

Transmucosal Immediate Release Fentanyl Products High Potency Narcotic Analgesics

Executive Summary

- All transmucosal immediate release fentanyl products (TIRFs) provide rapid onset analgesia with clinically meaningful pain relief achieved 30 minutes post dose.
- TIRF products are not interchangeable on a mcg per mcg basis. Patients being switched from a TIRF should be initiated at the lowest dose of the new product following the recommended dose titration protocol.
- The shared TIRF REMS mandates that all outpatients, healthcare professionals who prescribe TIRFs, as well as pharmacies and distributors be enrolled in the program and ensures appropriate use within FDA-approved labeling.
- In the absence of head-to-head trials, TIRF selection should be based on individual patient characteristics, likelihood of adherence, patient preferences, as well as cost.

Table 1: Uniform Formulary Recommendations for the High Potency Narcotic Analgesics from Previous Formulary Decisions

UF Status	Medications	Formulation	Generic
BCF	<ul style="list-style-type: none"> • Morphine sulfate 12-hour • Morphine sulfate 	ER tablets IR tablets	Yes Yes
UF	<ul style="list-style-type: none"> • Hydromorphone (Exalgo) • Morphine/Naltrexone (Embeda) • Codeine • Fentanyl • Hydromorphone (Dilaudid) • Meperidine • Methadone • Morphine (Avinza, Kadian) • Oxycodone (Oxycontin) • Oxymorphone (Opana) • Tapentadol ER (Nucynta ER) 	ER tablets ER capsules Oral tablets Transdermal, Transmucosal IR tablets Oral tablets Oral tablets Oral tablets ER-once daily IR, ER tablets, oral liquids IR, ER tablets ER tablets	Yes No Yes Yes Yes Yes Yes Yes Yes Yes Yes No
NF	<ul style="list-style-type: none"> • Tapentadol (Nucynta) • Oxycodone (Oxecta) 	IR tablets IR tablets	No No

Table 2: Transmucosal Immediate Release Fentanyl Products — Subclass Definition

Brand	Dosage Form	FDA Approval	Patent Expiration	Generic Availability
Abstral (Galena Biopharma)	Sublingual Tablet	Jan 7, 2011	Sept 24, 2019	
Actiq (Cephalon)	Transmucosal Lozenge	Nov 4, 1998		Y (PAR, Mallinckrodt)
Fentora (Cephalon)	Buccal Tablet	Sept 25, 2006	Mar 2019 – Jun 2028	-
Lazanda (Depomed)	Nasal Spray	June 30, 2011	Apr 2018 – Oct 2024	-
Onsolis (Meda)	Buccal Film	July 16, 2009	Discontinued	N/A
Subsys (Insys)	Sublingual Spray	Jan 4, 2012	April 27, 2030	-

FDA-Approved Indications

All of the TIRFs are indicated 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 (opioid tolerant). The definition of opioid tolerant, according to the FDA, is those patients who are regularly taking daily doses of at least 60 mg oral morphine, 30 mg oral oxycodone, 8 mg oral hydromorphone, 25 mg oral oxymorphone, 25 µg transdermal fentanyl per hour, or an equianalgesic dose of another opioid for one week or longer.

Generic Availability

Only the fentanyl citrate transmucosal lozenge (Actiq) is available in generic form. The other TIRFs have patents that extend as far as 2030.

