OPTUMRx

Therapeutic Class Overview
Fentanyl Immediate Release Products

INTRODUCTION

- Pain is one of the most common symptoms associated with cancer. Patients with cancer experience both chronic and acute pain, and it is important to distinguish the 2 from each other when determining appropriate management strategies. Breakthrough pain (BTP) is commonly defined as a transient increase in pain, occurring either spontaneously or in relation to a trigger, in a patient with relatively stable and adequately controlled background pain (*Zeppetella et al 2014*).
- BTP can broadly be divided into two types: incident BTP (when an obvious trigger precipitates the event) and spontaneous BTP (when no specific triggers are identified) (*Mercadante 2015*).
- On average, a typical duration of untreated BTP is approximately 30 minutes, with a mean time to peak intensity of about 10 minutes. However, BTP is a heterogeneous condition, varying between and within individuals (*Mercadante 2015*).
- Supplemental opioid doses are used to manage episodes of BTP *(National Comprehensive Cancer Network [NCCN] 2018, Portenoy et al 1990).* Any of the available short-acting opioids have the potential to be utilized for the management of BTP; however, immediate-release fentanyl products, due to a fast onset of action, are specifically Food and Drug Administration (FDA) approved for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to around-the-clock therapy for their underlying persistent cancer pain. Five different dosage forms of immediate-release fentanyl are currently available: a sublingual tablet (Abstral), a transmucosal lozenge (Actiq), a buccal tablet (Fentora), a nasal spray (Lazanda), and a sublingual spray (Subsys). A sixth immediate-release fentanyl product (Onsolis, a buccal film) was approved in the United States but is not currently available; the pharmaceutical company has stated that options for commercializing Onsolis are still being investigated (*BioDelivery Sciences 2017*). Currently, only the fentanyl transmucosal lozenge is available generically.
- Clinical trials have consistently demonstrated the effectiveness of immediate-release fentanyl in the management of BTP in patients with cancer; however, head-to-head trials are limited.
- Medispan class: Immediate-release fentanyl products are classified within the opioid agonist class of medications.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Abstral (fentanyl sublingual tablet)	-
Actiq (fentanyl oral transmucosal lozenge)	✔
Fentora (fentanyl buccal tablet)	-
Lazanda (fentanyl nasal spray)	-
Onsolis (fentanyl buccal soluble film)*	-
Subsys (fentanyl sublingual spray)	-

*Drug not currently available; the pharmaceutical company has stated that options for commercializing Onsolis are still being investigated.

(*BioDelivery Sciences 2017, Drugs@FDA 2018, Orange Book: Approved drug products with therapeutic equivalence evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Abstral (fentanyl sublingual tablet)	Actiq (fentanyl oral transmucosal lozenge)	Fentora (fentanyl buccal tablet)	Lazanda (fentanyl nasal spray)	Onsolis (fentanyl buccal soluble film)	Subsys (fentanyl sublingual spray)
Management of breakthrough pain in cancer patients **18 years of age** and older who are already receiving and are tolerant to around-the-clock opioid therapy for underlying persistent cancer pain.	✔		✔	✔	✔	✔
Management of breakthrough pain in cancer patients **16 years of age** and older who are already receiving and are tolerant to around-the-clock opioid therapy for underlying persistent cancer pain.		✔				

(Prescribing information: Abstral 2016, Actiq 2016, Fentora 2016, Lazanda 2017, Onsolis 2016, Subsys 2016)

