PUBLIC SUMMARY DOCUMENT

Product: Fentanyl citrate, nasal spray, 6 pack of single-dose nasal spray bottles 50 microgram, 100 microgram, 200 microgram;10-dose nasal spray bottle, 50 microgram per dose, 100 microgram per dose and 200 microgram per dose;20-dose nasal spray bottle, 50 microgram per dose,100 microgram per dose and 200 microgram per dose, Instanyl®

Sponsor: Takeda Pharmaceuticals Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested an Authority required (STREAMLINED) Palliative Care Schedule listing for treatment of breakthrough pain in a patient with cancer who is receiving opioids, and where further escalation of morphine for breakthrough pain results in intolerable adverse effects.

2. Background

The PBAC has not previously considered this formulation of fentanyl citrate.

3. Registration Status

The submission was considered under the TGA/PBAC parallel process. At the time of PBAC consideration, the Clinical Evaluation Report and TGA Delegate's overview were available.

4. Listing Requested and PBAC's View

Section 85 Palliative Care Schedule
Authority required (STREAMLINED)
For breakthrough pain in a patient with cancer who is receiving opioids for their persistent pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects.

The PBAC noted that the requested restriction was largely consistent with the current palliative care schedule listing for the comparator OTF, but that the OTF restriction specifies use in palliative care patients.

The PBAC considered that any listing for NF should use the same restrictions as currently listed OTF, with the single-dose and 10-dose sprays being listed for initial supply and the 20-dose sprays for continuing supply.

5. Clinical Place for the Proposed Therapy

Fentanyl is a pure opioid agonist, acting primarily through interaction with micro-opioid receptors in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system. The most clinically useful pharmacological effect is analgesia.

Nasal fentanyl (NF) is proposed as an alternative to oral transmucosal fentanyl (OTF), for treatment of breakthrough pain in palliative care patients with cancer who are receiving maintenance opioids for chronic pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects i.e. as a second-line opioid in the treatment of breakthrough cancer pain. OTF is currently the only fast-acting fentanyl (FAF) listed on the PBS for this indication.

The mainstay of care for cancer patients with moderate to severe persistent cancer pain is chronic opioid therapy, titrated to effect. NF is only intended for treatment of transient exacerbations of pain in cancer patients whose background pain is well controlled by the use of chronic opioid therapy, who are experiencing no more than four episodes of breakthrough pain per day and who are intolerant to an increase in opioid dose.

6. Comparator

The submission nominated oral transmucosal fentanyl citrate as the comparator. The PBAC considered that OTF was an appropriate comparator but noted that other short-acting opiods, including immediate-release morphine, would also be appropriate comparators.

7. Clinical Trials

The submission presented one randomised open-label, cross-over trial (Trial 019) comparing NF with OTF in 139 patients with cancer who were receiving stable background opioid treatment and who were experiencing breakthrough pain episodes of a severity warranting additional analgesics.

The trial comprised three phases: a pre-treatment screening phase, a titration phase, and an efficacy phase. The efficacy phase was up to two week's duration, during which, the aim was to treat six breakthrough pain episodes. Following completion of the titration and efficacy phases with the first investigational drug, the patient repeated the titration and efficacy periods with the second drug.

Publication details are presented in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Trial 019 Mercadante et al	A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial.	*Current Medical Research and Opinion* 2009, 25 (11): 2805-2815

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

The primary outcome in Trial 019, was time to onset of meaningful pain relief as determined by the patient. The submission based its claim of comparative effectiveness and safety of NF and OTF on the post hoc outcome of the proportion of treated breakthrough pain episodes in which clinically meaningful pain relief was achieved. This outcome was the key patient relevant outcome nominated by the submission.

Results for the primary outcome are presented in the table below.

