

PUBLIC SUMMARY DOCUMENT

Product: FENTANYL, tablet: sublingual, 100 microgram, 200 microgram and 400 microgram, Abstral[®]

Sponsor: A.Menarini Australia Pty Ltd.

Date of PBAC Consideration: March 2014

1. Purpose of Application

To request Authority Required listing on the palliative care schedule for fentanyl sublingual (SL) tablets for the management of breakthrough pain in patients with cancer who are already receiving maintenance opioid therapy for chronic pain and are unable to tolerate further escalation of morphine for breakthrough pain.

2. Background

Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain.

Fentanyl sublingual tablets had not previously been considered by the PBAC.

3. Registration Status

Fentanyl sublingual tablets were TGA registered on 22 August 2013 for the management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic for pain.

4. Listing Requested and PBAC's View

Authority required (palliative care)

Breakthrough pain:

Treatment phase: continuing treatment

The treatment criteria is: Patient must be undergoing palliative care,

AND the Clinical criteria is: Patient must have cancer,

AND the Clinical criteria is: Patient must be receiving opioids for their persistent pain,

AND the Clinical criteria is: Patient must be unable to tolerate further escalation in the dose of morphine for breakthrough pain due to adverse effects.

Listing was requested on a cost-minimisation basis with fentanyl lozenges.

The PBAC noted that the submission requested a restriction identical to that of fentanyl lozenges.

The PBAC agreed with DUSC, that there is likely to be use outside of the restriction, including for:

- settings other than palliative care
- patients who can tolerate dose escalation of morphine or an alternate opioid
- non-breakthrough pain or persistent use when background therapy is

inadequate

- patients with cancer or who have had cancer in the past, but who now have pain from other causes
- incident pain or use in anticipation of pain (e.g. prior to showering, changing of wound dressings, etc).

The PBAC considered that being able to titrate the dose of analgesic according to a patient's response is essential for ensuring both effectiveness and safety and the new formulation proposed in this submission has less dosing options than fentanyl lozenges. The PBAC noted that the submission sought listing only for 100mcg, 200mcg and 400mcg strengths of fentanyl SL tablets. The PBAC noted that additional strengths (300mcg, 600mcg and 800mcg) were available in other markets. The PBAC considered that if these additional strengths were also available in Australia, it would aid in dose titration.

5. Clinical Place for the Proposed Therapy

Breakthrough cancer pain describes a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy.

Fentanyl is an opioid agonist, interacting predominantly with the μ -opioid receptor. The primary therapeutic actions are analgesia and sedation.

The sponsor's Pre-Sub-Committee Response stated that market research data highlight three main types of breakthrough cancer pain:

1. Inadequate baseline therapy
2. Incident pain (e.g. moving a patient), and
3. Unpredictable quick onset pain.

Fentanyl sublingual tablets were proposed to be used as second-line therapy for patients in the palliative care setting, currently using morphine for the treatment of breakthrough cancer pain, but for whom the current morphine dose is inadequate and where an increase in the morphine dose is clinically inappropriate due to renal impairment or adverse reactions.

The PBAC considered that the appropriate clinical place for fentanyl SL tablets was unclear. The PBAC acknowledged that there was potential for confusion with respect to the clinical place in therapy with the current listing for fentanyl lozenges. The PBAC considered the restriction may be open to interpretation, i.e. whether eligible patients are those unable to tolerate further escalation of morphine itself, morphine equivalents (another opioid such as oxycodone), or tried all other suitable immediate acting opioids.

The PBAC considered that potential confusion about the place in therapy of fentanyl lozenge led to similar confusion regarding the place in therapy of the sublingual tablet.

6. Comparator

The submission nominated oral transmucosal fentanyl citrate (lozenge) as the comparator. The PBAC accepted that fentanyl lozenge was an appropriate comparator in the proposed second-line setting. However, the PBAC considered that other immediate-release opioids may also be appropriate comparators.

