

7.04 FENTANYL CITRATE

**100 microgram tablet: sublingual, 10 & 30,
 200 microgram tablet: sublingual, 10 & 30,
 300 microgram tablet: sublingual, 10 & 30,
 400 microgram tablet: sublingual, 10 & 30,
 600 microgram tablet: sublingual, 10 & 30,
 800 microgram tablet: sublingual, 10 & 30,
 Abstral®, A.Menarini Australia Pty Ltd.**

1 Purpose of Application

- 1.1 Authority Required (Palliative Care Schedule) listing for fentanyl sublingual tablets for treatment of breakthrough pain in patients undergoing palliative care for cancer.

2 Requested listing

2.1

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
FENTANYL CITRATE sublingual tablet Tablets 100 microgram Tablets 200 microgram Tablets 300 microgram Tablets 400 microgram Tablets 600 microgram Tablets 800 microgram	10 & 60	Nil	Abstral®	A.Menarini

Condition:	Breakthrough cancer pain
Episodicity	As needed
Severity	Moderate to severe
Treatment phase:	Initial treatment for dose titration Continuing treatment
Restriction:	Authority Required (Palliative Care Schedule)
Treatment criteria:	<ul style="list-style-type: none"> ▪ Patient must be undergoing palliative care for cancer ▪ Initiation must be in consultation with a specialist where a specialist is defined as <ul style="list-style-type: none"> • Palliative Care Specialist and Nurse Practitioner • Med Oncologist, Radiation Oncologist and Haematologist • Pain Specialist ▪ Continuation can be written by any clinician providing the initiation is made in consultation with a specialist ▪ Continuation includes patient stabilised on the drug in hospital in an in-patient setting where the initiation was in consultation with a Specialist.
Clinical criteria:	Patient must have cancer, AND Patient must have been experiencing transient exacerbations of pain which is rapid in onset and short in duration, despite relatively stable and adequately controlled background pain management, AND

	<p>Patient must be assessed as receiving adequate background opioid pain management for chronic cancer pain, AND Patient must have previously experienced inadequate pain relief following administration of adequate doses of an oral, immediate-release opioid for the treatment of breakthrough pain, e.g. morphine, hydromorphone or oxycodone OR Patient must have previously experienced adverse effects following an oral immediate-release opioid for treatment of breakthrough pain, or patient cannot take oral medication</p>
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- 2.2 The listing was requested on a cost minimisation basis compared to fentanyl lozenges, adjusted for a proportion of substitution of immediate-release opioids.
- 2.3 Compared to the previous requested restriction, the proposed restriction is narrower and more detailed, in that patients must have previously experienced inadequate pain relief or adverse events with an oral, immediate-release opioid. The previous restriction only specified inability to tolerate increased doses of morphine due to adverse events. The proposed restriction does not specify that patients need to have trialled all immediate-release oral opioids before moving to fentanyl sublingual tablets. There is potential for patients to be prescribed fentanyl sublingual tablets when there are other immediate-release opioid treatment options still available.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 Fentanyl sublingual (100mcg, 200mcg, 400mcg) was TGA registered on 26 August 2013 for the management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain. The sponsor has sought TGA registration for additional tablet dose strengths: 300mcg, 600mcg and 800mcg to be considered at the June 2015 ACPM meeting. At the time of the evaluation the Round 1 Clinical Evaluation Report was available for the consideration of these additional dose strengths.
- 3.2 A TGA approval letter for fentanyl sublingual strengths (300mcg, 600mcg and 800mcg) was received 1 July 2015.
- 3.3 A submission for fentanyl sublingual was considered at the March 2014 PBAC meeting, and was rejected on the basis of inadequately supported claims of non-inferior comparative efficacy and safety versus fentanyl lozenges.
- 3.4 The PBAC previously 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.
- 3.5 The PBAC previously considered that uptake of the fentanyl sublingual tablets would likely be higher than predicted due to ease of use and faster onset of action compared to fentanyl lozenges. 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.

- 3.6 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.
- 3.7 The table below outlines the concerns of the PBAC in the previous submission and the measures this resubmission undertook to address those concerns.

