



**North East Treatment
Advisory Group**

**Novel oromucosal
(Abstral®, Effentora®)
and nasal (Instanyl®) fentanyl
for breakthrough pain
associated with cancer:**

**Updated appraisal including
nasal fentanyl (PecFent®)**

Author: William Horsley
Lead Pharmacist for NETAG
July 2011
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Summary

- NETAG has previously not recommended use of the novel fentanyl products Abstral®, Effentora® and Instanyl®. The group gave an undertaking to re-appraise these products with respect to any new clinical evidence and clinical experience. In addition, another novel fentanyl product, PecFent®, has become available and is also appraised.
- The products being considered include two oromucosal tablets (one sublingual [Abstral®] and one buccal [Effentora®]) and two nasal sprays (Instanyl® and PecFent®). In-line with the general conclusion of the previous appraisal, the clinical evidence demonstrates that they each provide effective and rapid analgesia. However, dose titration is complex and there is a high drop-out rate during this phase (~25%). In addition, only two the nasal sprays have been evaluated against active comparators and in both cases these were less commonly used opiates for breakthrough cancer pain. None have been compared with the most commonly used opiate for breakthrough cancer pain; morphine oral solution.
- No unexpected or unusually high frequency of adverse effects was observed in clinical studies. Adverse effects were generally mild or moderate in severity and consisted primarily of those common to other opiates such as drowsiness, nausea, vomiting, and constipation.
- There were small rates of local adverse reactions relating to the mode of administration however in the absence of direct comparisons between the products it is not possible to confirm apparent differences between them.
- Fentanyl products are substantially more costly compared with other opiates commonly used for breakthrough pain. All are similarly priced at about £5 to £6 per dose or episode. Only Instanyl® is licensed for repeat dosing of the same pain episode and it has a greater estimated mean cost per pain episode.
- Primary and secondary care prescribing audit data has demonstrated low levels of use of the novel fentanyl products within NHS North East and therefore overall good compliance with the NETAG recommendation of October 2009.
- Due to their mode of administration and perceived more rapid analgesic effect these novel fentanyl products may be particularly useful for specific patient groups or therapeutic scenarios.

Introduction

In September 2009 the North East Treatment Advisory Group conducted an appraisal of novel fentanyl formulations (Abstral®, Effentora® and Instanyl®) at the request of the Palliative Care Clinical Group of the North East Cancer Network. ¹ The appraisal considered the use of these products within their licensed indications for breakthrough pain associated with cancer. NETAG subsequently issued a recommendation in October 2009 that these products are not used within NHS North East. ² The Palliative Care Clinical Group has requested reconsideration of this recommendation on the basis of the availability of new evidence since and on the submission of audit data from their own experiences of using these novel fentanyl products. In addition, the group has requested that NETAG also consider PecFent®, another nasal fentanyl preparation, in the updated appraisal. This appraisal report should be considered in conjunction with the earlier NETAG appraisal report. ¹

Clinical evidence including safety

Abstral®

Four additional studies were identified involving Abstral® in breakthrough pain associated with cancer. ³⁻⁶

The first was a small limited-dose study in 27 patients with metastatic cancer already on background opiate analgesia but still experiencing ≥ 4 episodes of breakthrough pain in a 14-day period. Each patient received treatment for four day-time episodes of breakthrough pain with a random sequence of sublingual fentanyl 100, 200 and 400 micrograms and placebo. The trial was double-blind with respect to the actual sequence of tablets. Twenty-three patients used all four doses and four patients received less than four doses. The primary outcome was the difference between doses in pain score measured on a 100 mm visual analogue score at a range of time points from 5 to 30 minutes. The difference was statistically significant only between the 400 microgram dose and placebo and then only at time points between 15 and 30 minutes ($p \leq 0.02$). The overall treatment effect (any dose of fentanyl vs. placebo) was significantly in favour of fentanyl ($p = 0.027$) however at no time point did the difference in mean pain scores meet the predefined clinically significant threshold of 20 mm with the maximum differential being < 11 mm. The study results were characterised by a relatively high placebo effect. ³

Fifteen adverse effects were experienced by 13 patients, with only three considered related to study treatment (moderate nausea/vomiting and mild dizziness). ³