7. Clinical Trials

The PBAC noted that no head-to-head trials were available and the submission was based on an indirect comparison of one randomised trial of sublingual fentanyl (EN005) and one randomised trial of fentanyl lozenges (Farrar 1998), with placebo as the common comparator. Details of the trials and associated reports are presented in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Randomised trials – sublingual fentanyl		
EN005	A double-blind, randomized, placebo-controlled multicentre study to evaluate the efficacy and safety of EN3267 for the treatment of breakthrough pain in opioid tolerant cancer patients followed by an up to 12 month non-randomized, open-label extension to assess long-term safety.	18 June 2009
Rauck 2009	Rauck RL, Tark M, Reyes, E, <i>et al.</i> Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain.	<i>Current Medical Research & Opinion</i> 2009; 25 (12):2877-2885
Randomised trials – fentanyl lozenge		
Farrar 1998	Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: Randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients.	<i>Journal of the National Cancer Institute</i> 1998; 90 (8):611-616

The PBAC noted that the clinical trials used restricted doses. The PBAC considered that in clinical practice, patients will likely titrate-to-effect and will use a greater variety of doses (even if not recommended in the Product Information). As a consequence, more tablets per dose may be required in clinical practice than in the trials.

The key features of the trials used in the indirect comparison are summarised in the table below.

Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Sublingual fentanyl vs. placebo					
EN005	66	R, DB, MC, ≤2 weeks	Unclear	Adult cancer patients w/ BTCP	SPID, PID, PR, TOTPAR, GP, response rate, QoL
Fentanyl lozenges vs. placebo					
Farrar 1998	92	R, DB, MC, <2 weeks	Unclear	Adult cancer patients w/ BTCP	SPID, PID, PR, TOTPAR, GP, response rate

Abbreviations: DB, double blind; MC, multi-centre; R, randomised; BTCP, breakthrough cancer pain; SPID, sum of pain intensity difference; PID, pain intensity difference; PR, pain relief; TOTPAR, total pain relief; GP, global performance of medication; QoL, quality of life.

Measures of pain in both trials were based on the Pain Intensity Numeric Rating Scale, an 11-point scale, where 0 represents no pain, and 10 “pain as bad as you can imagine”. Pain intensity was rated immediately before treating a breakthrough cancer pain episode with study medication (0 minutes), and for trial EN005 at 10, 15, 30 and 60 minutes after treatment and at the time of treatment with rescue medication, if applicable. Farrar 1998 reported measurements of pain intensity at 15, 30, 45 and 60 minutes.

The PBAC noted that no consumer comments were submitted in relation to this submission.

The sponsor of this submission did not request a hearing.

8. Results of Trials

The submission presented an indirect comparison of response rates (episode level data) from the sublingual fentanyl trial EN005 ($\geq 30\%$ reduction in pain intensity at 30 minutes) and the fentanyl lozenge trial Farrar 1998 ($\geq 33\%$ reduction in pain intensity at 30 minutes). Results are presented in the table below.

Indirect comparison between sublingual fentanyl and fentanyl lozenges: proportion of episodes with a reduction in pain intensity at 30 minutes $\geq 30\%$ for Trial EN005 and $\geq 33\%$ for Farrar 1998

Response rate ^a	Trial EN005 (N = 61)		Farrar 1998 (N = 86)		Indirect comparison
	Sublingual fentanyl	Placebo	Placebo	Fentanyl lozenges	
	213/364 (63.5%)	64/153 (41.8%)	89/245 (36.3%)	351/556 (63.1%)	NA
Odds Ratio	1.96 (1.34, 2.88)		3.00 (2.20, 4.10)		0.65 (0.40, 1.07)
Relative Risk	1.40 (1.14, 1.72)		1.74 (1.46, 2.08)		0.81 (0.61, 1.06)
Risk Difference	0.167 (0.074, 0.260)		0.268 (0.796, 0.340)		-0.101 (-0.347, 0.145)
NNT	6 (4, 14)		4 (3,5)		

^a Response rate is $\geq 30\%$ decrease in pain intensity at 30 min for sublingual fentanyl and $\geq 33\%$ at 30 min for fentanyl lozenges

