

Final Appraisal Report

Fentanyl (Instanyl[®]▼)

Nycomed UK Ltd

Advice No: 0710 – April 2010

Recommendation of AWMSG

Fentanyl intranasal spray (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.

Fentanyl intranasal spray (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.

Fentanyl intranasal spray (Instanyl[®]▼) may be suitable for shared care but should be initiated by, and remain under the supervision of, a physician experienced in the management of opioid therapy in cancer patients.

Statement of use:

No part of this advice may be used without the whole of the advice being quoted in full.

This report should be cited as:

ABBREVIATIONS

AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
BSA	Body surface area
BTCP	Breakthrough cancer pain
BTP	Breakthrough pain
CI	Confidence interval
CHMP	Committee of Medicinal Products for Human Use
EPAR	European Public Assessment Report
EU	European Union
ICER	Incremental cost effectiveness ratio
ITT	Intent-to-treat
IV	Intravenous
MA	Market Authorisation
MTC	Mixed Treatment Comparison
NHS	National Health Service
PI	Pain Intensity
PID	Pain Intensity Difference
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RMP	Risk Management Plan
SPID	Sum of the Pain Intensity Difference
SPC	Summary of Product Characteristics
WMP	Welsh Medicines Partnership

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 28th April 2010

The recommendation of AWMSG is:

Fentanyl intranasal spray (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.

Fentanyl intranasal spray (Instanyl[®]▼) may be suitable for shared care but should be initiated by, and remain under the supervision of, a physician experienced in the management of opioid therapy in cancer patients.

Additional note:

Fentanyl intranasal spray (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.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Fentanyl intranasal spray (Instanyl[®]▼) is indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain¹.

See glossary for a definition of breakthrough pain and maintenance opioid therapy.

2.2 Dosing

Before patients are titrated with Instanyl[®]▼, it is expected that their background persistent pain is controlled by use of chronic opioid therapy and that they are experiencing no more than four episodes of breakthrough pain per day¹.

The initial strength should be one dose of 50 micrograms in one nostril, titrating upwards as necessary through the range of available strengths (50, 100 and 200 micrograms). If the patient has insufficient pain relief, redosing with the same strength (in the other nostril) can be done, prior to administering the next dose, and at the earliest 10 minutes after the first dose. Once the dose has been established, the patient should be maintained on this strength¹.

The maximum daily dose is the treatment of up to four breakthrough pain episodes, each with no more than two doses separated by at least 10 minutes. The patient should wait at least four hours before treating another breakthrough pain episode during both titration and maintenance therapy. Generally, the maintenance strength of fentanyl should be increased when a patient requires more than one dose per breakthrough pain episode for several consecutive episodes¹.

Further information regarding administration of Instanyl[®]▼ can be found in the Summary of Product Characteristics (SPC)¹.

2.3 Market authorisation date

20 July 2009²

2.4 UK Launch date

12 October 2009²

3.0 DECISION CONTEXT

3.1 Background

Breakthrough cancer pain (BTCP) is a transitory exacerbation of pain experienced by most cancer patients occurring on a background of otherwise stable persistent pain. BTCP is generally self-limiting, with a peak intensity occurring on average at three minutes after onset and lasting for an average of 30 minutes. Patients may experience several episodes per day²⁻⁶. BTCP 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^{2,7}.

BTCP has been estimated to affect 50-90% of patients with cancer⁸. The company estimate that in 2009 the number of patients receiving treatment for BTCP in Wales was 2, 574².

Traditionally, oral morphine has been the most widely used treatment for BTCP, though the slow onset of action and long duration of effect do not mirror the temporal characteristics of most breakthrough pain episodes. Oral transmucosal fentanyl has a

more rapid onset of action and currently available products include fentanyl buccal lozenges (Actiq[®]), fentanyl buccal tablets (Effentora[®]▼) and fentanyl sublingual tablets (Abstral[®]▼)^{3,9}.

Fentanyl is an opioid analgesic interacting primarily with the μ -opioid receptor as a pure agonist with low affinity for the δ - and κ -opioid receptors¹. Fentanyl formulated for intranasal administration (Instanyl[®]▼) is absorbed very rapidly through the nasal mucosa¹; pain relief is seen within 10 minutes post-dose^{3,10} and the nasal route of absorption avoids first-pass metabolism of the active substance³.

3.2 Comparators

- Fentanyl buccal lozenges (Actiq[®])
- Fentanyl buccal tablets (Effentora[®]▼)
- Fentanyl sublingual tablets (Abstral[®]▼)

The company state in their submission that Actiq[®] is the current standard practice formulation of fentanyl administered transmucosally (and market leader)².

3.3 Guidance and related advice

There are no specific guidelines relating to the use of Instanyl[®]▼². The most relevant guidelines relating to the treatment of BTCP include:

