

# Fentanyl lozenges (Actiq) for breakthrough cancer pain

(FENT-a-nil)

## Summary

- Fentanyl lozenges are an oromucosal formulation for breakthrough cancer pain in people stabilised on regular opioid therapy for persistent cancer pain. They have a rapid onset of action compared with oral opioids.
- Oral morphine is the opioid of first choice on the basis of familiarity, cost and dosing flexibility. Consider fentanyl lozenges if an increase in morphine dose to control breakthrough pain causes intolerable adverse effects.
- Be aware of the following important safety issues:
  - **Do not use fentanyl lozenges in opioid-naïve patients** because of the risk of respiratory depression.
  - **Prevent accidental or deliberate misuse** by instructing patients and carers on the correct use, storage and disposal of fentanyl lozenges.
  - **Keep intact or partially used lozenges away from children.** They can be fatal if consumed by a child. Any lozenge that remains on the handle needs to be dissolved under hot running water and must not be discarded whole.
- To maximise oromucosal absorption of fentanyl, the lozenges should be moved along the cheek lining, not chewed, and swallowing of saliva minimised if possible until the lozenge is finished.
- Fentanyl lozenges have a side-effect profile typical of that of other opioids. Instruct patients and carers to remove the lozenge immediately if excessive side effects occur during use.
- **There is no dose equivalence between fentanyl lozenges and other opioid formulations.** The optimal dose cannot be predicted by the dose of regular opioid or previous breakthrough opioid. It should be individually titrated by starting at the lowest dose (200 micrograms).

## PBS listing

### Authority required

Breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent pain and when further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects.

Initial supply for dose titration is up to 3 packs of 3 units (9 lozenges) per prescription. Different dosages may be prescribed (each strength of lozenge requires an individual prescription). First continuing supply for

maintenance therapy is provided for up to 3 months (maximum of 20 packs of 3 units [total 60 lozenges] plus 2 repeats).

Second and subsequent continuing supply is provided for up to 3 months when consultation with a palliative care specialist or service has occurred. Otherwise a second continuing supply is for up to 1 month (no repeats).

Refer to the palliative care section of the *Schedule of Pharmaceutical Benefits* (see Section 2 or online ([www.pbs.gov.au/html/healthpro/browseby/palliative-care](http://www.pbs.gov.au/html/healthpro/browseby/palliative-care))) for more details on maximum quantities and repeats for patients receiving palliative care.

## Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended the listing of fentanyl lozenges as a Palliative Care benefit on the basis of high but acceptable cost-effectiveness compared with placebo.<sup>1</sup> The PBAC recognised the clinical need for an alternative opioid for breakthrough cancer pain in people who cannot tolerate escalating doses of morphine.

## Place in therapy

Fentanyl is a potent opioid analgesic. The oromucosal formulation consists of a fentanyl citrate lozenge attached to a plastic applicator.<sup>2</sup> Fentanyl lozenges are a treatment option for breakthrough cancer pain in people stabilised on regular opioid therapy for persistent cancer pain.<sup>2,3</sup>

Breakthrough pain is a transient flare in pain of moderate to severe intensity that occurs on a background of otherwise stable cancer pain controlled by chronic opioid therapy.<sup>4</sup> Breakthrough pain may last for seconds to hours, and in one study the median duration was 30 minutes.<sup>4</sup>

Fentanyl lozenges have a fast onset of action (5–10 minutes) due to rapid absorption of 25% of the dose across the oral mucosa.<sup>3</sup> The remaining dose is swallowed and slowly absorbed in the intestine.<sup>2,5</sup> About 50% of the total fentanyl dose becomes systemically available, with peak plasma concentrations at 20–40 minutes.<sup>2,3,5</sup>

Oral morphine is the opioid of first choice for breakthrough cancer pain because of its familiarity, cost and dosing flexibility.<sup>3,6,7</sup> Consider switching patients to fentanyl lozenges if an increase in their breakthrough dose of morphine causes intolerable adverse effects.

### Fentanyl lozenges have a faster onset of effect than oral opioids

Four randomised controlled trials provide data on the efficacy of fentanyl lozenges among a total of 393 opioid-tolerant patients with breakthrough cancer pain.<sup>8–12</sup> Patients were stabilised on opioid therapy for persistent cancer pain (usually oral morphine or transdermal fentanyl) and most previously used oral morphine or oxycodone for breakthrough pain.<sup>8–12</sup>

Differences in pain intensity (0 = no pain to 10 = worst pain) and pain relief scores (0 = none to 4 = complete) were small and mostly  $\leq 1$  point between fentanyl lozenges and breakthrough oral opioids or placebo.<sup>8,10–12</sup> The proportion of breakthrough pain episodes requiring additional medication did not differ significantly between fentanyl lozenges (2%) and oral morphine (1%).<sup>9</sup>