- 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 consistently demonstrated the effectiveness and safety of all available dosage forms of immediate-release fentanyl in the management of BTP in patients with cancer. Several trials have compared the agents to placebo and other short-acting opioids, including oxycodone, morphine, hydrocodone, hydromorphone, and codeine. Due to the nature of the disease in which immediate-release fentanyl is utilized, many of the efficacy clinical trials are open-label, dose titration trials. Patients were typically enrolled in a baseline phase in which the efficacy of their usual BTP medication was assessed and/or the dose of the studied immediate-release fentanyl product was titrated to an effective dose (*Christie et al 1998, Coluzzi et al 2001, Davies et al 2011, Fallon et al 2011, Hanks et al 2004, Jandhyala et al 2013, Kress et al 2009, Masel et al 2017, Mercadante et al 2007, Mercadante et al 2009, Payne et al 2001, Portenoy et al 1999, Portenoy et al 2006, Portenoy et al 2010, Rauck et al 2009, Rauck et al 2010, Rauck et al 2012, Slatkin et al 2007, Ueberall et al 2016, Vissers et al 2010, Zeppetella et al 2010*).
- Trials conducted to compare immediate-release fentanyl to oral short-acting opioids have generally shown immediate-release fentanyl products to improve pain relief shortly after dosing.
  - Two studies demonstrated significantly greater pain intensity difference (PID) scores as early as 10 and 15 minutes after administration of fentanyl nasal spray when compared to immediate-release morphine ($p < 0.05$) (*Davies et al 2011, Fallon et al 2011*).
  - A network meta-analysis of 10 randomized controlled trials evaluating fentanyl in various forms (nasal spray, sublingual tablets, buccal soluble film, buccal tablets, and oral transmucosal lozenge), as well as immediate-release morphine, demonstrated that all tested medications provided pain relief, but the fentanyl products provided greater pain relief in a shorter time frame than oral morphine. It was further noted that the intranasal fentanyl spray provided clinically meaningful pain relief at 15 minutes, whereas other medications did not provide clinically meaningful relief until later time points (*Zeppetella et al 2014*).
  - Another meta-analysis compared fentanyl buccal tablets, sublingual tablets, and transmucosal lozenges to both placebo and immediate-release morphine. Authors of this study found that the probability of each formulation being superior to placebo, in regards to PID over 60 minutes, was 97%, 72%, and 81% for buccal tablets, sublingual tablets, and transmucosal lozenges, respectively. The probability of immediate-release morphine being superior to placebo was 61%. The probabilities of greater pain relief for the fentanyl products compared to immediate-release morphine

were 68%, 57%, and 66% for the buccal tablet, sublingual tablet, and transmucosal lozenge, respectively. Similarly, when the fentanyl preparations were compared with immediate-release morphine over the first 30 minutes post-dosing, the likelihood of superiority estimates were 58%, 56%, and 62% for buccal tablets, sublingual tablets, and transmucosal lozenges, respectively (*Jandhyala et al 2013*).

- In contrast to the studies above, fentanyl transmucosal lozenge demonstrated a slower onset of action when compared to intravenous morphine (*Mercadante et al 2007*).
- There is limited evidence comparing the efficacy among all the various formulations of immediate-release fentanyl products; however, there are data comparing the fentanyl nasal spray to the transmucosal lozenge and to the buccal tablet.
  - One open-label, crossover study evaluated the efficacy of fentanyl nasal spray compared to fentanyl transmucosal lozenge. The primary efficacy endpoint, defined as the time to onset of meaningful pain relief, was 11 minutes for the fentanyl nasal spray group and 16 minutes for the fentanyl transmucosal lozenge group; 65.7% of patients had a faster onset of meaningful pain relief with the intranasal fentanyl spray ($p < 0.001$). Secondary outcomes included PID scores at 10 and 30 minutes (PID_{10}, PID_{30}). The adjusted mean PID_{10} and PID_{30} were significantly greater for the fentanyl nasal spray group compared to the fentanyl lozenge group ($p < 0.001$) (*Mercandante et al 2009*).
  - A meta-analysis by Vissers et al found that differences in PID scores at 15 minutes (PID_{15}) favoring fentanyl nasal spray were 1.2 points better (95% Bayesian credible interval [CrI], 0.8 to 1.5) compared to the buccal tablet and 1.3 points better (95% CrI, 0.9 to 1.6) compared to the transmucosal lozenge. The significant differences in PID scores favoring fentanyl nasal spray were maintained at the 30 minute time point compared to the buccal tablet and at the 30 and 45 minute time points compared to the transmucosal lozenge (*Vissers et al 2010*).

