OPTUMRx

# Therapeutic Class Overview
## Opioid Partial Agonist for Management of Opioid Dependence - Buprenorphine

### INTRODUCTION

- The American Psychiatric Association (APA) defines opioid dependence as a syndrome characterized by a problematic pattern of opioid use, leading to clinically significant impairment or distress (American Psychiatric Association, 2013).
    - Opioid dependence affects about 4.5 million people in the United States and leads to approximately 17,000 deaths annually (Substance Abuse and Mental Health Services Administration, 2012; Substance Abuse and Mental Health Services Administration, 2014).
- Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence (Micromedex® 2.0, 2016).
    - Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs may dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (Code of Federal Regulations, Title 42, Sec 8).
    - The Drug Addiction Treatment Act of 2000 (DATA 2000) expanded the clinical context of medication-assisted opioid addiction treatment by allowing qualified physicians to dispense or prescribe specifically approved medications, like buprenorphine, for the treatment of opioid addiction in treatment settings other than the traditional Opioid Treatment Program. In addition, DATA reduced the regulatory burden on physicians who choose to practice opioid addiction therapy by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act (Center for Substance Abuse Treatment, 2004).
- All buprenorphine products are Schedule III controlled substances (Drugs@FDA, 2016).
- In 2012, Reckitt Benckiser Pharmaceuticals, Inc. notified the FDA that they were voluntarily discontinuing production of SUBOXONE® (buprenorphine/naloxone) sublingual tablets as a result of increasing concerns over accidental/unsupervised pediatric exposure with the tablets compared to the film formulation. The unique child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduce exposure rates in children. Distribution of brand SUBOXONE (buprenorphine/naloxone) sublingual tablets was discontinued in March 2013; however, generic formulations remain available.
- Included in this review are the buprenorphine products that are FDA-approved to be used in the induction and maintenance treatment of opioid dependence.
- Medispan Class: Opioid Partial Agonists

**Table 1. Medications Included Within Class Review**

| Drug | Manufacturer | FDA Approval Date | Generic Availability |
|---|---|---|---|
| **Single Entity Agents** | | | |
| SUBUTEX (buprenorphine)* sublingual tablet | Various | 10/08/2002 | ✔ |
| **Combination Products** | | | |
| BUNAVAIL™ (buprenorphine/naloxone) buccal film | Biodelivery Sciences | 06/06/2014 | - |
| SUBOXONE‡ (buprenorphine/naloxone) sublingual tablets | Various | 10/08/2002 | ✔ |
| SUBOXONE (buprenorphine/naloxone) sublingual film | Indivior | 08/30/2010 | - |
| ZUBSOLV® (buprenorphine/naloxone) sublingual tablets | Orexo US | 07/03/2013 | - |

*SUBUTEX was discontinued; however, generic formulations are available.
‡SUBOXONE tablets were discontinued; however, generic formulations are available and brand name SUBOXONE is available as a film.

(Drugs@FDA, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2016)

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

| Indication | Single Entity Agent | Combination Products | | | |
|---|---|---|---|---|---|
| | SUBUTEX (buprenorphine) sublingual tablets | BUNAVAIL (buprenorphine/ naloxone) film | SUBOXONE (buprenorphine/ naloxone) sublingual tablets | SUBOXONE (buprenorphine/ naloxone) film | ZUBSOLV (buprenorphine/ naloxone) sublingual tablets |
| Treatment of opioid dependence | | | | ✔ | ✔ |
| Treatment of opioid dependence and is preferred for induction | ✔ | | | | |
| Maintenance treatment of opioid dependence | | ✔ | ✔ | | |

