PUBLIC SUMMARY DOCUMENT
Product: Fentanyl citrate, lozenge with integral applicator, 200 microgram, 400 microgram, 600 microgram, 800 microgram, 1200 microgram and 1600 microgram, Actiq®
Sponsor: Orphan Australia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission requested an authority required 'palliative care' listing for all registered strengths of fentanyl lozenges for the treatment of breakthrough pain in palliative care patients who are receiving opioids for their underlying persistent cancer pain where morphine is contraindicated due to renal impairment or adverse reactions which require cessation or change of therapy.

2. Background

At the June 2003 PBAC meeting, the PBAC rejected a submission seeking a Section 100 listing of fentanyl lozenges for the management of breakthrough cancer pain in patients with malignancies who meet certain criteria because of a lack of evidence in the proposed patient group with resulting uncertain clinical benefit and uncertain cost-effectiveness.

At the July 2004 PBAC meeting, the PBAC considered an application for an authority required 'palliative care' listing for the management of breakthrough cancer pain by specialists in palliative care patients who are receiving opioids for their underlying persistent cancer pain and where morphine and one other opioid are each precluded from use due to certain circumstances. The PBAC rejected the application because of uncertain clinical benefit and the resulting uncertain and unfavourable cost effectiveness.

3. Registration Status

Actiq was TGA registered on 15 November 2002 for the management of breakthrough cancer pain in patients with malignancies who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain.

As stated in the approved PI, use of oral transmucosal fentanyl citrate is contraindicated in opioid naïve patients. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 microgram transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

4. Listing Requested and PBAC's View

Authority required

For the treatment of breakthrough pain in palliative care patients who are receiving opioids for their underlying persistent cancer pain where morphine is contraindicated due to:
(1) Renal impairment defined as estimated glomerular filtration rate (eGFR) of less than 50 mL/min/1.73 m^2; or
(2) Adverse reactions which require cessation or change of therapy, and defined in the National Cancer Institute of the National Institute of Health Common Terminology Criteria for Adverse Events (CTCAE) (2003) as follows:
Nausea (Grade 2) – persisting after 2 to 3 doses despite adequate trials of antinauseants; or
Vomiting (Grade 2) – persisting after 2 to 3 doses despite adequate trials of antinauseants; or
Constipation (Grade 2) – persisting for up to a week despite adequate trials of laxatives, or
Depressed level of consciousness (Grade 2) - persisting after 2 - 3 doses, or Confusion (Grade

3) – persisting for more than 24 hours, or Hypersensitivity (Grade 2) – defined as rash, flushing, dyspnoea and drug fever ≥ 38˚C
Maximum Quantity: 3 (Initiation pack of 3), 20 (Maintenance pack of 3). Repeats: Nil

For PBAC's view of the requested restriction, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Fentanyl has a number of advantages in patients with renal impairment in that it is metabolised in the liver to inactive metabolites and has a short half-life. For patients with renal impairment, accumulation of active metabolites of other opioids may contribute to the adverse effects of opioids.

The Sponsor has agreed to initiate an extensive best practice education program on correct prescribing to limit fentanyl lozenges to the patient population as intended in the restriction and on correct titration to achieve optimum results.

6. Comparator

The submission nominated placebo as the comparator in the proposed PBS population. This was previously accepted by the PBAC.

7. Clinical Trials

No new clinical data was presented in the submission. The pivotal trial, AC 200/013, used in support of this submission was the same as that in the previous submissions.

This study has been published as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Farrar J et al	Oral transmucosal fentanyl citrate: randomised, double-blind, placebo-controlled trial for treatment of breakthrough pain in cancer patients.	Journal of the National Cancer Institute 90(8):611-6,1998
Farrar JT	Clinically important changes in acute pain outcome measures: a validation study.	Journal of Pain & Symptom Management 25(5):406-11, 2003

8. Results of Trials

The key results are summarised in the table below.