A larger and longer-term study was conducted in adult patients with stable cancer-related pain managed with opiate therapy but who were still experiencing between 1 and 4 episodes of breakthrough pain per day. 131 patients entered a dose-titration phase with 78 completing, of whom 66 entered a double-blind efficacy phase which 60 completed. 12 patients went straight from the titration phase to a follow-up safety phase which, combined with the 60 efficacy phase completers, provided a follow-up phase population of 72. During the efficacy phase patients received a random sequence of 10 doses of study medication including 7 fentanyl and 3 placebo doses. The primary efficacy outcome was the sum of pain score differences measured at 10, 15 and 30 minutes after taking a dose. Pain scores were measured on an 11-point scale ranging from 0 (no pain) to 10 (maximum pain). The fentanyl and placebo scores at 30 minutes were 49.5 and 36.6 points respectively (difference 12.9 points, $p < 0.001$). The active treatment effect was maintained at 60 minutes (143.0 vs. 104.5 points, difference 38.5 points, $p < 0.001$). Overall median treatment duration was 51 days.⁴

The overall safety population consisted of those exposed to at least one dose of study drug ($n = 131$) with 73% experiencing at least one treatment-emergent adverse effect and 43% of these experiencing an adverse reaction that was considered possibly or probably related to study medication. The most common adverse reactions were nausea (12%), vomiting (5%) and tiredness (5%). Only one patient experienced oral effects which were considered to be related to Abstral®. Seventeen patients discontinued treatment due to effects considered related to study medication. No fatalities were considered related to study medication. Results of the follow-up phase ($n = 72$, median treatment duration 162 days, 52 patients treated ≥ 3 months) are not reported separately.⁴

Another large long-term study was conducted in a similar population of adult patients with cancer on stable opiate pain relief but still experiencing 1 to 4 episodes of breakthrough pain per day. Enrolment ceased after the 'effectiveness and tolerability profiles of the study medication [had been characterised]'. Consequently, 139 patients entered the titration phase with 96 completing, all of whom entered a 12-month maintenance phase which 19 completed. This was a non-randomised open-label study in which all patients received active treatment. Effectiveness was assessed using quality-of-life and patient satisfaction measures and demonstrated generally stable effects on various aspects of quality-of-life. In terms of patient satisfaction with medication, there was a clear trend towards greater satisfaction with study medication compared with medication prior to the study.⁵

One-hundred and thirty-nine patients received at least one dose of study medication and form the primary safety population with 84% experiencing at least one adverse effect during the study. The most common effects were nausea (23%), fatigue (15%) and vomiting (13%). Thirty-five per cent of patients reported

adverse effects considered related to study medication with the most common being nausea, constipation and tiredness (each < 10%). Twenty-seven per cent of patients withdrew due to adverse event with the most common being nausea. Of the 96 patients who entered the follow-up phase (median duration 149 days, 65% \geq 3 months), 87 (91%) experienced at least one adverse effect. No serious adverse effects were considered related to study medication. There were no instances of oral adverse effects considered related to study medication.⁵

A non-comparative study from Germany reports outcomes relative to pre-treatment with Abstral® using a 28-day observation period in patients initiated on Abstral® and receiving background opiate therapy for cancer pain. Of 217 enrolled patients, 181 completed the observation period and associated clinical visits. Only 83 patients had prior use of other opiate therapy for breakthrough pain. The size of population on which efficacy outcomes are based is not clear. Nonetheless, mean pain score (11 point scale, range 0 to 10) decreased from 7.8 at baseline to 2.6 after treatment with Abstral® ($p < 0.001$). Time to first analgesic effect was \leq 10 minutes for 83% of episodes and time to maximum effect was \leq 30 minutes for 63% of episodes. Of the patients with prior breakthrough opiate experience, the majority (\geq 85%) reported that Abstral® was better for each of; speed of action, strength of action, duration of action, tolerability, and ease of handling. At study end 151 patients (84% of completers) chose to continue with Abstral®. Quality of life measures focusing on pain, disability, depression and anxiety all demonstrated substantial and significant improvements after treatment with Abstral® compared with baseline. The median number of doses of Abstral® used per day was one (range 0 to 8, mean 1).⁶

Of 217 enrolled patients, 33 (15%) experienced at least one adverse effect during the observation period, for whom 12 (6%) were considered related to Abstral®. The most common treatment-related adverse effects were nausea, tiredness, dizziness and vomiting (each < 3%). No deaths were considered related to Abstral®.⁶

Effentora®

The only relevant new published data identified for Effentora® both relate to the two pivotal populations previously reported.^{1 [ref 15,16]}

