AWMSG Secretariat Assessment Report – Advice no. 0911
Fentanyl (PecFent®▼) for the management of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic cancer pain

This assessment report is based on evidence submitted by Archimedes Pharma UK Ltd on 1 February 2011.

1.0 PRODUCT DETAILS

Licensed indication	Fentanyl pectin nasal spray (PecFent®▼) for the management of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain. Patients receiving maintenance opioid therapy are those who are receiving: • ≥ 60 mg of oral morphine daily; • ≥ 25 micrograms of transdermal fentanyl per hour; • ≥ 30 mg of oxycodone daily; • ≥ 8 mg of oral hydromorphone daily; • An equianalgesic dose of another opioid for a week or longer.
Dosing	The initial dose of PecFent®▼ to treat episodes of BTP is always 100 micrograms (one spray), even in patients switching from other fentanyl containing products for their BTP. Dose titration should be performed as per the Summary of Product Characteristics (SPC), and once established patients should take this dose up to a maximum of four times per day. One dose of PecFent may include administration of one spray (100 microgram or 400 microgram doses) or two sprays (one per nostril; 200 microgram or 800 microgram total doses) of the same dose strength (either 100 microgram or 400 microgram strength)[1]. PecFent®▼ therapy should be discontinued if patients no longer experience BTP. A gradual downward titration requires careful monitoring to avoid withdrawal effects[1].
Marketing authorisation date	31 August 2010[2,3]
UK Launch date	6 October 2010[2]

2.0 DECISION CONTEXT

2.1 Background

BTP is a severe transient exacerbation of pain that reaches peak intensity within a few minutes, and occurs on a background of otherwise controlled persistent pain. The prevalence of BTP in patients with chronic cancer pain is high (64–89%), where the average BTP episode lasts 30 min and the median frequency is 1.5–6 episodes per day[3–5]. The occurrence of BTP can be activity-related, however 40–50% of episodes

occur unexpectedly[3,4]. BTP can have a severe impact on a patient's physical and emotional functioning and may lead to hospital admissions and other interventions that are inconvenient for the patient and costly to the health service[6,7]. The company estimates that 34,771 chronic cancer patients in Wales suffer from BTP, of which 90% are eligible for opioid treatment and that approximately 0.2% of this population are likely to be prescribed PecFent®▼ by 2014[2].

Fentanyl is an opioid analgesic available in different formulations (transmucosal, intravenous, transdermal, intranasal) that primarily target μ-opioid receptors in the brain, spinal cord and smooth muscle. PecFent®▼ is a short-acting intranasal fentanyl preparation delivered as a controlled quantity with rapid systemic absorption and a rapid onset of action, which more closely mirrors the temporal characteristics of most BTP episodes than traditionally used oral morphine. Furthermore, the intranasal route of absorption facilitates gastrointestinal and hepatic bypass, enhancing PecFent®▼ bioavailability[3].

The company state that PecFent®▼ is intended for first-line treatment for BTP, as an alternative to other short-acting fentanyl preparations when oral morphine is unsuitable, and second-line treatment when immediate-release morphine sulphate (IRMS) or other short-acting fentanyl preparations have failed[2].

2.2 Comparators

The Welsh Medicines Partnership (WMP) requested the following comparators:

- Fentanyl intranasal spray (Instanyl®▼)
- Fentanyl buccal lozenges (Actiq®)
- Fentanyl buccal tablets (Effentora®▼)
- Fentanyl sublingual tablets (Abstral®▼)