Matters of concern	How the resubmission addressed it	June 2015 ESC Comment
7.2 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.	Expanded clinical section (Section B.6) with an updated literature search, supportive data from external network meta-analyses and a Cochrane review, and a formal indirect comparison using patient-level data for key efficacy outcomes.	The ESC considered that these re-analyses support the non-inferior comparative efficacy of sublingual fentanyl compared vs fentanyl lozenges, within the limits of indirect comparisons. While there are outstanding theoretical concerns about potential increased risk of local and systemic adverse effects with sublingual fentanyl in the PBS population, there is no difference in safety outcomes from the indirect comparisons supplied.
7.3 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 resubmission tightened the proposed restriction to ensure only patients in cancer palliative care are eligible for fentanyl sublingual.	The ESC considered that it remains unclear whether the place in therapy for sublingual fentanyl (and other immediate release fentanyl formulations) is 2 nd line (as claimed by the sponsor) or whether it should be 3 rd and subsequent lines.
7.4 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 resubmission included a supplementary analysis of efficacy comparing fentanyl sublingual with an immediate-release opioid (liquid morphine). The resubmission also incorporated the substitution of immediate-release opioids in estimation of financial implications.	The ESC noted that this concern was well addressed in the resubmission as it considers use of sublingual fentanyl in second or later line therapy.
7.6 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 for net harm	Greater detail was provided in the resubmission of the sponsor's post-marketing educational programs.	The ESC noted that whilst these strategies address prescribing issues, the potential for illicit diversion remains high.

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Matters of concern	How the resubmission addressed it	June 2015 ESC Comment
associated with the use of sublingual fentanyl tablets, given concerns regarding diversion, misuse and overdose.		
7.7 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 resubmission also clarified the definition of breakthrough cancer pain and demonstrated that incident pain is one possible manifestation of breakthrough cancer pain. The resubmission re-iterated the sponsor's willingness to enter into a risk share arrangement.	The ESC agreed that incident pain is a component of breakthrough cancer pain, and this is supported by the palliative care literature. The ESC noted that the proposed risk share arrangement could address potential higher than anticipated use.
6.24 Uncertain dose relativity between fentanyl sublingual and fentanyl lozenges. The resubmission did not take into account the financial implications of patients requiring more than one fentanyl sublingual tablet per dose.	The sponsor sought the registration of additional doses of fentanyl sublingual, and proposed a flat pricing structure for all fentanyl sublingual dose strengths. The cost of treating breakthrough cancer pain as calculated in the resubmission was the same irrespective of the titrated dose.	The ESC agreed that the additional dose strengths and flat pricing structure proposed by the resubmission adequately addressed the effects of a lack of equi-effective dosing on the cost minimisation calculations. This is reasonable for short acting fentanyl for breakthrough pain because only a single dose is used for each episode, and dose is titrated to effect for each patient and is highly variable.
6.27 Potential underestimation of cost, which did not consider the possibility of fentanyl sublingual substituting for other breakthrough cancer pain treatments such as immediate-release opioids (e.g. oxycodone)	Financial estimates take into account substitution of fentanyl lozenges, market growth from patient populations eligible for fentanyl lozenges but not currently treated due to limitations of the lozenge presentation, and patients treated or undertreated with immediate-release opioids.	The ESC agreed that this has been adequately addressed, and welcomed the proposed risk share arrangement.

4 Clinical place for the proposed therapy

4.1 Second-line therapy for patients undergoing palliative care for cancer. Patients must have been experiencing breakthrough cancer pain despite relatively stable and adequately controlled background pain management, and must have previously experienced inadequate pain relief or adverse effects from an oral immediate-release opioid. Although it is clear that the place in therapy for fentanyl sublingual is not first-line therapy (which must be an oral immediate-release opioid), it is unclear, based on

the proposed restriction, whether fentanyl sublingual may be used subsequent to the trial of only one immediate-release opioid or whether all possible other immediate-release opioids must be trialled ahead of fentanyl sublingual.

