

**FAST FACTS AND CONCEPTS #331
COMPARISON OF FENTANYL ORAL AND NASAL FORMULATIONS
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Background: Transmucosal fentanyl formulations are available via a variety of non-traditional routes (e.g. buccal, intranasal, sublingual). They are FDA approved for breakthrough cancer pain in patients \geq 16 years of age who are tolerant of \geq 60 mg of oral morphine equivalents per day (1-7). Off-label uses include non-cancer pain and painful procedures in children (8-10). This *Fact Fact* compares the catalogue of oral/nasal fentanyl preparations. *Fast Fact* #103 has more information on fentanyl lozenges (Actiq®).

Pharmacology (1-7): Fentanyl's marked lipophilicity and high rate of first pass metabolism renders traditional oral pill formulations relatively ineffective. Yet, these same pharmacologic properties lead to a quicker onset and duration of action for transmucosal or intranasal fentanyl compared with other short acting oral opioids (e.g. morphine, hydromorphone, oxycodone). Hence, they may have theoretical advantages for short onset, incident pain such as cancer related bone pain elicited by ambulation. Metabolism takes place in the liver primarily by CYP 3A4 to inactive metabolites which are excreted by the kidneys. Significant drug interactions can occur when used with other CYP 3A4 active drugs. In those with impaired liver function, many experts recommend initiate at 50% of the typical starting dose.

Comparative Effectiveness: In comparison to traditional oral short acting opioids, transmucosal fentanyl formulations are 20-200 times more expensive. Hence, most insurances do not cover them as a first line analgesics. Instead, they are considered if the first-line analgesic is not tolerated due to adverse effects, route issues, or an inability to control the rapid onset of breakthrough pain. A meta-analysis for breakthrough cancer pain found a likelihood of superiority over IR oral morphine ranging between 57-68% especially during the first 30 min of treatment (11). However, other controlled, clinical studies not included in this meta-analysis, have yielded mixed results (9-18).

Formulations (1-7): There is no known evidence clearly demonstrating superiority among the short acting fentanyl formulations; rather selection is primarily dependent on cost, preference, and insurance coverage. Other prescribing pearls include:

- Transmucosal absorption can result in variable bioavailability depending on the formulation and the individual ingesting it. Hence, there is little dose reliability between formulations.
- If rotating from a different opioid or converting between formulations, start at the initial dose recommendation and titrate to effect as specified in the package insert, regardless of the patient's past or current opioid requirement.
- Nasal decongestive agents may lead to lower peak plasma concentrations of intranasal formulations due to local vasoconstriction limiting bioavailability.
- Outpatient access to these formulations are only available through a Risk Evaluation and Mitigation Strategy (REMS) program. REMS programs are implemented to create a framework to promote patient safety for high-risk medications that may cause a serious adverse effect. Patients, prescribers, pharmacies and distributors all must be registered in a REMS program; this may limit access to these medications.

Form	Pricing	Pharmacokinetics	Dosing/Titration Pearls
Transmucosal lozenge (Actiq)	Between \$1800 - \$5600 for 30 lozenges.	<i>Starting Dose (SD):</i> 200mcg <i>Onset:</i> 15 - 20min <i>Peak:</i> 20 - 40min <i>Duration of Action (DOA):</i> 4 hrs	<ul style="list-style-type: none"> • place between cheek and gum for ~15 minutes • may re-dose after 30 min • maximum of 2 doses/breakthrough episode • wait 4 hours between breakthrough episodes

Form	Pricing	Pharmacokinetics	Dosing/Titration Pearls
Sublingual tab (Abstral)	Between \$1300 - \$3800 for 28 tablets.	<i>SD:</i> 100mcg <i>Onset:</i> 15 - 30min <i>Peak:</i> 30 - 60min <i>DOA:</i> 2 hrs	<ul style="list-style-type: none"> • dissolve under the tongue for ~15 minutes • may re-dose after 30 min • maximum of 2 doses/breakthrough episode • wait 2 hours between breakthrough episodes
Transmucosal lozenge	Between \$560 - \$1700 for 30 lozenges.	<i>SD:</i> 200 mcg <i>Onset:</i> 15 – 20 min <i>Peak:</i> 20 – 40 min <i>DOA:</i> 4 hrs	<ul style="list-style-type: none"> • dissolve under the tongue for ~15 minutes • may re-dose after 30min • maximum of 2 doses/ breakthrough episode • wait 4 hours between breakthrough episodes
Buccal tab (Fentora)	Between \$1440 - \$4300 for 28 tablets	<i>SD:</i> 100 mcg <i>Onset:</i> 15 – 30 min <i>Peak:</i> 35 – 45 min <i>DOA:</i> 2 hrs.	<ul style="list-style-type: none"> • may re-dose after 30 min • maximum of 2 doses per breakthrough episode • wait 4 hours between breakthrough episodes
Nasal spray (Lazanda)	Between \$1600 - \$2400 for 24 sprays	<i>SD:</i> 100mcg <i>Onset:</i> 10 - 15 min <i>Peak:</i> 15 - 20 min <i>DOA:</i> 2 hrs	<ul style="list-style-type: none"> • should not blow nose for 30 min after administration • wait 2 hours between breakthrough episodes • limited to ≤4 breakthrough episodes per day
Sublingual spray (Subsys)	Between \$480 - \$4900 for 10 sprays	<i>SD:</i> 100mcg <i>Onset:</i> 10 - 40min <i>Peak:</i> 40 - 75min <i>DOA:</i> 4 hrs	<ul style="list-style-type: none"> • maximum of 2 doses per breakthrough episode • wait 4 hours between breakthrough episodes • <u>caution:</u> avoid in ≥ grade 2 mucositis due to increased absorption.

Patient Counseling (1-7): Patients need specific instructions regarding:

- Factors that may decrease absorption: reduced saliva; recent use of liquids that reduce oral pH (coffee, cola, fruit juices); placement of product on tongue or gums; chewing gum.
- Factors that may increase absorption: mucositis or mouth ulcerations.
- Storage and Disposal: because some of these formulations may be dangerous for children, patients should store in original packaging at room temperature in childproof containers. Unused medications should be disposed in water (sink, toilet).
- For more specific counseling instructions, refer to these resources:
Actiq: <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm085817.pdf>
Abstral: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM239930.pdf>
Fentora: <http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088597.pdf>
Subsys: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM287863.pdf>
Lazanda: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM263032.pdf>

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