Note: calculations performed using Canadian HTA calculator

Abbreviations: NNT, number needed to treat; NA, not applicable

The submission claimed the results demonstrate non-inferiority, based on the lack of a statistically significant difference in response rates between the two trials. However, the PBAC noted that differences in the thresholds used to define response in each trial may have meant that more episodes in the EN005 trial were classed as a response compared to the fentanyl lozenge trial. The PBAC noted that episode-level data were used in the indirect comparison rather than patient level data. The PBAC recalled its previous consideration that it was inappropriate to analyse episodes of breakthrough pain treated as independent events (March 2013 Public Summary Document – Fentanyl citrate nasal spray).

The submission also presented a naïve comparison between SL fentanyl and fentanyl lozenges based on the available outcomes shared between the two trials – pain intensity difference (PID) and pain relief (PR) at 30 and 60 minutes. Results are shown in the table below.

Naïve comparison between sublingual fentanyl and fentanyl lozenges

Outcome	Sublingual fentanyl (EN005) n = 61			Fentanyl lozenge (Farrar 1998) n = 86		
	LS Mean diff (95% CI) p-value	Fentanyl Mean (SD)	Placebo Mean (SD)	Placebo Mean (SD)	Fentanyl Mean (SD)	Mean difference , p-value
Pain intensity difference (PID, using 11-point rating scale)						
30 min	0.87 (0.43, 1.30) p=0.0002	2.9 (1.7)	2.0 (2.1)	1.6 (NR)	2.5 (NR)	0.87, p<0.001

Outcome	Sublingual fentanyl (EN005) n = 61			Fentanyl lozenge (Farrar 1998) n = 86		
	60 min	0.98 (0.46, 1.50) p=0.0004	3.4 (1.9)	2.5 (2.4)	2.8 (NR)	3.5 (NR)
Pain relief (PR, using 5-point rating scale)						
30 min	0.54 (0.27, 0.82) p=0.0002	1.8 (0.7)	1.3 (1.0)	1.2 (NR)	1.9 (NR)	0.66, p<0.001
60 min	0.53 (0.20, 0.86) p=0.0022	2.0 (0.9)	1.5 (1.2)	1.7 (NR)	2.3 (NR)	0.61, p<0.001

Abbreviations: min, minutes; SD, standard deviation; NR, not reported; PID, pain intensity difference; PR, pain relief; LS mean diff, least squares mean difference; CI, confidence intervals

The PBAC noted that no formal comparison of other outcomes was presented in the submission. The results of naïve indirect comparison suggested broadly similar results for sublingual fentanyl and fentanyl lozenge for pain intensity difference and pain relief.

Overall, the PBAC considered that the evidence presented in the submission was inadequate to reliably determine the comparative effectiveness of fentanyl SL tablets versus fentanyl lozenges.

A summary of the adverse events reported in the EN005 and Farrar 1998 trials was presented in the submission. The PBAC noted that all adverse events occurring during the trials appeared to have been attributed to the active study medication. The most frequently reported (>5%) treatment-related adverse events for trial EN005 were nausea and vomiting. In Farrar 1998, the most frequently reported treatment-related adverse events were dizziness, nausea, somnolence, constipation and asthenia. The PBAC noted that adverse events in both trials were similar and consistent with the established safety profile of fentanyl.

The PBAC agreed with the ESC that sublingual fentanyl tablets delivered immediately as a complete dose is potentially less safe than lozenges, as lozenges take 15 minutes to dissolve and may be removed if the patient is getting narcotised. The PBAC considered that this may have safety implications that are important in the proposed PBS population as there are older patients with poorer functional status in the proposed PBS cohort than the populations in the trials.

The PBAC considered that the evidence presented in the submission was inadequate to reliably determine the comparative safety of fentanyl SL tablets versus fentanyl lozenges.

A summary of the comparative benefits and harms for sublingual fentanyl versus fentanyl lozenge is presented in the table below.