- Scottish Intercollegiate Guidelines Network (SIGN [2008]). Control of pain in adults with cancer - these recommend that the opioid for treating BTCP should ideally have pharmacokinetics which mirror the time features of the majority of patients' specific breakthrough pain (i.e. a rapid onset of action, high analgesic potency, fast offset of action)¹¹.
- Association for Palliative Medicine of Great Britain and Ireland. The management of cancer-related breakthrough pain (2008) - no recommendations were made about any individual interventions but 12 recommendations were made about general strategies mostly based on limited evidence⁹.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The company submission includes a dose ranging placebo-controlled efficacy trial (FT-017-IM); a dose titration, placebo-controlled efficacy and safety follow-up trial (FT-018-IM) and an open-label crossover trial (FT-019-IM) comparing the efficacy of Actiq[®] and Instanyl[®]▼. In FT-019-IM, 139 adult (≥ 18 years) cancer patients receiving stable opioid treatment for background pain but experiencing BTCP (≥ 3 BTCP episodes per week, but ≤ 4 BTCP episodes per day) were randomised to receive either Instanyl[®]▼ followed by Actiq[®] or Actiq[®] followed by Instanyl[®]▼. The primary endpoint of median time to onset of 'meaningful' pain relief was shorter with Instanyl[®]▼ versus Actiq[®]; indicating a faster time to pain relief when using Instanyl[®]▼. In both treatment sequences, a significantly greater number of patients had a faster onset of meaningful pain relief with Instanyl[®]▼ compared to Actiq[®]. Secondary endpoints including the difference in pain intensity (PI) scores at various time points and the time to 50% reduction in PI support a faster time to pain relief with Instanyl[®]▼ compared with Actiq[®]. Furthermore, ease of administration, general impression scores and patient preference were statistically significantly favourable for Instanyl[®]▼ compared to Actiq[®]. Overall, all doses of Instanyl[®]▼ were shown to be well tolerated and the safety profile for Instanyl[®]▼ was consistent between trials. No significant safety concerns were identified in the 10-month long-term safety phase of trial FT-018-IM and similar adverse event profiles were observed for Actiq[®] and Instanyl[®]▼ in trial FT-019-IM.

4.2 Review of the evidence on cost-effectiveness

The company submission describes a primary cost utility analysis comparing Instanyl[®]▼ with Actiq[®], based on a *post hoc* analysis of secondary endpoint data from trial FT-019-IM. A secondary analysis has also been conducted to compare Instanyl[®]▼ against Actiq[®], Effentora[®]▼ and Abstral[®]▼, based on an indirect, mixed treatment comparison (MTC). Only fentanyl formulations are considered as comparators, as requested by WMP. No evidence is presented on the cost effectiveness of Instanyl[®]▼ relative to oral morphine.

The primary analysis demonstrated that Instanyl[®]▼ was both more effective and less expensive than Actiq[®], i.e. Instanyl[®]▼ was dominant. The secondary analysis confirmed this result and found an incremental cost per quality-adjusted life year (QALY) gained of £9,000 to £10,000 when Instanyl[®]▼ was compared against the buccal and sublingual tablets. There are a number of limitations to the analyses, including assumptions regarding resource utilisation and the lack of direct evidence of efficacy compared with the buccal and sublingual tablet formulations. One-way sensitivity analyses indicate the conclusions of the primary base case analysis are robust, although it is not immediately clear how all parameter values have been tested and there is no consideration of the combined impact of the uncertainty in multiple parameters. The incremental cost per QALY gained for Instanyl[®]▼ relative to the buccal and sublingual tablet formulations ranged from around £6,000 to £23,000 in the sensitivity analyses that have been conducted.

4.3 Limitations of the evidence

- The primary endpoint of time to onset of 'meaningful' pain relief was measured by the patient using a stopwatch. Measurements are therefore subjective and individualised to each patient. This method of measuring pain relief is considered relevant and a more sensitive method of detecting between-group differences than conventional pain assessments¹².
- There is a lack of direct comparative data for the intranasal spray and the buccal and sublingual tablet formulations of fentanyl, and indirect evidence has a number of inherent limitations.
- The evidence relates to a sub-set of the licensed indication, in that it provides no evidence against non-fentanyl treatments for the management of BTCP (e.g. oral morphine, oxycodone).

5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

5.1 Clinical evidence

Evidence presented in the company submission includes details of three clinical studies; a dose ranging placebo-controlled efficacy trial (FT-017-IM); a dose titration, placebo-controlled efficacy and safety follow-up trial (FT-018-IM) and FT-019-IM, a head-to-head comparative trial between Actiq[®] and Instanyl[®]▼². The company submission also includes an indirect comparison of Instanyl[®]▼ with the newer fentanyl transmucosal formulations (Effentora[®]▼ and Abstral[®]▼) and immediate release oral morphine².

5.1.1 Study FT-017-IM and FT-018-IM – Placebo controlled trials

FT-017-IM was a randomised, double-blind, placebo-controlled, crossover multicentre (27 sites) trial designed to demonstrate the efficacy of Instanyl[®] in the treatment of breakthrough pain in cancer patients (n=152). All Instanyl[®] doses provided significantly higher mean PID₁₀ scores (ranging from 1.82 to 2.65) compared with placebo (1.41; p≤0.001 for all Instanyl[®] doses)^{2,3}.

FT-018-IM was a randomised, double-blind, placebo-controlled, cross-over multi-centre trial (22 sites) designed to demonstrate the efficacy and safety of titrated doses of Instanyl[®] in the treatment of BTCP (n=111). Patients included in this study were already considered responders and tolerant to Instanyl[®]. The primary endpoint was PID₁₀ after the first dose of study medication. All Instanyl[®] doses provided higher mean PID₁₀ scores (ranging from 2.00 to 2.74) compared with placebo (1.28). The mean response rate after one dose at 10 minutes was 31%, 60%, 49% for Instanyl[®] 50, 100 and 200 micrograms and 21% for placebo².