The first is an open-label extension study which included 120 patients from the pivotal efficacy studies plus an additional 77 patients who were successfully titrated to an effective dose using the same protocol. Only 42 patients (21%) remained in maintenance treatment for ≥ 12 months. Most discontinuations ($n = 55$) were due to adverse effects ($n = 70$) with the majority unrelated to study medication. Three patients discontinued due to lack of efficacy. There were 60 fatalities, all of which were considered related to the underlying cancer. One serious adverse effect was considered related to study medication; drug withdrawal syndrome. The most common adverse effects during the maintenance phase were: nausea (32%), vomiting (24%), fatigue (18%), peripheral oedema (15%), anaemia (15%), and constipation (15%). Overall, 93% of patients reported at least one adverse effect. Most patients remained on their initial dose although there was a trend towards higher doses during the maintenance phase. Fifteen patients (6% of all exposed patients including titration) reported application site adverse effects, all of which were considered to be related to study medication.⁷

The other new source of data for Effentora® is a combined analysis of the two pivotal efficacy studies (combined $n = 150$). The general conclusion is inline with those of the separate placebo-controlled studies, with Effentora® demonstrating superior efficacy to placebo. The combined analysis is useful inasmuch that single outputs are generated for each outcome. For example the proportion of patients with a ≥ 2 point improvement in pain score (measured on an 11-point scale) at 30 minutes was 59% with fentanyl and 36% with placebo, and 74% and 44% respectively at 45 minutes ($p < 0.001$). The most common adverse effects were nausea (17%), dizziness (17%), headache (10%), fatigue (10%), vomiting (8%) and constipation (7%). Application site reactions were observed in 18 patients resulting in discontinuation in three.⁸

In addition, an in-house indirect comparison of Effentora® with Actiq® and Abstral® found similar cumulative pain intensity score differences at 15 and 30 minutes between all three products. At 45 and 60 minutes Effentora® was superior to Abstral® which was in turn superior to Actiq®. A probabilistic sensitivity analysis which included comparison with oral morphine found that Effentora® was more likely to provide superior pain relief compared with all comparators. The methodology appears sound although the analysis has not been published.⁹

Instanyl®

Two additional published studies were identified regarding Instanyl®. ^{10,11}

The first was an open-label active-comparator crossover study which was reported in the previous appraisal report and referred to as study 019. ^{1 [ref 18,21,22]} The results reported previously are supported by the publication and in addition further analyses are provided. Efficacy was based on 101 patients for Instanyl® and 100 for the comparator group, fentanyl citrate lozenges (Actiq®). The difference between pain scores at 10 minutes was 1.19 ($p < 0.001$), 0.76 points at 30 minutes ($p < 0.001$). The results demonstrated a drastically faster onset of action with intranasal fentanyl compared with fentanyl lozenges, for example the proportion of patients with a reduction in pain score $\geq 33\%$ from baseline was 25% vs. 7% at five minutes and 51% vs. 24% at 10 minutes respectively (both $p < 0.001$). Patients reported a strong preference for treatment with intranasal fentanyl compared with fentanyl lozenges (77% vs. 23% respectively). 90% of patients reported that intranasal fentanyl was 'easy' or 'very easy' to use compared with 40% for the lozenges. 8% of intranasal fentanyl doses were supplemented with rescue medication compared with 5% of fentanyl lozenge doses. ¹⁰

As with the efficacy results the safety data concur with that reported in the previous appraisal report with some additional data provided. The most common potentially treatment-related adverse effects were (intranasal vs. lozenge respectively); nausea (8.2% vs. 7.6%), vomiting (4.9% vs. 3.4%), constipation (4.1% vs. 3.4%) and diarrhoea (3.3% vs. 2.5%). The majority of adverse effects were considered unrelated to study medication. There was one report of bilateral nasal ulceration in a patient who had used intranasal fentanyl with resolution after treatment discontinuation. ¹⁰

The other important source of new data regarding Instanyl® is a systematic review including indirect comparisons of efficacy vs. fentanyl lozenges (Actiq®), fentanyl buccal tablets (Effentora®) and standard morphine tablets. Six studies met the inclusion criteria for indirect comparison which were based on consistency of efficacy outcomes, patient characteristics and study design. The review was sponsored by the manufacturer of Instanyl®. Outcomes focused on the difference in pain score (11 point range) at specific time points and demonstrated that Instanyl® provided a faster reduction in pain score compared with all other comparators (including placebo). For example at 15 minutes after dose administration reductions in mean pain scores were 1.2 points greater compared with Effentora®, 1.3 points greater compared with Actiq® and 1.7 points greater compared with oral morphine (all $p < 0.05$). Although the difference was diminished at later time points (30, 45 and 60 minutes post-dose) Instanyl® remained the most effective treatment at those points (difference not significant vs. active comparators from 45 minutes). ¹¹

PecFent®

PecFent® is an intranasal fentanyl preparation licensed for the management of breakthrough pain in adults already receiving maintenance (background) opiate therapy for chronic cancer pain.¹² It became available in the UK in November 2010 and is available in bottles containing sufficient for eight sprays of either 100 or 400 micrograms of fentanyl.¹³ Each bottle costs £30.40¹⁴ equivalent to £3.80 per spray or between £3.80 and £7.60 per episode of breakthrough pain.

