

MTF Formulary Management for Transmucosal Immediate Release Fentanyl Products (TIRFs)

Defense Health Agency Pharmacy Operations Division
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Bottom-line:

- All TIRFs provide rapid onset of analgesia, with clinically meaningful pain relief achieved 30 minutes post dose.
- TIRF products are not interchangeable on a mcg per mcg basis. When switching patients from one TIRF to another, initiate the new product at the lowest dose, following the recommended dose titration protocol.
- The shared TIRF Risk Evaluation and Mitigation Strategies (REMS) mandates that all outpatients, healthcare professionals who prescribe TIRFs, as well as pharmacies and distributors be enrolled in the program, to ensure 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.

Uniform Formulary Decision: The Director, DHA approved the recommendations from the February 2015 DoD P&T Committee meeting on 5 May 2015, with an implementation date of 19 August 2015.

Uniform Formulary (UF) drugs		Non-Formulary (NF) drugs
BCF drugs - MTFs <u>must</u> have on formulary	MTFs <u>may</u> have on formulary	MTFs <u>must not</u> have on formulary
None	<ul style="list-style-type: none"> • Fentanyl transmucosal lozenge (Actiq, generics) 	<ul style="list-style-type: none"> • Fentanyl sublingual tablet (Abstral) • Fentanyl buccal tablet (Fentora) • Fentanyl pectin nasal spray (Lazanda) • Fentanyl sublingual spray (Subsys)

Clinical Summary

- Provide rescue doses of short-acting opioids to patients with cancer pain that is not relieved by around-the-clock opioid doses. (National Comprehensive Cancer Network Guideline) In the guideline preference is not given to one formulation or mode of delivering fentanyl transmucosally over another.
- All of the TIRFs are indicated for the management of breakthrough cancer pain (BTCP) in patients who are already receiving opioids, and who are tolerant to around-the-clock therapy for their underlying persistent cancer pain.
- All the available efficacy trials for the TIRFs currently marketed in the United States are randomized double-blind comparisons with placebo. No head-to-head comparisons have been conducted to date. Indirect comparisons are difficult to make, due to differences in 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.
- A network meta-analysis of 10 trials compared all opioids used in the treatment of BTCP. All the TIRFs showed greater pain intensity difference (PID) up to 60 minutes after administration, relative to placebo. All the BTCP medications produced clinically meaningful pain relief at 30 minutes post administration except morphine sulfate immediate release (MSIR), which did not show efficacy over placebo until 45 minutes post administration.
- A Cochrane review of 15 studies demonstrated that the TIRFs significantly improved pain intensity compared to placebo and MSIR at 10, 15, and 30 minutes post administration in patients with BTCP. Global assessment scores also favored the TIRFs over placebo and MSIR. The TIRFs were an effective treatment in the management of breakthrough pain, but there is a paucity of literature for managing BTCP, and a lack of head-to-head comparisons to help guide selection.

Safety and Tolerability

- 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.
- Adverse effects are similar for all the TIRFs and consistent with opioid therapy in cancer patients. Unique application site reactions include dental caries with the lozenge (Actiq) and nasal irritation with the nasal spray (Lazanda).

Other Factors

- All fentanyl products are part of the high-potency opioid safety edit, a type of prior authorization. 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 (lozenge) can be interrupted in case of toxicity and it is approved for adolescents 16 years and older. The sublingual formulations Abstral (tablet) and Subsys (spray) have faster dissolution than Actiq (lozenge) and Fentora (buccal tablet). Lazanda (nasal spray) is convenient and can be administered by caregivers.
- Unique disadvantages: The sugar content in the Actiq lozenge may cause formation of dental caries and subsequent tooth loss. Additionally, Actiq is associated with variable absorption and takes 15 minutes to dissolve completely. Lazanda may be unsuitable for patients with respiratory illnesses. Co-administration of Lazanda with a vasoconstrictive nasal decongestant (e.g., oxymetazoline) may lead to reduced fentanyl plasma concentrations.

References

- DoD P&T Committee minutes: <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee/Meeting-Minutes>
- Current/future drug classes under review by the DoD P&T Committee: <http://www.health.mil/About-MHS/Other-MHS-Organizations/DoD-Pharmacy-and-Therapeutics-Committee>
- TRICARE Formulary Search Tool: <http://www.express-scripts.com/tricareformulary>
- Prior Authorization/Medical Necessity forms: See TRICARE Formulary Search Tool above.
- Point of contact for additional information: usarmy.jbsa.medcom-ameddcs.list.pecuf2@mail.mil

TIRF Price Comparison at MTF	
Drug & Dosage Form	MTF cost/month (February 2015)
Basic Core Formulary	
None	
Uniform Formulary	
Fentanyl transmucosal lozenge (Actiq, generics)	\$ "Most Cost-Effective"
Non-Formulary	
Fentanyl sublingual tablet (Abstral)	\$\$ "Less Cost-Effective"
Fentanyl pectin nasal spray (Lazanda)	\$\$ "Less Cost-Effective"
Fentanyl buccal tablet (Fentora)	\$\$ "Less Cost-Effective"
Fentanyl sublingual spray (Subsys)	\$\$ "Less Cost-Effective"
Legend:	
\$ = "Most Cost-Effective" Represents Rx's with the <u>lowest cost</u> and best clinical efficacy	
\$\$ = "Less Cost-Effective" Represents <u>higher cost</u> Rx's similar clinical efficacy	
\$\$\$ = "Less Cost-Effective" Represents <u>next higher cost</u> Rx's with similar clinical efficacy	
\$\$\$\$ = "Least Cost-Effective" Represents Rx's with the <u>highest cost</u> with similar clinical efficacy	