Results for the pre-specified primary outcome, time to meaningful pain relief across the direct randomised trial, ITT analysis set[a]

Trial 019	NF/OTF N=71	OTF/NF N=68

	NF	OTF	Within patient difference	NF	OTF	Within patient difference
Censored data[b]						
n	60	47	47	41	53	39
Missing	11	24	24	27	15	29
Median (Q_L, Q_U)	10.2 (6.3, 15.2)	18.3 (11.7, 24.1)	5.6 (0.8, 12.2)	11.5 (7.5, 15.3)	15.0 (10.0, 23.9)	2.5 (-0.7, 9.7)
Overall						
	NF		**OTF**		**Within patient difference**	
Censored data[b]						
n	101		100		86	
Missing	38		39		53	
Median (Q_L, Q_U)	10.6 (6.6, 15.3)		15.7 (10.8, 24.0)		4.3 (0.0, 11.5)	

NF = nasal fentanyl; OTF = oral transmucosal fentanyl; Q_L = lower quartile; Q_U = upper quartile

[a] The submission states this is the ITT analysis set but patients without data for both treatment phases were excluded from the analysis.

[b] Times were censored at 60 minutes if rescue medication was taken within 60 minutes from taking test treatment and before any meaningful pain relief was recorded, or if the time to onset of pain was longer than 60 minutes.

The PBAC noted the results from trial 019 showed the median time to meaningful relief for the ITT analysis set was a within patient difference of 4.3 minutes. The PBAC considered that the clinical importance of this difference was uncertain.

The submission did not provide a statistical analysis for the primary outcome and claimed that statistical significance of this result is not calculable. However, the PBAC noted that statistical procedures are available for analysing clustered failure time data. The PBAC also noted that patients without data for both treatment phases were excluded from the analysis.

The key outcome nominated in the submission was the proportion of treated breakthrough pain episodes in which clinically meaningful pain relief was achieved. This was a post hoc outcome. The Statistical Analysis Protocol (SAP) stated that for the treatment difference, the analyses include the odds ratio calculated from the two rates and the corresponding 95% confidence intervals (CI), p-values calculated through a Generalised Estimating Equation (GEE) analysis. The results are presented in the table below.

Results of proportion of treated breakthrough pain episodes in which a meaningful pain response was achieved- *post hoc* analyses

Outcome	NF n/N (%)	OTF n /N (%)	Absolute difference, % (95% CI)	Odds Ratio (95%CI)	p-value*
Sum of pain intensity difference ≥ 2 points[a]					
$SPID_{0-30}$	392/577 (67.9%)	249/577 (43.2%)		2.79 (2.2, 3.5) *2.807 (2.0, 3.9)*	<0.0001 *<0.0001*
$SPID_{0-60}$	474/577 (82.1%)	433/577 (75.0%)		1.53 (1.2, 2.0) *1.479 (1.0, 2.1)*	0.0480 *0.0480*
Time specific pain intensity difference ≥ 2 points[a]					
PID_{30}	519/577	491/577	4.9	1.57	0.171

	(89.9%)	(85.1%)	(1.0, 8.7)	(1.1, 2.2) *1.433* *(0.9, 2.3)*	 *0.1713*
PID_5	179/577 (31.0%)	64/577 (11.1%)	19.9 (15.4, 24.5)	3.61 (2.6, 4.9) *3.150* *(2.0, 5.0)*	<0.001 *<0.0001*
PID_{10}	341/577 (59.1%)	174/577 (30.2%)	29.0 (23.6, 34.5)	3.35 (2.6, 4.3) *3.288* *(2.2, 4.9)*	<0.001 *<0.0001*
PID_{15}	447/577 (77.5%)	319/577 (55.3%)	22.5 (17.2, 27.8)	2.78 (2.2, 3.6) *2.726* *(1.8, 4.1)*	<0.001 *<0.0001*
PID_{20}	490/577 (84.9%)	420/577 (72.8%)	12.5 (7.8, 17.2)	2.11 (1.6, 2.8) *2.031* *(1.3, 3.1)*	0.003 *0.0030*
PID_{60}	536/577 (92.9%)	541/577 (93.8%)	-0.2 (-3.2, 2.7)	0.87 (0.5, 1.4) *0.896* *(0.5, 1.6)*	0.737 *0.7370*
Percentage pain intensity difference from baseline ≥ 33%[a]					
PID% $_{30}$	526/577 (91.1%)	462/577 (80.1%)	11.1 (7.1, 15.1)	2.57 (1.8, 3.7) *2.116* *(1.3, 3.4)*	0.011 *0.0053*
PID% $_{5}$	146/577 (26.3%)	39/577 (6.8%)	18.6 (14.5, 22.7)	4.67 (3.2, 6.8) *3.771* *(2.3, 6.2)*	<0.001 *<0.0001*
PID% $_{10}$	294/577 (51.0%)	136/577 (23.6%)	27.5 (22.1, 32.8)	3.37 (2.6, 4.3) *3.114* *(2.1, 4.6)*	<0.001 *<0.0001*
PID% $_{15}$	414/577 (71.8%)	247/577 (42.8%)	29.2 (23.7, 34.6)	3.39 (2.7, 4.3) *3.125* *(2.1, 4.6)*	<0.001 *<0.0001*
PID% $_{20}$	490/577 (84.9%)	358/577 (62.0%)	23.2 (18.3, 28.1)	3.45 (2.6, 4.6) *3.161* *(2.1, 4.8)*	<0.001 *<0.0001*
PID% $_{60}$	541/577 (93.8%)	541/577 (93.8%)	0.6 (-2.2, 3.5)	1.00 (0.6, 1.6) *0.879*	0.720 *<0.0001*