2.3 Guidance and related advice

- Scottish Intercollegiate Guidelines Network (SIGN). Control of pain in adults with cancer. Guideline 106. November 2008[8].
- Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. The management of cancer-related breakthrough pain. April 2009[9].
- All Wales Medicine Strategy Group (AWMSG) Final Appraisal Report. Fentanyl (Instanyl®▼) - April 2010; Instanyl®▼ is recommended as an option for use within NHS Wales for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain. Instanyl®▼ should only be considered as an option for the management of breakthrough cancer pain when immediate release oral opioids (e.g. morphine, oxycodone) are either inadequate or unsuitable[10].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submission includes two multicenter, phase III trials: a placebo-controlled, double-blind, randomised, crossover study (CP043)[11] and an active-controlled, double-blind, double-dummy, crossover study (CP044)[12]. The submission also includes a multicenter, open-label long-term safety and tolerability study (CP045) which included patients from CP043 and CP044, and newly enrolled patients[13]. In CP043 and CP044, patients were eligible for the double-blind phase if, after an open-label dose-titration period, two BTP episodes were successfully treated without unacceptable adverse events (AEs)[11,12]. The primary endpoint for CP043 was the cumulative sum of the recorded difference between pain intensity (PI) and baseline at

each time point from 5 to 30 min post-dose (SPID30); in contrast to that for CP044 the difference between PI and baseline at 15 min post-dose. In the intention-to-treat (ITT) data set for CP043 (n=73), SPID30 was significantly greater for patients receiving PecFent®▼ as compared to placebo (6.57 ± 4.99 vs. 4.45 ± 5.51, p<0.0001). Moreover, the PI difference for PecFent®▼ was significantly greater at all time points from 10 min (p<0.05) to 60 min (p<0.0001) after dosing. Clinically meaningful pain relief (PR; reduction in PI ≥2) occurred rapidly (5–10 min) in one third of BTP episodes and was evident in over three quarters of episodes by 60 min[11]. In CP044 (ITT n=79), PecFent®▼ had a significantly faster onset of action compared to IRMS (5 min post-dose, 61% vs. 51.6% of BTP episodes had a PR score increase of ≥1 point, p<0.001) and provided a significantly greater difference in pain reduction than IRMS at 15 min post-dose (3.02 ± 0.21 vs. 2.69 ± 0.18, p<0.05)[12]. No formal efficacy analysis was performed in CP045, but during the study >90% of patients (n=356) did not require an altered dose of PecFent®▼, and 94% did not require alternative 'rescue' BTP medication in a 60 min assessment period[13].

In the absence of direct comparative data for PecFent®▼ and other fentanyl products (Instanyl®▼, Actiq®, Effentora®▼, Abstral®▼), the company has made efforts to undertake a formal indirect mixed treatment comparison (MTC) of the available trial data. All of the studies included were blinded randomised controlled trials[11,12,14–17], except one that was open-label[18]. The MTC did not include comparisons with Effentora®▼ or Abstral®▼. PecFent®▼ and Instanyl®▼ may be incomparable in the MTC provided by the company as the studies are based on single- and multi-dose approaches, respectively[2]. However, results suggest that multi-dose Instanyl®▼ may be more efficient than single-dose PecFent®▼ in reducing pain, whereas Actiq® and PecFent®▼ had a very similar therapeutic effect.

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

In the aforementioned phase III studies, AEs were typical of that associated with opioid treatment, and most were mild to moderate in severity[12,13,17], with no apparent increase in frequency or severity with escalating dose[12]. In CP045, treatment-associated AEs considered as possibly, probably or definitely linked to PecFent®▼ were reported in 24.6% of patients. The highest overall incidence of AEs (20.1%) was present in the 800 microgram dose group. Less than 1% of patients withdrew from the studies due to adverse nasal drug reactions, although this figure could not be verified; no association was detected between PecFent®▼ and nasal AEs during a four-month follow-up period[1,11–13].

In contrast to Instanyl®▼, the PecFent®▼ delivery device aids dose monitoring by producing an audible, tactile and visible confirmation of an administered dose. This further provides an end-of-use stop mechanism after the eighth dose indicating the device should no longer be used[19]. The company suggests that Instanyl®▼ may not have been well received by health boards/professionals due to the lack of any such dose monitoring mechanism[2].