5.1.2 Study FT-019-IM – Comparison of Instanyl[®] and Actiq[®]

FT-019-IM was a randomised, open-label, cross-over study designed to compare the efficacy of Instanyl[®] and Actiq[®] in 139 adult cancer patients receiving stable background opioid treatment and experiencing BTCP. Patients receiving Instanyl[®] were titrated to one or two single doses of 50, 100 or 200 micrograms and patients receiving Actiq[®] were titrated to one or two doses of 200, 400, 600, 800, 1200 or 1600 micrograms (the algorithm for dose adjustment in the titration phase is included in Appendix 1). The trial was initially conducted in three stages; one week screening period; four week (on average) titration with Instanyl[®] or Actiq[®] until treatment with a given dose was effective (i.e. effective treatment of three out of four BTCP episodes) and a two week efficacy phase (treating six BTCP episodes) with the titrated fentanyl product. The titration and efficacy phase were then repeated with the other fentanyl product (see Appendix 1)^{2,12}. In trial FT-019-IM 95 (68.3%) and 90 (64.7%) patients reached successful doses during the titration phase for Instanyl[®] and Actiq[®], respectively².

The primary endpoint was patient-recorded time to onset of analgesia (i.e. 'meaningful' pain relief). Among the intent-to-treat (ITT) analysis set (n=139), efficacy data was obtained from 101 patients treated with Instanyl[®] and 100 patients treated with Actiq[®]. The median time to onset of 'meaningful' pain relief was 10.6 minutes with Instanyl[®] compared to 15.7 minutes with Actiq[®] and the median within patient difference was 4.3 minutes (n=86). Overall, 65.7% of patients reported fastest pain relief using Instanyl[®] compared with Actiq[®] (p<0.001; 95% confidence interval [CI]: 57.1, 73.6)^{2,12}. *Post hoc* analysis evaluated PID at 5, 15, 20 and 60 minutes. This showed a statistically significant (p<0.01) difference in pain intensity between the Instanyl[®] and Actiq[®] groups in favour of Instanyl[®]; this was evident as early as 5 minutes and was maintained until 60 minutes¹². For secondary endpoints refer to Table 1A, Appendix 1.

5.1.3 Mixed Treatment Comparison (MTC)

A systematic literature review was conducted to identify active or placebo controlled, randomised trials of the four available fentanyl formulations. This is reported to have identified two placebo-controlled trials for Effentora[®], and one placebo-controlled and one immediate release morphine sulphate-controlled trial for Actiq[®], in addition to the direct comparative trial of Instanyl[®] and Actiq[®]¹², and one of the two placebo-controlled trials of Instanyl[®] (FT-018-IM). The other placebo controlled trial of Instanyl[®] (FT-017-IM) was not included in the MTC as this did not include a dose titration phase². No randomised controlled trials for Abstral[®] met the inclusion criteria for the systematic review, and so the efficacy of this formulation is assumed to be the same as the lozenge formulation in the MTC analysis (see section 7.4). The primary

outcome for the MTC was the difference in pain intensity from the start of the BTCP episode to different time points up to 60 minutes. This was estimated for each of the formulations relative to placebo, and had to be adjusted for differences in the time points used for evaluation of pain intensity in the different trials. The results showed that Instanyl[®]▼ provided the greatest reduction in pain relative to placebo (for up to 45 minutes) and the highest probability of being the best treatment in terms of providing pain relief for up to 60 minutes after break through pain episode relative to Effentora[®]▼, Actiq[®] and oral morphine².

5.2 Safety

The majority of adverse events in clinical trials were considered to be mild to moderate in severity and there were no significant differences in adverse events between Instanyl[®]▼ and Actiq[®]. All doses of Instanyl[®]▼ were shown to be well tolerated and the most frequent treatment related adverse events were typical of opioid treatment and included nausea and vomiting^{2,11}. In trial FT-019-IM the number of patients who withdrew due to adverse events were similar for Instanyl[®]▼ and Actiq[®] (8.2% versus 6.8%, respectively)¹². One patient treated with Instanyl[®]▼ developed two small ulcers of the nasal mucosa (one in each nostril); however the patient recovered nine days after treatment withdrawal¹². In trial FT-018-IM, moderate epistaxis was the only adverse event possibly related related to the nasal administration of Instanyl[®]▼ and in trial FT-017-IM, treatment unrelated nasopharyngitis was the only reported adverse event of nasal symptomatology². No treatment related deaths were recorded².

In a pharmacokinetic study with oxymetazoline the maximum concentration of Instanyl[®]▼ was reduced by 50% and the time to reach maximum concentration was doubled. As this may reduce the efficacy of Instanyl[®]▼ it is recommended that concomitant use of nasal decongestants is avoided¹.

The company submission states that although no new safety issues have emerged during the development of Instanyl[®]▼ the adverse event profile will continue to be monitored by the company in clinical practice². The adverse event profile of Instanyl[®]▼ will be further defined in the risk management plan (RMP)³.

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 use¹.

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- Results from trial FT-019-IM showed that Instanyl[®]▼ produced superior clinically important pain relief ($\geq 33\%$ PI reduction) versus Actiq[®] up to 30 minutes post-dosing ($p < 0.05$) and as early as 5 minutes ($p < 0.001$)^{2,12}.
- In trial FT-019-IM a proportion of treated BTCP episodes required rescue medication in the efficacy phase. This proportion was higher after administration of Instanyl[®]▼ (all doses combined, 45 of 577 episodes [7.8%]) compared with Actiq[®] (28 of 577 [4.9%]). However, rescue medication could be taken 20 minutes after the first dose and 10 minutes after the second dose of Instanyl[®]▼, whereas rescue medication could not be taken until 45 minutes or 60 minutes after start of administration of the first Actiq[®] dose (depending on whether one or two lozenges were administered^{2,12}).
- In trial FT-019-IM, due to the subjective nature of the primary endpoint, consideration should be given as to whether the open label design of the study may have biased the results.