				(0.5, 1.7)	
Global performance ≥2 points[b]					
GI score 60	509/574 (88.7%)	461/572 (80.6%)		1.89 (1.4, 2.6) *1.729 (1.1, 2.8)*	0.0383 *0.7197*

CI = confidence interval; GI = global impression; NF = nasal fentanyl; OTF = oral transmucosal fentanyl; PID_t = pain intensity difference at t minutes; $SPID_{0-t}$ = sum of pain intensity difference from baseline to t minutes
* Generalised estimating equation (GEE) p-value
[a] Pain intensity was measured using a numeric rating scale of 0-10
[b] Global impression was assessed on a scale of 0-4.

The PBAC noted that in general, the adverse events reported in trial 019 were either related to the patients' underlying disease or were recognised adverse events associated with fentanyl. Overall, the trial results did not indicate any major differences in the safety profiles of NF and OTF. However, the PBAC noted that it was possible that adverse events were under-reported in the trial, as patients were not required to record them in the patient diary.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described NF as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over OTF. The PBAC did not accept the submission's claim.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

Despite the claim of superior comparative effectiveness, the submission presented a cost-minimisation analysis based on the assumption that NF is non-inferior to OTF in terms of the proportion of treated breakthrough pain episodes in which a meaningful pain response was achieved.

The PBS price for a pack of 30 OTF lozenges is the same irrespective of strength. Similarly, the submission proposed that the price for each 20-dose nasal spray bottle of NF will be the same, regardless of strength. As a result, the cost per breakthrough pain episode was only dependent on the number of units of OTF and NF taken per episode (where a unit is defined as one lozenge of OTF or one spray of NF), not on the quantity of fentanyl administered.

The submission's calculation of the equi-effective doses was based on the average number of OTF lozenges and the average number of sprays of NF administered per treated breakthrough pain episode in the efficacy phases of Trial 019.

The equi-effective doses were estimated as 1.58 units of NF per treated breakthrough pain episode and 1.30 units of OTF per treated breakthrough pain episode.

The PBAC noted that the equi-effective doses did not take into account the relative dose rates during dose titration.

11. Estimated PBS Usage and Financial Implications

The submission's estimated net cost per year to the PBS was less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

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

However, the PBAC rejected the submission for NF because of the poor quality of the clinical data presented in support of the claim of superiority of NF over OTF and uncertainty regarding non-inferiority of NF compared with OTF, with regard to comparative safety. The PBAC considered the equi-effective doses used in the cost-minimisation analysis were uncertain as they did not take into account relative dose rates during the titration phase of the trial. While the PBAC accepted that OTF was an appropriate comparator, it considered that a mixed comparator including other short acting opioids would also be appropriate. Furthermore, the PBAC considered that there was a potential for net harm associated with use of NF given the numerous safety issues identified by the Advisory Committee on Safety of Medicines (ACSOM) and the Australian and New Zealand College of Anaesthetists (ANZCA).

The PBAC noted that patients included in trial 019 were not required to be intolerant to further increases in the background opioid dose, and therefore may not have been fully representative of the requested PBS population. The PBAC noted that the risk of bias in the trial was high, given its open-label design and subjective outcomes.

