

5.06 FENTANYL CITRATE

**100 microgram tablet: buccal, 4 & 28,
200 microgram tablet: buccal, 4 & 28,
400 microgram tablet: buccal, 4 & 28,
600 microgram tablet: buccal, 4 & 28,
800 microgram tablet: buccal, 4 & 28,
Fentora®, Teva Pharmaceuticals Australia Pty Ltd.**

1 Purpose of application

- 1.1 Authority Required (Palliative Care Schedule) listing for fentanyl buccal tablets for treatment of breakthrough cancer pain.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
FENTANYL CITRATE			Fentora® Teva
Oral (buccal) disintegrating tablet			
100mcg titration pack			
200mcg titration pack			
400mcg titration pack	8	0	
600mcg titration pack			
800mcg titration pack			
Oral (buccal) disintegrating tablet			
100mcg maintenance pack			
200mcg maintenance pack			
400mcg maintenance pack	56	0	
600mcg maintenance pack			
800mcg maintenance pack			

Authority Required (Palliative Care Schedule)

Treatment of breakthrough pain in patients with cancer AND who are receiving opioids for their persistent pain AND who must be unable to tolerate further escalation in the dose of short acting opioids (which may include morphine) for breakthrough pain due to adverse effects AND who must be undergoing palliative care.

- 2.1 The proposed restriction is ambiguous regarding the place in therapy for fentanyl products on the PBS (i.e. it is unclear whether fentanyl may be used as second-/third-/subsequent-line therapy in patients with other non-fentanyl treatment options or only as a last-line therapy in patients with no other options).
- 2.2 The Pre-Sub-Committee Response's (PSCR) clarification that the intended place in therapy is third and subsequent line treatment. The ESC suggested the restriction wording incorporate 'unable to tolerate further escalation in the dose of two or more short acting opioids...' to ensure use restricted to third or subsequent line.
- 2.3 The listing was requested on a cost minimisation basis compared to fentanyl lozenges.

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

3 Background

- 3.1 TGA status: Fentanyl buccal tablets were registered by the TGA on 5 February 2015 for the treatment of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.
- 3.2 The PBAC has not previously considered fentanyl buccal tablets for any indication.

4 Clinical place for the proposed therapy

- 4.1 Breakthrough cancer pain is a term used to describe transitory exacerbations of pain in cancer patients whose background pain is well-controlled by the use of chronic opioid therapy.
- 4.2 The submission positioned both fentanyl buccal tablets and fentanyl lozenges as third-line treatment options after the failure of two or more immediate-release opioids (primarily morphine, oxycodone and/or hydromorphone). Results of the sponsor-commissioned physician survey indicated that while fentanyl products are predominantly used as third and subsequent-line treatments they are also considered as second-line or even first-line therapy in some patients.
- 4.3 The PBAC noted the comments of the sponsor and the ESC in reference to the clinical place of therapy. The PBAC considered that withholding fentanyl buccal 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 buccal 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. The evaluation considered this an appropriate main comparator. Various formulations of other immediate-release opioids are likely to be relevant secondary comparators in the second-line, third-line and subsequent-line settings.
- 5.2 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 There were no consumer comments for this item.

Clinical trials

6.3 The submission was based on an indirect comparison of pain outcomes between fentanyl buccal tablets (Study 14, Study 3039, Kosugi et al 2014) and fentanyl lozenges (Farrar et al 1998) using a placebo common comparator.

6.4 Two head-to-head non-randomised studies (Berardi et al 2012 [abstract only], Graffi et al 2011 [abstract only]) were identified as supportive evidence. Additional long-term safety studies of fentanyl buccal tablets were also provided as supportive evidence in the extended assessment of harms (Study 15, Davies et al 2015, Lofti et al 2011 [abstract only]).