Pain outcomes mostly differed between treatments in the first 15–30 minutes of dosing.<sup>8,9,11</sup> This is consistent with the faster onset of effect of fentanyl lozenges compared with breakthrough oral opioids (e.g. morphine liquid has an onset of 30 minutes).<sup>3</sup> In one trial, patients obtained more than half of their total change in pain intensity (56%) and pain relief (65%) within 15 minutes of their fentanyl lozenge dose.<sup>11</sup> This was significantly greater than the corresponding changes in this period with their usual breakthrough opioid.<sup>11</sup>

## Safety issues

Fentanyl lozenges have typical opioid adverse effects.<sup>2</sup> Those most commonly reported in trials included somnolence, dizziness, nausea and constipation.<sup>8–11,13</sup> Respiratory depression is the most serious safety issue with opioids.<sup>3</sup>

Most patients in trials tolerated fentanyl lozenges, with  $\leq 5\%$  stopping treatment because of adverse effects.<sup>8–11,13</sup> Fentanyl may cause less constipation, nausea, vomiting and confusion than morphine.<sup>3,6</sup>

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with Australian Prescriber. For information about reporting adverse reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

### Use fentanyl lozenges only in people who are already stabilised on opioid therapy for persistent cancer pain

The safety of fentanyl lozenges has only been studied in people with breakthrough cancer pain who are opioid-tolerant (i.e. exposed to at least 60 mg/day of morphine, transdermal fentanyl 50 micrograms/hour or an equivalent dose of another opioid, for at least 1 week).<sup>2,8–11,13</sup>

**Do not use fentanyl lozenges in opioid-naïve patients, or in those with severe respiratory depression or severe obstructive lung conditions.<sup>2</sup>**

Opioid-naïve patients who use fentanyl lozenges are more susceptible to respiratory depression at any dose.<sup>2,5</sup>

**Prevent accidental or deliberate misuse**

Provide instructions on how to use, store and dispose of fentanyl lozenges safely, to help prevent accidental or deliberate misuse (see Information for patients and carers). Fentanyl lozenges have an onset of effect that is comparable to that of intravenous morphine.<sup>5</sup> Deliberate misuse of fentanyl via the oromucosal route has been reported.<sup>14</sup>

**Keep intact or partially used fentanyl lozenges out of sight and reach of children.<sup>2,15</sup>** The amount of fentanyl contained in an intact or partially used lozenge can be fatal to a child.<sup>2,15</sup> Any lozenge that remains on the handle needs to be dissolved under hot running water and must not be discarded whole (see Information for patients and carers).

## Dosing issues

Optimise the regular opioid dose before starting fentanyl lozenges.<sup>2,5</sup>

The initial dose of fentanyl lozenges is 200 micrograms.<sup>2</sup> Titrate if needed using the available dosage units (200, 400, 600, 800, 1200 and 1600 micrograms).<sup>2</sup> The maximum daily dose is four units of any strength.<sup>2,5</sup>

Each lozenge is placed in the mouth against the cheek and is moved around the mouth to maximise oromucosal absorption over 15 minutes.<sup>2</sup> The lozenge should not be consumed in less than 15 minutes or be chewed, as this can result in inadequate control of breakthrough pain.<sup>2</sup>

**The optimal dose of fentanyl lozenges cannot be converted from the dose of other opioid formulations**

**Start every patient on 200 micrograms** and titrate to a dose that adequately controls each breakthrough pain episode with acceptable side effects.<sup>2</sup> The dose cannot be determined from the daily dose of regular opioid therapy (including fentanyl patches) or the breakthrough opioid dose that was previously used.

Titration doses of fentanyl lozenges in trials did not correlate with the doses of oral or transdermal opioids used for persistent pain.<sup>8,9,11,16</sup> More than half of patients in one trial were effectively controlled on 200 or 400 micrograms regardless of their daily dose of regular opioid.<sup>11</sup> Pooled data from 3 trials also found no dose equivalence between fentanyl lozenges and oral opioid formulations used for breakthrough pain.<sup>16</sup>

If a single lozenge does not adequately relieve pain 15 minutes after it is finished, a second lozenge of the same strength may be taken.<sup>2,5</sup> Increase the dose to the next higher strength if two lozenges are repeatedly needed for each episode of breakthrough pain.<sup>2</sup> Use a lower dose if excessive side effects occur (e.g. sedation) before a lozenge is fully consumed.<sup>2</sup>

Most patients switching treatment to fentanyl lozenges can be titrated to an effective dose within a short period. About three-quarters of patients in trials were successfully titrated.<sup>8,9,11</sup> Titration to an optimal dose in one trial was completed in a median of 5 days (range 1–22 days).<sup>9</sup>

**Low doses are effective for most patients**

Most patients in trials achieved adequate pain relief with the lower-strength lozenges (200, 400 and 600 micrograms).<sup>8,9,11</sup> Half of the patients in one trial found the starting dose of 200 micrograms to be effective, and few needed doses higher than 600 micrograms.<sup>8,9,11</sup> A longer-term study (mean 3 months) also found that many patients (61%) maintained their final titrated dose without further dose escalation.<sup>13</sup>

**Review the regular opioid if fentanyl lozenges are needed frequently**

Regular opioid therapy should be reviewed if more than four fentanyl lozenges at an effective strength are needed per day.<sup>2,5</sup> Fentanyl lozenges were not studied in people with uncontrolled or rapidly escalating pain. Patients in trials had relatively stable cancer pain and no more than four daily breakthrough episodes.