- In study FT-018-IM, more than 50% of the patients needed two doses of Instanyl[®]▼ to treat their breakthrough pain³. The Committee of Medicinal Products for Human Use (CHMP) considered that as Instanyl[®]▼ is effective in about 50% of patients who take one dose, and as patients who took a second dose achieved a clinical and significant additional benefit, the doses and mode of administration are acceptable³.
- In trial FT-019-IM, a second dose of Actiq[®] was permitted 30 minutes after the first, if required^{3,12}; however the SPC states that if adequate analgesia is not obtained within 15 minutes after the patient completes consumption of a single Actiq[®] unit, a second Actiq[®] unit of the same strength may be consumed¹⁴.
- It is of note that Actiq[®] is reported in the MTC-based analyses to have the lowest effectiveness of the fentanyl formulations (see section 7.4)².
- Instanyl[®]▼ bypasses the oral route and may be convenient for patients with nausea and vomiting, dry mouth syndrome, oral mucositis and impaired gastrointestinal function, which are common symptoms in cancer patients³.

Additional information was provided to members as commercial in confidence.

7.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

7.1 Context

The company submission² describes cost utility analyses of Instanyl[®]▼ compared against other short-acting fentanyl formulations for the management of BTCP, as requested by WMP. Neither short acting oral morphine, nor oxycodone which may be suitable for patients intolerant of morphine¹⁵, are considered as comparator treatments for BTCP in these analyses. As the licensed indication does not limit the use of Instanyl[®]▼ to those in whom oral morphine is not an option¹, these analyses may be considered to relate to a sub-set of the licensed indication for Instanyl[®]▼.

A primary cost utility analysis has been conducted to compare Instanyl[®]▼ against Actiq[®]. *Post hoc* data from trial FT-019-IM¹² are used for this analysis. A secondary cost utility analysis compares Instanyl[®]▼ against Actiq[®] and against fentanyl buccal tablets (Effentora[®]▼) and sublingual tablets (Abstral[®]▼). There are no direct comparative data for Instanyl[®]▼ against the buccal and sublingual tablet formulations, and this analysis is based on indirect data derived from a MTC². The perspective of the analyses is NHS Wales and a one-year time horizon of analysis is used, as it is considered that most eligible patients will be undergoing palliative care and have limited remaining lifetime². The model has not been provided to WMP.

7.2 Methods

Modelling approach: A decision analytic model has reportedly been developed to represent the course of pain intensity associated with BTCP. This is based on pain intensity scores over the duration of each BTCP episode. For the base case model it is assumed that patients have a background pain intensity score of 2 on a scale of 0-10, and experience three BTCP episodes that require treatment per day, for 96 days each year². The basis of the background pain intensity score and the three BTCP episodes per day appears to be the mid-range of inclusion criteria of the comparative trial¹², which specified background pain intensity ≤ 4 and experiencing four or fewer BTCP episodes per day. The basis of the 96 days over which patients experience BTCP per year is referenced to company market research and is not further discussed. All BTCP episodes are assumed to last for 60mins or less, as this was the maximum period over which pain intensity associated with BTCP was recorded in the clinical trial¹². Treatment benefit from each formulation is assumed to be constant over time (i.e. no further dose adjustments are made over the one-year time frame). Resource use is assumed to be linearly related to the combined duration and intensity of the BTCP

episodes, which the company acknowledges to be unlikely and is explored in scenario analyses.

Inputs: For the primary analysis, the pain intensity scores at time 0, 5mins, 10mins, 15mins, 20mins, 30mins and 60mins are derived from trial FT-019-M comparing Instanyl[®]▼ and Actiq[®]12. The pain intensity difference was reported to be statistically significantly greater at all time points for Instanyl[®]▼ than for Actiq[®], although it should be noted that pain intensity was a secondary endpoint in the trial, and *post hoc* analysis has been undertaken to derive values for all but the 10min and 30min time points^{2,12} (see Section 5).

For the secondary analysis, pain intensity scores for each time point have been derived from a MTC² (see Section 5). The primary outcome for the MTC was the difference in pain intensity from the start of the BTCP episode to different time points up to 60 minutes. This was estimated for each of the formulations relative to placebo, and had to be adjusted for differences in the time points used for evaluation of pain intensity in the different trials.

Utility values for eight health states that are thought to be representative of a 60 minute BTCP episode have been generated via an elicitation study using time trade-off techniques in members of the public². The eight health states were reportedly developed and tested with specialist health professionals and patients. This study is reported to show that mean utility was positively related to the rate of reduction in BTCP intensity. The company reports that a literature search was conducted to inform utility values but no relevant data were identified and it has not been possible to compare their results from this elicitation study with that of others². From the utility values obtained for these eight health states, a regression analysis has been conducted to generate a linear equation to represent utility values for any given pain intensity over any time point within the 60 minutes time frame². This is used to estimate utility values for the different formulations based on their estimated rate of reduction in BTCP intensity.

Resource use associated with BTCP episodes has been derived from company-sought expert opinion. It is reported that eight UK clinical experts were interviewed and provided consensus on the probabilities and frequencies of health professional visits, hospital visits and hospice stays, etc., for cancer patients with BTCP episodes and those without BTCP episodes. These items of resource use were costed using published list prices. Drug costs are assumed to consist of only the short acting fentanyl drug costs used for relief of BTCP episodes, and are based on list prices².

Several one-way sensitivity analyses have been conducted to explore uncertainty in pain intensity levels with no treatment and with each of the four formulations, resource use, background pain intensity and uncertainty in utility values. Ranges of 75% to 125% of the base case values appear to have been explored for the parameters relating to background pain intensity and the number of BTCP episodes per day, but it is unclear what ranges have been explored for other parameters. In addition, three scenario analyses have been performed:

- A) Background pain intensity score of 3, instead of 2
- B) Only drug costs included in the resource use estimates
- C) Reduced BTCP episode duration of 30mins, with linear reduction to background pain intensity, instead of 60mins duration for BTCP episode.