(Prescribing information: buprenorphine sublingual tablets, 2016; buprenorphine/naloxone sublingual tablets, 2016; BUNAVAIL, 2014; SUBOXONE film, 2016; ZUBSOLV, 2015)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (Amass et al, 2004; Fiellin et al, 2008).
- Studies have shown that in adult patients with opioid dependence, the percentage of opioid negative urine tests was significantly higher for both buprenorphine and buprenorphine/naloxone compared to placebo, while no significant difference was seen between the two active treatment groups (Daulouede et al, 2010; Fudala et al, 2003). In addition, a small randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone (Strain et al, 2011).
- Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or self-reported drug use with longer treatment duration compared to detoxification; however, one of the studies showed no significant difference in the percentage of positive urine tests between the two treatment groups at 12 weeks (Kakko et al, 2003; Woody et al, 2008; Weiss, 2011).
- In a meta-analysis of 21 randomized controlled trials, patients receiving buprenorphine at doses ≥16 mg/day were more likely to continue treatment compared to patients receiving doses <16 mg/day; however, no significant difference was seen in the percentage of opioid positive urine tests between the high and low dose groups (Fareed et al, 2012[b]).
- Studies that compared different dosing regimens of buprenorphine showed no difference in rate of treatment retention, percentage of urine tests positive for opioids, or withdrawal symptoms (Bickel, et al, 1999; Gibson, et al 2008; Petry et al 1999; Schottenfeld et al, 2000).
- One study found that buprenorphine/naloxone sublingual film was comparable to the sublingual tablet form in dose equivalence and clinical outcomes (Lintzeris et al, 2013).
- Approval of BUNAVAIL (buprenorphine/naloxone) buccal film was based on results of a 12-week, Phase 3 study in 249 patients who were converted from SUBOXONE sublingual tablet or film to BUNAVAIL. The majority of patients who participated found BUNAVAIL easy to use and pleasant in taste. Additionally, there was some resolution in constipation complaints experienced with SUBOXONE (Biodelivery Sciences press release, 2014; Sullivan et al, 2014; Sullivan et al, 2015).
- 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 (Farre et al, 2002; Gibson, et al, 2008; Gowing et al, 2009; Johnson et al,

1992; Kamien et al, 2008; Meader et al, 2010; Minnozi et al, 2013; Perry et al, 2013; Petitjean et al, 2001; Soyka et al, 2008; Strain et al, 2011). However, when low doses of buprenorphine were studied (≤8 mg/day), high doses of methadone (≥50 mg/day) proved to be more efficacious (Farre et al, 2002; Ling et al, 1996; Mattick et al, 2014; Schottenfeld et al, 1997).

- A double-blind, 12-week randomized clinical trial was conducted in an outpatient research clinic in 70 adult patients with prescription opioid dependence and positive urine samples that were willing to undergo detoxification. The trial evaluated the relative efficacy of varying buprenorphine tapering regimens (one, two, and four weeks) and subsequent naltrexone maintenance in prescription opioid dependent patients who had been briefly stabilized on combination buprenorphine/naloxone. The main outcomes included the percentage of participants negative for illicit opioid use, retention, naltrexone ingestion, and favorable treatment response (i.e., retained in treatment, opioid abstinent, and receiving naltrexone at the end of the study). The study was conducted in two phases: phase 1 included weeks 1 to 5 (after randomization) and daily clinic visits while phase 2 included weeks 6 to 12 and thrice weekly clinic visits. In both phase 1 and 2, the 4-week taper resulted in greater opioid abstinence than the shorter tapers (P=0.02 and P=0.03, respectively). Additionally, the 4-week taper resulted in more treatment responders (P=0.03) and greater retention and naltrexone use than the shorter tapers (both P=0.04). According to the authors, the results suggest that a subset of prescription opioid-dependent outpatients may respond positively to a 4-week taper plus naltrexone maintenance intervention (Sigmon et al, 2013).
- An open-label, single-site, 14-week randomized clinical trial enrolled 113 patients with prescription opioid dependence to determine the efficacy of buprenorphine taper compared to ongoing maintenance therapy in primary care-based treatment of patients with prescription opioid dependence. The study included a two week induction and stabilization period, 14 weeks of treatment, and two weeks of continuing clinical care. Patients were randomized to buprenorphine taper (taper condition) or ongoing buprenorphine maintenance therapy (maintenance condition). The buprenorphine taper was initiated after 6 weeks of stabilization, lasted for 3 weeks, and included medications for opioid withdrawal, after which patients were offered naltrexone treatment. The maintenance group received ongoing buprenorphine therapy. All patients received physician and nurse support and drug counseling. The primary outcome measures were the overall percentage of opioid-negative urine samples, patient-reported days per week of illicit opioid use, and patient reported maximum consecutive weeks of abstinence from illicit opioids. Secondary outcomes included the percentage of patients meeting criteria for protective transfer and treatment retention (number of days from randomization to last clinical contact). During the trial, the mean percentage of urine samples negative for opioids was lower for patients in the taper group (35.2%; [95% CI, 26.2 to 44.2%]) compared with those in the maintenance group (53.2%; [95% CI, 44.3 to 62%]). Patients in the taper group (n=57) reported more days per week of illicit opioid use than those in the maintenance group (n=56) once they were no longer receiving buprenorphine (mean use, 1.27 [95% CI, 0.6 to 1.94] vs 0.47 [95% CI, 0.19 to 0.74] days). Patients in the taper group had fewer maximum consecutive weeks of opioid abstinence compared with those in the maintenance group (mean abstinence, 2.7 [95% CI, 1.72 to 3.75] vs 5.2 [95% CI, 4.16 to 6.2] weeks). Patients in the taper group were less likely to complete the trial (6 of 57 [11%] vs 37 of 56 [66%]; P<0.001). Sixteen patients in the taper group reinitiated buprenorphine treatment after the taper owing to relapse. The authors concluded that tapering is less efficacious than ongoing maintenance treatment in patients with prescription opioid dependence (Fiellin et al, 2014).
- The American Psychiatric Association, American Society of Addiction Medicine, United States Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment, and the Veterans Health Administration publish guidelines for the treatment of opioid dependence. These guidelines support the access of pharmacological therapy for the management of opioid dependence without preference of one agent over another. However, they do suggest that combination buprenorphine products should be used for maintenance treatment (Center for Substance Abuse Treatment, 2004; Kleber et al, 2006; Kraus et al, 2011; Veterans Health Administration, 2015).

