

BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The applicant Cephalon Europe submitted on 21 February 2007 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Effentora, through the centralised procedure under Article 3 (2) b of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 1 June 2006. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / Known active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

Licensing status:

Effentora has been given a Marketing Authorisation in the United States of America.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Karl Broich

Co-Rapporteur: Eva Skovlund

2. Steps taken for the assessment of the product

- The application was received by the EMA on 21 February 2007.
- The procedure started on 21 March 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 June 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2007. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 10-12 July, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 12 July 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 3 October 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 November 2007.
- During the CHMP meeting on 10-13 December 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing.
- During the meeting on 21-24 January 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Effentora on 24 January 2007. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 January 2008.

SCIENTIFIC DISCUSSION

1.1 Introduction

Effentora is a fentanyl buccal tablet (FEBT) which is indicated for the management of breakthrough pain (BTP), recurrent episodes of acute transitory pain, in patients who are already receiving maintenance opioid therapy for chronic cancer pain.

BTP is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain and the adequate treatment is a significant clinical problem. BTP is usually severe, reaching peak intensity within a few minutes, and has a variable duration with an average of about 30 minutes.. The ability to achieve a rapid analgesic effect in this case is essential. Treatment should be part of an overall pain management programme and medication to manage BTP should be titrated individually.

Opioids are usually administered both for background medication and for BTP management. BTP are usually treated with short-acting or normal-release opioid analgesics. It has been shown that Fentanyl is suited for the management of BTP. Oral transmucosal fentanyl citrate (OTFC) is currently the only opioid analgesic approved in the United States (US) and some European countries specifically for BTP in patients with cancer who are receiving around-the clock (ATC) opioid therapy for background pain.

FEBT has been developed using proprietary technology for efficient and rapid delivery of fentanyl. The tablet is designed for placement and retention within the oral cavity, between the gum and the inside of the cheek. Disintegration is expected to provide improved absorption compared with the currently available transmucosal formulation of fentanyl.

The prevalence of BTP is high, with 64% to 89% of patients with chronic cancer pain experiencing such events, and the median number of episodes is 4 per day. The occurrence of between 40% and 50% of episodes is unpredictable.

Fentanyl citrate is a potent opioid analgesic (ATC N02AB). Fentanyl, a pure opioid agonist, acts primarily through interaction with μ receptors located in the brain, spinal cord, and smooth muscle to produce its pharmacologic effect. Its analgesic potency is approximately 80 times that of morphine. The primary site of therapeutic action is the central nervous system (CNS). Fentanyl is a widely approved medicinal active substance with well known pharmacodynamic, pharmacokinetic and toxicological properties, available since 1960s in different formulations, including subcutaneous, intravenous, transdermal and transmucosal dosage forms.

Fentanyl buccal tablet (FEBT) 100, 200, 400, 600 and 800 μg is a novel formulation, designed to facilitate rapid delivery and enhanced absorption of fentanyl via the oral mucosa, resulting in accelerated rapid analgesic effect. FEBT technology is based on the idea that transient pH changes may optimize dissolution and absorption of the substance through the oral mucosa.

FEBT indication is proposed for the management of breakthrough pain (BTP), recurrent episodes of acute transitory pain, in patients who are already receiving maintenance opioid therapy for chronic cancer pain.

Effentora is individually titrated and to a so called “successful dose” that provides adequate analgesia and minimises undesirable effects. This titration process is described in detail in the SPC.

The excipients contained in FEBT are well known and covered by Ph.Eur monographs.

1.2 Quality aspects

Introduction

Cephalon Europe has applied for a marketing authorisation through the centralised procedure for Effentora (fentanyl citrate) 100 µg, 200 µg, 400 µg, 600 µg and 800 µg buccal tablets. The tablets are designed to disperse and release the active substance in the buccal cavity to ensure rapid onset of action.

Active Substance

Fentanyl is a synthetic opioid analgesic, belonging to the piperidine derivatives, and it is chemically related to pethidine.

Fentanyl citrate is a white to almost white powder, soluble in water, freely soluble in methanol and sparingly soluble in alcohol.

- **Manufacture**

Fentanyl citrate is an established active substance and the quality of the active substance has been granted a certificate of suitability (CEP).

Fentanyl citrate is milled prior to its further use in the manufacturing process of the finished product.

All known impurities are limited by the respective Ph. Eur. monograph. Any other impurities are limited to not more than 0.1%.

- **Specification**

Fentanyl citrate is a compendial substance. For compendial analytical methods no additional validation data is deemed to be necessary.

A laser scattering method is used for the measurement of fentanyl citrate particles. The method is validated.

- **Stability**

In the CEP, type III amber glass or polyethylene bag inside a HDPE drum is mentioned as primary packaging material for the active substance.

A re-test period of 3 years is stated if stored in the above mentioned container materials.

Medicinal Product

The product is a buccal tablet of five different strengths. The product is packed in aluminium/PVC foil blisters. The 200 µg – 800 µg strengths can be distinguished from each other by debossed numbers on one of the tablet's faces. The 100µg strength is different in size.

- **Pharmaceutical Development**

The buccal tablets are designed for transmucosal administration. A major advantage of the buccal route is the avoidance of first-pass metabolism. The application site and the fast disintegration of the tablets, partly due to the effervescent components of the formulation, lead to a rapid and increased permeation of the active substance through the mucosal barrier.

