Scottish Medicines Consortium

fentanyl, 100, 200, 400, 600 and 800 microgram buccal tablet (Effentora®) No. (510/08)
Cephalon UK Ltd

10 October 2008 (*Issued January 2009)*

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 buccal tablets (Effentora®) are accepted for restricted use within NHS Scotland for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

When compared with placebo, the tablets showed an improvement in patient assessment of the intensity of breakthrough pain. Use of fentanyl buccal tablets should be restricted to patients who are unsuitable for other short-acting opioids e.g. oral morphine.

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Fentanyl buccal tablets are indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

Dosing information

Fentanyl buccal tablets (FBT) should be individually titrated to an "effective" dose that provides adequate analgesia and minimises undesirable effects. In clinical studies, the effective dose was not predictable from the daily maintenance dose of opioid. Patients should wait at least 4 hours before treating another BTP episode with these tablets during titration or maintenance therapy.

The dose should be titrated upwards through the range of available tablet strengths, up to a dose of 800 micrograms.

Treatment should be initiated by and remain under the guidance of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential of abuse of fentanyl.

Product availability date

19 January 2009

Summary of evidence on comparative efficacy

Breakthrough pain (BTP) is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain. It is usually severe, reaching peak intensity within a few minutes and has a variable duration with an average of about 30 minutes. Opioids are usually administered both for background medication and for BTP management. BTP episodes are usually treated with short-acting or normal-release opioid analgesics. It has been shown that fentanyl is suitable for the management of BTP.

There are two pivotal phase III studies and an additional long-term safety study, which was an extension study of the first two but also recruiting new patients. The two pivotal trials were randomised, placebo-controlled and had similar design. Each consisted of a dose-titration open-label period and a randomised double-blind treatment period in which each patient was their own control; each phase lasted 21 days. The long-term study had the same dose titration period, but was followed by an open-label treatment phase of at least 12 months duration, but which was to continue until the closure of the trial.

All trials recruited adult patients with cancer who were on maintenance treatment of opioid analgesics for at least 1 week. The dose ranges for inclusion were the equivalent of 60-1000mg morphine/day or 50-300 microgram/hour of transdermal fentanyl in the first trial; in the second and third trials the fentanyl dose was from 25 microgram/hour and in the second trial there were no upper limits. Patients were required to be experiencing 1 to 4 episodes of BTP most days which were alleviated by additional fast-acting opioids. The dose titration period was designed to find a successful dose, defined as the dose of FBT that provided adequate analgesia (sufficient pain relief within 30 minutes after placing the tablet for two consecutive episodes of BTP that occurred at least 4 hours apart) without unacceptable side effects. They were not allowed to titrate above 800 micrograms per dose. For the treatment period, in the first two trials, patients were supplied with ten tablets, seven of the successful dose of FBT and three matching placebo, to be taken in a predefined randomised order. In

the long-term trial, patients were given a supply of FBT at their successful dose. They were only allowed to treat a maximum of four episodes per day and instructed to wait at least 4 hours after treating a previous episode before using study drug again. Patients were allowed to use their standard rescue medication if pain relief was inadequate 30 minutes after using study drug. For each dose of study drug taken, patients recorded pain intensity (PI) scores on an 11 point visual analogue scale (VAS), pain relief (PR) scores on a five point VAS, the use of rescue medication, and conducted a global medication performance assessment. In the first trial, parameters were recorded at 15, 30, 45 and 60 minutes; in the second, they were recorded at 5, 10, 15, 30, 45, 60, 90 and 120 minutes.

For the first two trials, the primary endpoint was the summed pain intensity difference (SPID), calculated across each episode of BTP; up to 30 min in the first trial and up to 60 min in the second. Safety was the primary endpoint in the third trial, and will not be discussed further in this section. Secondary endpoints included SPID at 15, 45 and 60 min (first trial) and at 30, 90 and 120 min in the second; pain intensity difference (PID) and PR at all time-points and mean total pain relief (TOTPAR) score and global medication performance at specified time-points.

For the first trial, 123 patients were enrolled, 80 identified a successful dose during the titration period and 77 entered the treatment phase. The full analysis set comprised 72 patients and 68 (55%) completed the study. In the full analysis set the mean age was 58 years and mean baseline around the clock (ATC) dose was equivalent to 242 mg morphine; mean rescue medication dose was 21 mg morphine equivalent. Mean PI score was 6.9.