Clinical evidence and safety

The pivotal study demonstrating the efficacy of PecFent® is a phase III randomised double-blind placebo-controlled crossover study in patients with chronic cancer pain still experiencing 1 to 4 episodes of breakthrough pain per day despite background opiate therapy. An effective dose was identified following a dose titration phase (n = 114). Patients (n = 83) then received 10 doses of study medication containing a random sequence of 7 active and 3 placebo doses. The primary outcome measure was the mean sum of the difference between baseline and post-dose pain scores (11 point scale) at various time points (5, 10, 15 and 30 minutes post-dose) per patient. The primary outcome results were 6.57 points with PecFent® and 4.45 points with placebo (difference 2.12 points, p < 0.001). The proportion of episodes that achieved a ≥ 2 point reduction in pain intensity (11 point scale) was significantly greater than placebo at all time points from 10 to 60 minutes post-dose. For example, 33% vs. 25% at 10 minutes post-dose, 66% vs. 40% at 30 minutes post-dose and 76% vs. 49% at 60 minutes post-dose. Additional rescue medication was used in 9.4% of fentanyl episodes and 20% of placebo episodes within 60 minutes of study dose medication. Patients were more satisfied with the overall use of PecFent® and with the speed of onset and reliability compared with placebo (p < 0.001). About 70% of patients were 'satisfied' or 'very satisfied' with the ease of use and convenience of PecFent®. At the end of the study 87% of patients opted to continue using PecFent® in an open label extension study.^{15,16}

Treatment-emergent adverse events within 24 hours of last study dose were more common with PecFent® than placebo with 51% of PecFent® episodes and 5% of placebo episodes reporting any adverse event. The most common adverse events with PecFent® were vomiting (11%), nausea (9%), dizziness (8%), disease progression (4%), and nose bleed (4%). Nine patients discontinued treatment due to adverse events. No fatalities were linked to use of study medication. Nasal tolerability across 10 symptoms was assessed separately and demonstrated little change from pre-study medication use. Where symptoms were experienced, severity was always mild or moderate with none reporting severe symptoms.^{15,16}

A more recent publication reports the efficacy of PecFent® compared with encapsulated morphine tablets in a double-dummy double-blind randomised study. Patients were similar to those in other studies of breakthrough analgesia in cancer, having stable cancer-related pain managed with background opiates but still experiencing 1 to 4 episodes of breakthrough pain per day. Patients (n = 106) were titrated to an effective dose of PecFent®. Those successfully titrated (n = 84) were then treated with a random sequence of five PecFent® plus placebo capsules and five morphine doses plus placebo nasal spray. The primary outcome measure was the mean per patient difference in pain score (11 point scale) at 15 minutes post-dose. Efficacy results have not yet been fully reported. The difference in primary outcome was significantly in favour of PecFent® (p = 0.04). Other efficacy outcomes related to the speed of onset and demonstrated faster onset of pain relief with PecFent® than with morphine (onset of pain relief in 58% of pain episodes at five minutes and 98% at 30 minutes with PecFent®, both p < 0.05 vs. morphine). The proportion of patients with ≥ 2 point reduction in pain score compared with pre-dose was (PecFent® vs. morphine respectively); 25% vs. 23% at 5 minutes post-dose (p > 0.05), 52% vs. 45% at 10 minutes (p < 0.05), 76% vs. 69% at 15 minutes (p < 0.05) and > 80% for both preparations at 30, 45 and 60 minutes (each p > 0.05). The proportion of episodes which required additional rescue medication was 3% with PecFent® and 4% with morphine.^{17,18}

Patient acceptability and satisfaction was also assessed using a 4 point scale (range 1 to 4, higher score representing greater satisfaction). The mean score for satisfaction with 'speed of relief gained with the nasal spray' was 2.92 with PecFent® and 2.62 with morphine (p ≤ 0.01) measured at 30 minutes, and 3.01 vs. 2.72 (p ≤ 0.01) respectively measured at 60 minutes. Satisfaction with the overall acceptability and convenience of the nasal spray was high (~ 80%) with 70% of patients opting to continue therapy with PecFent® in an open-label extension study.¹⁷

