

fentanyl 100microgram/dose and 400microgram/dose nasal spray solution (PecFent[®]) SMC No. (663/10)

Archimedes Pharma

17 December 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

fentanyl nasal spray (PecFent[®]) is accepted for restricted use within NHS Scotland.

Indication under review: management of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic cancer pain.

SMC restriction: restricted to use in patients unsuitable for short-acting oral opioids, as an alternative to other fentanyl preparations.

Fentanyl pectin nasal spray offers an advantage in the time to onset of pain relief and reduction in pain intensity of breakthrough pain compared with placebo and immediate release morphine sulphate. Indirect comparison indicates broadly comparable efficacy to an oral transmucosal fentanyl formulation and an existing fentanyl nasal spray.

Prescribers should be aware of the differing absorption and elimination characteristics of the available nasal fentanyl preparations; doses are not interchangeable.

Overleaf is the detailed advice on this product.

**Chairman
Scottish Medicines Consortium**

Indication

Management of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of pain that occurs on a background of otherwise persistent pain.

Patients receiving maintenance opioid therapy are those who are taking at least 60mg of oral morphine daily, at least 25microgram of transdermal fentanyl per hour, at least 30mg of oxycodone daily, at least 8mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Dosing Information

Initially 100microgram intranasally and titrated to an effective dose that provides adequate analgesia without causing undue (or intolerable) adverse reactions. Doses may be taken every four hours to a maximum of four doses per day. Treatment should be initiated by and remain under the supervision of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential for abuse of fentanyl.

Product availability date

6 October 2010

Summary of evidence on comparative efficacy

This preparation contains fentanyl in a pectin-based gel that is administered intranasally for breakthrough cancer pain (BTCP). It is the second fentanyl nasal spray marketed in the UK for this indication. The manufacturer has requested that SMC consider the use of the preparation in patients unsuitable for short-acting oral opioids (e.g. oral morphine) and used as an alternative to other fentanyl preparations.

In a phase III crossover study 83 adults, who had an average of one to four BTCP episodes per day while receiving daily opioid equivalent to at least 60mg oral morphine, successfully completed an open-label dose titration phase and were randomised to double-blind fentanyl nasal spray or placebo to treat up to ten episodes of BTCP, with a maximum of four doses per day and at least four hours between doses i.e. re-dosing was not permitted. The patient's usual medication for BTCP could be taken as rescue medication if pain relief was inadequate 30 minutes after study drug or another episode of BTCP occurred within four hours. The primary efficacy endpoint was summed pain intensity difference (SPID) from baseline over 30 minutes post-dose, with pain intensity measured on an 11-point numeric rating scale (0=no pain to 10=worst possible pain) and where a difference of at least two points would be judged clinically important. This was assessed via analysis of covariance in a modified intent-to-treat population (mITT) comprising all randomised patients with at least one active- and one placebo-treated evaluable episode. Mean SPID over 30 minutes post-dose for BTCP episodes treated with fentanyl nasal spray was significantly greater than those treated with placebo, 6.57 versus 4.45. There were also significant effects on secondary endpoints, including, SPID at other time points, pain intensity difference, rescue medication use (9.4% versus 20% of episodes at 60 minutes) and response analysis (76% versus 48% of episodes at 60 minutes), where response is a reduction in pain intensity of at least 2 points.

In a similarly designed phase III crossover study, 84 adults, who had an average of one to four BTCP episodes per day while receiving daily opioid equivalent to at least 60mg oral morphine, successfully completed an open-label dose titration phase and were randomised to double-blind fentanyl nasal spray or immediate release morphine sulphate for BTCP to a maximum of four episodes per day. Patients were requested not to take rescue medication within 30 minutes of study drug, however, five patients in the fentanyl nasal spray group took rescue medication in this period. The primary efficacy endpoint, pain intensity difference (PID) from baseline at 15 minutes post-dose, was assessed via analysis of covariance in a mITT population, as defined for the previous study. Mean PID at 15 minutes post-dose for BTCP episodes treated with fentanyl nasal spray was significantly greater than those treated with immediate release morphine sulphate, 3.02 versus 2.69. There were significant effects on PID at other timepoints, but there were no consistent significant differences between treatments for SPID or response analyses. Rescue medication use was similar in both groups (3.0% and 3.8% of episodes at 60 minutes, respectively).