For the primary endpoint in the full analysis set, the least squares (LS) mean (standard error (SE) of LS mean) SPID for the first 30 minutes for the 7 episodes in which FBT was taken was 3.0 (0.12) compared to 1.8 (0.18) for the 3 placebo episodes, being significantly in favour of FBT. For secondary end-points, SPID at 15, 45 and 60 minutes also significantly favoured FBT as did PID, PR, and TOTPAR at all time-points (15, 30, 45 and 60 minutes) and patient global assessment at the measured time-points of 30 and 60 minutes.

In the second trial, 129 patients were enrolled, 87 achieved a successful dose and entered the treatment phase. The full analysis set comprised 78 patients and 75 (58%) completed the study. In the full analysis set, the mean age was 54 and mean morphine equivalent doses were 225 mg for ATC and 26 mg for rescue therapy. Mean PI score was 6.4.

SPID assessed at 60 minutes had a LS mean (SE) value of 9.8 (0.26) for the FBT treated episodes compared to 5.0 (0.38) for the placebo treated episodes; this difference was significant. After 30, 90 and 120 minutes, the results also significantly favoured FBT treatment, as they did with PID at all time points except 5 min. The significance at these time points was echoed in the results for PR. FBT scored significantly better for TOTPAR at 60, 90 and 120 min and global medication performance assessment at 60 and 120 min (the only times at which these were measured).

Summary of evidence on comparative safety

Over both the titration and treatment periods, adverse events were generally those attributable to fentanyl. In the first study, 38% of patients reported at least 1 treatment-related adverse event; in the second study, that number was 34%. In the long-term study, 232 patients were exposed to FBT for a mean of 158 days; for the 197 patients who entered the maintenance phase, this became 182 days. Fifty-three percent received FBT for less than 6 months while only 16% received it for at least 12 months. The mean daily dose was

1,981 micrograms. One hundred and eight patients (47%) reported a treatment-related adverse event.

Of interest were adverse events due to tablet placement e.g., application site pain, ulcer, or burning, which may necessitate switching to another therapy. In the first study, 6 (4.9%) patients reported such adverse events and 2 of these withdrew from the study; in the second, 12 (9.6%) patients reported an adverse event and 1 withdrew. In the long-term study, these figures were 15 (6.5%) patients reporting an event and 4 withdrawing.

Summary of clinical effectiveness issues

Fentanyl buccal tablets have not been directly compared to alternative opioid regimens for breakthrough pain, including oral transmucosal fentanyl lozenges (Actiq®).

There are no guidelines on a starting dose for FBT based on the around the clock dose therefore a titration period is needed. This may cause some initial delay in patient benefit, causing unnecessary pain. The need for titration to achieve a successful dose, even if switching between opioid products, may lead to confusion or indeed error.

The different pharmacokinetic profiles of fentanyl buccal tablets and oral transmucosal fentanyl lozenges (Actiq) constitute a risk management issue. The two products are not dose equivalent. Dose reductions and close monitoring are required if switching from the lozenges to the buccal tablets.

The results from the pivotal trials were based on responder-rich patient groups who identified successful doses during the titration period. This may not reflect the response rates that would be expected in a treatment-naive population.

With respect to onset of action, in the pivotal trials there was a significant response compared with placebo at 10 minutes, but not at 5 minutes, after dose administration. The magnitude of the effect at the early time points is rather small, although highly significant when compared to placebo.

Patient response has only been assessed up to 2 hours despite the fact that another dose could not (and cannot, according to the licence) be given until 4 hours has passed. The required time interval may not cover all episodes of BTP experienced by a patient, therefore additional therapy may be needed for these episodes. There are also prescribing risk management issues with regard to this required minimal interval between doses. The terminal elimination half-life of FBT is reported to be 22 hours, compared with 7 hours for the oral transmucosal fentanyl lozenges. If the dosing interval is not strictly observed, there is the potential for accumulation.

Responses to doses above 800 micrograms were not tested, even though sufficient analgesia was not achieved in all patients. However, the licensed dose range has been proven to be effective for a large proportion of patients.