7.3 Results

7.3.1 Primary analysis

The primary base case analysis indicates Instanyl[®]▼ is both less expensive and is more effective than Actiq[®] (incremental QALYs gained 0.021 and costs £50 lower than with Actiq[®]), i.e. Instanyl[®]▼ dominates Actiq[®], based on the *post hoc* data derived from the comparative trial. Instanyl[®]▼ remained dominant in all of the one-way sensitivity analyses and scenario analysis A². In scenario analysis B, Instanyl[®]▼ and Actiq[®] costs are exactly the same, and Instanyl[®]▼ is more effective. Scenario analysis C has not been performed as the company reports that the trial upon which this analysis was based demonstrated that both treatments reduced pain to below background pain intensity at 60mins.

Table 1. Base case primary analysis – Instanyl[®]▼ versus Actiq[®] using *post hoc* data from head-to-head trial (FT-019-IM)²

	Instanyl [®] ▼	Actiq [®]
QALYs	0.152	0.131
Total costs	£1,738	£1,789
ICER	Instanyl [®] ▼ dominates Actiq [®]	

7.3.2 Secondary analyses

The secondary analyses indicate Instanyl[®]▼ remains dominant over Actiq[®], including in the one-way sensitivity analyses and the scenario analyses (in scenario analysis B, the costs are exactly the same for both formulations, and the Instanyl[®]▼ is associated with a gain of 0.023 QALYs compared with the Actiq[®]).

For the comparisons of Instanyl[®]▼ against the buccal tablet, the incremental cost per QALY gained is £9,037 in the base case analysis. The range of incremental cost effectiveness ratios (ICERs) reported in the sensitivity and scenario analyses is £5,839 to £17,620 per QALY gained. When compared with the sub-lingual tablet, the base case ICER is £10,094 and ranges from £6,188 to £22,776 in the sensitivity and scenario analyses.

Table 2. Base case secondary analyses – Instanyl[®]▼ versus Actiq[®], buccal tablet and the sublingual tablet using data derived from MTC²

	Instanyl [®] ▼ vs. Actiq [®]	Instanyl [®] ▼ vs. buccal tablet	Instanyl [®] ▼ vs. s/l tablet
QALYs	0.133 vs. 0.110	0.133 vs. 0.112	0.133 vs. 0.110
Total costs	£1,731 vs. £1,758	£1,731 vs. £1,538	£1,731 vs. £1,499
ICERs (Instanyl[®]▼ vs. comparator)	Instanyl [®] ▼ dominant	£9,037	£10,094
s/l = sublingual tablet			

7.4 WMP critique of the company's economic evidence

It is not clear that the base case analyses presented in the company submission provide the most plausible point estimates of utility gain and costs with Instanyl[®]▼ compared with the other fentanyl formulations. There are a number of strengths and limitations to the evidence that has been presented.

Strengths of the economic evidence provided in the company submission include:

- The availability and use of direct comparative data for the analysis of Instanyl[®]▼ compared against Actiq[®].
- In the absence of direct comparative evidence for Instanyl[®]▼ and the buccal tablet, systematic literature searches and reviews have been conducted to derive data for the MTC.
- A plausible approach to utility value elicitation has been used in the absence of other sources.
- Multiple one-way sensitivity and scenario analyses have been conducted to explore the impact of parameter value assumptions.

Limitations of the economic evidence provided in the company submission include:

- Efficacy data for the primary analysis are derived from a *post hoc* analysis of secondary endpoint data from the comparative trial.
- The lack of robust, direct comparative efficacy data for Instanyl[®]▼ and the buccal and sublingual tablet formulations.
- The assumption of constant benefit per BTCP episode over time, although this assumption applies to all formulations considered in the analyses and so on average may not favour one comparator over another.
- There is no specific consideration of the greater use of a second dose of Instanyl[®]▼ compared with second dose of Actiq[®] in the comparative clinical trial (see section 6). However, the trial protocol permitted earlier use of rescue doses for Instanyl[®]▼ than for Actiq[®]¹², which may have contributed to this finding.
- The use of expert opinion to derive resource use. The model also assumes a linear relationship between BTCP episodes and resource use, which is unlikely to be the case in practice.
- The combined impact of uncertainty in multiple parameters has not been explored. This may be particularly relevant for the comparison against the sublingual tablet, which has the lowest acquisition costs of the four formulations, but in the absence of data is simply assumed to have the same effectiveness as Actiq[®]. It is of note that Actiq[®] is reported in the MTC-based analyses to have the lowest effectiveness of the fentanyl formulations.
- The range of values explored in the sensitivity analyses is unclear for some key parameters.
- The economic model has not been provided by the company, which precludes verification of the reported model inputs and outputs.

7.5 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of Instanyl[®]▼ for the management of BTCP.

8.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

8.1 Methods

The budget impact estimates relate to the use of Instanyl[®]▼ as an alternative to other fentanyl formulations and oral morphine (c.f. oral morphine was not a comparator in the economic model). The submission uses Welsh population estimates and predicted growth rate, and the assumption that annual mortality rate due to cancer (0.25% based on Cancer Research UK statistics for the UK¹⁶) is an appropriate proxy for the rates of advanced cancer, to estimate the number of patients with advanced cancer in each of the next five years. The proportion of these patients estimated to be in pain is 70%, based on a news article that reported results of a questionnaire study of cancer patients in 2000¹⁷. The proportion of these patients with BTCP episodes is estimated to be 89%, based on a survey of hospice patients in 1998¹⁸. Based on company market research, 65% of patients who experience BTCP receive opioid treatment for background pain and of these, 85% will receive treatment for BTCP episodes².