More patients experienced adverse events following treatment with active PecFent® than active morphine (actual data not published). Most adverse events were mild to moderate in severity. Six patients discontinued treatment following treatment of their most recent episode with PecFent® compared with two discontinuing following use of morphine.¹⁷

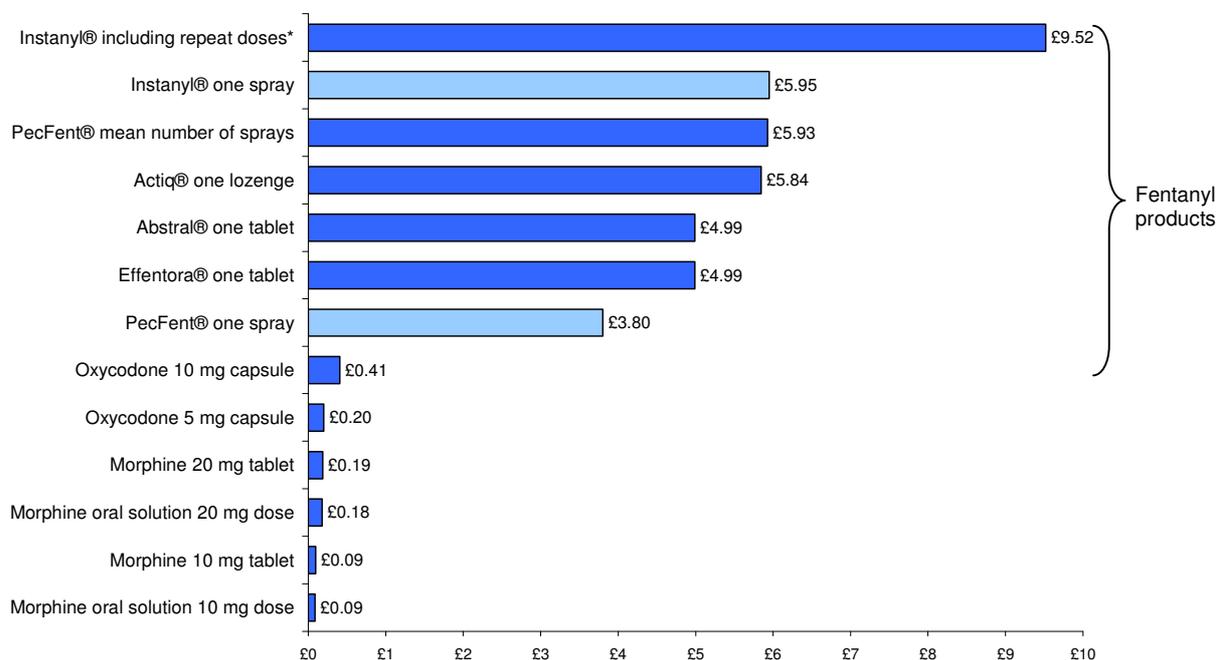
Nasal tolerability was assessed separately both objectively by clinicians and subjectively by patients. Objective assessment identified only a few adverse effects both before and after use of nasal sprays with no obvious causal links. Subjective assessment was made across ten nasal-specific symptoms with no significant differences between PecFent® or morphine active treatment episodes.¹⁷

Longer-term follow-up with PecFent® was reported in a 16-week study of 356 patients¹⁹ including 122 patients from the two other studies previously reported.¹⁵⁻¹⁷ Only 110 patients completed the 16 weeks with most premature discontinuations due to study closure (n = 95) or death (n = 59). The study was designed to collect data on safety and tolerability and not efficacy parameters and included 403 patients as titration failures were also included. One-quarter of patients experienced adverse events considered to be related to study treatment although not necessarily PecFent® as background and rescue analgesia was also in use. The most common adverse effects were those typical of opiates such as dizziness, vomiting, constipation, tiredness and nausea. Nasal effects were separately investigated (n = 312) and found that the majority of patients did not experience any nasal symptoms (> 85% for each individual symptom). Only six nasal symptom reports were categorised as severe, with most categorised as mild. Rescue medication was required for 6% of episodes during the treatment phase (i.e. excluding the titration phase).¹⁹

Cost analysis for PecFent®

PecFent® is available in bottles containing sufficient for eight sprays of either 100 or 400 micrograms of fentanyl. Each bottle costs £30.40 equivalent to £3.80 per spray. Thus each dose per episode of breakthrough pain will cost between £3.80 and £7.60 depending on the number of sprays required for the dose.¹⁴ Using a weighted mean dose derived from the pivotal phase III study of PecFent®¹⁵ the mean cost per dose is estimated at £5.93. Figure 1 demonstrates the cost per dose for a range of opiate medicines licensed or otherwise commonly used for the management of breakthrough pain in cancer.