## SAFETY SUMMARY

- These products are contraindicated in patients with known hypersensitivity to the active ingredients.
- Warnings and precautions include abuse potential, central nervous system depression, dependence, impairment in operating heavy machinery, orthostatic hypotension, neonatal withdrawal, respiratory depression, precipitation of opiate withdrawal, and hepatic impairment.
- Similar to other opiate products, these products may increase intracholedochal pressure, increase cerebrospinal fluid pressure, and obscure diagnosis or exacerbate acute abdominal symptoms.
- These products should not be used as analgesics.

- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome.
- All of the buprenorphine-containing products have an associated risk evaluation and mitigation strategy (REMS) program (REMS@FDA, 2016).

(Micromedex 2.0, 2016)

## DOSING AND ADMINISTRATION

**Table 2a. Dosing and Administration**

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| **Single Entity Agents** | | | | |
| SUBUTEX (buprenorphine) | Sublingual tablet: 2 mg, 8 mg | Opioid dependence: Initial: dose should be individualized based on type and degree of opioid dependence and timing of last use; titrate rapidly to clinically effective dose; buprenorphine plus naloxone replace buprenorphine typically after 2 days; Maintenance: (for patients who cannot tolerate naloxone) typical range is 4 to 24 mg daily; adjust dosage in 2 or 4 mg increments/ decrements to level that holds patient in treatment and suppresses opioid withdrawal effects | To avoid precipitating withdrawal, induction should be undertaken when objective and clear signs of withdrawal are evident. | Buprenorphine sublingual tablets should be placed under the tongue until dissolved.<br><br>For doses requiring the use of more than two tablets, patients are advised to either place all the tablets at once or alternatively, place two tablets at a time under the tongue. |
| **Combination Products** | | | | |
| BUNAVAIL, SUBOXONE, ZUBSOLV (buprenorphine/ naloxone) | Buccal film (BUNAVAIL): 2.1 mg/0.3 mg 4.2 mg/0.7 mg 6.3 mg/1 mg<br><br>Sublingual film (SUBOXONE): 2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg<br><br>Sublingual tablet (generics, ZUBSOLV): 2 mg/0.5 mg* 8 mg/2 mg* 1.4 mg/0.36 mg† 2.9 mg/0.71mg† | Opioid dependence: Buccal film (BUNAVAIL): Maintenance; the recommended dose is 8.4 mg/1.4 mg buprenorphine/ naloxone per day administered as a single dose (range 2.1 mg/0.3 mg to 12.6 mg/2.1 mg)<br><br>Sublingual film (SUBOXONE): Induction; up to 8 mg/2 mg is recommended on Day 1, given as an initial dose of 2 mg/0.5 mg or 4 mg/1 mg and | | Buprenorphine/ naloxone sublingual tablets should be placed under the tongue until dissolved. For doses requiring the use of more than two SUBOXONE tablets, patients are advised to either place all the tablets at once or alternatively, place two tablets at a time under the tongue. Patients requiring more than one ZUBSOLV tablet are advised |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | 5.7 mg/1.4 mg†<br>8.6 mg/2.1 mg†<br>11.4 mg/2.9 mg† | titrated in 2 mg to 4 mg increments of