Substantial differences may exist in the pharmacokinetic profile of immediate-release fentanyl products, which result in clinically important differences in the rate and extent of absorption of fentanyl. Therefore, when switching between fentanyl containing products indicated for treatment of breakthrough pain, including intranasal formulations, it is essential that patients are again titrated with the new product, and not just switched.

As with Instanyl®▼, due to the potential risk of overdose and danger for children and family circles, the nasal spray solution should be placed in the child-resistant box immediately after use[1,6]. Furthermore, like other fentanyl-based medicines, PecFent®▼ requires a 'special' prescription and has stricter conditions than normal, due to potential misuse and addiction[3].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The company state that PecFent®▼ is intended for first-line treatment, as an alternative to other short-acting fentanyl products, when oral morphine is unsuitable and second-line treatment when IRMS or other short-acting fentanyl preparations have failed[2]. In comparison to IRMS (CP044), PecFent®▼ had a faster onset of action and significantly reduced pain intensity, suggesting it may be a more appropriate treatment for second-line BTP in cancer patients[12].
- WMP requested Instanyl®▼, Actiq®, Effentora®▼ and Abstral®▼ as comparators. In the absence of direct comparative studies, the company included an indirect MTC to compare PecFent®▼ with Actiq® and Instanyl®▼. Instanyl®▼ is an intranasal fentanyl formulation and therefore should be considered the most appropriate direct comparator for PecFent®▼. However, in accordance with market research conducted by Intercontinental Medical Statistics (IMS) Health in 2009-2010, the company used Actiq® as the main comparator for the economic evaluation as it accounted for 76% of the Welsh short-acting fentanyl BTP market by value and 72% by volume, whereas Instanyl®▼ had less than 0.17% by value[2]. A secondary, supportive analysis was provided for Instanyl®▼, but Effentora®▼ and Abstral®▼ were not presented in the company submission[2].
- The maximum dose used in the PecFent®▼ studies was higher than that used in the Instanyl®▼ studies (800 and 200 micrograms, respectively). Despite this, a four-month safety study demonstrated that AEs associated with PecFent®▼ treatment remained typical of those associated with opioid treatment[13]. However, safety assessment over longer time periods would be valuable and results of a two-year follow-up study to CP045 are expected in the next 6–12 months[2].
- All patients included in the Instanyl®▼ phase III efficacy study were known responders from the phase II programme, in contrast to the PecFent®▼ phase III efficacy studies where patients were treatment-naive. This may have implications for response rate and tolerability[20].
- PecFent®▼ is short-acting with rapid systemic absorption and a rapid onset of action, which more closely mirrors the temporal characteristics of most BTP episodes than traditionally used oral morphine. Furthermore, the intranasal route of absorption facilitates gastrointestinal and hepatic bypass, enhancing PecFent®▼ bioavailability[11,21].
- In contrast to Instanyl®▼, the PecFent®▼ delivery device aids dose monitoring by producing a tactile, audible and visible confirmation of dose administration. In addition, an end-of-use locking mechanism is engaged after eight doses.
- Instanyl®▼ is an aqueous-based nasal spray solution whereas PecFent®▼ uses a blend of pectin with sucrose, which gels on contact with calcium ions forming a well dispersed spray plume appropriate for nasal delivery[3]. This is considered a novel nasal spray excipient that has not been previously used in approved pharmaceutical products[3].
- Nasal administration does not depend on saliva production; therefore cancer patients with salivary gland dysfunction, mucositis and xerostomia may gain particular benefit from intranasal fentanyl administration.

- In a study carried out in four European countries including the UK (n=320), 26% of patients (13% from the UK) said they would definitely not use an intranasal fentanyl formulation for BTP treatment; the reason provided was "*I don't like the idea of such a product*"[22]. However, there was no commercially available intranasal fentanyl product when this data was collated.

