PUBLIC SUMMARY DOCUMENT

Product: FENTANYL, 100 micrograms/actuation nasal spray, 8 actuations and 400 micrograms/actuation nasal spray, 8 actuations, PecFent®
Sponsor: AstraZeneca Pty Ltd.
Date of PBAC Consideration: March 2014

1. Purpose of Application

To request Authority Required listing on the palliative care schedule for the management of breakthrough pain in adults 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

A submission for an alternative intranasal fentanyl preparation (Instanyl®) claiming superiority compared to fentanyl lozenges was rejected by the PBAC at the March 2013 meeting.

A previous application seeking PBS listing for intranasal fentanyl (PecFent®) was withdrawn by the sponsor prior to the July 2013 PBAC meeting.

3. Registration Status

PecFent 100 microgram and 400 microgram were TGA registered on 15 and 13 August 2012 respectively for the management of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy.

4. Listing Requested and PBAC's View

Authority required (palliative care schedule)
Breakthrough cancer pain in patients unable to tolerate further escalation in the dose of morphine due to adverse effects.

Listing was requested on a cost-minimisation basis with fentanyl lozenges based on a claim of non-inferiority.

The PBAC noted that the requested listing was consistent with the current listing for fentanyl lozenges.

5. Clinical Place for the Proposed Therapy

Breakthrough cancer pain is a term used to describe moderate/severe transient exacerbations of pain in cancer patients whose background pain is well controlled by the use of chronic opioid therapy.

The PBAC noted the clarification in the sponsor's Pre-Sub-Committee Response (PSCR, p1) that the intended place in therapy of intranasal fentanyl was last line after exhausting all non-

fentanyl treatment options. This position is aligned with the main comparator, fentanyl lozenges.

The PBAC considered that the appropriate clinical place for fentanyl nasal spray 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 nasal sprays.

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, wound dressings, etc).

6. Comparator

The submission nominated fentanyl lozenges as the main comparator. The main argument provided in support of this nomination was that fentanyl lozenges are the only immediate-release opioid listed on the PBS as a second-line treatment for breakthrough cancer pain.

The submission nominated immediate-release morphine (as a proxy for all opioids/formulations) as a supportive comparator in the first-line setting (outside the requested PBS restriction); and the alternative formulation of intranasal fentanyl (Instanyl®) as an additional comparator.

The PBAC considered that fentanyl lozenges are an appropriate comparator, but that other immediate-release opioids may also be appropriate comparators in the requested treatment setting.

The PBAC recalled its consideration from March 2013, which determined that other immediate-release opioids (other than fentanyl) were also appropriate comparators for Instanyl® (intranasal fentanyl) for the same indication.

7. Clinical Trials

The submission was based on a series of direct and indirect comparisons between intranasal fentanyl and the nominated comparators:

- Indirect comparison of intranasal fentanyl (CP043) vs. fentanyl lozenge (Farrar et al 1998) using a placebo common comparator.
- Indirect comparison of intranasal fentanyl (CP044) vs. fentanyl lozenge (Coluzzi et al 2001) using immediate-release morphine as the common comparator.
- Direct comparison of intranasal fentanyl vs. immediate-release morphine (CP044)
- Indirect comparison of intranasal fentanyl (PecFent®; CP043) vs. intranasal fentanyl (Instanyl®; Kress et al 2009) using a placebo common comparator.

The submission also presented longer-term observational data for both intranasal fentanyl (CP045; extension study from CP043 and CP044 with additional newly enrolled patients) and fentanyl lozenges (Payne et al 2001; extension study from Farrar 1998).

