin is approved for use as a single application only and is not indicated for retreatment.[7]
    - Reasons for treatment failure with the topical scabicide and pediculicide products include misdiagnosis, noncompliance, failure to follow instructions correctly, not enough pediculicide applied, reinfestation, and resistance. If resistance is suspected, retreatment should be with a different chemical entity than initially used.[34]

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Therapeutic Class Overview
Second and Third Generation Oral Fluoroquinolones

Therapeutic Class

Overview/Summary: The second and third generation quinolones are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-8] They are broad-spectrum agents that directly inhibit bacterial deoxyribonucleic acid (DNA) synthesis by blocking the actions of DNA gyrase and topoisomerase IV, which leads to bacterial cell death.[9,10]

The quinolones are most active against gram-negative bacilli and gram-negative cocci.[10] Ciprofloxacin has the most potent activity against gram-negative bacteria. Ciprofloxacin and ofloxacin have limited activity against streptococci and many anaerobes while levofloxacin and moxifloxacin have greater potency against gram-positive cocci, and moxifloxacin has enhanced activity against anaerobic bacteria.[9,10] Gemifloxacin, levofloxacin and moxifloxacin are considered respiratory fluoroquinolones. They possess enhanced activity against *Streptococcus pneumoniae* while maintaining efficacy against *Haemophilus influenzae*, *Moraxella catarrhalis* and atypical pathogens. Resistance to the quinolones is increasing and cross-resistance among the various agents has been documented. Two mechanisms of bacterial resistance have been identified. These include mutations in chromosomal genes (DNA gyrase and/or topoisomerase IV) and altered drug permeability across the bacterial cell membranes. [9,10]

Clinical Guidelines support the use of fluoroquinolones in children and adults for a variety of indications including infective endocarditis, valvular heart disease, encephalitis, meningitis, skin and soft tissue infections, infectious diarrhea, as travel medicine, certain sexually transmitted diseases, urinary tract infections, cystitis, pyelonephritis, anthrax, plague, chronic obstructive pulmonary disease, pneumonemia (community and hospital acquired), intra-abdominal infections, cancer-related infections, and prophylaxis.[11-37]

The fluoroquinolones have been the subject of several Food and Drug Administration (FDA) advisories which have included updates to their boxed warnings. The warnings now state that the benefits outweigh the risks in for serious bacterial infections, including anthrax, plague and bacterial pneumonia; however, their use in uncomplicated infections (e.g., acute bacterial sinusitis, acute exacerbation of chronic bronchitis and uncomplicated urinary tract infections) should be limited to when no other options are available.[38]

This review excludes intravenous dosage forms and encompasses only the oral dosage forms.

Table 1. Medications Included Within the Therapeutic Class Review[4-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Second Generation Fluoroquinolones			
Ciprofloxacin (Cipro®*, Cipro XR®*)	Bone and joint infections, urethritis/cervicitis (gonococcal), infectious diarrhea, inhalational anthrax§, intra-abdominal infections, prostatitis, pyelonephritis†, respiratory tract infections (lower), sinusitis, skin and skin-structure infections, typhoid fever, urinary tract infections†,§	Suspension: 250 mg/5 mL 500 mg/5 mL Tablet (extended-release): 500 mg 1,000 mg Tablet (immediate-release): 100 mg 250 mg 500 mg 750 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Levofloxacin (Levaquin®*)	Acute exacerbations of chronic bronchitis, inhalational anthrax (post-exposure)#, plague#, pneumonia (community-acquired and nosocomial), prostatitis, pyelonephritis, sinusitis, skin and skin-structure infections, urinary tract infections	Solution: 250 mg/10 mL Tablet: 250 mg 500 mg 750 mg	✔
Ofloxacin*	Acute exacerbations of chronic bronchitis, cystitis, urethritis/cervicitis (gonococcal and non-gonococcal), pelvic inflammatory disease, pneumonia (community-acquired), prostatitis, skin and skin-structure infections, urinary tract infections	Tablet: 200 mg 300 mg 400 mg	✔
Third Generation Fluoroquinolones			
Gemifloxacin (Factive®)	Acute exacerbations of chronic bronchitis, pneumonia (community-acquired)	Tablet: 320 mg	-
Moxifloxacin (Avelox®*, Avelox ABC Pack®)	Acute exacerbations of chronic bronchitis, Intra-abdominal infections, Pneumonia (community-acquired), sinusitis, skin and skin-structure infections, urethritis/cervicitis (gonococcal), prostatitis, urinary tract infections	Tablet: 400 mg	-