Breakthrough pain just before a scheduled dose of regular opioid (i.e. 'end-of-dose failure') may be controlled by adjusting the regular opioid dose.<sup>17</sup> If the regular opioid dose is increased to improve pain control, the dose of fentanyl lozenges may need to be reviewed.<sup>2</sup> End-of-dose failure needs to be distinguished from incident pain (i.e. caused by movement), as this is managed separately.<sup>6</sup>

## Information for patients and carers

Instruct patients and carers on how to use fentanyl lozenges when needed for breakthrough pain. **They must only be given to people who are regularly taking another opioid for their persistent cancer pain and not to anyone else.**

### Advise patients, carers and relatives of the safety risk to children and others with fentanyl lozenges.

Tell them how to safely store and dispose of the lozenges, in particular:

- not to open the tamper-proof packaging until the patient is ready to use the lozenge
- keep used or partially used lozenges out of sight and reach of children and other people who are not the patient or carer
- dissolve partially used lozenges as soon as possible under hot running water, or return to a pharmacy for disposal
- discard handles in a waste container that is out of reach of children.<sup>2,3,15</sup>

Inform patients and carers that fentanyl is absorbed through the lining of the mouth as the lozenge dissolves. To maximise this absorption, the lozenges should be moved along the cheek lining, not chewed, and swallowing of saliva should be minimised if possible until the lozenge is finished.<sup>2,5</sup>

Some patients with cancer who have xerostomia (dry mouth) may be unable to finish the fentanyl lozenges, or they may take longer to dissolve.<sup>18</sup> Water can be used to moisten the oral cavity before using a lozenge.<sup>2</sup>

To minimise the risk of overdosing, instruct patients and/or carers:

- to wait 15 minutes after finishing a lozenge before taking a second dose if pain is not adequately controlled by the first lozenge
- not to use more than two lozenges per episode of breakthrough pain
- to remove the lozenge immediately if excessive side effects occur.<sup>2</sup>

Patients and carers need to be aware that fentanyl lozenges are a strong opioid analgesic. They can act as quickly as an injection, and side effects (such as drowsiness, dizziness and nausea) can occur while the lozenge is being used. Reassure patients and carers that side effects may stop or reduce in severity over time.<sup>2,5</sup>

Suggest or provide the Actiq consumer medicine information (CMI) leaflet, which provides illustrations on the administration of fentanyl lozenges.

## References

1. Department of Health and Ageing. November 2007 PBAC outcomes — positive recommendations. <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacrec-Nov07-positive> (accessed 15 January 2008).
2. Orphan Australia Pty Ltd. Actiq product information. 6 November 2002.
3. Australian Medicines Handbook 2007.
4. Portenoy RK, Hagen NA. *Pain* 1990;41:273–81.
5. Aronoff GM, et al. *Pain Med* 2005;6:305–14.
6. Palliative Care Expert Group. Therapeutic Guidelines: Palliative Care [revised August 2005]. In: eTG complete [CD-ROM]. Melbourne: Therapeutic Guidelines Limited, November 2007.
7. National Prescribing Centre. The use of strong opioids in palliative care. MeReC Briefing 2003. [http://www.npc.co.uk/MeReC\\_Briefings/2002/briefing\\_no\\_22.pdf](http://www.npc.co.uk/MeReC_Briefings/2002/briefing_no_22.pdf) (accessed 18 December 2007).
8. Christie JM, et al. *J Clin Oncol* 1998;16:3238–45.
9. Coluzzi PH, et al. *Pain* 2001;91:123–30.
10. Farrar JT, et al. *J Natl Cancer Inst* 1998;90:611–6.
11. Portenoy RK, et al. *Pain* 1999;79:303–12.
12. Zeppetella G, Ribeiro MDC. *Cochrane Database Syst Rev* 2006:CD004311.
13. Payne R, et al. *J Pain Symptom Manage* 2001;22:575–83.
14. Liappas IA, et al. *J Psychopharmacol* 2004;18:277–80.
15. *Prescrire Int* 2002;11:106–7.
16. Hagen NA, et al. *J Palliat Med* 2007;10:47–55.
17. Emanuel E, Emanuel L. Palliative and end-of-life care. In: Kasper DL, ed. *Harrison's Principles of Internal Medicine* [online]. New York: McGraw-Hill, 2005. <http://ovidsp.tx.ovid.com/spb/ovidweb.cgi> (accessed 5 February 2008).
18. Davies AN, Vriens J. *J Pain Symptom Manage* 2005;30:496–7.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.