6.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost-effectiveness evidence

6.1.1 Context

The company's submission describes a primary cost-minimisation analysis (CMA) of PecFent®▼ against Actiq® for the management of BTP in adults receiving maintenance opioid therapy for chronic cancer pain[2]. A secondary cost-utility analysis (CUA) compares PecFent®▼ with Instanyl®▼ fentanyl nasal spray. No comparisons have been made against IRMS, which limits the economic evidence to situations in which IRMS is not an appropriate option.

No studies directly comparing PecFent®▼ with Actiq® or with Instanyl®▼ have been conducted. Based on a Bayesian indirect MTC of PecFent®▼, Actiq® and Instanyl®▼ trials, it is assumed that PecFent®▼ and Actiq® are therapeutically equivalent[2]. Therefore, as company conducted market research indicates that Actiq® is the most frequently used fentanyl formulation for BTP in cancer patients in Wales, the company's chosen primary approach to address the cost-effectiveness of PecFent®▼ was to consider a CMA of PecFent®▼ versus Actiq®.

The secondary CUA is based on small differences observed in favour of Instanyl®▼ in terms of changes in PI scores. As effectiveness and overall costs of PecFent®▼ are both estimated to be lower than for Instanyl®▼, the company has presented the results of the CUA as the incremental costs per quality-adjusted life year (QALY) gained for Instanyl®▼ over PecFent®▼ (which is equivalent to the incremental saving per QALY lost with PecFent®▼). The base case analyses assume that the average frequency of BTP episodes is 2.6 per day and that the duration of treatment is 180 days. See Appendix 1 for further details.

6.1.2 Results

Results of the base case CMA of PecFent®▼ versus Actiq® are summarised in Table 1. The cost of comparators per treatment of a BTP episode included the probability of re-dosing, estimated as 30% for Actiq® (administration of PecFent®▼ does not allow re-dosing). The estimated costs per BTP episode were £7.61 for Actiq® and £5.71 for PecFent®▼. Titration costs were assumed to be £80.07 for Actiq® and £43.26 for PecFent®▼. Other healthcare costs were not considered, since the company assumed that there would be no difference in the costs associated with providing and monitoring the use of the three fentanyl products.

Table 1. Company-reported results of base case CMA of PecFent®▼ versus Actiq®

	Total number of BTP episodes	Cost per BTP episode (£)	Product cost over evaluation period (£)	Titration cost (£)	Total cost (£)
PecFent®▼	468	5.71	2,672.16	43.26	2,715.42
Actiq®	468	7.61	3,552.12	80.07	3,642.12
Difference	-	-1.90	-879.96	-36.80	-926.70

Sensitivity analyses of PecFent®▼ versus Actiq® treatment assumed that:

- No re-dosing is required for Actiq®;
- Average duration of treatment is one year;
- Titration costs are excluded;
- Titration re-dosing costs are excluded.

All scenarios resulted in net cost savings for PecFent®▼ treatment with the largest saving, of £1,817 per patient, reported when the duration of treatment was one year, and the lowest saving, of £61 per patient, when costs associated with titration and Actiq® re-dosing were excluded from the analysis.

Results of the CUA are presented in Table 2. The large incremental cost per QALY gained is driven by the very small difference in QALYs observed for Instanyl®▼ versus PecFent®▼.

Table 2. Company-reported results of the CUA of Instanyl®▼ versus PecFent®▼

	Instanyl®▼	PecFent®▼	Difference
Drug costs (£)	4,482.99	2,672.16	1,810.83
Other healthcare costs (£)	4,802.08	5,055.44	-253.36
Total cost (£)	9,285.07	7,727.60	1,557.47
QALYs gained	0.209	0.203	0.006
Incremental cost per QALY gained (£)*	**250,455.37**		

CUA: Cost-utility analysis; QALY: Quality-adjusted life year.
*Note this analysis was conducted to assess cost-effectiveness of Instanyl®▼ versus PecFent®▼, but is equivalent to £250,455.37 saved per QALY lost with PecFent®▼ versus Instanyl®▼