*Generic is available in at least one dosage form or strength.
†Extended-release formulation in addition to instant-release formulation
§Approved for patients ≥1 year of age
#Approved for patients ≥6 months of age

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the second and third generation quinolones.[39-71]
- Kaushik et al evaluated azithromycin to ciprofloxacin for the treatment of cholerae in young children aged 2 to 12 years. There was a statistically significant difference in clinical cure favoring azithromycin compared to ciprofloxacin (relative risk [RR], 1.34; 95% confidence interval [CI], 1.16 to 1.54; P<0.001); however, there was not a significant difference in bacteriological success (RR, 1.05; 95% CI, 1.00 to 1.10; P=0.06).[39]
- Clinical trials have demonstrated comparable efficacy and safety profiles among the quinolones for the treatment of skin and soft-tissue infections, genitourinary infections, respiratory tract infections, and other miscellaneous infections.[39-70]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Endocarditis: native/ prostatic valve endocarditis empiric therapy (ciprofloxacin for six months) or treatment of blood culture-negative endocarditis (quinolone for 6 to 18 months).[11-14]
    - Use in prevention of infections after surgery in combination with other antibiotics.[18,37]

- Recommend use of levofloxacin, moxifloxacin or levofloxacin/ciprofloxacin (in combination with clindamycin) for empiric therapy of diabetic foot infections.[19]
- First or second line in the treatment of infectious diarrhea, depending on specific cause.[20,22]
- Quinolones are the first line for chemoprophylaxis and treatment of traveler's diarrhea.[21]
- Quinolones are first line or alternative therapies for sexually transmitted diseases such as chancroid, chlamydia, epididymitis and non-gonococcal urethritis.[23]
- Second line for uncomplicated urinary tract infections and first line for acute pyonephritis.[24,25]
- First line for inhalation anthrax; second line for plauge[26,27]
- Treatment for acute exacerbation of chronic obstructive pulmonary disease should be based on bacterial resistance patterns, but generally quinolones are not considered first line.[28]
- Outpatient treatment of community-acquired pneumonia with moxifloxacin, gemifloxacin or levofloxacin is first line in patients with risk factors for drug resistant strains, presence of certain comorbidities, immunosuppressing conditions or use of antimicrobials within the previous three months and as an alternative to patients who cannot tolerate other first line agents.[29-32]

- Other Key Facts:
  - Ofloxacin and levofloxacin are eliminated mostly via the kidney, moxifloxacin is eliminated mostly via the liver, and the others are eliminated via a mix of kidney and liver.[9]
  - Ciprofloxacin (immediate-release) and levofloxacin are the only medications approved for use in patients <18 years of age for certain indications. Ciprofloxacin may be used in patients >1 year of age and levofloxacin is approved for children >6 months of age.[1,4]
  - Moxifloxacin is the only oral quinolone that does not need to adjusted in patients with renal disease.[5]
  - All second and third generation quinolones are available in an oral tablet. Ciprofloxacin is also available in an extended-release tablet. Ciprofloxacin and levofloxacin are formulated as an oral suspension and solution respectively.[1-6]
  - Ciprofloxacin (extended-release), gemifloxacin, levofloxacin and moxifloxacin are approved for once daily dosing.[1-76]
  - Ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin are available in at least one generic formulation.

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Therapeutic Class Overview
Selective Serotonin Reuptake Inhibitors

Therapeutic Class

- **Overview/Summary:** The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa), and premenstrual dysphoric disorder.[1-16] Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder, and unspecified anxiety disorder.[17] Some antidepressants have also been used in nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis, and tobacco abuse.[1-17]

  Treatment for psychiatric disorders includes psychotherapy, pharmacotherapy or the combination of the two. The decision to implement psychotherapy is dependent upon patient willingness and severity of illness. Despite the variety of pharmacologic options available, all antidepressants appear to be equally efficacious for mood disorders. Therefore, initial treatment should depend on the individual's overall medical condition and current medication profile.[18-27]Pharmacology, tolerability and safety profiles differ among these classes and among individual agents. However, for all antidepressants, the Food and Drug Administration (FDA) requires manufacturers to include a black-box warning notifying prescribers of the potential for antidepressants to increase suicidal thoughts in children and adults.[18-27]

  The antidepressants can be classified in several ways, such as by chemical structure and/or presumed mechanism of activity. The agents included in this review belong to the category, selective serotonin-reuptake inhibitors (SSRIs). The SSRIs include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. These agents are believed to exert their effects through potentiating the serotonergic activity in the central nervous system.[1-16] All but fluvoxamine are Food and Drug Administration (FDA)-approved for the treatment of major depressive disorder.[1-16]