- 4.2 The Pre-Sub-Committee Response clarifies the intention of the restriction to only require lack of efficacy in one immediate release opioid prior to the use of fast-acting fentanyl. The PSCR (p2) also argues that fast acting fentanyl should be used clinically in the second-line setting, as the pharmacokinetic profiles of other fast acting (immediate release) opioids are all similar. The ESC did not consider that this claim was reasonable, considering the differences in metabolism, drug interactions and clearance of these agents.
- 4.3 The PBAC noted the concerns of the ESC in reference to the clinical place in therapy being at second-line. The PBAC considered that withholding fentanyl sublingual to third- and subsequent lines for breakthrough pain may not be practical or reasonable. The Committee further considered that any concerns for diversion may be controlled adequately in the second line listing under a palliative care setting.
- 4.4 The PBAC considered that, in rare circumstances, fentanyl sublingual may be used in a first-line setting, by patients that are unable to swallow oral immediate-release opioids and who would otherwise require subcutaneous morphine.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 Fentanyl lozenges, with immediate-release opioids (represented by oral immediate-release morphine) as a supplementary comparator. These were considered the appropriate comparators. Immediate-release opioids were not considered as comparators in the previous submission.
- 5.2 In the resubmission's estimates of utilisation, fentanyl sublingual uptake from 'non-fentanyl lozenge use' (i.e., from sub-optimal immediate-release opioid treatment) was greater than the uptake from fentanyl lozenge treatment (75% and 25% of the estimated patient uptake, respectively).
- 5.3 The PBAC considered both immediate-release oral opioids and fentanyl lozenges to be appropriate comparators. In addition, the PBAC considered that in rare circumstances, for the small group of patients who are unable to swallow oral opioids, subcutaneous morphine is an appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health professionals (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with fentanyl sublingual, including:
- i) the rapid onset of action and short duration of effect being ideal for the ease of use in frail, elderly patients and the reduction in burden on carers;
 - ii) the improved analgesia for movement or activity related breakthrough pain with a shorter duration; and
 - iii) avoiding excess opioid accumulation when used for incident pain.

Clinical trials

- 6.3 The resubmission was based on an indirect comparison of fentanyl sublingual (n=61) and fentanyl lozenges (n=89), with placebo as common comparator. The trials used in the indirect comparison were the same as in the previous submission but different outcomes were used in the resubmission. The resubmission also included a non-randomised comparison of fentanyl sublingual and immediate-release oral morphine, as a proxy for immediate-release opioids (n=40).
- 6.4 Details of the trials presented in the resubmission are provided in the table below.

Table 1: Trials (and associated reports) presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Indirect comparison of fentanyl sublingual and fentanyl lozenges, placebo common comparator		
Fentanyl sublingual		
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. NCT: 00262678	Clinical Study Report, 18 June 2009.
Rauck 2009	Rauck RL, Tark M, Reyes, E, et al. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain.	Current Medical Research & Opinion 2009; 25 (12):2877-2885

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Trial	Protocol title/ Publication title	Publication citation
EN007	A multiple-dose, non-randomized, open-label, multicentre study to evaluate the long-term safety and effectiveness of EN3267 in the treatment of breakthrough pain in cancer patients. NCT: 00263575.	Clinical Study Report, 18 June 2009
Nalamachu 2011	Nalamachu, Hassman, Wallace et al. Long term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain.	Current Medical Research & Opinion 2011; 27(3):519-530
Fentanyl lozenges		
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.	Journal of the National Cancer Institute 1998; 90(8):611-616
Payne 2001	Payne R, et al. Long term safety of oral transmucosal fentanyl citrate for breakthrough cancer pain.	Journal of Pain and Symptom Management 2001; 22(1):575-583
Supplementary meta-analyses		
Zeppetella 2014	Zeppetella G, Davies A, Eijgelshoven I, Jansen JP. A network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes.	Journal of Pain and Symptom Management 2014; 47(4):772-785.
Jandhyala 2013	Jandhyala R, Fullarton JR, Bennett M. Efficacy of rapid-onset oral fentanyl formulations vs. oral morphine for cancer-related breakthrough pain: A meta-analysis of comparative trials.	Journal of Pain and Symptom Management 2013; 46(4):573-580
Zeppetella 2013	Zeppetella G, Davies AN. Opioids for the management of breakthrough pain in cancer patients.	Cochrane Database of Systematic Reviews 2013 (online) (10): CD004311
Fentanyl sublingual vs immediate-release opioids		
Velazquez Rivera 2014	Velazquez Rivera I, Munoz Garrido JC, Garcia Velasco P, de Enciso I, Clavarana L. Efficacy of sublingual fentanyl vs. oral morphine for cancer-related breakthrough pain.	Advanced Therapeutics 2014; 31:107-117