Summary of the Evidence

- According to the National Comprehensive Cancer Network (NCCN), rescue doses of short-acting opioids should be provided to patients with cancer pain that is not relieved by around-the-clock opioid doses. Though the guideline states that consideration should be given to TIRFs, preference is not given to one formulation or mode of delivering fentanyl transmucosally over another.
- All the available efficacy trials for the TIRFs currently marketed in the United States have been randomized double-blind comparisons with placebo. No head-to-head comparisons have been conducted to date. All the trials differ in terms of patient selection criteria, severity of breakthrough pain episodes and titration as well as repeat dosing protocols. Other differences include the extent of placebo response and proportion of patients with a neuropathic component to their pain, all of which could affect the study results and make indirect comparisons difficult among the TIRF formulations.
- A network meta-analysis of 10 trials compared all opioids used in the treatment of breakthrough cancer pain (BTCP). Fentanyl buccal tablets, sublingual tablets and film transmucosal lozenges, an intra-nasal spray (INFS, only available in Europe), and a pectin nasal spray were compared to both placebo and immediate-release morphine sulfate (MSIR). The primary endpoint was the pain intensity difference (PID) relative to placebo up to 60 minutes after administration. All the TIRFs showed greater PIDs relative to placebo; INFS, pectin nasal spray, fentanyl buccal tablets, and the transmucosal lozenges showed greater PIDs as early as 15 minutes post administration compared to placebo, but only INFS produced clinically meaningful pain relief (absolute PID ≥ 2) at this time point. All the BTCP medications produced clinically meaningful pain relief at 30 minutes post administration except MSIR, which did not show efficacy over placebo until 45 minutes post administration.
- A Cochrane review of 15 studies evaluating transmucosal fentanyl citrate for cancer-related breakthrough pain demonstrated that TIRFs significantly improved pain intensity compared to placebo and immediate-release morphine sulfate at 10, 15, and 30 minutes post administration. Global assessment scores also favored the TIRFs over placebo and MSIR. The authors concluded that the TIRFs were an effective treatment in the management of breakthrough pain. They noted the paucity of literature for the management of breakthrough pain and the lack of head-to-head comparisons to help guide selection.

Safety

- All TIRFs share the same black box warning highlighting the risk of respiratory depression, the potential for medication errors when switching from TIRF to TIRF, as well as the abuse potential given the potency of fentanyl as an opioid. Patients should not be converted on a mcg per mcg basis from other TIRF products.
- There is a shared Risk Evaluation Mitigation Strategy (REMS) access program for all the TIRF products. This shared REMS mandates that all outpatients, healthcare professional who prescribe TIRFs, as well as pharmacies and distributors be enrolled in the program. The goals of the REMS are to ensure appropriate patient selection (use in opioid-tolerant patients only), prevent inappropriate conversion between fentanyl products, prevent accidental exposure to children and others, and educate providers and patients on the potential for misuse, abuse, addiction, and overdose.
- Adverse effects were similar for all the TIRFs and consistent with opioid therapy in cancer patients. With the exception of unique application site reactions: dental caries (Actiq) and nasal irritation (Lazanda).

Other Factors

- All fentanyl products are part of the high-potency opioid safety edit. This is a pharmacy safety program designed to reduce the use of highly potent opioids in opioid-naïve patients.
- All TIRFs have a rapid onset of analgesia and provide alternative options for patients with difficulty swallowing or persistent nausea/vomiting.
- Unique advantages: administration of Actiq can be interrupted in case of toxicity and it is approved for adolescents 16 years and older. The sublingual formulations Abstral and Subsys have faster dissolution than the oral and buccal formulations, Actiq and Fentora. Lazanda, the nasal spray, is convenient and can be administered by caregivers.

- Unique disadvantages: Actiq is associated with variable absorption; training is also required to ensure correct use (move lozenge along the inside of cheek until complete dissolution), takes about 15 minutes to dissolve completely, lollipop may be considered childish, sugar content has resulted in formation of dental caries and tooth loss. Lazanda may be unsuitable for patients with respiratory illnesses. Coadministration of a vasoconstrictive nasal decongestant, such as oxymetazoline, to treat allergic rhinitis leads to reduced fentanyl plasma concentrations in patients taking Lazanda.

Conclusion

- Minor differences in pharmacokinetics of the TIRF formulations do not result in clinically relevant differences in pain relief. All TIRFs provide rapid onset analgesia with clinically meaningful differences in pain intensity achieved after 30 minutes of administration.
- In the absence of head-to-head trials, TIRF selection should be based on individual patient characteristics, likelihood of adherence, patient preferences, as well as cost.
- Though not as ideal, short-acting opioids remain a viable option for the treatment of BTCP.

References

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Abbreviations

The following abbreviations are used in this review:

BTCP	– breakthrough cancer pain
INFS	– intra-nasal spray
MSIR	– immediate-release morphine sulfate
NCCN	– National Comprehensive Cancer Network
PID	– pain intensity difference
REMS	– Risk Evaluation Mitigation Strategy
TIRF	– transmucosal immediate release fentanyl