One-way sensitivity analyses (for a comparison of PecFent®▼ versus Instanyl®▼) indicate that if the rate of Instanyl®▼ re-dosing is reduced to half that assumed in the base case analysis, the incremental cost-effectiveness ratio (ICER) is around £111,000 saved for each QALY lost with PecFent®▼ versus Instanyl®▼. If re-dosing occurs in all BTP episodes with both Instanyl®▼ and PecFent®▼, the ICER increases to £283,000 saved per QALY lost. When the QALY gains with Instanyl®▼ are increased to an equivalent level as those adopted for the comparison of Instanyl®▼ against Actiq® in the previous AWMSG submission for Instanyl®▼[10], the ICER for PecFent®▼ versus Instanyl®▼ decreases to £46,000 saved per QALY lost.

Probabilistic sensitivity analysis is reported to demonstrate a 61% probability that the costs saved per QALY foregone would exceed £30,000 with the use of PecFent®▼ compared with Instanyl®▼.

6.1.3 WMP Critique

Strengths of the economic evidence include:

- In the absence of direct comparative data for PecFent®▼ and other fentanyl products, the company has made efforts to undertake formal indirect comparisons of the available trial data to inform the economic analyses.

Limitations of the economic evidence include:

- There is a lack of direct comparative data to assess the relative effectiveness of available fentanyl preparations, and indirect comparisons have inherent limitations which warrant cautious interpretation of the resultant efficacy estimates.
- Adoption of a cost-minimisation approach for the comparison of PecFent®▼ with Actiq®, based on results of indirect treatment comparisons, assumes equivalence in all health outcome domains. This has not been demonstrated and ignores potentially important differences in the route of administration and patient preferences.
- A significant contributor to the large ICER reported in the CUA of Instanyl®▼ versus PecFent®▼ is the small QALY gains that make up the denominator. These QALY gains are derived from the efficacy data generated by the indirect treatment comparison, combined with utility data that are also subject to uncertainty. As noted by the company, the QALY differences are expected to be modest given that the BTP episodes in the model only account for 0.05 of a year and the difference in PI between PecFent®▼ and Instanyl®▼ during these episodes is small. It should be noted that Instanyl®▼ is recommended for restricted use in NHS Wales in this patient population[10], and this analysis indicates that PecFent®▼ is less costly than Instanyl®▼, and also possibly less effective. In this context, the results of the CUA should be interpreted with caution.

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and methods

Based on Welsh Cancer Intelligence Survival Unit data for 2007[23], and Welsh population estimates, the company estimates there were 89,156 patients with cancer in Wales in 2010, rising to 129,059 in 2014. Trends in incidence and mortality are assumed to remain constant. The incidence of BTP among cancer patients in Wales has been estimated using data from a published review[5]. It is assumed that 60% of cancer patients experience chronic pain, of which 65% suffer from BTP. About 90% of patients with BTP are expected to receive opioid treatment. As assumed in the economic models, each patient is expected to experience 2.6 BTP episodes per day, for 180 days. Combined with company market research data, this is reported to indicate that the vast majority of these patients are managed with oral immediate-release morphine, with 0.7% receiving short-acting fentanyl. The estimated number of patients with BTP currently treated with fentanyl is 210, which is expected to rise to 301 in 2014 (assuming no change in the proportion of patients managed with fentanyl).

The company assumes that only Actiq® will be displaced by the uptake of PecFent®▼, and anticipates a 2.5% uptake rate for PecFent®▼ in 2010, rising to 20% in 2014. The number of people who will be managed with PecFent®▼ is therefore expected to increase from 5 in 2010 to 61 in 2014. The estimated number of patients treated with PecFent®▼ and the associated costs over the five year period are shown in Table 3.