Source: Table B-6, pp60-61 of the resubmission

6.5 The key features of the included trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Fentanyl sublingual vs placebo					
EN005	61	R, DB, MC, ≤2 weeks; ≤12 mth extension	Unclear	Adult cancer patients w/ BTCP	SPID, PID, PR, [redacted]
EN007	96	OL, MC, single arm, ≤12 mth extension	Unclear	Adult cancer patients w/ BTCP naïve to fentanyl sublingual	[redacted], QoL
Fentanyl lozenges vs placebo					
Farrar 1998 / Payne 2001	92	R, DB, MC, <2 weeks	Unclear	Adult cancer patients w/ BTCP	SPID, PID, PR, TOTPAR, GP, response rate
Fentanyl sublingual vs immediate-release oral morphine					
Velazquez Rivera 2014	40	DB, SC, non-randomised, 30 days	High	Adult cancer patients w/ BTCP	Pain intensity, frequency of BTCP, time to onset of pain relief

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

Source: compiled during the evaluation

Comparative effectiveness

6.6 The previous submission presented an indirect comparison of responder rates using episode-level data for fentanyl sublingual and fentanyl lozenges. The current resubmission presented a formal indirect comparison of patient-level data for fentanyl sublingual and fentanyl lozenges on pain intensity difference and pain relief measures. There were no statistically significant differences demonstrated between fentanyl sublingual and fentanyl lozenges for the pain intensity difference and pain relief outcomes at the 15, 30 or 60 minute time points. The resubmission claimed non-inferiority of fentanyl sublingual over fentanyl lozenges based on a lack of statistically significant differences between the two treatments on measures of pain intensity difference and pain relief. There are no established non-inferiority margins for pain outcomes. However, the mean pain scores and confidence intervals for each treatment overlap considerably, indicating that results for the two treatments were very similar for these outcome measures. However, the ESC considered the reliability of this comparison is limited by the indirect comparison.

Table 3: Indirect treatment comparison on Mean Difference PID and PR

Time-point	Sublingual fentanyl (EN005) n = 61			Fentanyl lozenge (Farrar 1998) n = 89			Indirect Comparison Mean difference (95%CI)
	Mean diff (95% CI)	Fentanyl Mean (SD)	Placebo Mean (SD)	Placebo Mean (SD)	Fentanyl Mean (SD)	Mean diff (95% CI)	
Pain intensity difference (PID, using 11-point rating scale)							
15 min	0.55 (0.23, 0.87)	2.0 (1.4)	1.5 (1.6)	1.1 (NR)	1.7 (NR)	0.58 (0.3, 0.9)	0 (-0.5, 0.5)
30 min	0.87 (0.43, 1.30)	2.9 (1.7)	2.0 (2.1)	1.6 (NR)	2.5 (NR)	0.87 (0.5, 1.2)	0 (-0.6, 0.6)
60 min	0.98 (0.46, 1.50)	3.4 (1.9)	2.5 (2.4)	2.8 (NR)	3.5 (NR)	0.66 (0.2, 1.1)	0.3 (-0.4, 1.1)
Pain relief (PR, using 5-point rating scale)							
15 min	0.36 (0.16, 0.56)	1.4 (0.7)	1.0 (0.8)	1.0 (NR)	1.5 (NR)	0.47 (0.2, 0.7)	-0.1 (-0.5, 0.2)
30 min	0.54 (0.27, 0.82)	1.8 (0.7)	1.3 (1.0)	1.2 (NR)	1.9 (NR)	0.66 (0.4, 0.9)	-0.1 (-0.5, 0.3)
60 min	0.53 (0.20, 0.86)	2.0 (0.9)	1.5 (1.2)	1.7 (NR)	2.3 (NR)	0.61 (0.3, 0.9)	-0.1 (-0.5, 0.4)

Abbreviations: CI, confidence intervals; Mean diff, mean difference; min, minutes; NR, not reported; SD, standard deviation

Source: Table B-38, p95; Table B-39, p96; Table B-40, p97 of the resubmission

- 6.7 The resubmission also presented the results of a non-randomised double blind study comparing fentanyl sublingual with immediate-release oral morphine in patients with breakthrough cancer pain (Velazquez Rivera 2014). Outcomes were reported as difference in pain intensity from baseline on days 3,7,15 and 30. Results from this study were unable to be interpreted in the context of breakthrough cancer pain relief. For each assessment day, it is unclear which patients were included, what episodes were counted, and which time point was used to measure pain intensity.