CLINICAL GUIDELINES

- The European Association for Palliative Care (EAPC) guidelines recommend that breakthrough cancer pain be evaluated to ensure that true breakthrough pain is differentiated from uncontrolled background pain. Around-the-clock opioid therapy should be optimized before a rescue opioid is considered. True breakthrough cancer pain can then be treated with immediate-release oral opioids or with oral or intranasal fentanyl formulations (*Caraceni et al 2012*).
- Breakthrough cancer pain should be treated with agents that have a quick onset and short duration in order to mirror the characteristics that define this type of pain. Standard practice is to administer a rescue dose of short-acting opioids equivalent to 10% to 20% of the total daily dose of the maintenance opioid being used to manage the underlying persistent cancer pain. It is preferred to use the same opioid for breakthrough pain that is being used to manage the persistent pain; however, this is not always possible (*Caraceni et al 2012, Caraceni et al 2013, Hagen et al 2007, NCCN 2018*).
- The 2018 NCCN clinical practice guidelines on adult cancer pain state that transmucosal immediate-release fentanyl (TIRF) medications offer rapid onset of analgesic effect and may be considered only for opioid-tolerant patients with breakthrough pain not attributed to inadequate dosing of the maintenance opioid regimen. The NCCN guidelines further indicate that there is no data to support use of one TIRF product over another, only that patients should be started on the lowest dose of the formulation and titrated to effect (*NCCN 2018*).

SAFETY SUMMARY

- Contraindications:
  - Fentanyl immediate-release products are contraindicated in opioid non-tolerant patients, in the management of acute or postoperative pain, in patients with acute or severe bronchial asthma in an unmonitored setting or without access to resuscitative measures, and in patients with suspected gastrointestinal obstruction.
  - Fentanyl immediate-release products are contraindicated in patients with a known intolerance or hypersensitivity to fentanyl or to any of the products' components.

Boxed Warning for Abstral, Actiq, Fentora, Lazanda, Onsolis, and Subsys

WARNING
• Due to the risk of fatal respiratory depression, these medications are contraindicated in opioid non-tolerant patients and in the management of acute or postoperative pain, including headache/migraines. Monitor closely, especially upon initiation or following a dose increase. • Keep out of reach of children. Accidental ingestion can result in a fatal overdose of fentanyl. • Use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) may cause fatal respiratory depression. • Concomitant use with benzodiazepines or other central nervous system (CNS) depressants may result in profound sedation, respiratory depression, or death. • When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product. • When dispensing, do not substitute with any other fentanyl products. • Fentanyl is a Schedule II controlled substance with abuse liability similar to other opioid analgesics. • Available only through a restricted program called the TIRF Risk Evaluation and Mitigation Strategy (REMS) Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program. • Prolonged use in pregnant women can result in neonatal opioid withdrawal syndrome (NOWS).