Table 3. Company-reported costs associated with PecFent®▼ treatment

	Year 1 (2010)	Year 2 (2011)	Year 3 (2012)	Year 4 (2013)	Year 5 (2014)
Number of patients treated for BTP	31,294	34,701	38,170	41,703	45,300
Number of patients treated with fentanyl	210	233	256	280	304
PecFent®▼ uptake (%)	2.50	5.00	10.00	15.00	20.00
Number of PecFent®▼ treated patients	5	12	26	42	61
Cost of PecFent®▼ (£)	13,361.40	32,067.36	69,479.28	112,235.80	163,009.10
Offset cost of Actiq® (£)	-17,760.60	-42,625.44	-92,355.12	-149,189.00	-216,679.30
Net cost (£)	-4,399.20	-10,558.08	-22,875.84	-36,953.28	-53,670.24
BTP: Breakthrough pain.					

No sensitivity analysis of budget impact is presented in the company's submission.

7.1.2 WMP critique

In the absence of Welsh-specific data, a number of assumptions have been made to estimate the number of cancer patients experiencing BTP. The number of patients with cancer is estimated based on Welsh incidence and prevalence data, and it is assumed that 60% of cancer patients on active treatment experience pain. However, it is not clear whether these patients would experience immediate and ongoing pain that is managed in practice with chronic opioid medication, therefore the number of patients eligible for fentanyl BTP treatment may be overestimated. As per the economic models, it is assumed that patients experience 2.6 BTP episodes per day for 180 days on the basis that these patients typically have a short life expectancy, but it is unclear how this relates to the mortality rates assumed in deriving the net number of cancer patients eligible for BTP treatment. Collectively, there would appear to be significant uncertainty in the estimated patient numbers and, consequently, in the budget impact estimates.

7.2 Comparative unit costs

WMP identified fentanyl products Actiq®, Instanyl®▼, Effentora®▼ and Abstral®▼ as the most appropriate PecFent®▼ comparators in the management of BTP in adults receiving maintenance opioid therapy for chronic cancer pain. Acquisition costs for these comparators are shown in Table 4.

Table 4. Acquisition costs of fentanyl-based medication

Fentanyl preparation	Example dose per pain episode*	Example cost per pain episode (£)**
PecFent®▼ nasal spray 100, 400 mcg	100 or 400 mcg	3.80
	200 or 800 mcg	7.60
Actiq® lozenges 200, 400, 600, 800, 1200, 1600 mcg	200, 400, 600, 800, 1200, 1600 mcg	5.84
Instanyl®▼ nasal spray 50, 100, 200 mcg	50 , 100 or 200 mcg	5.95
	400 mcg	11.90
Effentora®▼ tablets 100, 200, 400, 600, 800 mcg	100, 200, 400, 600, 800 mcg	4.99
Abstral®▼ tablets 100, 200, 300, 400 600, 800 mcg	100, 200, 300, 400 600, 800 mcg	4.99

mcg: microgram.
*If more than four episodes of BTP occur each day, background analgesia should be adjusted.
**Costs are based on BNF[24] and MIMS[25] list prices, assuming the dose can be delivered with the lowest number of dose units available. Costs could be greater during titration phase or if inadequate response is achieved with one dose – See individual SPCs for full dosing recommendations.
This table does not imply therapeutic equivalence of drugs or the stated doses.

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that PecFent®▼ may be suitable for shared care within NHS Wales, but should be initiated by, and remain under the supervision of, a physician experienced in the management of opioid therapy in cancer patients.

Physicians should be aware of the potential abuse of fentanyl[1].

8.2 Ongoing studies

The company submission highlighted that results from the extension period of the open-label safety study CP045[13] are likely to be available within 6-12 months, and will report on the long-term (up to two years) tolerability of PecFent®▼[2].