Comparative harms

- 6.8 Adverse events from trials EN005 and Farrar 1998 were not re-presented from the previous submission. Long-term safety data presented from the fentanyl sublingual trial EN007 and fentanyl lozenge trial Payne 2001 were similar and consistent with the established safety profile of fentanyl (e.g. nausea, vomiting, constipation, somnolence, dizziness, and headache). Safety data reported in the fentanyl sublingual vs immediate-release morphine study (Velazquez Rivera 2014) were also consistent with the established safety profile of other opioid agents.
- 6.9 In regard to adverse events related to the mode of administration, both fentanyl sublingual tablets (█.█% of patients from Trial EN005) and fentanyl lozenges (approximately 1-10% of patients based on product information) are associated with mucosal irritation (including bleeding, pain and ulceration). The ESC noted the theoretical potential for a higher prevalence of mucositis or mucosal irritation with fentanyl sublingual tablets when compared with fentanyl lozenges due to more localised administration.

Clinical claim

- 6.10 The resubmission described fentanyl sublingual as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over fentanyl lozenges. The body of evidence supporting the claim of non-inferiority between fentanyl sublingual tablets and fentanyl lozenges was weak: indirect comparison of trials with uncertain risk of bias and limited applicability to the PBS population, subjective and highly variable outcomes, no widely accepted non-inferiority margins and the possibility of higher prevalence of adverse local and systemic effects with fentanyl sublingual, especially in the PBS population.
- 6.11 The resubmission did not make a clinical claim for fentanyl sublingual over immediate-release opioids. The resubmission claimed that fentanyl sublingual is non-inferior to the reference treatments, immediate-release opioids, in treating an episode of breakthrough cancer pain. The evaluation considered that the claim was not adequately supported. The ESC agreed with the commentary that the data comparing fentanyl to immediate release opioids cannot be reliably applied.
- 6.12 The PBAC noted the weak body of evidence for comparison of fentanyl sublingual tablets with fentanyl lozenge and immediate-release opioids. In the context of a clinical need in the palliative care population for a non-parenteral opioid formulation with a faster onset of action and short duration, the PBAC accepted non-inferior comparative effectiveness and non-inferior comparative safety.

Economic analysis

- 6.13 The resubmission presented a cost-minimisation analysis, adjusted for a proportion of use substituting for immediate-release opioids (offered as a ■■■% discount on the price of fentanyl lozenges). The previous submission also presented a cost-minimisation analysis with a ■■■% discount on the price of fentanyl lozenges. No additional costs or offsets were included in the economic analysis.
- 6.14 Equi-effective doses for fentanyl sublingual and fentanyl lozenges were not estimated, but the resubmission's economic analysis assumed that each pain episode would be treated with one sublingual tablet or one lozenge. The sponsor's decision to apply to the TGA for registration of three further dose strengths (300, 600 and 800mcg) means that the previous submission's concerns that patients may require two sublingual tablets to achieve similar doses to one lozenge, may no longer be applicable. The ESC considered that the registration of the additional strengths adequately addressed this issue for this case of short acting fentanyl for breakthrough cancer pain, where only one dose is used per episode and dose is titrated to effect in each patient and is highly variable.