- Key additional warnings and precautions include:
  - Opioid analgesics impair the mental and/or physical ability required for potentially dangerous tasks (eg, driving a car or operating machinery).
  - Respiratory depression is the chief hazard of opioid agonists; it is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients.
  - Products contain an amount of medication which can be fatal in children, in individuals for whom they are not prescribed, and in those who are not opioid-tolerant.
  - Products may produce bradycardia; use with caution in patients with bradyarrhythmias.
  - Products are not recommended for use in patients who have received monoamine oxidase inhibitors within 14 days due to the risk of serotonin syndrome.
  - Products may produce adrenal insufficiency, severe hypotension, increased intracranial pressure, and increased seizure frequency in patients with seizure disorders.
  - In clinical trials for Fentora, 10% of patients reported application site reactions which ranged from paresthesia to ulceration and bleeding.
- Common adverse reactions of immediate-release fentanyl products are consistent with the opioid class, including dizziness, somnolence, constipation, nausea, vomiting, and dyspnea.
- Products may cause fetal harm; available data in pregnant women is insufficient to inform a drug-associated risk for major birth defects and miscarriage.
- Fentanyl is excreted in breast milk; breastfeeding is not recommended.
- Reduced fertility may occur in females and males of reproductive potential after chronic use of opioids. It is unknown if these effects are reversible.
- Safety and efficacy have not been established in pediatric patients below 16 years of age for Actiq, and below 18 years of age for all other products.
- Products in this class share a REMS program, the TIRF REMS. The purpose of the TIRF REMS access program is to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with these agents (*REMS@FDA 2017, TIRF REMS Program*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Abstral (fentanyl)	Sublingual tablet	Once titrated to an effective dose, use 1 tablet at onset of BTP episode. May repeat dose after 30 minutes if adequate analgesia is not obtained. Must wait at least 2 hours before treating another BTP episode. Limit to treatment of 4 or fewer BTP episodes per day.	Administer with caution in patients with renal and hepatic impairment.
Actiq (fentanyl)	Transmucosal lozenge	Once titrated to an effective dose, use 1 lozenge at onset of BTP episode. May repeat dose after 15 minutes if adequate analgesia is not obtained. Must wait at least 4 hours before treating another BTP episode. Limit to use of 4 or fewer units per day.	Administer with caution in patients with renal and hepatic impairment.
Fentora (fentanyl)	Buccal tablet	Once titrated to an effective dose, use 1 tablet at onset of BTP episode. May repeat dose after 30 minutes if adequate analgesia is not obtained. Must wait at least 4 hours before treating another BTP episode.	Administer with caution in patients with renal and hepatic impairment.
Lazanda (fentanyl)	Nasal spray	Once titrated to an effective dose, use 1 dose at onset of BTP episode. Must wait at least 2 hours before treating another BTP episode. Limit treatment to 4 or fewer BTP episodes per day.	Administer with caution in patients with renal and hepatic impairment.
Onsolis (fentanyl)	Buccal soluble film	Once titrated to an effective dose, use 1 unit at onset of BTP episode. Must wait at least 2 hours before treating another BTP episode. Limit to 4 doses per day.	Administer with caution in patients with renal and hepatic impairment.
Subsys (fentanyl)	Sublingual spray	Once titrated to an effective dose, use 1 unit at onset of BTP episode. May repeat dose after 30 minutes if adequate analgesia is not obtained. Must wait at least 4 hours before treating another BTP episode. Limit to 4 or fewer doses per day.	Administer with caution in patients with renal and hepatic impairment. Exposure to Subsys is greater in cancer patients with mucositis leading to an increased risk of respiratory depression and central nervous system depression. Patients with Grade 1 mucositis should be closely monitored. Subsys should be avoided in patients with Grade 2 mucositis or higher unless the benefits outweigh the risks.

See the current prescribing information for full details

CONCLUSION

- Immediate-release fentanyl products are short-acting opioids FDA-approved for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to around-the-clock therapy for their underlying persistent pain. Five different dosage forms of immediate-release fentanyl are currently available: a sublingual tablet (Abstral), a transmucosal lozenge (Actiq), a buccal tablet (Fentora), a nasal spray (Lazanda), and a sublingual spray (Subsys). A sixth immediate-release fentanyl product (Onsolis, a buccal film) is approved in the United States but is not

currently available; the pharmaceutical company has stated that options for commercializing Onsolis are still being investigated *(BioDelivery Sciences 2017)*. Currently, only the fentanyl transmucosal lozenge is available generically.

- Immediate-release fentanyl has a fast onset of action, making it well-suited for the management of cancer-related BTP as this type of pain is characterized by a rapid onset, severe intensity and a self-limiting course. Currently, these products are the only short-acting opioids specifically FDA-approved for use in the management of cancer pain.
- Current clinical guidelines support the use of immediate-release fentanyl products as an option for the treatment of breakthrough cancer pain in opioid tolerant patients. There is no evidence to support use of one product over another, and patients should be started on the lowest available dose and titrated to effect.
- The effectiveness of these products is well documented in clinical trials. There are limited head-to-head trials comparing efficacy among all dosage forms; however, there is some evidence supporting a faster onset of action for fentanyl nasal spray when compared to the fentanyl lozenge or buccal tablet.
- Bioavailability differs among products and the different formulations are not interchangeable. Appropriate dose titration is important.
- All products share a boxed warning for the risk of life-threatening respiratory depression, accidental ingestion (especially by children), drug interactions, medication errors, abuse potential, REMS, and NOWS.
- Products in this class are only available through a REMS program, the TIRF REMS. The purpose of the TIRF REMS access program is to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with these agents.

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