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Appendix 1. Additional health economic information

Table 1A. Health economic model detail

	Base Case Model	Appropriate?
Comparator(s)	PecFent®▼ fentanyl nasal spray is compared against Actiq® (fentanyl lozenges) in what the company considers to be its primary CMA comparator and against Instanyl®▼ fentanyl nasal spray in a secondary CUA.	These fentanyl preparations are appropriate comparators, although other fentanyl preparations (e.g. Effentora®▼ buccal tablets, Abstral®▼ sublingual tablets) that are licensed for the management of BTP have not been considered (based on company-reported market share data). No comparisons have been made against IRMS, which limits the economic evidence to situations in which IRMS is not an option.
Population	Adults with chronic cancer pain receiving maintenance opioid therapy and are experiencing BTP.	Yes, in line with the licensed indication, although the choice of comparators limits the patient population to those in whom IRMS is not an option.
Analysis type	CMA comparing PecFent®▼ and Actiq®.	A primary CMA has been conducted on the basis of an indirect MTC, which is reported to have demonstrated no statistically or clinically significant difference between PecFent®▼ and Actiq® in terms of PI differences from baseline to different time periods of up to an hour. It should be noted that the CMA framework assumes equivalence in all health outcome domains. The company has not provided evidence of equivalence in domains other than PI differences, which may be important given that differences in fentanyl routes of administration and formulations might influence patient preference.
	CUA comparing PecFent®▼ and Instanyl®▼.	As the indirect MTC indicated PecFent®▼ was possibly less effective than Instanyl®▼, and as overall costs were estimated to be lower for PecFent®▼ than for Instanyl®▼, the CUA presented by the company uses Instanyl®▼ as the comparator against PecFent®▼. It should be noted that Instanyl®▼ is recommended as a treatment option for use in NHS Wales when IRMS is either inadequate or unsuitable[10].
Perspective	The CMA considers direct medical costs only, from the perspective of NHS Wales. The CUA includes non-specific elements of wider care costs.	Appropriate to consider direct costs from the perspective of NHS Wales and Personal Social Services.
Time Horizon	Analysis assumes time horizon of 180 days.	Yes, the company has justified the time horizon based on the life expectancy of the relevant patient population. A one year time horizon has been explored in sensitivity analysis.

Table 1A. Continued

	Base Case Model	Appropriate?
Discount rate	Discounting was not applied, since time horizon is less than one year.	Yes.
Efficacy	There are no direct comparative data for PecFent®▼ with other fentanyl preparations. Therefore, efficacy data (relative PI scores) were generated from a Bayesian indirect MTC using data from two studies comparing PecFent®▼ with placebo and oral morphine[11,12], two studies comparing Actiq® with placebo and oral morphine[14,15], and two studies comparing Instanyl®▼ with placebo and Actiq®[16,18]. This indirect MTC is reported to have indicated no statistical or clinical significant difference between PecFent®▼ and Actiq®, which the company assumes is demonstration of equivalence between these two formulations and is the basis for conducting a CMA. For the CUA of Instanyl®▼ versus PecFent®▼, the mean absolute PI scores for PecFent®▼ were reportedly 6.89 (95%CI 6.48-7.30) before administration and 3.32 (95%CI 2.85-3.79) 60 minutes after administration. For Instanyl®▼, the mean absolute PI scores decreased from 6.89 (95%CI 6.48-7.30) before administration to 2.93 (95%CI 0.10-5.76) 60 minutes after administration.	In the absence of direct comparative data, an indirect MTC would be appropriate, although it should be noted that indirect comparisons have inherent limitations which warrant cautious interpretation of the resultant efficacy estimates. The trials employed in the indirect comparison had different baseline PI scores and, as the trials generally involved a titration period to establish an effective dose before efficacy was formally assessed, it is possible that the effectiveness of fentanyl preparations in practice will be lower than that observed in the trials.
Adverse effects	AEs assumed to be the same for PecFent®▼, Actiq® and Instanyl®▼.	Yes. AE data from the clinical trials are limited but appear to be typical of opioid-related AEs. The nasal formulation appears to have been well tolerated.
Utility values	Utility data were not collected in fentanyl trials[11,12,14–16,18]. To obtain utility weights, PI scores were mapped to utility data derived from a published study[26], in which members of the public (not patients) completed a time-trade-off exercise and physicians experienced in the management of chronic pain completed EQ-5D questionnaires as patient proxies. The base case analysis uses the physician-derived utility weights.	Details of the methodology of imputing utility values are limited. The company has used physician-derived proxy utility weights, which generate larger differences in QALY gains compared with those utility weights derived from members of the public. Sensitivity analysis includes use of utility values reported in the AWMSG Final Appraisal Report for Instanyl®▼[10].