No studies have been performed specifically to explore dwell time and absorption of FBT in patients with xerostomia. These subjects are instructed to drink water prior to administration of FBT to moisten the oral cavity. If following this recommendation does not result in an appropriate response, these patients may need to switch to another therapy.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing the fentanyl buccal tablet (FBT) with the oral transmucosal fentanyl lozenge. The use of the oral transmucosal fentanyl lozenge as a comparator effectively niches the product to a role in patients who are unsuitable for other short-acting opioids e.g. oral morphine. Efficacy data on pain relief and use of rescue medication were taken from an indirect comparison of two placebo-controlled FBT trials and one placebo-controlled oral transmucosal fentanyl lozenge trial. QALYs were estimated using the relationship between pain intensity and utility values from a study of patients with chronic back pain. The only costs considered were the acquisition costs of the medicines as other costs were not expected to differ between FBT and the comparator. The manufacturer estimated that if all Scottish patients currently using the lozenge switched to the buccal tablet there would be a saving of £123,496 and a QALY gain of 0.64 over the course of one year.

There are three concerns:

- The evaluation was presented as the management of a single, 60-minute episode of breakthrough pain. This was extended to a one-year time horizon by simply multiplying the results for the single episode by the expected number of episodes per day (4) and the expected number of days of treatment (91). This assumes episodes are homogeneous and that treatment effectiveness is constant, which is clinically unlikely. Since the assumption applies to both FBT and the lozenge it probably does not affect the outcomes of the health economic case.
- There are no directly comparative clinical studies of FBT and oral transmucosal fentanyl lozenge and therefore an indirect comparison was necessary. This is a weaker form of evidence and there were some concerns about the comparability of patients in the different studies and different doses of drugs being used.
- The clinical trials carried out failed to include a generic measure of quality of life that could be converted into a QALY. As a result the manufacturer used the results of a study of patients with chronic back pain.

The sensitivity analysis provided some reassurance that the above weaknesses would not seriously affect the results.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN) guidelines (June 2000) for control of pain in patients with cancer recommends that every patient on opioids for moderate to severe pain should have access to breakthrough analgesia. These guidelines are currently under review, to be published summer 2008.

Additional information: previous SMC advice

Following a full submission, the Scottish Medicines Consortium (SMC) issued advice in October 2004: oxycodone (Oxynorm®) injection is accepted for restricted use within NHS Scotland only for the treatment of moderate to severe pain in patients with cancer. Use of this drug should be restricted to patients who have difficulty in tolerating morphine or diamorphine therapy. Limited data indicate that it provides analgesia similar to parenteral morphine at similar doses. However, there are no comparative data with diamorphine, the opioid recommended by Scottish Intercollegiate Guidelines Network (SIGN) for patients with cancer who require parenteral opioids. Oxycodone is more expensive than diamorphine and the economic case for this product replacing the other products has not been clearly demonstrated.

Additional information: comparators

The most common opioids used for breakthrough pain have been examined. There are no licensed doses for breakthrough pain in the majority of cases, so the mean dose used at baseline in the trials has been used, using standard conversion factors from the American Pain Society (2003). There are licensed ranges for the two fentanyl preparations, however, so these have been used.

Cost of relevant comparators

Drug	Dose regimen	Cost per dose (£)
fentanyl buccal tablet	**100 to 800micrograms**	**5 ***
fentanyl lozenge	200 to 3,200micrograms	6 to12
hydromorphone	5mg	<1
oxycodone	10mg	<1
morphine	20mg	<1

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 6th August 2008. * Price supplied by manufacturer, June 2008.

Additional information: budget impact

The manufacturer estimated the net budget impact to be a saving of £124k in year 1 rising to £175k in year 5, based on 325 patients in Scotland requiring treatment in year 1. Since only medicines costs are considered this is also the manufacturer's estimate of the net drug budget impact.

The figures quoted assume 100% switching from the oral transmucosal fentanyl lozenge to the buccal tablet. The manufacturer also supplied estimates for lower switch rates but these are simply pro rata to the projected saving (e.g. 50% switch means half the savings).

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.

This assessment is based on data submitted by the applicant company up to and including 01 December 2008.

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.

The undernoted references were supplied with the submission.

Portenoy RK, Taylor D, Messina J, Tremmel L. (2006) A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain; 22(9): 805-11.

Slatkin NE, Xie F, Messina J, Segal TJ. (2007) Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. J Support Oncol; 5(7): 327-34.