The company expects uptake of Instanyl[®]▼ to be 0.2% on year 1, rising to 7.2% in year 5. The current and expected market share of the other fentanyl formulations (lozenge, buccal tablet, sublingual tablet) and oral morphine are presented, based on company market research. These suggest that the main changes in market shares over the next five years will be a reduction in the proportion of treatments provided as oral morphine and the fentanyl Actiq[®] and an increase in treatments provided as the Instanyl[®]▼ and the buccal (Effentora[®]▼) and sublingual (Abstral[®]▼) tablet. The drug costs for the treatment of BTCP are reported to be based on three episodes of BTCP per day and an expected number of days of treatment per patient per year of 96, as per the economic model. The approach to other resource use is also as per the economic model, which assumed an unlikely linear relationship between BTCP episodes and resource use.

8.2 Results

The annual budget impact estimate included in the company submission is summarised in Table 3. By far the main driver of the increase in costs reported in each of the five years is drug acquisition costs; savings in other resource use from the use of Instanyl[®]▼ amount to only around 3% of the additional drug acquisition costs.

Table 3. Annual budget impact estimate for each of the next 5 years

	2009	2010	2011	2012	2013
Number of patients to be treated with Instanyl[®]▼	5	59	117	160	190
Total costs with Instanyl[®]▼	£1,104,458	£1,195,527	£1,237,923	£1,311,567	£1,353,085
Total costs without Instanyl[®]▼	£1,097,691	£1,117,662	£1,082,998	£1,101,292	£1,103,461
Net budget impact	£6,767	£77,865	£154,924	£210,274	£249,624

8.3 Critique

The budget impact estimates rely on the same assumptions as the economic model, which are associated with a degree of uncertainty as discussed in section 7. Additional areas of uncertainty include the assumed annual death rate of 0.25%, which appears to relate to the UK as a whole. The Cancer Research UK figures suggest an annual death rate closer to 0.3% for Wales¹⁶, which would increase patient numbers by 20% over those estimated in the submission. The use of survey data from pre-2000 to inform estimates of BTCP and rates of control may also be a source of uncertainty. No further sensitivity or scenario analyses have been provided.

8.4 Comparative unit costs

Table 4 provides example costs per dose for Instanyl[®]▼ and the comparators.

Table 4. Example comparator costs^{1,15}

BTCP treatment	Example dose in BTCP episode	Acquisition cost/dose
Fentanyl intranasal spray (Instanyl [®] ▼)	0.05mg to 0.2mg	£5.95
Fentanyl lozenge (Actiq [®])	0.2mg to 1.6mg	£5.95
Fentanyl buccal tablet (Effentora [®] ▼)	0.1mg to 0.8mg	£5.14
Fentanyl sublingual tablet (Abstral [®] ▼)	0.1mg to 0.8mg	£4.99
Oxycodone (OxyNorm [®])	5mg to 50mg	<£2.00
Oral morphine (Oramorph [®])	One-sixth of 24hour background morphine dose, e.g. 10mg to 50mg	<£0.50
This table does not imply therapeutic equivalence of the regimens and doses		

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

Instanyl[®]▼ should be initiated under the supervision of a physician experienced in the management of opioid therapy in cancer patients. Patients must be carefully monitored during the titration process and titration to a higher dose necessitates contact with the health care professional¹. This product may be suitable for shared care.

9.2 Ongoing studies

The company state that there are no ongoing or updated trial analyses for Instanyl[®]▼ relevant to this submission.

9.3 Other

- There are no specific guidelines on how to change from one fentanyl product to another, but based on how often a dose can be taken, it could be assumed that a different preparation should not be used within four hours of the original one¹⁰.
- There is a potential for prescribing and dispensing errors if more than one formulation of immediate release fentanyl is available locally or prescribed in the community, as the strengths are similar. In order to prevent such errors, the brand name of the correct product should be used on the prescription¹⁰.
- Patients and carers will need to be provided with guidance on the correct storage and disposal of Instanyl[®]▼. Any used or unused bottles should be systematically discarded in the child-resistant outer box according to local policy or returned to the pharmacy¹.

9.4 Patient organisation information

One patient organisation submission was made by Myeloma UK.

9.5 Medical expert summary

Medical expert opinion was provided to members.

GLOSSARY

Breakthrough pain:

A transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain¹.

Ease of drug administration:

In trial FT-019-IM ease of drug administration was assessed by the patient at the end of each efficacy phase using a 5-point verbal scale rating ranging from 0=very easy to 4= very difficult¹²

General Impression Score:

General Impression was measured using a 5-point verbal rating scale (VRS) ranging from 0=poor to 4=excellent¹²

Maintenance opioid therapy:

At least 60mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30mg oxycodone daily, at least 8mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer¹.

Meaningful Pain Relief:

This was defined/determined by the patient (no advice from healthcare professionals/researchers) and recorded using a stop watch¹².

Pain Intensity Score:

Pain intensity was assessed 60 minutes after commencement of Instanyl[®]▼/Actiq[®] administration using a standard 11-point numerical rating scale (NRS), ranging from 0=no pain to 10=worst possible pain¹².