Table 1. Current Medications Available in the Therapeutic Class[1-2,5-13]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Citalopram (Celexa®*)	Depression (includes major depressive disorder),	Solution: 10 mg/5 mL Tablet: 10 mg 20 mg 40 mg	✔
Escitalopram (Lexapro®*)	Depression (includes major depressive disorder), generalized anxiety disorder,	Solution: 5 mg/5 mL Tablet: 5 mg 10 mg 20 mg	✔
Fluoxetine (Prozac®*, Prozac Weekly®*,	Bulimia nervosa, depression (includes major depressive disorder), obsessive-compulsive disorder, panic disorder,	Delayed-release capsule: 90 mg Immediate-release capsule:	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Sarafem®)	premenstrual dysphoric disorder,	10 mg 20 mg 40 mg Immediate-release tablet: 10 mg 20 mg 60 mg Solution: 20 mg/5 mL	
Fluvoxamine (Luvox®, Luvox® CR)	Obsessive-compulsive disorder,	Extended release capsule: 100 mg 150 mg Immediate release tablet: 25 mg 50 mg 100 mg	✔
Paroxetine hydrochloride (Paxil®*, Paxil CR®*)	Depression (includes major depressive disorder), generalized anxiety disorder*, obsessive-compulsive disorder*, panic disorder, premenstrual dysphoric disorder†, posttraumatic stress disorder*, social anxiety disorder	Extended release tablet: 12.5 mg 25 mg 37.5 mg Suspension, oral: 10 mg/5 mL Immediate release tablet: 10 mg 20 mg 30 mg 40 mg	✔
Paroxetine mesylate (Brisdelle®, Pexeva®)	Depression (includes major depressive disorder), obsessive-compulsive disorder, panic disorder, vasomotor symptoms associated with menopause; (moderate to severe)#	Immediate release capsule: 7.5 mg Immediate release tablet: 10 mg 20 mg 30 mg 40 mg	-
Sertraline (Zoloft®)	Depression (includes major depressive disorder), obsessive-compulsive disorder, panic disorder, premenstrual dysphoric disorder, posttraumatic stress disorder, social anxiety disorder	Oral concentrate: 20 mg/mL Tablet: 25 mg 50 mg 100 mg	✔

*Immediate-release only
†Extended-release only
#Brisdelle® only; Brisdelle® is not indicated for the treatment of any psychiatric condition.

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the serotonin and norepinephrine reuptake -inhibitors for their FDA-approved indications.[28-82]
- In one study which compared fluoxetine, imipramine and desipramine for duration of initial therapy, fluoxetine was taken for a longer period of time than desipramine or imipramine (P<0.001 for either desipramine or imipramine).[28] Statistical comparisons between the two TCAs were not done but they were numerically similar. The difference in duration of therapy was due primarily to less tolerability of desipramine and imipramine. Only 9% of the patients switched from fluoxetine due to adverse events while 27% and 28% assigned to desipramine and imipramine respectively switched due to adverse events (P<0.001 for both TCAs compared to fluoxetine).
- The overall length of antidepressant therapy (if the patient switched to another agent) was not different regardless of which agent was initiated first. In addition, response to medication as measured by the Hamilton Depression Rating Scale (HDRS) was equivalent.[29]
- One study comparing health care costs of fluoxetine versus imipramine and fluoxetine versus desipramine compared outpatient costs to primary care and to mental health. The authors found no difference in primary care visit cost in either comparison (fluoxetine versus desipramine; P=0.19 and fluoxetine versus imipramine; P=0.98). There was also no difference in mental health outpatient visit cost in either comparison group (fluoxetine versus desipramine; P=0.33 and fluoxetine versus imipramine; P=0.73).[31]
- A meta-analysis evaluated venlafaxine compared to SSRIs in treatment of major depressive disorder. Using a random effect model showed that venlafaxine was has statistically higher rates of achieving remission (odds ratio [OR], 1.13; 95% CI, 1.0 to 1.28; P=0.05) and response (OR, 1.17; 95% CI, 1.03 to 1.34; P=0.02). Subgroup analysis found that venlafaxine had a significantly better response rate than fluoxetine (OR, 1.28; 95% CI, 1.05 to 1.55; P=0.01). There were no significant differences in response or remission between venlafaxine and other individual SSRIs. There was no significant difference in all cause discontinuation between venlafaxine and SSRIs (OR, 1.10; 95% CI, 0.97 to 1.25; P=0.15). Venlafaxine had significantly higher discontinuation due to adverse events compared with SSRIs (OR, 1.41, 95% CI, 1.10-1.79, P=0.006).[38]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - National and international treatment guidelines for the treatment of depression state that selecting an agent should be driven by anticipated side effects, tolerability, patient preference, and quantity and quality of available clinical data, and that the effectiveness of antidepressants is usually comparable within and between medication classes.[18-27]
    - Guidelines also state that medications that can be considered first-line therapy for most patients include selective serotonin reuptake inhibitors (SSRIs), SNRIs, mirtazapine, or bupropion, while monoamine oxidase inhibitors (MAOIs) should be reserved for patients who are unresponsive to other available medications. These guidelines do not recommend one SSRI, SNRI or MAOI over another.[18-27]
    - Antidepressants are recommended as first-line treatment for GAD, with the following agents considered treatment options: SSRIs, SNRIs, and nonsedating tricyclic antidepressants (TCAs).[38]
- Other Key Facts:
    - Fluoxetine is the only agent within the class that carries indications for treating bulimia nervosa, while Brisdelle® (paroxetine mesylate) is the only SSRI that is FDA-approved for the treatment of vasomotor symptoms associated with menopause.
    - All of the SSRI products have a Black Box Warning regarding the potential for antidepressants to increase suicidal thoughts in children and young adults.[1-16]