6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Key studies		
Study 14	Cephalon Clinical Study Report (2005). A multicentre, double-blind, placebo-controlled study of ORAVESCENT® fentanyl citrate for the treatment of breakthrough pain in opioid-tolerant cancer patients.	Internal study report.
	Portenoy et al (2006). A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer.	Clinical Journal of Pain 22: 805-811
Study 3039	Cephalon Clinical Study Report (2007). A double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety and tolerability of ORAVESCENT® fentanyl citrate in opioid-tolerant patients with cancer and breakthrough pain.	Internal study report
	Slatkin et al (2007). Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain.	Journal of Supportive Oncology 5: 327-334
Kosugi 2014	Kosugi et al (2014). A randomized, double-blind, placebo-controlled study of fentanyl buccal tablets for breakthrough pain: efficacy and safety in Japanese cancer patients.	Journal of Pain and Symptom Management 47: 990-1000
Farrar 1998	Farrar et al (1998). Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients.	Journal of the National Cancer Institute 90: 611-616
	Farrar et al (2000). Defining the clinically important difference in pain outcome measures.	Pain 88: 287-294
Supportive studies		
Berardi 2012	Berardi et al (2012). Oral transmucosal fentanyl citrate (OTFC) vs. fentanyl buccal tablet (FBT) for breakthrough cancer pain (BTcP).	Supportive Care in Cancer 20:S118 [abstract only]
Graffi 2011	Graffi et al (2011). Oral transmucosal fentanyl citrate (OTFC) vs tablet form of fentanyl citrate (TFFC) for cancer-related breakthrough pain (BTCP).	European Journal of Pain S5: 173 [abstract only]
Long-term safety studies		
Study 15	Cephalon Clinical Study Report (2007). A multicentre, open-label, long-term study of ORAVESCENT® fentanyl citrate for the treatment of breakthrough pain in opioid-tolerant cancer patients.	Internal study report
	Weinstein et al (2009). Fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic cancer pain: a long-term, open-label safety study.	Cancer 115: 2571-2579
Lotfi 2011/2012	Lotfi et al (2011). Fentanyl buccal tablets for breakthrough cancer pain treatment – results of a non-interventional study evaluating its routine use in Germany/Austria.	European Journal of Pain Supplements 5 :173 [abstract only]
	Lotfi et al (2012). Routine use of fentanyl buccal tablets for breakthrough cancer pain in Germany/Austria: results of a non-interventional study as part of a European risk management plan.	Palliative Medicine 26: 550-551 [abstract only]
Davies 2015	Davies et al (2015). Improved patient functioning after treatment of breakthrough cancer pain: an open-label study of buccal tablets in patients with cancer pain.	Supportive Care in Cancer. Published online 4 January 2015.

Source: Table B.2-1 (p 12-14), Section B of the submission

6.6 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	Outcomes
Fentanyl buccal tablets vs. placebo					
Study 14	77	R, DB, MC, CO 10 pain episodes	Uncertain	Patients with BTCP	Pain intensity/pain relief, global medication performance, rescue medication use
Study 3039	87	R, DB, MC, CO 10 pain episodes	Uncertain	Patients with BTCP	Pain intensity/pain relief, global medication performance, patient acceptability measures, rescue medication use
Kosugi 2014	73	R, DB, MC, CO 9 pain episodes	Uncertain	Patients with BTCP	Pain intensity/pain relief, patient acceptability measures, rescue medication use
Meta-analysis	237/164	Meta-analysis of Study 14 and Study 3039 with and without Kosugi 2014			Pain intensity/pain relief, global medication performance, rescue medication use
Fentanyl lozenges vs. placebo					
Farrar 1998	92	R, DB, MC, CO 10 pain episodes	Uncertain	Patients with BTCP	Pain intensity/pain relief, global medication performance, rescue medication use

Abbreviations: BTCP, breakthrough cancer pain; CO, cross-over; DB, double blind; MC, multi-centre; R, randomised
Source: Constructed during the evaluation

- 6.7 The cross-over design used in the clinical trials may have introduced confounding due to the potential for carry-over treatment effects (with either study drug or rescue medications) given that both active and placebo treatments could be used within a few hours of each other.
- 6.8 The ESC noted that the trials of both fentanyl buccal tablets and fentanyl lozenges included run-in periods to find an effective tolerable dose of fentanyl prior to randomisation. The ESC considered that this may have implications for interpretation of the safety data as some patients do not continue to randomisation due to adverse events resulting in underestimates of adverse drug events. Furthermore, only patients who had effective pain relief with fentanyl were randomised, which may result in overestimates of the efficacy of fentanyl.
- 6.9 There are differences between the trial populations and the requested PBS population which may limit the applicability of trial results (trials were not restricted to palliative care patients and did not require patients to have a prior history of treatment failure). The submission acknowledged the limited applicability of the Kosugi et al 2014 trial (Japanese population, lower than recommended doses, hospitalised patients) to the requested PBS population.

Comparative effectiveness

- 6.10 The main analyses presented in the commentary were based on data from the evaluable analysis set population from the Farrar trial (primary analysis of the trial), excluded the Kosugi trial (due to applicability issues), assumed independence between active and placebo values (assumption used in the primary analysis presented in the submission), and were analysed using a random effects model (approach used in the primary analysis presented in the submission).