The PBAC further noted that following suspicion of misconduct at site 17 in Trial 019, the European Medicines Agency (EMA) undertook an inspection to verify whether two trials (018 and 017), submitted in support of marketing approval of NF, were conducted in compliance with Good Clinical Practice. The inspections identified major and critical findings regarding the quality and validity of the efficacy data reported in the two trials. In addition, the safety data reported in these trials were not considered reliable as under-reporting of adverse events was observed. However, the PBAC also noted that as the results obtained were consistent between the efficacy studies, the Committee for Medicinal Products for Human Use (CHMP) concluded that the deficiencies found in the quality system of the sponsor were unlikely to invalidate the quality of the efficacy and safety data.

The PBAC noted that the unit of analysis in the post hoc outcome was episodes of breakthrough pain treated, rather than patients. The PBAC considered that it was inappropriate to analyse these episodes as independent events, as each patient may have reported outcomes for up to 6 episodes in each treatment period. Additionally, some patients would not have contributed any data, and others would only have data available for one investigational drug.

Notwithstanding the concerns about the clinical data, overall, the PBAC accepted that the point estimates for the pre-defined primary outcome, and the p-values calculated through a Generalised Estimating Equation (GEE) analysis for the post hoc analyses suggest that NF is likely to be non-inferior in terms of comparative effectiveness to OTF.

The PBAC noted that in general, the adverse events reported in trial 019 were either related to the patients' underlying disease or were recognised adverse events associated with fentanyl. Overall, the trial results did not indicate any major differences in the safety profiles

of NF and OTF. However, the PBAC noted that it was possible that adverse events were under-reported in the trial, as patients were not required to record them in the patient diary.

The PBAC also considered that there was significant potential for harms associated with NF based on use of repeated doses to relieve pain, and patients not waiting four hours between doses. Thus, a potential for overdosing exists. The PBAC noted the recommendation by the Advisory Committee on Safety of Medicines (ACSOM) that the container for nasal fentanyl, not be approved until it is re-designed to include a lock out mechanism and dose counter. In addition, the ACSOM identified problems with the child-resistant outer packaging, adsorption of fentanyl onto the packaging components if the container is not stored in an upright position, a likely increased risk of overdose due to number of doses in the presentation, and a likely high desirability of this presentation for diversion and misuse.

The PBAC also noted concerns raised by the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists (ANZCA), in relation to the potential for leakage arising from of the rapid onset of action in the management of incident pain, where the rapid onset of effect may result in a pattern of behaviour that leads to dependence on the drug.

The PBAC did not accept the submission's claim of superior comparative effectiveness considering the issues around the integrity of trial 019, the post hoc nature of the nominated efficacy outcome and the uncertain clinical significance of a difference of 4.3 minutes for the pre-specified primary outcome of trial 019. Rather, the PBAC considered that NF is likely to be non-inferior in terms of comparative effectiveness to OTF. The PBAC considered the submission's claim of non-inferior comparative safety, not reasonable and that potential for net harm associated with use of NF existed.

The PBAC noted the Drug Utilisation Sub-Committee (DUSC) advice that due to considerable variation in the published values for most of the data upon which the submission's utilisation calculations were based, the estimates of the eligible population were highly uncertain. The PBAC agreed with the DUSC that the estimates presented in the submission for the palliative care schedule were likely underestimates, based on uncertainty regarding the size of the eligible PBS population. The PBAC agreed that there is considerable potential for use in non-cancer pain and in patients who do not have 'intolerable' adverse events associated with increased background opioid dose. Furthermore, the scope of palliative care in clinical practice is changing, which may increase the eligible patient population. The PBAC also considered the uptake rate used in the submission was uncertain and that the uptake of NF would be rapid and extensive given the fast onset of action and ease of administration.

The PBAC also considered that NF may be used for incident pain associated with dressing changes and other painful procedures including patient transfer, further adding to the uncertainty in the estimated usage and uptake.

The PBAC also agreed with the DUSC in relation to concerns regarding potential misuse and/or diversion of NF to unsanctioned settings.

The PBAC noted that the submission is eligible for an Independent Review.

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 has comment.