The main advantage that PecFent® appears to offer against oral morphine is more rapid analgesia as it has demonstrated superior analgesic efficacy only at specific time points.^{17,18} However the most commonly used formulation for breakthrough pain in the UK is oral morphine solution which might reasonably be expected to result in more rapid drug absorption than encapsulated morphine tablets. Therefore, on current evidence, it is not possible to conclude that PecFent® is superior to all commonly used morphine formulations including oral morphine solution.

Figure 1. Costs of various opiate medicines used for breakthrough pain ¹³

Key: Light blue bars represent single dose costs however each has a corresponding dark blue bar representing mean cost per episode based on dose frequencies from clinical studies. Doses do not imply therapeutic equivalence.

* : Mean cost per episode for Instanyl® is based on an estimate of 60% of episodes treated with a second (repeat) dose. ^{20,21} However it is not clear whether this rate also includes dose titration phases. Estimates from Nycomed (UK) indicate that mean cost per episode excluding titration phases is about £6.50. ²²

As can be seen in figure 1, all fentanyl preparations are substantially more costly than other non-fentanyl opiates for breakthrough pain, typically being of the order 15 to 60 times more costly per episode.

PecFent® is similarly priced to other fentanyl products licensed for breakthrough pain at a mean cost of about £5 to £6 per dose. The only other nasally administered product (Instanyl®) has a greater estimated mean cost at over £9 per episode although it is not clear whether this includes repeat dosing during titration phases. The other novel fentanyl products (Abstral®, Effentora® and Instanyl®) have not changed in price since the previous appraisal report was published.¹ A range of single-dose Instanyl® nasal spray products has recently been approved and are expected to be available in the UK before the end of 2011, however the price is not yet known. ²³

Instanyl® is the only novel fentanyl product which is licensed for repeat dosing of the same episode of pain. If rescue analgesia is required for the same episode of pain with the other fentanyl products then repeat dosing would represent off-license use.

Prescribing audit

Data removed as potentially commercially sensitive.^{24, 25}

Clinical audit data

Data has been presented from the UK Breakthrough Cancer Pain Registry which was established specifically to collect data on the use of Abstral® in the UK. This demonstrates a successful titration rate of 70% (23 out of 33 patients) which is broadly similar to the rate obtained in clinical studies. Most patients commenced titration with the lowest Abstral® dose of 100 micrograms and most achieved a final dose of 400 or 800 micrograms, broadly in agreement with the prescribing data from NHS North East. Dose titration took between 0 and 18 days (median 4 days and mean 5.1 days). One-third of clinicians rated titration as easy, most rated it as acceptable (55%) with 14% rating it as difficult. These corresponded well to patient assessments (31%, 56% and 13% respectively). Twelve out of 16 patients who stated a preference preferred Abstral® to their previous medication, two preferred their previous medication and two had no preference. Reasons for preference included 'reliable pain relief' (n = 10), 'ease of use' (n = 7), quick pain relief (n = 6), 'less side effects' (n = 5) and 'better taste' (n = 4).²⁶

Guidelines and other recommendations

All four novel fentanyl products (Abstral®, Effentora®, Instanyl® and PecFent®) have been recommended for use within NHS Scotland by the Scottish Medicines Consortium, each restricted to use only when oral morphine preparations are not considered suitable (not otherwise specified).²¹

The All Wales Medicines Strategy Group has recommended Instanyl® only in situations when other standard opiate preparations are considered unsuitable or inadequate.²⁷ The AWMSG has not issued a recommendation regarding Abstral®, Effentora® or PecFent®.

No national guidelines applicable to UK practice which explicitly define the place in therapy for any of the novel fentanyl preparations were identified.

Points to consider

A large amount of additional data regarding the novel fentanyl preparations Abstral®, Effentora® and Instanyl® has been published since the first NETAG appraisal report was completed in September 2009.

Most of the new data pertains to Abstral® which had the least published data available at the time of preparation of the previous report. Data relating to Effentora® only includes a minority of evidence relating to a new patient cohort however it does provide evidence relating to longer-term efficacy and safety and an additional pooled analysis of the pivotal phase III studies. Similarly, the additional data relating to Instanyl® consists of the publication of the pivotal active-comparator study which has permitted further evaluation of efficacy and safety, and an indirect comparison of Instanyl® with other treatments.