- 6.11 The nominated primary outcome of the submission was summed pain intensity difference at 60 minutes.

Table 3: Indirect comparison of summed pain intensity difference and total pain relief between fentanyl buccal tablets and lozenges

Trial	Fentanyl buccal tablets	Placebo	Fentanyl lozenge	Mean difference (95% CI)
Summed pain intensity difference at 30 minutes				
Study 14 (N = 72)	3.2 (2.6)	2.0 (2.2)	-	1.20 (0.78, 1.62)
Study 3039 (N = 78) ^a	3.3 (2.2)	1.8 (1.9)	-	1.44 (1.07, 1.80)
Farrar 1998 (N = 86)	-	2.5 (2.3)	4.0 (2.4)	1.50 (0.79, 2.21)
Meta-analysis of fentanyl buccal trials; I ² =0%				1.33 (1.06, 1.61)
Indirect estimate of effect, results > 0 favour fentanyl buccal tablets				-0.17 (-0.93, 0.59)
Summed pain intensity difference at 60 minutes (primary outcome)				
Study 14 (N = 72)	10.5 (6.0)	6.2 (5.5)	-	4.40 (3.36, 5.44)
Study 3039 (N = 78) ^a	9.7 (5.6)	4.9 (4.4)	-	4.75 (3.87, 5.64)
Farrar 1998 (N = 86)	-	6.6 (5.4)	10.1 (5.2)	3.55 (1.96, 5.14)
Meta-analysis of fentanyl buccal trials; I ² =0%				4.61 (3.93, 5.28)
Indirect estimate of effect, results > 0 favour fentanyl buccal tablets				1.06 (-0.66, 2.78)
Total pain relief at 60 minutes				
Study 14 (N = 72)	6.1 (2.5)	3.9 (2.9)	-	2.20 (1.61, 2.79)
Study 3039 (N = 78)	7.0 (3.1)	4.4 (3.6)	-	2.75 (2.21, 3.28)
Farrar 1998 (N = 86)	-	4.7 (3.2)	7.4 (2.9)	2.70 (1.78, 3.62)
Meta-analysis of fentanyl buccal trials; I ² =44%				2.49 (1.95, 3.02)
Indirect estimate of effect, results > 0 favour fentanyl buccal tablets				-0.21 (-1.27, 0.85)

Abbreviations: CI, confidence interval

Source: Table B.6-1 (p 59), Table B.6-2 (p 60), Table B.6-6 (p 68), Table B.6-9 (p 71), Section B of the submission; Table 3-11 (p 27-28) and Table 3-12 (p 29-30) of the FDA Actiq statistical report

Summed pain intensity difference measured on a 0-20 scale (30 minutes) or 0-40 scale (60 minutes); Total pain relief measured on a 0-16 scale (60 minutes)

^a Summed pain intensity measures for Study 3039 were weighted to account for additional assessment points at 5 and 10 minutes

- 6.12 There was no difference in summed pain intensity difference or total pain relief between fentanyl buccal tablets and fentanyl lozenges. Additionally, there was no statistically significant difference in rescue medication use between treatments (rate ratio 0.96; 95% CI 0.60, 1.53).
- 6.13 The analysis was sensitive to outcomes reported for different patient datasets from the Farrar et al (1998) trial. An analysis using the ITT population rather than the evaluable analysis set population suggested a statistically significant improvement in summed pain intensity difference at 60 minutes with fentanyl buccal tablets compared to fentanyl lozenges (mean difference 1.87; 95% CI 0.90, 2.84).
- 6.14 Fentanyl buccal tablets met the nominated non-inferiority margin for summed pain intensity difference at 60 minutes (lower CI bound > -1.0 to -1.5). However, the non-inferiority margin used in the submission was not well established. Following consideration of the PSCR, the ESC concluded that the non-inferiority margin used may not be adequately justified.
- 6.15 Overall, both formulations appeared to have broadly similar results on pain outcomes (similar point estimates with highly overlapping confidence intervals). However, in

view of the limitations of the indirect comparison and lack of established non-inferiority margins, the reliability of these estimates is uncertain.

Comparative harms

- 6.16 Adverse events reported with fentanyl buccal tablets and fentanyl lozenges were generally consistent with the established safety profile of fentanyl (e.g. nausea, vomiting, constipation, somnolence, dizziness, headache, confusion, asthenia, pruritus and fatigue).
- 6.17 In regards to adverse events related to the mode of administration, the submission noted that both fentanyl buccal tablets (approximately 5-10% of patients) and fentanyl lozenges (not reported, approximately 1-10% of patients based on product information) are associated with mucosal irritation (including bleeding, pain and ulceration).