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Therapeutic Class Overview
Short-acting β2-Agonists

Therapeutic Class

- **Overview/Summary:** Respiratory short acting β_2-agonists (SABAs) are Food and Drug Administration (FDA)-approved indications include asthma, chronic obstructive pulmonary disease, exercise-induced bronchospasm (EIB), and/or and reversible bronchospasm. Respiratory β_2-agonists act preferentially on the β_2-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-15] The β_2-agonists can be divided into two categories: short-acting and long-acting. The short-acting respiratory β_2-agonists consist of albuterol (ProAir HFA®, ProAir RespiClick®, Proventil HFA®, Proventil HFA®, Ventolin HFA®), levalbuterol (Xopenex®, Xopenex HFA®), metaproterenol and terbutaline. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-15] As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all albuterol metered dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. These inhalers were replaced by MDIs which use hydrofluoroalkanes (HFAs). There is no difference in the safety or efficacy of the HFA inhalers compared to the CFC inhalers; however, there may small differences in taste and/or feel with the HFA inhalers. The deadline for removal of the pirbuterol (Maxair®) CFC inhaler is December 31, 2013.[16]

Table 1. Current Medications Available in the Therapeutic Class[1-15]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Short-Acting β_2-agonists			
Albuterol (AccuNeb®*, ProAir HFA®, ProAir RespiClick®, Proventil HFA®, Ventolin HFA®, VoSpire ER®*)	Relief of bronchospasm in patients with asthma†,‖, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†‡§, prevention of exercise-induced bronchospasm†‡	Dry Powder Inhaler: 90 µg Meter dose aerosol inhaler (HFA): 120 µg albuterol sulfate# Solution for nebulization: 0.63 mg 1.25 mg 2.5 mg 0.5% concentrated solution (3 mL unit dose vials) Sustained-release tablet: 4 mg 8 mg Syrup:	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		2 mg/5 mL Tablet: 2 mg 4 mg	
Levalbuterol (Xopenex®*, Xopenex HFA®)	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†	Meter dose aerosol inhaler (HFA): 59 µg¶ Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (3 mL vials)	✔
Metaproterenol*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	✔
Terbutaline*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	✔

*Generic available in at least one dosage form or strength.
†Inhalation solution.
‡Metered-dose inhaler.
§Dry powder inhaler.
‖Oral formulations.
¶Delivering 45 µg levalbuterol base.
#Delivering 108 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy SABAs in providing relief from reversible bronchospasms and EIA.[21-41]
- Safety and efficacy of albuterol dry powder inhaler (ProAir Respiclick®) was evaluated in two 12-week randomized, double-blind, placebo-controlled studies. Forced expiratory volume in one second (FEV_1) was significantly improved with albuterol dry powder inhaler compared with placebo (no P value reported).[7]
- In clinical trials that comparing albuterol to levalbuterol, inconsistent results have been reported and have not consistently demonstrated improved outcomes with levalbuterol compared to albuterol. Moreover, studies have shown no significant differences between the two agents in the peak change in FEV_1 or the number and incidence of adverse events.[21-31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Short-acting β_2-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.[17-20]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis. [17-20]

  - Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs.[17-20]
  - The addition of a systemic corticosteroid may be required if patients do not respond immediately to treatment with a SABA or if the exacerbation is severe.[17-20]
  - The use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[17]
- Other Key Facts:
  - Studies have failed to consistently demonstrate significant differences between products.
  - Albuterol oral solution, oral tablets, and solution for nebulization, levalbuterol solution for nebulization, metaproterenol oral solution and oral tablets, and terbutaline oral tablets and solution for injection are available generically.
  - There are currently branded albuterol hydrofluoroalkanes (HFA) inhalers and one dry-powder inhaler; however, no generic equivalents are available.

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Therapeutic Class Overview
Topical Antivirals

Therapeutic Class

- **Overview/Summary:** Both acyclovir (Zovirax®) and penciclovir (Denavir®) are synthetic nucleoside analogs derived from guanine that are approved for the management of initial herpes genitalis, recurrent herpes labialis and/or non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients. In addition, a combination of acyclovir and hydrocortisone (Xerese®) is approved to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in recurrent herpes labialis. These agents are active against various herpes simplex virus including types 1 and 2 (HSV-1 and HSV-2).[1-5] The two most common cutaneous manifestations of the herpes simplex virus infection are orolabial and genital herpes. Orolabial herpes presents most commonly as cold sores and is the most prevalent form of mucocutaneous herpes infection. Approximately 35 to 60% of Caucasians in the United States have serologic evidence of having been infected by HSV-1.[6] Genital herpes, is one of the most common viral sexually transmitted diseases in the world, but has demonstrated a decreased prevalence over the past few years. A majority of patients infected with HSV-2 have not been diagnosed, as symptoms may be mild in many cases and the presentation is highly variable between patients. Although infections may be mild or unrecognized, the virus continues to be shed intermittently in the genital tract. After resolution of primary infection, the virus persists in the nerve roots of the sacral plexus, causing recurrent (often less severe) outbreaks.

  Prior to the introduction of acyclovir as an antiviral drug in the early 1980s, cutaneous HSV infection was managed with drying agents and other local care. Today, treatment options include multiple oral, intravenous and topical antiviral agents. Oral antiviral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and those with severe disseminated infection.[6] Topical antivirals reduce the duration of viral shedding and the length of time before all lesions become crusted; however, the topical treatment is much less effective compared to oral or intravenous therapies. No antiviral agent currently available will eradicate HSV, and treatment is aimed at managing symptoms and reducing disease duration rather than curing the disease. Currently, acyclovir ointment is available generically.

Table 1. Current Medications Available in the Therapeutic Class[2-5]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Acyclovir (Zovirax®*)	Management of initial herpes genitalis†, treatment of recurrent herpes labialis‡, management of non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients†	Cream: 5% (2, 5 g tubes) Ointment: 5% (5, 15, 30 g tube)	✔
Penciclovir (Denavir®)	Treatment of recurrent herpes labialis	Cream: 1% (1.5 g tube)	-
Combination Products			
Acyclovir/ hydrocortisone (Xerese®)	Treatment of recurrent herpes labialis#	Cream: 5%/1% (5 g tube)	-

*Generic available in at least one dosage form or strength.
† Acyclovir 5% ointment only.
‡ Acyclovir 5% cream only.
#To reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time.