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Appendix 1. Additional Clinical Information

Algorithm for dose adjustment in the titration phase (trial FT-019-IM)²:

BTCP treatment	Successful		Unsuccessful	
Undesirable effects	No	Yes	No	Yes
Decision	Go to Phase 2	One strength down For 50mcg Instanyl®/ 200mcg Actiq®: withdrawal	One strength up For 200mcg Instanyl®/ 1600mcg Actiq®: withdrawal	Withdrawal
mcg = micrograms				

Successful treatment of one BTCP episode²:

- No need for rescue analgesia within the first 60 min
- A score of ≥ 2 on the general impression scale by the patient at 60 min after start of each treatment
- No severe undesirable effects such as pronounced hypoventilation, unacceptable sedation or drowsiness

Trial Design (trial FT-019-IM)²:

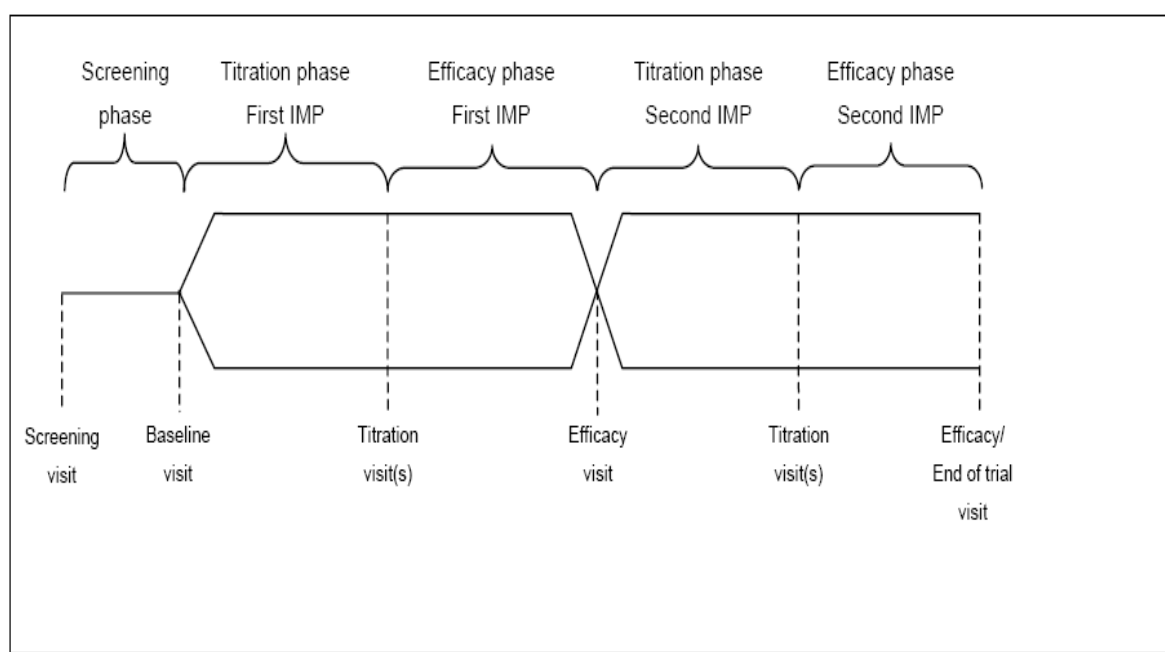


Table 1A. Trial FT-019-IM: A comparison study of Instanyl®[▼] versus Actiq® for the treatment of breakthrough cancer pain

Ref	Study type	No. patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (Instanyl® [▼] versus Actiq®)
Merca dante S et al ^{2, 12}	Open-label, cross-over trial 44 sites in 7 European countries (including 8 in UK) 13 weeks (assuming average titration time for each fentanyl product) Maximum duration of study was 26 weeks	Enrolled: n=196 Randomised n=139 ITT: n=139 Completed: n=86 Instanyl/Actiq treatment sequence: n=71 Actiq/Instanyl treatment sequence: n=68 Instanyl efficacy data set: n=101 Actiq efficacy data set: n=100	Inclusion: ▪ Aged ≥18 years ▪ ≥3 BTCP episodes/week but ≤4 BTCP episodes/day ▪ Stable opioid treatment for background pain* ▪ Prescribed a strong opioid for at least partial relief of BTCP, but additional analgesics are needed for severe intensity BTCP ▪ Life expectancy ≥3month Exclusion: ▪ Hepatic impairment ▪ Oral/nasal surgery or radiotherapy ▪ Treatment with MAO inhibitor within 14 days, methadone within 32 days, buprenorphine within 16 days ▪ Recent therapy which could alter pain or response to analgesics ▪ Neurological, psychiatric impairment, head injury, primary brain tumour ▪ Hypersensitivity to fentanyl/opioids ▪ Pathological conditions of the nasal cavity ▪ Nasogastric feeding ▪ Intranasal administration of other therapies ▪ Impaired respiratory function affected by fentanyl	Female: 60 Males: 79 Caucasian: 100% Mean Age: 62yrs (range 22-94) Mean BMI: 24.3kg/m ² (range 14.7-35.5) Mean weight: 69.7kg (range 45-115) Mean height: 169cm (range 149-200)	Two treatment sequences: ▪ Instanyl followed by Actiq ▪ Actiq followed by Instanyl Initial three stages: (1) 1-week screening, (2) 4-week titration phase, Instanyl: initially 50mcg followed by a second dose at 10 mins if insufficient pain relief; then one or two single doses of 100 or 200mcg until successful BTCP treatment [†] . Actiq: initially 200mcg followed by a second dose at 30 mins if insufficient pain relief; then one or two single doses of 400, 600, 800, 1200 or 1600mcgs until successful BTCP treatment ^{†14} (3) 2-week efficacy phase. Six BTP episodes were treated with the identified effective Instanyl/Actiq dose This was followed by 4-week titration phase and 2-week efficacy phase for other product Rescue analgesics were allowed, as needed 45mins (if a second dose of Instanyl was not taken) or 60mins (if a second dose of Instanyl was taken) after administration.	Primary Endpoint (Instanyl n=101; Actiq n=100): Median time to onset of meaningful pain relief: ▪ Instanyl: 10.6 minutes ▪ Actiq: 15.7 minutes Secondary Endpoints: PID₁₀ (mean for all doses [range]): Instanyl: 2.39 (1.63-3.00) Actiq: 1.10 (0.51-1.43) LS mean treatment difference: 1.19 (p<0.001; CI: 1.04, 1.34). PID₃₀ (mean for all doses [range]): Instanyl: 4.54 (3.90-5.08) Actiq: 3.69 (1.99-4.31) LS mean treatment difference: 0.76 (p<0.001; CI: 0.62, 0.90). SPID₀₋₁₅ (mean for all doses (range): Instanyl: 1.77 (1.25-2.14) Actiq: 0.85 (0.40-1.09) LS mean treatment difference: 0.82 (p<0.001; CI: 0.72, 0.92). SPID₀₋₆₀ (mean for all doses (range): Instanyl: 3.85 (3.27-4.33) Actiq: 3.06 (1.83-3.51) LS mean treatment difference: 0.70 (p<0.001; CI: 0.60, 0.80). Median time to 50% reduction in PI score Instanyl: 15 minutes; Actiq: 30 minutes Overall 61% had fastest median time to 50% reduction using Instanyl versus 24.3% using Actiq (p=0.025) (14.8% no difference) Ease of administration: Mean score for Instanyl was 0 (very easy) and for Actiq was 2 (OK) General impression Score at 60 minutes: Mean total Instanyl score: 2.2 Mean total Actiq score: 2.1 (p<0.001; CI: 0.1,0.2) Patient Preference: 77.4% preferred Instanyl and 22.6% preferred Actiq (p<0.001) Number of patients in which Instanyl was considered fastest to meaningful pain relief : ▪ Instanyl/Actiq: 47/71 (66.2%; p=0.009; CI:54, 77) ▪ Actiq/Instanyl: 43/66 (65.2%) (p=0.019; CI: 52.4, 76.5)