Summary of evidence on comparative safety

The adverse effect profile is typical of an opioid analgesic. The European Medicines Agency noted that issues pertaining to dosage forms with rapid increases in plasma concentrations of opioids are known and that there were no specific concerns with this formulation. Objective and subjective nasal tolerance assessments undertaken systematically did not reveal any clinically significant effects that would limit the use of this formulation.

Summary of clinical effectiveness issues

Only patients who achieved an effective dose during the open-label titration phase entered the double-blind treatment phase of the studies. The treatment effect and response rates observed in the studies may therefore be greater than those in practice.

A Bayesian indirect comparison, and a supporting Bucher analysis, of fentanyl nasal spray and oral transmucosal fentanyl citrate (OTFC) were provided to support the assumption of their comparable efficacy. These only included studies with placebo or immediate release morphine sulphate as comparators, omitting studies with other active comparators, for example fentanyl nasal spray (Instanyl®) versus OTFC. The outcome of the indirect comparisons showed considerable overlap of credible limits of the weighted mean pain intensity difference at 30 minutes between the two formulations. There were baseline differences in pain intensity across the studies, which were higher in the fentanyl nasal spray studies (6.9 to 7.8) compared to the OTFC studies (5.9 to 6.9). However, it is considered that adjusting for this difference would not alter the conclusion of the indirect comparison that there is no difference in efficacy between the two fentanyl formulations.

There are no direct comparative data with the other fentanyl nasal spray, Instanyl®.

The nasal route of administration may be preferable to patients with reduced saliva production who would experience difficulties with oral transmucosal administration of fentanyl.

The titration schedule is 100microgram, 200microgram, 400microgram then 800microgram, which can be administered by one or two doses of the available 100microgram and 400microgram per dose formulations. Compared to alternative fentanyl preparations (Effentora®, Abstral® and Actiq®) that are available in a greater variety of evenly priced dose formulations, there is less scope to vary dose at a fixed cost.

Differences may exist in absorption and elimination characteristics between immediate-release fentanyl preparations and doses are not interchangeable. When switching to fentanyl nasal spray (PecFent) from another immediate-release fentanyl preparation, including intranasal formulations, the patient should be titrated to an effective dose via the recommended titration schedule and not switched on a dose-for-dose basis.

Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis comparing fentanyl nasal spray with OTFC in patients experiencing breakthrough cancer pain who are unsuitable for other short acting oral opioids (e.g. oral morphine) as an alternative to other fentanyl preparations. The analysis was conducted over a 6-month time horizon which seems appropriate given the patient population. A Bayesian network analysis and two separate indirect comparisons using the Bucher method (using oral morphine and placebo as common comparators and described above) were provided to demonstrate comparable efficacy of fentanyl nasal spray and OTFC.

Costs in the model included drug acquisition costs, titration costs (which included additional prescriptions, wasted preparations plus visits to a doctor), re-dosing and rescue medication costs. The cost per dose of fentanyl nasal spray was based on the percentage of patients on each dose from the trial, resulting in an average of 1.5 doses per patient at an average cost of £5.71 per dose. The pricing structure of OTFC is such that the cost per dose does not vary with a cost of £5.84 per dose.

In the base case analysis the manufacturer estimated savings of £1,080 per patient over a 6-month period. This included savings from reduced drug acquisition, rescue medication and titration costs but was largely due to the different assumptions applied in relation to re-dosing requirements. Using drug costs alone the savings were estimated to be £71 per patient, assuming no re-dosing, rescue medication or titration costs.