Clinical claim

- 6.18 The submission described fentanyl buccal tablets as non-inferior in terms of efficacy and non-inferior in terms of safety compared to fentanyl lozenges.
- 6.19 The PBAC noted the weak body of evidence for comparison of fentanyl buccal tablets with fentanyl lozenge. However, noting the challenges in developing high-quality data in this clinical context the PBAC considered that the claims of non-inferior comparative effectiveness and non-inferior comparative safety were adequately supported.
- 6.20 The PBAC noted that the submission did not make a claim capturing the possibility of fentanyl buccal tablets substituting for other breakthrough pain treatments such as other immediate release opioids. The PBAC considered that this omission was not appropriate in view of the risk of this product replacing other immediate-release opioids.

Economic analysis

- 6.21 The submission presented a cost-minimisation analysis of fentanyl buccal tablets compared to fentanyl lozenges.
- 6.22 The proposed equi-effective doses were 100mcg fentanyl buccal tablets and 152mcg fentanyl lozenges. This estimate was derived from the mean doses reported in the included clinical trials. This estimate was considered unreliable as there is no established dose equivalency (on a microgram to microgram basis) between various fentanyl products.
- 6.23 The proposed equi-effective dose was not used as the basis for the cost minimisation analysis. Instead, the submission proposed a flat pricing structure across available dose strengths assuming that one fentanyl buccal tablet was equivalent to one fentanyl lozenge. This approach appeared reasonable and is consistent with the current pricing structure for fentanyl lozenges. The ESC noted and agreed with the PSCR's comment regarding equi-effective dosing to be less of an issue for pricing due to flat pricing structure throughout varying doses, particularly for this drug and

indication, due to limitation to the administration of one dose per episode of breakthrough pain in most cases, and highly variable inter-individual titration to response for opioids.

- 6.24 Based on this analysis the submission estimated a flat DPMQ of \$ [REDACTED] for two initiation packs (8 tablets) and \$ [REDACTED] for two maintenance packs (56 tablets) of fentanyl buccal tablets.

Drug cost/patient/90 days

- 6.25 Fentanyl buccal tablets: \$ [REDACTED] (assuming DPMQ price, maintenance treatment and 3 breakthrough episodes a day)
- 6.26 Fentanyl lozenge: \$ [REDACTED] (assuming DPMQ price, maintenance treatment and 3 breakthrough episodes a day)

Estimated PBS usage & financial implications

- 6.27 This submission was not considered by DUSC.
- 6.28 The submission used a market share approach to estimate the utilisation/financial implications associated with the PBS listing of fentanyl buccal tablets.

Table 4: Estimated utilisation and cost to the PBS of fentanyl buccal tablets in the first five years of listing

	Year 1 (2015-2016)	Year 2 (2016-2017)	Year 3 (2017-2018)	Year 4 (2018-2019)	Year 5 (2019-2020)
One fentanyl formulation available on the PBS					
Cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Fentanyl units dispensed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Second fentanyl formulation available on the PBS (growth in market 5% year 1; 10% subsequent years)					
Fentanyl units dispensed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
FBT market share	% [REDACTED]	% [REDACTED]	% [REDACTED]	% [REDACTED]	% [REDACTED]
FBT units dispensed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
OTFC market share	% [REDACTED]	% [REDACTED]	% [REDACTED]	% [REDACTED]	% [REDACTED]
OTFC units dispensed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total PBS/RPBS fentanyl market cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Incremental difference in fentanyl market PBS cost with and without fentanyl buccal tablets					
With FBT	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Without FBT	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Abbreviations: FBT, fentanyl buccal tablets; OTFC, fentanyl lozenges; RPBS, Repatriation Pharmaceutical Benefits Scheme; PBS, Pharmaceutical Benefits Scheme

Source: Constructed during the evaluation based on the Fentora Section E base case Excel Spreadsheet

- 6.29 The redacted table above shows that at year 1, the estimated number of units dispensed was more than 200,000 and the net cost to the PBS would be less than \$10 million. At year 5, the estimated number of units dispensed was more than 200,000 and the net cost to the PBS estimated to be less than \$10 million.