Despite this new data, the overall evaluation of these novel fentanyl formulations is still confounded by the absence of any comparisons with the most commonly used opiate preparation for breakthrough pain; oral morphine solution (Oramorph®).

The new data, which provides a greater volume of evidence focused on longer follow-up, is useful in ascertaining the safety profiles of each product. This does not indicate any unexpected or excessive burden of adverse effects. There are some adverse effects which are specific to the product formulation and mode of administration although this is not true for all of the products and has a low incidence where these effects do occur.

The data regarding PecFent®, which wasn't appraised in the first report, demonstrates similar outcomes to that available for the other fentanyl products. PecFent® has been directly compared with oral morphine although not in a presentation that is commonly used for breakthrough pain in the UK. In summary, PecFent® appears to provide effective analgesia more rapidly than placebo and encapsulated morphine tablets with a predictable adverse effect profile.

The evidence indicates that all of these novel fentanyl products experience high drop-out rates during dose titration, often due to the inability to achieve a stable dose or due to adverse effects. This aspect will have a bearing on their practical application with each requiring intensive monitoring and supervision during the titration phase and additional strategies required for those in whom titration is not successful.

These novel fentanyl preparations are most innovative with respect to their mode of administration; two are formulated as nasal sprays (Instanyl® and PecFent®) and two as oromucosally absorbed tablets that don't require swallowing. Both routes of administration negate use of the gastro-intestinal tract and could enable

use in patients with poor or absent swallowing function. However, local application site reactions have occurred and the nasal preparations require a certain level of dexterity and co-ordination which could prove problematic for some patients. Further, use in this patient sub-population has not been specifically investigated with any of these products.

All fentanyl preparations for breakthrough pain are similarly priced at about £6 per episode. Instanyl® may prove to be more costly although it is also the only one licensed for repeat dosing of the same pain episode. Fentanyl products are substantially more costly than other commonly used opiate preparations for breakthrough pain (figure 1). There is no conclusive evidence that any of the new fentanyl products are clinically and meaningfully more effective than non-fentanyl comparators. Where superiority has been demonstrated this only relates to temporal parameters of onset of analgesia, with the differences being small and of uncertain practical significance. In addition, most studies used a placebo comparator and the two active comparators (Actiq® lozenges and encapsulated morphine tablets) are not commonly used preparations for breakthrough pain.

These novel fentanyl preparations are priced within the same bracket as the established fentanyl lozenges, Actiq®, and may represent cost-effective substitutes within the fentanyl class of breakthrough analgesia. However, if fentanyl breakthrough analgesia was to demonstrate similar growth vs. other opiates as has been observed with fentanyl transdermal patches,²⁸ then the cost of managing breakthrough pain could increase substantially without evidence of meaningful clinical benefit.

Outside of dose titration or adjustment, only Instanyl® is licensed for repeat dosing for the same pain episode, at a minimum interval of 10 minutes. In order to remain within the product license, the other novel fentanyl preparations would require additional rescue analgesia for the same episode. Rates of use of rescue analgesia in clinical studies were 11% with Abstral®, 17% with Effentora®, and 6 to 9% with PecFent®. Rescue analgesia was used in about 8% of Instanyl® episodes too although it is not clear if repeat dosing was permitted in the studies.

PecFent® and Instanyl® nasal sprays both have a shelf-life of up to two years. However PecFent® should be discarded if it remains unused for any five consecutive day period, or once it is more than 14 days, since the product was first used.¹²

Evidence relating to use within NHS North East indicates good compliance with the negative NETAG recommendation of October 2009 although it is not known what level of usage there might have been in the absence of that recommendation. In addition, the primary care prescribing data is cumulative and concatenated and therefore temporal trends and small area variations are not observed.