The following weaknesses were noted:

- Other forms of fentanyl are available including another intranasal preparation that could be considered an appropriate comparator. The manufacturer did not provide such a comparison as part of their original submission but subsequently provided a secondary analysis where an alternative fentanyl nasal spray was used as the comparator. This suggested that, although the comparator fentanyl nasal spray was possibly more effective than the pectin-based fentanyl nasal spray under consideration in this submission, it was also more expensive and according to the relative cost-effectiveness ratio would not be a cost-effective use of resources
- An indirect comparison was conducted which showed that fentanyl nasal spray and OTFC have comparable efficacy. However, there were some potential weaknesses with the indirect comparison including the possible exclusion of some relevant studies from the network analysis. For example, the study comparing the other fentanyl nasal spray

with OTFC was excluded on the basis that it did not have a common comparator; however this is only necessary when the Bucher method is used.

- The 200microgram and 800microgram doses require two sprays of the drug which results in double the cost, whereas the cost per dose of OTFC does not vary. If more patients require the 200microgram and 800microgram doses in practice this is likely to result in fentanyl being more expensive than OTFC.
- The analysis involves some simplifying assumptions such as assuming each episode of pain is identical. However, this approach has been adopted in previous fentanyl submissions and applies to both treatment arms.

Despite these issues, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In November 2008 the Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 106, control of pain in adults with cancer. This recommends that patients with moderate to severe breakthrough pain should receive breakthrough analgesia and when using oral morphine for breakthrough pain the dose should be one sixth of the around the clock morphine dose and should be increased appropriately whenever the around the clock dose is increased. Also, it includes a good practice point that when using OTFC for breakthrough pain the effective dose should be found by upward titration independent of the around the clock opioid dose.

Additional information: comparators

Relevant comparators include alternative short-acting formulations of fentanyl e.g. fentanyl nasal spray (Instanyl[®]), oral transmucosal fentanyl lozenges (Actiq[®]), fentanyl buccal tablet (Effentora[®]) and fentanyl sublingual tablet (Abstral[®]).

Cost of relevant comparators

Drug	Dose Regimen	Cost per dose (£)
Fentanyl nasal spray (PecFent)	100 and 400 micrograms	3.80
	200 and 800 micrograms	7.60
Fentanyl nasal spray (Instanyl [®])	50, 100 and 200 micrograms	5.95
	400 micrograms	11.90
Fentanyl lozenge (Actiq [®])	200, 400, 600, and 800, micrograms	5.84
	1.2 and 1.6 mg	
Fentanyl buccal tablet (Effentora [®])	100, 200, 400, 600 and 800 micrograms	4.99

Fentanyl sublingual tablet (Abstral®)	100, 200, 300, 400, 600 and 800 micrograms	4.99
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Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 21 September 2010.

Additional information: budget impact

The number of BTCP episodes treated with short-acting fentanyl products was estimated to be 186,986 in year one rising to 527,944 in year five. The manufacturer estimated that fentanyl pectin-based nasal spray would have a 2.5% market share in year one rising to 20% in year five which equated to 4,675 treated episodes in year one rising to 105,589 in year five. On the basis of each patient being treated for 6 months and experiencing 3 episodes of BTCP per day, this equates to 9 patients being treated in year one rising to 196 in year five. Based on these assumptions the manufacturer indicated that fentanyl pectin-based nasal spray would result in savings of £608 in year one rising to £14k in year five.

References

The undernoted references were supplied with the submission. The references shaded in grey are additional to those supplied with the submission.

Archimedes Pharma. Clinical study report for CP043

Archimedes Pharma. Clinical study report for CP044

European Medicines Agency. European Public Assessment for PecFent

Taylor D, Galan V, Weinstein SM et al. Fentanyl pectin nasal spray in breakthrough cancer pain. J Support Oncol 2010; 8: 184-90

This assessment is based on data submitted by the applicant company up to and including 14 November 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

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

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.