buprenorphine at approximately 2 hour intervals based on the control of acute symptoms; on Day 2, a single dose of up to 16 mg/4 mg is recommended; Maintenance; recommended dose is 16 mg/4 mg buprenorphine/ naloxone per day administered as a single dose (range 4 mg/1 mg to 24 mg/6 mg)<br><br>Sublingual tablets (ZUBSOLV): Induction; initial dose of up to 5.7 mg/1.4 mg is recommended, given as an initial dose of 1.4 mg/0.36 mg followed by the remaining Day 1 dose divided into 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2 hour intervals; on Day 2, a single daily dose of up to 11.4 mg/2.9 mg is recommended; Maintenance; target dose buprenorphine/ naloxone 11.4 mg/2.9 mg once daily; typical dosage range, buprenorphine/ naloxone 2.9 mg/0.71 mg to 17.2 mg/4.2 mg daily<br><br>Buprenorphine/ naloxone generic sublingual tablets: Maintenance; recommended dose is 16 mg/4 mg buprenorphine/ naloxone per day administered as a | | to place all tablets in different places under the tongue at the same time. Do not crush, break, chew, or swallow the tablets.<br><br>The SUBOXONE sublingual film should be placed under the tongue close to the base on the left or right side (one film only). If more film is needed to achieve the dose, place an additional film under the tongue on the opposite side. Minimize overlap as much as possible. Keep the film under the tongue until completely dissolved. If a third film is needed, put it under the tongue after the first 2 films have dissolved. Do not cut, chew, or swallow the film. For induction, the sublingual route of SUBOXONE film is preferred. For maintenance, SUBOXONE film may be administered buccally or sublingually. For buccal use, one film can be placed on the inside of both the right and left cheeks until completely dissolved. If more than 2 films are needed, place additional film on |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | | single dose; range 4 mg/1 mg to 24 mg/6 mg daily | | the inside of the cheek after the first 2 films have dissolved.<br><br>The BUNAVAIL buccal film should be applied to the buccal mucosa (with the text on the film against the side of the cheek). Press and hold in place for five seconds and leave in place until dissolved; do not eat or drink until dissolved. Two films may be applied at once (one to each cheek). No more than two films should be applied to the inside of one cheek at a time. Do not cut or tear film.<br><br>Taper therapy to avoid withdrawal symptoms. |

*Generic buprenorphine/naloxone sublingual tablets.
†ZUBSOLV (buprenorphine/naloxone) sublingual tablets.

**Table 2b. Equivalent Doses of Buprenorphine/Naloxone Combination Products[a]**

| BUNAVAIL buccal film | buprenorphine/naloxone sublingual tablets and/or SUBOXONE sublingual film | ZUBSOLV sublingual tablets |
|---|---|---|
| - | 2 mg/0.5 mg | 1.4 mg/0.36 mg |
| 2.1 mg/ 0.3 mg | 4 mg/1 mg | 2.9 mg/0.71 mg |
| 4.2 mg/ 0.7 mg | 8 mg/2 mg | 5.7 mg/1.4 mg |
| 6.3 mg/1 mg | 12 mg/3 mg | 8.6 mg/2.1 mg |
| - | 16 mg/4 mg | 11.4 mg/2.9 mg |

[a] Systemic exposures of buprenorphine and naloxone may differ when patients are switched from tablets to films or vice versa.