Details of the trials and associated reports presented in the submission are presented in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Intranasal fentanyl (PecFent®) vs. placebo		
CP043	Archimedes Development Study Report (2009). A Multicenter, Placebo-Controlled, Double-Blind, Two-Phase Crossover Study of Nasalfent (Fentanyl Citrate Nasal Spray) in the Treatment of Breakthrough Cancer Pain (BTCP) in Subjects Taking Regular Opioid Therapy	Internal study report
	Portenoy et al (2010). A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain	Pain 151: 617-624
	Taylor et al (2010). Fentanyl pectin nasal spray in breakthrough cancer pain	Journal of Supportive Oncology 8: 184-190
Intranasal fentanyl (PecFent®) vs. immediate-release morphine sulfate tablets		
CP044	Archimedes Development Study Report (2009). A Multicentre, Double-Blind, Double-Dummy, Two-Phase Crossover Study of Nasalfent (Fentanyl Citrate Nasal Spray) Compared to Immediate-release morphine Sulphate Tablets in the Treatment of Breakthrough Cancer Pain (BTCP) in Subjects Taking Regular Opioid Therapy	Internal study report
	Fallon et al (2011). Efficacy and safety of fentanyl pectin nasal spray compared with immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: A multicenter, randomized, controlled, double-blind, double-dummy multiple-crossover study	Journal of Supportive Oncology 9: 224-231
	Davies et al (2011). Consistency of efficacy, patient acceptability, and nasal tolerability of fentanyl pectin nasal spray compared with immediate-release morphine sulfate in breakthrough cancer pain	Journal of Pain and Symptom Management 41: 358-366
Intranasal fentanyl (PecFent®) - open-label extension study		
CP045	Archimedes Development Study Report (2009). An Open-Label Study Investigating Long-Term Safety and Tolerability of Nasalfent (Fentanyl Citrate Nasal Spray) in the Treatment of Breakthrough Cancer Pain (BTCP) in Subjects Taking Regular Opioid Therapy	Internal study report

Trial ID	Protocol title/ Publication title	Publication citation
	Radbruch et al (2012). Long-term tolerability, efficacy and acceptability of fentanyl pectin nasal spray for breakthrough cancer pain	Supportive Care in Cancer 20: 565-73
	Portenoy et al (2012). Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioid-tolerant patients	Journal of Opioid Management 6: 319-328
Fentanyl lozenges vs. placebo		
Farrar (1998)	Farrar JT 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 JT et al (2000). Defining the clinically important difference in pain outcome measures.	Pain 88: 287-294
Fentanyl lozenges vs. immediate-release morphine		
Coluzzi (2001)	Coluzzi PH et al (2001). Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR).	Pain 91: 123-130
Fentanyl lozenges - open-label extension study		
Payne (2001)	Payne R et al (2001). Long-term safety of oral transmucosal fentanyl citrate for breakthrough cancer pain.	Journal of Pain and Symptom Management 22: 575-583
Intranasal fentanyl (Instanyl®) vs. placebo		
Kress (2009)	Kress HG et al (2009) Efficacy and tolerability of intranasal fentanyl spray 50 to 200 µg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period.	Clinical Therapeutics 31: 1177-1191

The submission acknowledged that included trial populations were not representative of the requested PBS population but argued that any differences were unimportant.

The PBAC noted that the clinical trials used restricted doses. The PBAC agreed with the ESC 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 sprays per dose may be used in clinical practice than in the clinical trials.

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 main outcomes presented in the submission were responder analyses based on pain intensity (PI) and pain relief (PR) scales.

Results of the indirect comparison of intranasal fentanyl versus fentanyl lozenges using placebo as the common comparator are presented in the table below.

Indirect comparison of pain intensity and pain relief over time with intranasal fentanyl vs. fentanyl lozenges using a placebo common comparator (patient-level data)