Benefit/harm summary - sublingual fentanyl vs. fentanyl lozenges

Outcome	No studies (No episodes)	Indirect RR estimate (95%CI)	Event rate/100 episodes		Increment
			SLFC	OTFC	
Benefits					
Pain intensity difference ≥ 30% at 30 minutes (≥ 33% for fentanyl lozenge)	2 (1318 in 147 pts)	0.805 (0.61, 1.06) ^a	58.5 vs 41.8 PBO (≤ 14 days)	63.1 vs 36.3 PBO (< 14 days)	-
Harms					
There are insufficient data to formally assess the comparative safety.					

Abbreviations: CI, confidence interval; SLFC, sublingual fentanyl; OTFC, fentanyl lozenges; PBO, placebo; RR, relative risk; pts, patients

^a Results > 1 favour sublingual fentanyl

The PBAC noted that although the results in the table above demonstrate that there is no statistically significant difference between sublingual fentanyl and fentanyl lozenges with regard to pain intensity, the point estimate favours fentanyl lozenges (RR 0.805 (95% CI: 0.61, 1.06)).

The PBAC noted that during Trial EN005, there were several instances of trial medication diversion (p49, EN005 clinical trial report). The PBAC also noted the Australian Public Assessment Report (AusPAR) for sublingual fentanyl states that the short T_{max} and high bioavailability relative to other forms of fentanyl suggests this product would be preferred by individuals likely to abuse opioids. The PBAC were concerned that there would be a high risk of diversion of sublingual fentanyl tablets.

The PBAC were also concerned that there is a high risk of overdose or misuse in patients who meet the PBS restriction criteria.

9. Clinical Claim

The submission described sublingual fentanyl as non-inferior in terms of efficacy and similar in terms of safety compared to fentanyl lozenges.

The PBAC did not accept the submission's claim in relation to comparative efficacy. While there was no statistically significant difference shown in the indirect comparison between sublingual fentanyl and fentanyl lozenges, the PBAC considered that the quality of the data was poor. On the basis of the evidence presented in the submission, the PBAC was unable to make a reliable assessment of the comparative efficacy of sublingual fentanyl versus fentanyl lozenges.

The PBAC considered that the safety profile of fentanyl is well established, but the PBAC expressed concern that sublingual tablet presentation introduced new safety concerns, as detailed above. Consequently, the PBAC did not consider the submission's claim of similar safety compared to fentanyl lozenges was adequately supported.

10. Economic Analysis

Given that the PBAC did not accept the clinical claim of non-inferiority, the Committee considered the cost-minimisation analysis presented in the submission was fundamentally not appropriate.

However, with regard to the cost-minimisation analysis, the PBAC noted that equi-effective doses had not been estimated in the submission. The submission utilised a nominal 1:1 dose relationship between the two fentanyl preparations, with a flat pricing structure across dose strengths. The administration of sublingual fentanyl requires different numbers of tablets to achieve target doses which results in a tiered pricing structure, as the 2-tablet doses (300mcg, 600mcg, 800mcg) are twice as expensive as 1-tablet doses (100mcg, 200mcg, 400mcg). Therefore it is important to establish some estimate of dose relativity between treatments.

The PBAC considered the approach used in the submission to nominate a dose relationship between sublingual fentanyl and oral transmucosal fentanyl was not appropriate.

The PBAC noted that the submission did not take into account the likelihood of patients requiring more than one sublingual fentanyl tablet per dose. The weighted average number of sublingual fentanyl tablets per dose for patients stabilised in Trial EN005 was 1.71, as shown in the table below. The PBAC noted that if the 300mcg, 600mcg and 800mcg tablets were available in Australia, as they are in other markets, patients would be unlikely to require more than one tablet per dose.

Distribution of patients by stabilised sublingual fentanyl dose (end of open-label titration)

Dose	Number of patients (%) N=66	Number of tablets required per dose
100mcg	4 (6.1)	1
200mcg	7 (10.6)	1
300mcg	16 (24.2)	2
400mcg	8 (12.1)	1
600mcg	9 (13.6)	2
800mcg	22 (33.3)	2
Weighted average number of tablets per dose		1.71

An alternative analysis was conducted during the evaluation based on the average number of sublingual fentanyl tablets required per dose for patients stabilised in Trial EN005 (1.71). The PBAC considered this to be a more appropriate basis for cost-minimisation.