BMI: body mass index; BTCP: breakthrough cancer pain; CI: confidence interval; dys: days; ITT: intent-to-treat; LS: least squares; MAO: monoamine oxidase; mcg: micrograms; PI: pain intensity; PID₁₀: pain intensity difference at 10 minutes; PID₃₀: pain intensity difference at 30 minutes; SPID: sum of the pain intensity difference; UK: United Kingdom.

*Treatment for mild background pain includes oral morphine, oxycodone, hydromorphone or transdermal fentanyl for at least one month at a dose equivalent to 60-500mg oral morphine per day or to transdermal fentanyl 25-200mcg/hour. †Successful treatment of one BTCP episode: (1) no need for rescue analgesia (2) a score of ≥2 on the general impression scale by the patient at 60 minutes after start of fentanyl treatment (3) no severe undesirable effects such as pronounced hypoventilation, unacceptable sedation or drowsiness

Appendix 2. Additional Health Economic Model Information

Table 2A. Health economic model detail²

Base Case Model		Appropriate?
Comparator(s)	Primary analysis: Fentanyl intranasal spray compared against fentanyl lozenges (Actiq®) Secondary analysis: Fentanyl intranasal spray (Instanyl) compared against fentanyl lozenges (Actiq®), fentanyl buccal tablets (Effentora®) and fentanyl sublingual tablets (Abstral®)	Yes – as requested by WMP. The licensed indication for fentanyl intranasal spray does not limit its use to those situations where oral morphine is not an alternative. Therefore, the economic evidence that is presented relates to a sub-set of the licensed indication.
Population	Hypothetical population of adults with cancer pain, experiencing 1-4 BTCP episodes per day	Yes – population meets licensed indication
Model type and description	Decision analytic model to represent the course of pain intensity associated with BTCP, based on pain intensity scores over the duration of each episode. Assumptions in the base case: - Patients experience 3 BTCP episodes requiring treatment per day for 96 days each year - All BTCP episodes are of 60mins or less - Treatment benefit for each formulation is constant - Resource use is linearly related to the combined duration and intensity of the BTCP episode	Model type appears adequate, but there are some limitations to the assumptions employed (see Section 7.4)
Perspective	Considers direct medical costs only, from perspective of NHS Wales	Yes
Time Horizon	One year	Yes – as most patients have limited life remaining and this treatment does not offer any survival benefit
Discount rate	N/A	Not applicable due to short time horizon of analysis
Efficacy	Primary analysis: Based on post hoc analysis of secondary endpoint data from the head-to-head trial of the intranasal and lozenge formulations. Secondary analysis: Based on indirect data derived from a mixed treatment comparison using available active and placebo-controlled trials identified in a structured literature search.	Primary analysis: Yes – but note limitations of post hoc analysis of secondary endpoint data (see Section 7.4) Secondary analysis: Yes – in the absence of alternative data, but acknowledge limitations of indirect comparisons (see Section 7.4)
Adverse effects	Not included in the model on the basis that the active compound in each of the formulations is the same.	The available safety data do not suggest meaningful differences in adverse events between the intranasal and lozenge formulations (see section 5.2)
Utility values	Obtained from an elicitation study conducted in members of the general population using time trade-off methods.	Yes in the absence of other sources. The submission describes an appropriate approach to utility value elicitation.
Resource use	Based on assumptions and expert opinion.	Not a robust method and potentially liable to biases.
Costs	Based mainly on published unit costs and BNF	Yes
Model Provided?	No	Not possible to verify model inputs and outputs
Other considerations		