References

1. Horsley W. Noval oramucosal (Abstral®, Effentora®) and nasal (Instanyl®) fentanyl for breakthrough pain associated with cancer. NHS North East Treatment Advisory Group, September 2009 www.netag.nhs.uk
2. NHS North East Treatment Advisory Group. Treatment appraisal: Decision summary for Novel oramucosal (Abstral®, Effentora®) and nasal (Instanyl®) fentanyl for breakthrough pain associated with cancer. October 2009 www.netag.nhs.uk
3. Lennernas B, Frank-Lissbrant I, Lennernas H et al. Sublingual administration of fentanyl to cancer patients is an effective treatment for breakthrough pain: results from a randomized phase II study. *Palliative Medicine* 2010;24(3):286-93
4. Rauck RL, Tark M, Reyes E et al. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. *Current Medical Research and Opinion* 2009;25:2877-85
5. Nalamachu S, Hassman D, Wallace MS et al. Long-term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain. *Current Medical Research and Opinion* 2011;27:519-30
6. Uberall MA, Muller-Schwefe GHH. Sublingual fentanyl orally disintegrating tablet in daily practice: efficacy, safety and tolerability in patients with breakthrough cancer pain. *Current Medical Research and Opinion* 2011;27(7):1385-94
7. Weinstein SM, Messina J, Xie F. Fentanyl buccal tablet for the treatment of breakthrough pain in opiate-tolerant patients with chronic cancer pain: A long-term, open-label safety study. *Cancer* 2009;115:2571-9
8. Zeppetella G, Messina J, Xie F, Slatkin NE. Consistent and clinically relevant effects with fentanyl buccal tablet in the treatment of patients receiving maintenance opiate therapy and experiencing cancer-related breakthrough pain. *Pain Practice* 2010;10(4):287-93
9. Cephalon (UK), June 2011.
10. Mercadante S, Radbruch L, Davies A 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;25:2805-15
11. Vissers D, Stam W, Nolte T et al. Efficacy of intranasal fentanyl spray versus other opiates for breakthrough pain in cancer. *Current Medical Research and Opinion* 2010;26:1037-45
12. PecFent® (Archimedes Pharma). Summary of product characteristics (version 21/03/2011). www.medicines.org.uk
13. *Pharmaceutical Journal* 2010;285:575
14. NHS dictionary of medicines and devices. May 2011. www.dmd.nhs.uk
15. Portenoy RK, Burton AW, Gabrail N et al. A multicenter, placebo-controlled, double-blind, multiple-crossover study of fentanyl pectin nasal spray (FPNS) in the treatment of breakthrough cancer pain. *Pain* 2010;151:617-24
16. Taylor D, Galan V, Weinstein SM et al. Fentanyl pectin nasal spray in breakthrough cancer pain. *Journal of Supportive Oncology* 2010;8:184-90

17. Davies A, Sitte T, Elsner F et al. Consistency of efficacy, patient acceptability, and nasal tolerability of fentanyl pectin nasal spray compared with immediate-release morphine sulphate in breakthrough cancer pain. *Journal of Pain and Symptom Management* 2011;41(2):358-66
18. Fallon M, Gatti A, Davies A et al. Fentanyl pectin nasal spray provides clinically meaningful pain relief and a more rapid onset of analgesia compared with immediate-release morphine sulphate in breakthrough cancer pain. *Palliative Medicine* 2010;24:S24. Abstract.
19. Portenoy RK, Raffaelli W, Torres LM et al. Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioid-tolerant patients. *Journal of Opioid Management* 2010;6(5):319-28
20. European Medicines Agency. Assessment report for Instanyl. Ref EMEA/H/C/959. July 2009
21. Scottish Medicines Consortium. Various SMC advice.
www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/DrugsBySubCategory?term=4.7%20Analgesics
22. Personal communication, Nycomed UK, July 2011 (ref INS-964-11)
23. www.inpharm.com/news/161511/nycomed-europe-cancer-pain-spray-instanyl-fentanyl
Accessed 4th July 2011
24. Data on file. NHS Regional Drug and Therapeutics Centre (Newcastle). May 2011.
25. Andrew I. Novel fentanyl preparations: Regional data collection. May 2011.
26. Ward J, Laird B, Fallon M. The UK breakthrough cancer pain registry: Origin, methods and preliminary data. *BMJ Supportive and Palliative Care* 2011;1(S1):A24
[Additional data from copy of actual poster presentation]
27. All Wales Medicines Strategy Group. Final appraisal report: Fentanyl (Instanyl®), Nycomed UK Ltd. Advice No: 0710 – April 2010.
www.wales.nhs.uk/sites3/Documents/371/fentanyl%20%28Instanyl%29%20FAR1.pdf
28. NHS Regional Drug and Therapeutics Centre (Newcastle). Drug Update number 63: Opioid analgesia in cancer. February 2009. www.nyrdtc.nhs.uk/docs/dud/DU_63_OPIOID.pdf

Author's declaration: The author has participated in an advisory board for the manufacturer of one of the novel fentanyl products although not concerning the fentanyl product.