Evidence-based Medicine

- When the efficacy of acyclovir 5% cream was evaluated compared to placebo for the treatment of genital herpes, there was only a significant decrease in the duration of itching with acyclovir treatment compared to placebo.[7] When penciclovir 1% cream was compared to acyclovir 3% cream for the treatment of genital herpes, the only significant difference seen between the two treatment groups was time to crusting of lesions, which favored penciclovir treatment.[8]
- In the treatment of recurrent herpes labialis, acyclovir 5% cream significantly shortens the mean clinician-assessed duration of herpes labialis episodes and mean patient-assessed duration of pain when compared to placebo. The lesion healing time and the number of episodes per month was not found to be significant between treatments.[9-13]
- The combination formulation of acyclovir/hydrocortisone 5%/1% cream was evaluated in a double-blind, active and placebo controlled study of more than 2,400 patients ≥18 years of age with a history of herpes simplex labialis who had experienced at least three recurrent episodes in the past year. The primary endpoint, prevention of ulcerative herpes simplex labialis lesions (frequency of patients with nonulcerative recurrences) was significantly greater in patients treated with acyclovir/hydrocortisone compared to patients treated with acyclovir or placebo (42 vs 35 and 26%, respectively; *P*<0.05 for both). [14]
- Compared to placebo, patients treated with penciclovir 1% cream experienced significant decreases in the overall lesion healing time, healing in early, late and vesicle stages, resolution of lesion pain and resolution of symptoms including itching, tingling, burning, numbness and tenderness.[15-17] Patients treated with penciclovir also were shown to have a significantly higher percent of cases healed at six and eight days. When penciclovir 1% cream was compared to acyclovir 5% cream, there was a significantly shorter time to crusting with penciclovir treatment compared to acyclovir. The percent of patients cured at seven days was not significantly different. [18,19]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - National and international guidelines including those published by the Centers for Disease Control and Prevention, state that the topical antiviral agents offer minimal clinical benefit and should not be recommended over other options in general use, such as the oral antivirals.[20,21]
- Other Key Facts
    - Acyclovir 5% ointment is the only topical antiviral agent available generically; however, several oral antiviral formulations are available generically in various formulations.

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Therapeutic Class Overview
Topical Vitamin D Analogs and Combinations

Therapeutic Class

- **Overview/Summary:** The focus of this review will be the topical vitamin D analogs and combination products. In general, these agents are Food and Drug Administration (FDA)-approved for the treatment of plaque psoriasis in adults. However, depending on the formulation, several products have been approved for use in children or for the treatment of plaque psoriasis.1-8 There are currently two topical vitamin D analogs, calcipotriene and calcitriol. Calcitriol is the active form of vitamin D3, cholecalciferol, which is synthesized in the body; calcipotriene is structurally similar to naturally occurring calcitriol. In addition, calcipotriene has been formulated in combination with betamethasone, a corticosteroid. The exact mechanism of action by which vitamin D analogs exert their effect for the treatment of plaque psoriasis is unknown. They are believed to involve the drug's ability to inhibit keratinocyte proliferation and stimulate keratinocyte differentiation.9

  Psoriasis is a common chronic skin disorder typically characterized by erythematous papules and plaques with a silver scale, although other presentations occur. Most cases are not severe enough to affect general health and are treated in the outpatient setting.[9] The options for treatment are topical or systemic and depend on the severity of the disease. Mild-to-moderate disease can often be managed with topical agents, while patients with moderate-to-severe disease may need systemic therapy. Moderate-to-severe disease is usually considered to effect more than 5 to 10% of the body. Topical therapy help provide symptomatic relief, minimize required doses of systemic medications (if being used) and may also be psychologically cathartic for some patients.[9] Treatment options for mild-to-moderate disease include topical corticosteroids, emollients, tar, topical retinoids and the vitamin D analogs. Most often, a combination of topical corticosteroids and either calcipotriene, calcitriol or tazarotene are prescribed.[9] Many patients find that certain medications are very messy or difficult to apply. For scalp psoriasis, many patients prefer lotions, solutions, gels, foams, or sprays as vehicles as opposed to creams and ointments.[9]

Table 1. Medications Included Within the Therapeutic Class Review[1-8]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
Single-Entity Agents			
Calcipotriene (Calcitrene®*, Dovonex®*, Sorilux®)	Treatment of plaque psoriasis (cream, ointment, foam)‖, Treatment of plaque psoriasis of the scalp (foam, solution¶)‖	Cream: 0.005% Foam: 0.005% Ointment: 0.005% Solution: 0.005%	✔
Calcitriol (Vectical®*)	Treatment of plaque psoriasis†	Ointment: 3 µg/g	✔
Combination Products			
Calcipotriene/ betamethasone (Enstilar®, Taclonex®*, Taclonex Scalp®*)	Treatment of plaque psoriasis‡, treatment of plaque psoriasis of the scalp (suspension)	Foam: 0.005%/0.064% Ointment: 0.005%/0.064% Suspension: 0.005%/0.064%	✔

