PHARMACY PROFILE: Oromucosal Fentanyl Preparations (Abstral® tablet, Actiq® lozenge and Fentora® tablet)

Key Messages

- There are three oromucosal fentanyl formulations for breakthrough pain available in Australia. They are indicated in patients stabilised on regular opioid therapy for cancer pain. These preparations have a rapid onset of action compared with other oral opioids.
- Oral morphine should remain first choice due to dosing flexibility, cost and familiarity. Consider transmucosal fentanyl if an increase in morphine dose for breakthrough pain leads to intolerable adverse effects.
- Abstral®, Actiq® and Fentora® are not interchangeable. When switching, start new brand with its recommended starting dose and titrate to minimise toxicity.
- A dose equivalence between transmucosal fentanyl products and other opioid formulations has not been established. The optimal dose cannot be determined by the dose of regular opioid or previous breakthrough opioid. It should be individually titrated by beginning at the lowest dose.
- Palliative care nurses play an important role in educating patients and their families about the management of immediate release fentanyl preparations.

Breakthrough cancer pain is an ephemeral exacerbation of pain that occurs in 50-90% of patients who have otherwise well controlled persistent pain. [1] Oromucosal fentanyl preparations (lozenge, buccal and sublingual tablets) are indicated for the management of breakthrough pain in patients stabilised on opioid analgesia equivalent to at least 60 mg of oral morphine daily for more than a week. The dose of oromucosal fentanyl should be titrated according to response and sedation score. The aim is to relieve an episode of breakthrough pain with a single dose and minimal opioid adverse effects. If the regular opioid dose is increased, the dose of fentanyl for breakthrough pain should be re-titrated. Like all opioids, patient cardiorespiratory status should be closely monitored.

Each fentanyl product should be titrated to the most effective dose that provides adequate analgesia and minimises adverse effects. Switching from one brand to another at a 1:1 ratio should not be attempted due to differences in pharmacokinetic profiles: it is essential to titrate the new formulation. [2,3] Substituting between formulations may cause a delay in patient benefit and unnecessary pain.


<table>
<thead>
<tr>
<th>Oral Preparation</th>
<th>Abstral® tablet</th>
<th>Actiq® lozenge</th>
<th>Fentora® tablet</th>
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<tbody>
<tr>
<td>Starting Dose</td>
<td>Sublingual 100 micrograms, if this is inadequate after 30 minutes, give another 100 microgram tablet and consider increasing the tablet strength for the first dose of the next episode.</td>
<td>Buccal 200 micrograms, if this is inadequate 30 minutes after starting lozenge, give a second dose of 200 micrograms.</td>
<td>Buccal 100 micrograms, if this is inadequate after 30 minutes, give another 100 microgram tablet and consider increasing the tablet strength for the first dose of the next episode.</td>
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<td>Dose Titration</td>
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<td>If a second dose was needed, increase to the next higher strength tablet. If this is inadequate after 30 minutes, usually give a 100 microgram tablet. However, consider giving 200 micrograms if the first dose was 400-600 micrograms (and was well tolerated).</td>
<td>If a second dose was needed for the previous episode, increase to the next higher strength tablet. If this is inadequate after 30 minutes, usually give a 100 microgram tablet. However, consider giving 200 micrograms if the first dose was 200-600 micrograms (and it was well tolerated).</td>
<td>If a second dose was needed, increase to the next higher strength for several episodes. If this is inadequate 30 minutes after starting lozenge, give a second dose of the same strength lozenge.</td>
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</table>

| Maximum dose per episode | 800 micrograms | 600 micrograms | 800 micrograms |

| Dose Maintenance and Retitratation | Wait at least 2 hours between treatment of episodes. Treat no more than 4 episodes in 24 hours. If >4 breakthrough episodes occur per day for 4 consecutive days, consider increasing the dose of the regular opioid. | Wait at least 4 hours between treatment of episodes. If >4 breakthrough episodes per day for 4 consecutive days, or 2 doses are needed to treat several consecutive episodes, adjust the dose of the regular opioid. | Wait at least 4 hours between treatment of episodes. If >4 breakthrough episodes occur per day for several consecutive days, or 2 doses are needed to treat several consecutive episodes, adjust the regular opioid dose. |