Cost/patient/90 days

- 6.15 \$■■■ (DPMQ \$■■■ for 60 tablets; 3 tablets/ day x 4.5 packs for 90 days)
Fentanyl lozenge cost/patient/90 days: \$■■■ (DPMQ \$■■■ for 60 lozenges; 3 lozenges/ day x 4.5 packs for 90 days)
Oxycodone immediate-release tablet cost/patient/90 days: \$■■■.
- 6.16 The costs presented above are estimates and represent approximate costs given certain assumptions:
- Costs for fentanyl sublingual and fentanyl lozenges are based on the DPMQ for a continuation script (60 tablets), disregarding dose titration period
 - Costs for immediate-release oxycodone tablets, used as a proxy for all other oral immediate-release opioids, were estimated in using a "theoretical pack" of oxycodone to treat the equivalent number of episodes as one pack of fentanyl sublingual.
 - Treatment duration for each patient is 90 days.
 - Each patient receives treatment with one tablet or lozenge or equivalent oxycodone tablet dose for each of 3 breakthrough pain episodes/day (based on patients in the key included fentanyl sublingual trial).

Estimated PBS usage & financial implications

- 6.17 This resubmission was not considered by DUSC. An epidemiological approach was taken in the resubmission compared to a market-share approach in the previous submission. The March 2014 submission did not consider uptake of fentanyl sublingual outside of the fentanyl lozenge market. The current resubmission estimated the extent of use from patients switching from fentanyl lozenges to fentanyl sublingual and from eligible patients not currently treated with fentanyl lozenges.

Table 4: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Number treated March 2014					
Uptake from fentanyl lozenge	%	%	%	%	%
Uptake from fentanyl lozenge March 2014	%	%	%	%	%
Uptake from IR opioids	%	%	%	%	%
Uptake from IR opioids March 2014	%	%	%	%	%
Total initiation scripts					
Total initiation scripts March 2014					
Total continuation scripts					
Total continuation scripts March 2014					
Estimated net cost to PBS					
Net cost to PBS	\$	\$	\$	\$	\$
Net cost to PBS March 2014	-\$	-\$	-\$	-\$	-\$

Note: patients were estimated to experience 3 breakthrough pain episodes per day, each episode treated with one sublingual fentanyl tablet. Treatment duration was estimated at 109 days.

Abbreviations: IR, immediate-release; NE, not estimated. Source: Compiled during the evaluation

- 6.18 The redacted table above shows that at year 1, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million. At year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$10 – 20 million.
- 6.19 The submission’s estimate of the net cost of listing fentanyl sublingual is based on the total cost of fentanyl sublingual, with cost offsets from substitution of fentanyl lozenges and immediate-release opioids. Whether this is an over- or under-estimate is unknown because of uncertainties around assumptions of uptake from the eligible patient groups. The ESC considered that the resubmission’s financial estimates were most sensitive to changes in the eligible patient population (proportion of patients with breakthrough cancer pain, proportion treated with an opioid, and proportion intolerant or unresponsive to first line agent), and the length of therapy.
- 6.20 The PBAC noted that the submission had appropriately taken an epidemiological approach rather than a market share approach as in the previous submission. The PBAC agreed with the resubmission that the size of the eligible population remains uncertain given the wide ranges in the published literature and the paucity of evidence underpinning a number of key assumptions. The PBAC considered that a risk share arrangement would be needed to address this uncertainty as well as manage the financial implications for any use beyond the restriction including into the first-line treatment of breakthrough pain in cancer patients.

Quality Use of Medicines

- 6.21 The resubmission presented a summary of the sponsor’s fentanyl sublingual educational program, mandatory for prescribers and dispensers of fentanyl sublingual, with additional information for patients and carers.
- 6.22 The PBAC recalled it has previously raised concern about potential for misuse and diversion of opioids. The PBAC considered that a telephone authority required listing may help to mitigate this risk. The PBAC noted that it will be considering the

Post-Market Review of Authority required listings, including opioids and the outcomes of an opioid stakeholder meeting.

Financial Management – Risk Sharing Arrangements

- 6.23 The sponsor indicated a willingness to enter into a Risk Share Arrangement (RSA). No details were provided in the resubmission.
- 6.24 The PBAC recommended that the RSA would be required to address the following uncertainties:
- Uncertain size of patient population, duration of treatment and uptake of use.
 - Further use beyond the restriction including outside of the palliative care breakthrough pain cancer population.
- 6.25 The PBAC considered that the main risk of higher than expected expenditure stems from fentanyl substituting for oral immediate-release opioids in patients able to tolerate immediate-release opioids. The Committee advised that the RSA should therefore include a [REDACTED].