*Generic is available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have consistently demonstrated the safety and efficacy of the topical psoriasis agents, calcipotriene, calcitriol and tazarotene either alone or in combination.[13-54]
- Calcipotriene monotherapy is an effective and safe treatment for the management of psoriasis and studies have evaluated its effectiveness versus placebo, coal tar and betamethosone.[13-18]
    - Calcipotriene was also found to be safe and effective for the treatment of scalp psoriasis.[19-21]
- The combination of calcipotriene and betamethasone was more effective than placebo or monotherapy with either agent alone at treating the signs and symptoms of psoriasis.[23-36]
    - The efficacy combination calcipotriene and betamethasone was also seen when treating patients who had a diagnosis of scalp psoriasis.[38-41]
- Calcitriol has been shown to be an effective treatment option for patients with psoriasis.[42-46]
- There have been several head-to-head studies evaluating the safety and efficacy of these agents.[47-54]
    - When calcipotriene was compared to calcitriol as monotherapies or in combination with a corticosteroid, the results of trials regarding "superiority" are conflicting, but suggest that both agents are effective. [48-51]
    - One study found that calcitriol is better tolerated that the calcipotriene, with perilesional erythema (P<0.001), perilesional edema (P<0.02) and stinging/burning (P<0.001) all less severe with calcitriol than with calcipotriol.[51]
    - Tazarotene plus mometasone was compared to calcipotriene monotherapy and was shown to be not significantly different in the percentage of patients achieving complete or almost complete clearance at any time during eight weeks of treatment.[52] Two other studies comparing calcipotriene to tazarotene showed similar results.[53,54]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Potent corticosteroids are recommended as first-line treatment for mild/moderate plaque psoriasis they have well documented efficacy and well known safety profile.[10-11]
    - For psoriasis not responsive to a potent steroid and treatment is required longer than four to eight weeks (depending on potency of steroid), topical vitamin D analogs, tazarotene and other agents such as coal tar can be used.
    - Special considerations need to be made depending on the location and severity of the disease. For areas of the face, flexures and genitals, which are highly sensitive to steroid atrophy, a short term of mild or moderate potency corticosteroids are recommended for a short period of time (two weeks maximum).[10]
    - For moderate to severe plaque psoriasis requiring systemic therapy, topical agents can be used as an adjunctive therapy to help with the signs and symptoms of the disease.[12]
- Other Key Facts:
    - Generic products are available for calcipotriene (cream, ointment, solution), calcitriol, and calcipotriene/betamethasone (ointment).

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Therapeutic Class Overview
Ulcerative Colitis Agents

Therapeutic Class

- **Overview/Summary:** Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms that include diarrhea, abdominal pain, bleeding and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic and immunologic factors.[1,2] Complications of IBD include hemorrhoids, rectal fissures, fistulas, perirectal abscesses and colon cancer.[3] Ulcerative colitis and Crohn's disease are the two forms of IBD and differ in their pathophysiology and presentation. Ulcerative colitis is limited to the rectum and colon, and affects the mucosa and sub-mucosa causing continuous lesions. Crohn's disease can involve any part of the gastrointestinal tract, and is a transmural process that causes discontinuous lesions frequently leaving "skip areas" of relatively normal mucosa.[1,3] The goals for the treatment of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations and maintain remission from acute inflammation or surgical palliation or cure.[3] The distribution and extent of the disease (i.e., disease location and degree of mucosal involvement) often dictate the route and formulation of drug therapy.[1] The 5-aminosalicylic acid (5-ASA) derivatives available in oral formulations include balsalazide, mesalamine, olsalazine and sulfasalazine. Balsalazide, mesalamine and olsalazine were developed to maintaining the overall therapeutic benefit of sulfasalazine while improving tolerability.[4-17] Upon oral administration mesalamine is absorbed in the small intestine and does not reach the colon. Pentasa® is an ethylcellulose-coated mesalamine formulation that slowly releases the drug throughout the gastrointestinal tract. Asacol® HD and Delzicol® tablets contain a pH-sensitive film that dissolves at a higher pH, thereby delivering mesalamine to the terminal ileum and proximal colon. Lialda® and Apriso® are formulated in a matrix that delays mesalamine release until it reaches the distal ileum and colon. Balsalazide, olsalazine and sulfasalazine are prodrugs that are cleaved in the colon following bacterial reduction to form mesalamine. Mesalamine is also available as an enema (Rowasa®) and as a rectal suppository (Canasa®).[4-16] Currently, balsalazide and sulfasalazine oral formulations as well as topical mesalamine are available generically.[17,18]