| Patient Counselling | Place the tablet well under your tongue; do not swallow the tablet; allow it to dissolve completely without chewing or sucking. If you have a dry mouth, moisten your mouth with water before using the tablet. | Place lozenge in the mouth against the cheek and move it around the mouth using the applicator. Let it dissolve over 15 minutes. Do not chew. Take particular care to ensure good dental hygiene as the lozenge contains sugar. Any partly used lozenges should be returned to the pharmacy for safe disposal. | Place tablet between the cheek and gum near the back molar teeth; alternatively, place tablet well under your tongue (if you are using more than one tablet at a time, put them on each side of your mouth). Do not swallow the tablet, allow it to disintegrate without chewing or sucking. If you have a dry mouth, moisten your mouth with water before using the tablet. Do not eat or drink when the tablet is in your mouth. Allow 30 minutes for absorption, then if there are any bits of tablet left, you can swallow them with a glass of water. |

| Products | 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, 800 mcg | 200 mcg, 400 mcg, 600 mcg, 800 mcg, 200 mcg, 1600 mcg | 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg |
Considerations for use in palliative care

- Immediate-release oral opioids are still considered first-line. Oral solution should be trialled if tablets are inadequate; only when pain is insufficiently controlled with regard to speed of onset of action or prolonged undesirable effects should the transmucosal products be considered. [5]

- A patient's circumstances should be considered carefully to ensure they fulfil the necessary requirements for use of a transmucosal product, e.g., current opioid dose, ability to access, use, store and dispose of the product reliably.

- It is recommended that patients with xerostomia/dry mouth or mucositis moisten their mouth before administration of Fentora, Actiq or Abstral. If this does not help, then switching to another product such as morphine sulphate oral solution is advisable.

- Re-dosing with any of the immediate-release products should not be done within at least 4 hours of the previous dose. There are no specific guidelines on how to change from one product to another, but based on how often a dose can be taken, it could be assumed that a different preparation should not be used within 4 hours of the original one.

Tips for palliative care nurses

- Patients should be advised to keep the medicine in the original blister package. Open the package right before use.

- Pain relief achieves within 15 minutes; peak plasma concentrations occur at approximately 20–40 minutes. [4]

- Do not mix different fentanyl products for treating breakthrough pain, use one brand only.

- These fentanyl products are not interchangeable (nor is there dose equivalence with any other opioid product),

- If needed to switch between brands, start the new brand with its starting dose and titrate, and discard the unwanted products safely.

Evidence of efficacy

- No studies comparing the fentanyl products with each other were reported. The majority of trials were placebo controlled.

- A prospective survey of 50 hospice patients with breakthrough pain conducted by Zeppetella [6] to compare patient assessments of time to relief among the various immediate release opioids prescribed found no difference in effectiveness among the oral opioids (morphine, n=10, oxycodone n=10, hydromorphone n=10, methadone n=10 or oral transmucosal fentanyl citrate (OTFC) n=10). OTFC was rated more effective than morphine, oxycodone and hydromorphone (p<0.01) and methadone (p=0.045). The issue to consider was the dose of the oral rescue opioid was ~18% of the total daily regular dose, compared with the OTFC does which was ~36% of the total daily regular dose. The average time to meaningful pain relief was 31 minutes (range 5-75). No difference was found between morphine, hydromorphone and oxycodone. Methadone was found to work faster than morphine (p<0.01) whilst OFTC worked faster than all other 4 medications (p<0.001).

- All fentanyl products were more effective than placebo in treating breakthrough cancer pain. [5]
Safety

- The concomitant use of sublingual fentanyl with any CYP3A4 inhibitor may cause potentially fatal respiratory depression.
- Substantial differences exist in the pharmacokinetic profiles of oromucosal fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose. When prescribing, do not convert patients on a mcg-per-mcg basis between fentanyl products.
- Transmucosal buccal tablets (Fentora), lozenges (Actiq) and sublingual tablets (Abstral) are contraindicated in the management of acute or postoperative pain (including headache, migraine, or dental pain), and in patients who are not opioid tolerant.
- The wide range of fentanyl products can lead to errors in dosing due to differences in pharmacokinetic/dynamic profiles.

References


Authors: Wassana Sorich, Clinical Pharmacist, Repatriation General Hospital, South Australia.

Useful resources

- Contact your local pharmacist or hospital drug information service.
- National Prescriber Service Website – ‘NPS Medicinewise’ is an excellent resource for consumers and health professionals.