11. Estimated PBS Usage and Financial Implications

The submission estimated the net cost per year to the PBS to be less than \$10 million in Year 5.

The submission used a market share approach to estimate the utilisation and financial implications associated with the requested PBS listing of fentanyl sublingual tablet. The PBAC agreed with the DUSC that the market share approach taken in the submission was likely to underestimate utilisation of sublingual fentanyl tablets. Only a small proportion of the population eligible for fentanyl lozenges are currently treated with this agent. This is possibly due to the lengthy administration time and administration method. The proportion of eligible patients treated with fentanyl sublingual tablets is likely to be larger than the proportion of eligible patients treated with fentanyl lozenges due to the ease of administration and the faster onset of action of the sublingual tablet. The PBAC agreed with the DUSC that that an epidemiological approach would be more appropriate in this instance.

The PBAC noted that the submission did not consider the possibility of sublingual fentanyl substituting for other breakthrough cancer pain treatments, e.g. immediate-release opioids such as oxycodone. The PBAC considered that this was inappropriate and may further underestimate the uptake and utilisation.

The PBAC also considered that there would be considerable risk of use beyond the proposed restriction including in settings other than palliative care, in patients who can tolerate further dose escalation of morphine/other opioids, and use in treatment of incident or anticipated pain.

12. PBAC Outcome

The PBAC acknowledged that a clinical need exists for alternative treatments for breakthrough pain in cancer patients.

However, the PBAC rejected the submission for fentanyl sublingual tablets for the treatment of breakthrough cancer pain. The PBAC considered the submission's claims of non-inferior comparative efficacy and safety versus fentanyl lozenges were inadequately supported by the data presented in the submission. The PBAC was therefore unable to accept the submission's cost-minimisation analysis.

The PBAC also considered that the appropriate clinical place of sublingual fentanyl was unclear, noting that it was possible that it would be used in a number of clinical settings in addition to that requested in the proposed restriction.

The PBAC accepted that fentanyl lozenge was an appropriate comparator in the proposed second-line setting. However, the PBAC considered that other immediate-release opioids may also be appropriate comparators.

The PBAC considered that the evidence presented in the submission was inadequate to reliably inform an assessment of the comparative effectiveness and comparative safety of fentanyl SL tablets versus fentanyl lozenges.

The PBAC considered that there were significant safety and quality use of medicines issues related to the use of sublingual fentanyl tablets. The Committee noted the risk management plan proposed by the sponsor but considered that there was still potential net for harm associated with the use of sublingual fentanyl tablets, given concerns regarding diversion, misuse and overdose.

The PBAC did not accept the utilisation estimates provided in the submission. The PBAC considered that uptake of the fentanyl sublingual tablets would likely be higher than predicted due to ease of use and faster onset of action. The PBAC also considered that there is likely to be use of fentanyl sublingual tablets in the management of other pain, such as incident pain in the acute care setting, which could lead to use beyond the requested population, further increasing uptake.

The PBAC acknowledged that there was potential for confusion with respect to the clinical place in therapy with the current listing for fentanyl lozenges. The PBAC considered the restriction may be open to interpretation, i.e. whether eligible patients are those unable to tolerate further escalation of morphine itself, morphine equivalents (another opioid such as oxycodone), or tried all other suitable immediate acting opioids. The PBAC recommended that the Department review and clarify the current listing for fentanyl lozenges to ensure the clinical place in therapy is clearly understood.

Recommendation:

Rejected

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

The sponsor is disappointed with the decision but welcomes the PBAC acknowledgement that a clinical need exists for alternative treatments for breakthrough pain in cancer patients. The sponsor will continue to work with the PBAC to secure a PBS listing for ABSTRAL[®].