(Micromedex 2.0, 2016)

## SPECIAL POPULATIONS

**Table 3. Special Populations**

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| **Single Entity Agents** | | | | | |
| SUBUTEX (buprenorphine) | Clinical studies did not include sufficient number of subjects aged 65 and over to determine whether they responded differently than younger subjects.<br><br>Dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range. | Safety and efficacy have not been established. | No dosage adjustment required. | Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half and monitor for signs and symptoms of toxicity or overdose.<br><br>Moderate hepatic impairment: No dose adjustment necessary. Use with caution and monitor for signs and symptoms of toxicity or overdose.<br><br>Mild hepatic impairment: No dosage adjustment necessary. | Pregnancy Category C*<br><br>Buprenorphine passes into breast milk. Caution should be exercised and infant monitored for increased drowsiness and breathing difficulties. |
| **Combination Products** | | | | | |
| BUNAVAIL, SUBOXONE, ZUBSOLV (buprenorphine/ naloxone) | Clinical studies did not include sufficient number of subjects aged 65 and over to determine whether they responded differently than younger subjects.<br><br>Dose selection for elderly patients should | Safety and efficacy have not been established. | No dosage adjustment required. | Unknown; because both drugs are extensively metabolized by the liver, plasma levels may be higher in patients with moderate and severe hepatic impairment.<br><br>Dosage should be adjusted and patients should | Pregnancy Category C*<br><br>Buprenorphine passes into breast milk. Caution should be exercised and infant monitored for increased drowsiness and breathing difficulties. |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| | be cautious, usually starting at the low end of the dosing range. | | | be watched for signs and symptoms for precipitated opioid withdrawal.<br><br>Since they are fixed dose combinations including naloxone, these formulations should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. | |

*Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

(Micromedex 2.0, 2016)

## CONCLUSION

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, BUNAVAIL (buprenorphine/naloxone) buccal film, SUBOXONE (buprenorphine/naloxone) sublingual film, and ZUBSOLV (buprenorphine/naloxone) sublingual tablets are used for the treatment of opioid dependence. Some products are indicated for maintenance treatment only, while others are indicated for both induction and maintenance.
- For patients unable to receive methadone-clinic based treatment, buprenorphine and buprenorphine/naloxone remain viable treatment options. Buprenorphine may be used for the earlier stages of therapy when treatment is observed since it does not have the naloxone component to deter inappropriate use. These agents are Schedule III controlled substances.
- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (Amass et al, 2004; Fiellin et al, 2008).
- Physicians prescribing buprenorphine for opioid dependency must undergo specialized training due to the potential for abuse and diversion. Because of these risks, buprenorphine monotherapy should be reserved for patients who are pregnant or have a documented allergy to naloxone (DATA, 2000; Center for Substance Abuse Treatment, 2004).
- Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence (Farre et al, 2002; Gibson, et al, 2008; Gowing et al, 2009; Johnson et al, 1992; Kamien et al, 2008; Meader et al, 2010; Petitjean et al, 2001; Soyka et al, 2008; Mattick et al, 2014; Strain et al, 2011).
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome. These products also have REMS criteria.
- The American Psychiatric Association, American Society of Addiction Medicine, United States Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment, and the Veterans Health Administration publish guidelines for the treatment of opioid dependence. These guidelines support the access of

pharmacological therapy for the management of opioid dependence without preference of one agent over another. However, they do suggest that combination products should be used for maintenance treatment (Center for Substance Abuse Treatment, 2004; Kleber et al, 2006; Kraus et al, 2011; Veterans Health Administration, 2015).

- Buprenorphine and buprenorphine/naloxone sublingual tablets are available generically.

**Table 4. Advantages and Disadvantages of Buprenorphine Products**

| Drug | Advantages | Disadvantages |
|---|---|---|
| **Single Entity Agents** | | |
| buprenorphine sublingual tablets | Available as a generic; preferred for induction | Does not contain naloxone component to deter abuse; not preferred for maintenance |
| **Combination Products** | | |
| BUNAVAIL (buprenorphine/naloxone) buccal film | Contains naloxone to deter abuse | Not available as a generic; indicated for maintenance treatment only |
| buprenorphine/naloxone sublingual tablets | Contains naloxone to deter abuse; available as a generic | Longer dissolution time compared to films; indicated for maintenance treatment only |
| SUBOXONE (buprenorphine/naloxone) sublingual film | Contains naloxone to deter abuse; can be used for induction and maintenance; can be administered either sublingually or buccally for maintenance treatment | Not available as a generic |
| ZUBSOLV (buprenorphine/naloxone) sublingual tablets | Contains naloxone to deter abuse; can be used for induction and maintenance | Not available as a generic |

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