Relative risk of responder (pain intensity difference of ≥33% at 30 mins) in Trial AC 200/013

Fentanyl N=556	Placebo N=245	Relative risk (95%CI)	*Risk difference (95%CI)*	*NNT (95%CI)*
351 (63.1%)	89 (36.3%)	1.74 (1.46, 2.08)	*0.27 (0.19, 0.34)*	*4 (3, 6)*

Efficacy of fentanyl lozenges across all scales using the optimal cut-off points in Trial AC 200/013 (secondary outcomes)

Trial AC 200/013	Scale	Cut-off point	Relative risk (95% CI)
% Max TOTPAR**(at 60 min)	0-100	≥33%	1.66 (1.36-2.03)
Pain relief (at 30 min)	0-4	0-1 vs. 2-4	1.64 (1.40-1.92)
PID(absolute change at 30 min)	0-10	0-1 vs. 2-10	1.78 (1.49-2.13)
SPID (sum of PID/h over 60 min)	0-10	0-2 vs. 3-10	1.74 (1.45-2.13)
Global performance (at 60 min)	0-4	0-1 vs. 2-4	1.83 (1.53-2.17)

PID = Pain Intensity Difference, TOTPAR = Total Pain Relief; SPID = Sum of Pain Intensity Difference
Pain Intensity measured on an 11-point scale (0=no pain, 10=worst pain)
Pain Relief measured on 5-point scale (0=no relief, 4=complete relief)
Global Performance and Global Satisfaction Rating measured on a 5-point scale (0=poor, 4=excellent)

No new toxicity data was presented in the submission.

9. Clinical Claim

The submission claimed that fentanyl lozenge is statistically significantly superior to placebo for all measures of pain relief in cancer breakthrough pain. The PBAC noted that fentanyl lozenges produce greater pain relief compared to placebo, but have more toxicity.

10. Economic Analysis

An updated preliminary economic evaluation was presented. A cost effectiveness analysis on a per patient basis was presented as well as a cost utility analysis. Two arms were considered, the responder and non-responder arm. The relative risk was used for both arms, using the definition of a patient achieving equal to or greater than 33% reduction in pain intensity difference at 30 minutes as a responder.

The submission calculated the trial-based incremental cost/extra responder to be less than $15,000.

No modelled economic evaluation was presented. The economic evaluation involved a trial based incremental cost per QALY approach. The base case modelled incremental cost/extra QALY was calculated to be in the range $45,000 - $75,000.

11. Estimated PBS Usage and Financial Implications

The net cost to the PBS of listing fentanyl lozenges was estimated to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of fentanyl lozenge on the Palliative Care Section of PBS for the treatment of breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent cancer pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects on the basis of a high but acceptable cost-effectiveness ratio.

The PBAC noted that renal function is not routinely monitored in palliative care patients and that this measure was therefore inappropriate to be one of the criteria for the restriction.

The PBAC considered that the utility gain of 0.7 for a responder over a non-responder was high but plausible for the identified patients with uncontrolled pain in the palliative care setting of a terminal illness. The PBAC also recognised the high clinical need of these patients.

The PBAC considered that the utilisation predictions by the submission were an underestimate and that the proposed risk sharing agreement would limit the increase in costs to the PBS due to usage outside the recommended restriction.

Recommendation

Restriction:

CAUTION: The risk of drug dependence is high.

Authority required
Initial supply for dose titration for breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects.

NOTE: No applications for increased repeats will be authorised.

Maximum quantity: 3 x finished packs of 3 units
Repeats: Nil

Authority required
1st continuing supply (for up to 3 months) for breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects.

NOTE: No applications for increased repeats will be authorised. Telephone approvals are limited to 1 month's therapy.

Maximum quantity: 20 x finished packs of 3 units
Repeats: 2

Authority required
Second and subsequent continuing supply (for up to 3 months) for breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects, where consultation with a palliative care specialist or service has occurred.

NOTE: No applications for increased repeats will be authorised. Telephone approvals are limited to 1 month's therapy.

Maximum quantity: 20 x finished packs of 3 units
Repeats: 2

Authority required

Second and subsequent continuing supply (for up to one month) for breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects.

NOTE: No applications for increased repeats will be authorised.

Maximum quantity: 20 x finished packs of 3 units
Repeats: 0

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Orphan welcomes this recommendation by the PBAC to list a treatment option for breakthrough cancer pain in palliative care patients who cannot receive further dose escalation of morphine because of intolerable side effects.