Table 1A. Continued.

	Base Case Model	Appropriate?
Resource use and costs	Cost data used in the analysis included cost of titration and cost of BTP treatment by PecFent®▼, Actiq® and Instanyl®▼. Costs were estimated per spray/lozenge, per dose and per BTP episode. The company assumed a single dose of PecFent®▼, 1.3 doses for Actiq® and 1.61 doses of Instanyl®▼ per BTP episode, taking into account the probability of re-dosing for Actiq® and Instanyl®▼. Since PecFent®▼ is available in strengths of 100 and 400 micrograms and some doses require two sprays, the average price of PecFent®▼ per BTP episode was equivalent to 1.5 doses. The estimated average frequency of BTP episode was 2.6 per day, and the duration of treatment was 180 days. Other healthcare costs were not considered in the CMA, since the company assumed that there will be no difference in costs beyond fentanyl acquisition costs. However, for the CUA, the company considers that the difference in BTP intensity scores between single-dose PecFent®▼ and multi-dose Instanyl®▼ observed in the indirect MTC could potentially lead to different levels of consumption of associated healthcare or social care resources. Therefore the costs of non-BTP have been assumed from a published costing study conducted in USA in 1998-99[27], and apportioned to PecFent®▼ and Instanyl® based on the small differences in BTP rates observed from the indirect MTC.	The costs of Instanyl®▼ include re-dosing observed in the active and placebo-controlled trials. The company assumes that all patients who require re-dosing will continue on their initial dose of Instanyl®▼; however, it is possible that a proportion of patients will be switched to a higher dose of Instanyl®▼, which may reduce the degree of re-dosing required per BTP episode. This scenario appears not to have been explored in sensitivity analysis. Dose titration to establish an effective dose is reportedly based on the titration schedules included in the respective SPC and the observed trial-based titration rates. The company appears to assume that inadequate pain relief obtained after the first dose initiates up-titration, and that doses remaining in the formulation pack are therefore wasted, but the extent to which these doses would be "wasted" in practice is unclear. An additional cost is assumed for the act of titrating patients' doses, which from the model provided by the company appears to be assumed to involve 10minutes of health professional time. The costing of that 10 minutes depends on the setting in which the dose titration is assumed to occur (assumed as 70% in the hospital/hospice setting, 10% in outpatient setting, 10% at the GP practice and 10% at home). Further details are lacking. There are many limitations to the approach used to include non-BTP costs in the CUA, as noted by the company, including the fact that resource use and costs in the USA from 12 years ago are unlikely to be representative of those in Wales today.
Uncertainty and scenario analyses	In the CMA, one-way sensitivity and scenario analyses included an increase in duration of treatment to one year, excluding titration costs and excluding re-dosing. In the CUA, uncertainty was assessed by both one-way sensitivity analyses and probabilistic sensitivity analysis. One-way sensitivity analyses included a two-fold increase in dose of both products, decrease in re-dosing of Instanyl®▼ by 30%, two times increase in duration of treatment, and healthcare costs and QALYs taken from other studies[2].	Few details are provided in relation to the probabilistic sensitivity analysis regarding the parameters that have been assumed to vary and the distributions used.
Model Provided?	The model was provided following request from WMP.	Yes.

AE: Adverse event; BTP: Breakthrough pain; CI: Confidence interval; CMA: Cost-minimisation analysis; CUA: Cost-utility analysis; IRMS: Immediate-release morphine sulphate; MTC: Mixed treatment comparison; PI: Pain intensity; QALY: Quality-adjusted life year.