Time (min)	CP043			Farrar (1998)			Indirect mean difference (95% CI)
	Mean difference (95% CI)	FPNS Mean (SD)	PBO Mean (SD)	PBO Mean (SD)	OTFC Mean (SD)	Mean difference (95% CI)	
Pain intensity difference (using an 11-point rating scale)							
15	0.65 (0.15, 1.15)	1.97 (1.51)	1.32 (1.57)	1.0 (NR)	1.65 (NR)	0.58 (0.33, 0.83)	0.07 (-0.49, 0.63)
30	0.96 (0.38, 1.54)	2.69 (1.65)	1.73 (1.90)	1.60 (NR)	2.47 (NR)	0.87 (0.53, 1.21)	0.09 (-0.58, 0.76)
45	1.12 (0.49, 1.75)	3.20 (1.85)	2.08 (2.03)	2.48 (NR)	3.11 (NR)	0.63 (0.26, 1.01)	0.49 (-0.26, 1.24)
60	1.35 (0.68, 2.02)	3.57 (1.97)	2.22 (2.14)	2.79 (NR)	3.45 (NR)	0.66 (0.25, 1.07)	0.69 (-0.10, 1.48)
Pain relief (using a 5-point rating scale)							
15	0.38 (0.07, 0.69)	1.49 (0.89)	1.11 (1.01)	0.98 (NR)	1.45 (NR)	0.47 (0.29, 0.65)	-0.09 (-0.45, 0.27)
30	0.62 (0.29, 0.95)	1.91 (0.85)	1.29 (1.16)	1.19 (NR)	1.85 (NR)	0.66 (0.44, 0.88)	-0.04 (-0.44, 0.36)
45	0.78 (0.45, 1.11)	2.17 (0.88)	1.39 (1.13)	1.64 (NR)	2.15 (NR)	0.50 (0.26, 0.74)	0.28 (-0.13, 0.69)
60	0.82 (0.48, 1.16)	2.32 (0.89)	1.50 (1.19)	1.67 (NR)	2.28 (NR)	0.61 (0.37, 0.85)	0.24 (-0.17, 0.66)

Abbreviations: CI, confidence interval; FPNS, intranasal fentanyl; NR, not reported; OTFC, fentanyl lozenges; PBO, placebo; SD, standard deviation

The PBAC noted that both fentanyl formulations were associated with statistically significant improvements in pain intensity and pain relief at all measured time points compared to placebo. However, based on the submission's nominated non-inferiority thresholds (minimum clinically important difference (MCID) of -2 for both pain intensity difference and pain relief), neither intranasal fentanyl nor fentanyl lozenge showed a clinically important improvement in pain outcomes compared to placebo.

The PBAC considered that the indirect comparison of intranasal fentanyl versus fentanyl lozenges using immediate-release morphine as the common comparator was not robust due to the lack of exchangeability between the CP044 and Coluzzi et al (2001) trials.

Results from the CP044 trial indicated that intranasal fentanyl was associated with a statistically significant improvement in pain intensity difference from 15 minutes onwards and a statistically significant improvement in pain relief from 30 minutes onwards compared to immediate-release morphine. However, due to the limitations of the CP044 trial and small magnitude of difference between treatments, the PBAC did not consider this information to be informative.

Overall, the PBAC considered that the evidence presented in the submission was inadequate to reliably determine the comparative effectiveness of intranasal fentanyl versus fentanyl lozenges. Similarly, the data for the comparison with immediate-release morphine were inadequate to determine the comparative effectiveness.

The PBAC considered the adverse event data reported in the included trials were insufficient to determine the comparative safety of each of the treatments due to the difficulty in

attributing adverse events when both treatments could be used within a few hours of each other.

In practice, the safety profile of fentanyl is well established (various formulations have been available for over twenty years). However, the PBAC noted that nasal fentanyl 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 becoming narcotised. The PBAC further noted that this may have safety implications that are important in the PBS population as there are older patients with poorer functional status in the PBS cohort than the populations in the trials.

A summary of the comparative benefits and harms for fentanyl intranasal spray versus fentanyl lozenges is presented in the table below.

Benefit/harm summary - intranasal fentanyl vs. fentanyl lozenges

Outcome	№ studies (№ episodes)	Indirect RR estimate (95%CI)	Event rate/100 episodes		Increment
			FPNS	OTFC	
Benefits					
Pain intensity difference ≥ 33% at 30 minutes	2 (1460 in 175 pts)	1.03 (0.78, 1.35)[a]	59.9 vs 33.5 PBO (≤ 21 days)	63.1 vs 36.3 PBO (≤ 14 days)	-
Harms					
There are insufficient data to formally assess the comparative safety.					

Abbreviations: CI, confidence interval; FPNS, intranasal fentanyl; OTFC, fentanyl lozenges; PBO, placebo; RR, relative risk

[a] Results > 1 favour intranasal fentanyl

9. Clinical Claim

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

The PBAC noted that there was no statistically significant difference in pain outcomes between intranasal fentanyl and fentanyl lozenge, in the indirect comparison, using placebo as the common comparator. The PBAC was concerned, however, that there was no clinically important difference in pain outcomes over placebo.