Table 1. Current Medications Available in the Class[4-16]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Balsalazide (Colazal®*, Giazo®)	Treatment of mildly to moderately active UC in patients ≥5 years of age (Colazal®), treatment of mildly to moderately active UC in male patients ≥18 years of age (Giazo®)	Capsule: 750 mg (Colazal®) Tablet: 1,100 mg (Giazo®)	✔
Mesalamine (Apriso®, Asacol® HD, Canasa®, Delzicol®, Lialda®, Pentasa®, Rowasa®*, SfRowasa®)	Induction of remission in adults with active, mild to moderate UC (Lialda®), induction of remission and for the treatment of patients with mildly to moderately active UC (Pentasa®), maintenance of remission of UC in adults (Apriso®, Lialda®), treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis (Rowasa®, SfRowasa®), treatment of mildly to moderately active UC and for the maintenance of remission of UC in patients ≥5 years of age (Delzicol®), treatment of mild to moderately active ulcerative proctitis (Canasa®), treatment of moderately active UC (Asacol® HD)	Delayed-release capsule: 400 mg (Delzicol®) Delayed-release tablet: 800 mg (Asacol® HD) 1,200 mg (Lialda) Extended-release capsules: 250 mg (Pentasa®) 500 mg (Pentasa®) Rectal enema: 4,000 mg/60 mL unit	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		(Rowasa®; SfRowasa®) Rectal suppository: 1,000 mg (Canasa®)	
Olsalazine (Dipentum®)	Maintenance of remission of UC in patients who are intolerant of sulfasalazine	Capsule: 250 mg (Dipentum®)	-
Sulfasalazine (Azulfidine®*, Azulfidine EN-Tabs®*)	Prolongation of the remission period between acute attacks of UC (Azulfidine®, Azulfidine EN-tabs®), treatment of mild to moderate UC, and as adjunctive therapy in severe UC (Azulfidine®, Azulfidine EN-tabs®), Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs, (Azulfidine EN-tabs®) and treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs] (Azulfidine EN-tabs®)	Delayed-release tablet: 500 mg (Azulfidine EN-tab®, Sulfazine®†) Tablet: 500 mg (Azulfidine®, Sulfazine®†)	✔

NSAIDs=nonsteroidal anti-inflammatory drugs, UC=ulcerative colitis
*Generic available in at least one dosage form or strength.
†Branded generic product

Evidence-based Medicine

- A Cochrane review of the 5-aminosalicylic acid (5-ASA) derivative oral preparations for the induction of remission in patients with ulcerative colitis, demonstrates that newer 5-ASA derivatives are significantly more effective compared to placebo with no statistically significant differences between 5-ASA preparations.[19]
- Results from a meta-analysis comparing mesalamine once daily to multiple daily dosing demonstrated that once-daily dosing is as effective and has a comparable safety profile as multiple dosing regimens for the maintenance treatment of ulcerative colitis. In addition, once-daily dosing is more effective for inducing remission in active ulcerative colitis compared to multiple daily dosing.[20]
- Oral sulfasalazine therapy has been shown to be less effective than rectal mesalamine therapy in patients with distal ulcerative colitis.[21]
- In another meta-analysis, rectal 5-ASA was significantly more effective compared to placebo and rectal corticosteroids for inducing remission in ulcerative colitis. Rectal 5-ASA was not more effective compared to oral 5-ASA for symptomatic improvement.[22]
- A meta-analysis that evaluated the efficacy of topical mesalamine concluded that topical mesalamine is more effective compared to placebo for the prevention of relapse of disease activity in quiescent ulcerative colitis. The time to relapse was longer with topical mesalamine in the two trials that reported this outcome, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy.[23]
- In a meta-analysis evaluating the efficacy of oral 5-ASA therapy compared to topical 5-ASA therapy or a combination of oral and topical 5-ASA therapy, combined 5-ASA therapy was more effective compared to oral 5-ASA therapy for induction of remission in mild to moderately active ulcerative

colitis. Moreover, intermittent topical 5-ASA therapy was more effective compared to oral 5-ASA therapy for preventing relapse of quiescent ulcerative colitis.[24]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - According to current guidelines by the American College of Gastroenterology, oral aminosalicylates (balsalazide, mesalamine, olsalazine and sulfasalazine) are effective for achieving and maintaining remission in distal disease.[25]
  - Topical mesalamine formulations are more effective than topical steroids or oral aminosalicylates; however, the combination of oral and topical agents more effective compared to each agent alone.[25]
  - Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission of disease, and combination oral and topical therapy is better than oral mesalamine alone. [25]
  - Sulfasalazine is recognized as a first-line agent in the management of mild to moderately active colitis, with balsalazide, mesalamine, olsalazine being effective for reducing the number of relapses and the maintenance of mild to moderate disease remission. [25]
- Other Key Facts:
  - Balsalazide and sulfasalazine oral formulations are available generically.[18]
  - Topical mesalamine enemas are available generically.[18]

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