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC recommended listing fentanyl citrate sublingual tablets as an Authority Required benefit on the Palliative Care Schedule for the treatment of breakthrough pain in patients undergoing palliative care for cancer.
- 7.2 The recommendation was made on a cost-minimisation basis with immediate-release opioids and fentanyl lozenge (Actiq). Equi-effective doses were not estimated, but assumptions were made for each pain episode to be treated with one sublingual tablet or one lozenge. The PBAC considered that the resubmission's request of flat pricing across dose strengths addressed the issue of variability during titration of short acting fentanyl for breakthrough pain.
- 7.3 Based on the data provided, the PBAC considered that in the context of a clinical need in the palliative care population for a non-parenteral opioid formulation with a faster onset of action and short duration, a non-inferior comparative effectiveness and non-inferior comparative safety may be acceptable.
- 7.4 The PBAC agreed that the likely clinical place in therapy for fentanyl sublingual would be a second-line listing in a palliative care setting, as withholding fentanyl sublingual to third- and subsequent lines for breakthrough pain may not be practical or reasonable. Furthermore, the Committee considered that, in rare circumstances, fentanyl sublingual may be appropriately used in first-line setting for patients unable to swallow oral immediate-release opioids.

- 7.5 The PBAC considered both immediate-release oral opioids and fentanyl lozenges to be appropriate comparators. In addition, for the small group of patients who are unable to swallow oral opioids, the PBAC considered that subcutaneous morphine may be an appropriate comparator.
- 7.6 The PBAC noted the comments from health professionals regarding the desire for a product with rapid action and short duration of effect. The PBAC acknowledged that a clinical need exists for alternative treatments for breakthrough pain in cancer patients and particularly for treatments which control breakthrough pain without the sedation associated with immediate-release oral opioids.
- 7.7 The PBAC agreed with the ESC that incident pain is a component of breakthrough pain, as supported by the palliative care literature.
- 7.8 The PBAC noted that the resubmission had appropriately taken an epidemiological approach rather than a market share approach as in the previous submission. The PBAC agreed with the resubmission that the size of the eligible population remains uncertain given the wide ranges in the published literature and the paucity of evidence underpinning a number of key assumptions. The PBAC considered that a robust risk-sharing arrangement would be needed to address this uncertainty as well as manage the financial implications for any use beyond the restriction including into the first-line treatment of breakthrough pain in cancer patients.
- 7.9 The PBAC considered that a telephone authority required listing may help to mitigate the risk of standing concerns regarding potential for misuse and diversion of opioids.
- 7.10 The PBAC requested the Department consult with peak clinical bodies for pain management to define the restriction wording and clinical place in therapy. The Committee advised that following finalisation of the restriction, any amendments should be flowed on to the current fentanyl lozenge listing.
- 7.11 The PBAC recommended that fentanyl citrate sublingual tablets should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.12 The PBAC advised that fentanyl citrate sublingual tablets are suitable for prescribing by nurse practitioners under a Shared Care model.
- 7.13 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.14 The submission is not eligible for an Independent Review as the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Restrictions to be finalised.

Add new items:

FENTANYL CITRATE

100 microgram tablet: sublingual, 10 & 30,
200 microgram tablet: sublingual, 10 & 30,
300 microgram tablet: sublingual, 10 & 30,
400 microgram tablet: sublingual, 10 & 30,
600 microgram tablet: sublingual, 10 & 30,
800 microgram tablet: sublingual, 10 & 30,
Abstral®, A.Menarini Australia Pty Ltd.

Amend existing/recommended listing:

FENTANYL CITRATE

Lozenge 200 micrograms, 9 & 30
Lozenge 400 micrograms, 9 & 30
Lozenge 600 micrograms, 9 & 30
Lozenge 800 micrograms, 9 & 30
Lozenge 1200 micrograms, 9 & 30
Lozenge 1600 micrograms, 9 & 30
Actiq®, Orphan Australia Pty Ltd

9 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.

10 Sponsor's Comment

A.Menarini Australia Pty Ltd welcomes the decision by the PBAC to make Abstral available to cancer patients with breakthrough pain who currently have a high need.