The PBAC noted that there were insufficient data presented in the submission to formally assess the comparative safety of intranasal fentanyl versus fentanyl lozenges. The PBAC considered that the safety profile of fentanyl is well established, however, the PBAC expressed concern that intranasal presentation introduced new safety concerns, as detailed above. Consequently, the PBAC did not accept the submission's claim of similar safety compared to fentanyl lozenges.

The submission described intranasal fentanyl as at least non-inferior and possibly superior in terms of efficacy compared to immediate-release morphine (as a proxy for all immediate-release opioids). The submission made no specific claim in terms of comparative safety.

The PBAC did not accept the submission's claim in relation to comparative efficacy with immediate release morphine. The PBAC considered limitations in the data set in relation to exchangeability and applicability meant that the indirect comparison was not informative for the purposes of decision making.

10. Economic Analysis

The submission presented a cost minimisation analysis of intranasal fentanyl versus fentanyl lozenge based on estimates of the average cost per patient of fentanyl lozenges over 100 days of treatment assuming 3 breakthrough pain episodes per day.

The submission estimated all drug costs based on the dispensed price per maximum quantity (DPMQ).

The submission argued that the dosing of intranasal fentanyl in the included studies is unlikely to be representative of clinical practice. This argument was based on the observation that PBS utilisation data for fentanyl lozenges are not consistent with the dose distribution reported in the clinical studies The submission did not estimate an equi-effective dose, as both intranasal fentanyl and fentanyl lozenges have flat pricing structures (same price for all initiation packs/same price for all continuation packs).

The submission assumed that distribution of intranasal fentanyl doses will follow the same pattern as fentanyl lozenge PBS data.

- Intranasal fentanyl 100mcg = 200mcg fentanyl lozenges
- Intranasal fentanyl 200mcg = 400mcg fentanyl lozenges
- Intranasal fentanyl 400mcg = 600mcg and 800mcg fentanyl lozenges
- Intranasal fentanyl 800mcg = 1200mcg and 1600mcg fentanyl lozenges

However, the PBAC noted that administration of intranasal fentanyl requires different numbers of sprays to achieve target doses which results in a tiered pricing structure as the two-spray doses (200mcg, 800mcg) are twice as expensive as the one-spray doses (100mcg, 400mcg). Therefore, the PBAC considered it would be important to establish some estimate of dose relativity between treatments.

The PBAC noted a number of issues with the submission's economic analysis including dose distribution assumptions, patient survival estimates, pharmacy/wholesaler mark-ups, estimated duration of titration phases and whether the two spray dose of intranasal fentanyl (which requires more scripts/packs) will increase GP visits.

The price of intranasal fentanyl is sensitive to the assumed dose distribution pattern of intranasal fentanyl, number of breakthrough pain episodes and patient survival. This sensitivity appears to be primarily due to the complexity and subsequent uncertainty associated with attempting to incorporate the titration period into the analysis.

The PBAC noted a simplified cost-minimisation analysis conducted during the evaluation (based on sprays per episode, intranasal fentanyl 1.54 sprays equals 1 fentanyl lozenge) resulted in slightly lower prices for both initiation and continuation packs. However, the Committee considered that the data presented in the submission did not adequately support the claims of non-inferior comparative efficacy and safety versus fentanyl lozenges. The

PBAC was therefore unable to accept the submission's cost-minimisation analysis or the simplified cost-minimisation analysis conducted during the evaluation.

11. Estimated PBS Usage and Financial Implications

The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the requested listing of intranasal fentanyl.

The submission the net cost per year to the PBS to be between $10-30 million in Year 5.

The PBAC noted the issues identified by the DUSC in relation to the submission's estimates:

- Estimated utilisation relies heavily on a small clinician survey (n=20) with variable results.
- There will be a high net cost to the PBS because more eligible patients are likely to use fentanyl nasal spray than lozenges because of the time and method of administration. Less than 10% of the use is expected to come from substitution of lozenges. Cost offsets for reduction in other BTCP treatments have not been included in the estimates.
- The definition of 'unable to tolerate further escalation of the dose of morphine' may be broadly interpreted in practice, resulting in higher than expected use.
- There is likely to be use outside of the restriction, including for
    - Patients who can tolerate increasing the dose of morphine.
    - Non-breakthrough pain or persistent use when background therapy is inadequate.
    - For 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. For example showering, wound dressings.