- 6.30 A market-share approach based on fentanyl lozenges may underestimate the utilisation of any new fentanyl formulation in the eligible patient population given the known under-utilisation of the lozenge formulation. This is possibly due to the lengthy administration time and administration method of the lozenge where patients need to move the lozenge around the mouth to aid mucosal absorption.
- 6.31 The main driver of the financial estimates was the growth rate applied to the fentanyl market with the introduction of a second fentanyl formulation. The submission assumed a growth rate of ■% in the first year and ■% in subsequent years based on the claim that the clinical benefits of fentanyl buccal tablets are not sufficiently different from fentanyl lozenges to expect a substantial change in prescribing habits. The lengthy administration time and method of the lozenge may be limiting its uptake. The PSCR provides epidemiologic estimates of less than 10,000 potential patients.
- 6.32 There is considerable risk of use outside the proposed restriction. This includes settings other than palliative care, use in patients who can tolerate further dose escalation of morphine/other opioids, and use in treatment of incident or anticipated pain. The PSCR argues that incident or anticipated pain is within the scope of 'breakthrough pain'. The ESC agreed that this was consistent with the palliative care literature. However, the stated concerns regarding use outside the restriction, either outside of the palliative care setting or in those who could tolerate dose escalation of other opioids, still remain.
- 6.33 The methodology used to transform government expenditure to number of fentanyl units dispensed was overly complex and non-transparent.
- 6.34 The PBAC agreed that the market share approach based on the use of fentanyl lozenge is likely to substantially underestimate the utilisation for fentanyl buccal tablets. The PBAC recalled previous advice (March 2014 – fentanyl sublingual Public Summary Document) and agreed that an epidemiological approach would have been a more appropriate estimation basis.
- 6.35 The PBAC considered that the size of the eligible population remains uncertain given the wide ranges in the published literature. 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

- 6.36 The submission acknowledged the risk of abuse, misuse and diversion associated with fentanyl buccal tablets. The submission did not make any specific claim regarding comparative risk between fentanyl buccal tablets and fentanyl lozenges. The sponsor has developed a comprehensive risk management plan for fentanyl buccal tablets and is committed to minimising the risk of misuse, abuse and diversion by supporting prescriber/patient educational activities as well as routine pharmacovigilance. The ESC noted, in the PSCR the sponsor expressed willingness to limit prescribers to those intimately involved in the care of palliative patients.

- 6.37 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 administrative processes for PBS-listed opioids is under consideration as part of the Post-Market Review of PBS Authorities.

Financial Management – Risk Sharing Arrangements

- 6.38 The submission did not propose a Risk Share Arrangement (RSA) for fentanyl buccal tablets. The PBAC noted the sponsor's statements in its PSCR and pre-PBAC responses that it did not see a reason for a risk share agreement. The PBAC did not consider that the sponsor's position on a risk share agreement was valid primarily because of the very high risk of use outside of the proposed restriction (see 6.32).
- 6.39 The PBAC recommended that a RSA is 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.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of fentanyl citrate buccal tablets for the treatment of breakthrough pain in patients undergoing palliative care for cancer. The PBAC considered that the submission had not adequately addressed immediate-release opioids as an appropriate comparator. Further, the PBAC did not consider that the submission's utilisation estimates were reliable, and was concerned that no strategy was proposed by the sponsor to mitigate this risk.
- 7.2 The PBAC considered that the likely clinical place in therapy for fentanyl buccal would be a second-line listing in a palliative care setting. The Committee considered that withholding fentanyl buccal to third- and subsequent lines for breakthrough pain may not be practical or reasonable. Furthermore, the Committee considered that, in rare circumstances, fentanyl buccal may be used in first-line setting for patients unable to swallow oral immediate-release opioids.
- 7.3 The PBAC considered the submission's claims of non-inferior comparative effectiveness and non-inferior comparative safety compared to fentanyl lozenges were adequately supported.
- 7.4 The PBAC noted that other immediate-release opioids had not been considered as an alternate comparator in the submission and a claim capturing the possibility of fentanyl buccal tablets substituting for other breakthrough pain treatments such as other immediate-release opioids was not made. The PBAC considered both other 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.

- 7.5 The PBAC agreed that the market share approach based on the use of fentanyl lozenges is likely to substantially underestimate the utilisation for fentanyl buccal tablets. The PBAC recalled its previous advice (March 2014 – fentanyl sublingual Public Summary Document) and agreed that an epidemiological approach would have been a more appropriate estimation basis.
- 7.6 The PBAC considered that the size of the eligible population remains uncertain given the wide ranges in the published literature. 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.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how many 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.

9 Sponsor's Comment

Teva Pharma Australia Pty Ltd will continue to work with the department to resolve the issues raised by the PBAC.