The PBAC noted the ESC advice stating the estimates of utilisation and financial cost were highly unpredictable due to the underlying assumptions relating to:

- dose distribution patterns (including the potential for more than 2 sprays per dose);
- patient survival;
- GP attendances;
- impact on extended-release fentanyl formulations; and
- the reliance on a small sponsor-commissioned survey of physicians as provided in the PSCR.

The PBAC noted the concerns raised by the sponsor in the pre-PBAC response in relation to the issues raised by the ESC and DUSC. The PBAC noted the sponsor had proposed a risk sharing arrangement (RSA) as a means to address or alleviate concerns associated with these issues.

The PBAC agreed with DUSC that use of published literature, particularly large population studies in countries with similar health systems, would provide a more robust basis for estimating use.

The PBAC also agreed with DUSC that despite fentanyl lozenge being nominated as the main comparator, less than 10% of the proposed use of fentanyl nasal spray is expected to arise from substitution of lozenges. There is likely to be a large additional cost to the PBS, the magnitude of which will depend on what other BTCP treatment patients are currently receiving.

The PBAC agreed with the DUSC that fentanyl nasal spray presents a high risk of overdose or misuse. Fentanyl spray is proposed to be available in 100 or 400 mcg per spray. The number of sprays per episode varies depending on the required dose. Accidental overdose with repeated actuations of a nasal spray may be more likely than with other dose forms.

The PBAC considered there is a high risk of diversion. The ability to divide the maintenance pack of 4 individual bottles would make diversion easier. The Substance Abuse and Mental Health Services Administration (SAMHSA) 2007-2008 National Survey on Drug Use and Health stated that 56% of respondents obtained their drugs free from friend/relative.

The PBAC noted that the submission acknowledged the potential for leakage outside the requested indication into the first-line treatment of breakthrough cancer pain. The submission also acknowledged the potential for off-label use for indications other than breakthrough cancer pain and suggested a RSA to manage this risk.

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 nasal spray for the treatment of breakthrough cancer. The PBAC considered that the data presented did not adequately support the submission's claims of non-inferior comparative efficacy and safety versus fentanyl lozenges. The PBAC was therefore unable to accept the submission's cost-minimisation analysis.

The PBAC also considered that the appropriate clinical place of intranasal 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 lozenges were an appropriate comparator for the place in therapy as clarified in the sponsor's PSCR. However, the PBAC considered that other immediate-release opioids would also be appropriate comparators.

The PBAC considered that the simplified cost-minimisation analysis conducted during the evaluation (based on sprays per episode, intranasal fentanyl 1.54 sprays equals 1 fentanyl lozenge) was a more appropriate method for calculation of price equivalence between fentanyl nasal spray and fentanyl lozenge. However, as the PBAC did not consider the clinical data to be supportive of the non-inferiority claim, the cost-minimisation analysis was not adequately supported.

The PBAC considered that there were significant safety and quality use of medicines issues related to the use of fentanyl nasal spray. The Committee considered that there was a large

potential for harm associated with the use of fentanyl nasal spray, given the concerns regarding diversion, misuse and overdose.

The PBAC were concerned about the complexity of the titration regimen in palliative care patients, who are likely to have poor functional status. Additionally, the PBAC considered that it would be very easy for a patient to accidently administer a second dose of fentanyl nasal spray inadvertently, leading to the possibility of accidental overdose.

Based on the advice provided by ESC and DUSC, the PBAC considered that the utilisation estimates provided in the submission were unlikely to be realised in practice. The PBAC considered it was difficult to predict the total cost to the PBS of the listing of intranasal fentanyl as the estimates of use could not be relied upon. The PBAC acknowledged the sponsors willingness to discuss options for a risk share arrangement, but considered that the implementation of a risk share arrangement would not be enough to offset all of the concerns raised.

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

Unfortunately, there are no further data and no way for AstraZeneca to address the PBAC's reasons for rejecting PecFent. Consequently, it is disappointing that PecFent will not be made available for palliative care patients experiencing breakthrough cancer pain.