All excipients have been widely used in commercial pharmaceutical dosage forms. All excipients are covered by Ph Eur Monographs.

The formulation development is based on three different formulations, starting from a small scale proof of concept formulation with unmilled active substance, over formulations with an optimized blending process to a formulation where finally compatibility of all excipients has been proved. Except for the inclusion of colorants and slightly deviating amounts of a filler the later developed formulations have been identical to the commercial formulation.

Fentora buccal tablets are packaged in moisture-resistant aluminium/PVC foil blister packs. Moisture resistance of the packaging material is crucial for this type of tablet. Permeation tests confirm that the blister material is acting as barrier against water vapour, oxygen and carbon dioxide. "Shipping studies" were initiated and the results showed that the blister material sufficiently protects the tablets against physical damage under defined shipping conditions.

- Adventitious Agents

None of the ingredients used in the manufacture or in the composition is of human or animal origin.

- Manufacture of the Product

The manufacture of the drug product is performed at two different manufacturing sites.

The manufacturing process basically involves standard mixing and compression techniques. The description of the manufacturing process is sufficient.

Critical steps in the manufacture were identified and adequate in-process controls were established. Two separate process validation studies on a commercial batch scale have been performed, one for coloured tablets and the other for the non-coloured tablets as finally proposed for commercial use. The results of the validation data support the quality and reproducibility of the process.

All of the excipients are well known and commonly used in the manufacture of pharmaceutical products and meet Ph. Eur. compendial standards. No additional controls are required. None of the excipients is novel or of human or animal origin.

Representative Certificates of Analysis for all excipients were provided.

The packaging is manufactured from two laminate components. Individual tablets are placed in blister cells, cold formed from a laminate consisting of aluminium foil and polyvinylchloride films (PVC/Polyamide/Al-foil/PVC). This laminate is then sealed to a second laminate of paper/polyester/aluminium foil with heat-seal coating lacquer (paper/PET/Al-foil/HSC).

- Product Specification

The specification for batch release includes tests for appearance, identification and assay of fentanyl, content uniformity, disintegration, fentanyl related substances, hardness, loss on drying, and microbiological quality. The related substances limits of the release and shelf specifications are within the limits set in the ICH-guideline Q3.

The analytical procedures and test methods have been adequately described. The description of the method development is comprehensive. The validation was performed in accordance to the ICH Q2 after selectivity had been successfully shown.

The results of 35 batches covering all dosage strengths and manufacturing sites were provided. The batches are covering the entire production scale range. The batches have been manufactured on equipment identical to the one used for routine production. All tablets are packaged in the same container closure proposed for the commercial product.

- Stability of the Product

Batch analysis results from 28 batches covering all dosing strengths and manufacturing sites are presented. The data demonstrates good compliance with the release specification.

The stability results presented for Effentora buccal tablets consist of results from 26 batches, production scale size, stored under long-term (25 C/60% RH) and accelerated (40°C/75% RH) conditions. These batches were tested for the following stability indicating parameters: appearance, disintegration, fentanyl content, related substances, hardness, loss on drying, and microbiological quality. The results from long-term and accelerated stability testing demonstrate only a slight degree of decomposition. Photostability of the packaged product has been proven. The buccal tablets were packaged in the container closure system proposed for marketing. Stability data support the proposed shelf life and storage conditions as defined in the SPC.

Due to the effervescent properties of the buccal tablets moisture resistance is a crucial quality requirement of the packaging material. Extensive permeation test data confirm that the blister material is acting as barrier against water vapour, oxygen and carbon dioxide. The suitability of the selected packaging material has further been verified by the results of the accelerated and long term stability studies.

Discussion on chemical, pharmaceutical and biological aspects

Generally, satisfactory documentation has been provided. The active substance is of compendial quality.

Regarding the finished product, the manufacturing process is adequately described and controlled. It should ensure a consistent quality for the product.

1.3 Non-clinical aspects

Introduction

The submission contains a comprehensive literature overview of the non-clinical safety profile of fentanyl concerning non-clinical pharmacology, pharmacokinetics and toxicology. In addition, the dossier contains non-clinical studies which were originally performed for the authorisation of another oral transmucosal fentanyl (OTFC) product that is marketed in the EU. Further safety pharmacology and toxicological studies conducted in direct support of the current procedure have also been submitted.

As the pharmacodynamic, pharmacokinetic and toxicological properties of fentanyl are well known, the main toxicological concerns the potential additional toxicity within this product is whether FEBT administration enhances toxicity, due to increased systemic exposure, or causes local toxic effects.

Most of the bibliographical data are based on studies performed up to 30 years ago, and are generally not GLP-compliant. Of the submitted original studies, studies on safety pharmacology and genotoxicity are in accordance with GLP, whereas the pharmacokinetic studies are not GLP-compliant.

Pharmacology

- **Primary pharmacodynamics**

Fentanyl is a selective opioid agonist interacting primarily at μ opioid receptors located within the central nervous system. Fentanyl possesses analgesic activity with a potency 80-fold higher than morphine, but with shorter duration of action as well as sedative effects. The formulation of Effentora is not expected to affect the well known pharmacodynamic properties of fentanyl.

- **Secondary pharmacodynamics and Safety pharmacology programme**

The applicant has submitted original core safety pharmacology studies on cardiovascular, respiratory and central nervous system in rats and telemetered dogs. In addition, the applicant has provided a review of published literature regarding fentanyl-related effects on cardiovascular, cerebrovascular, respiratory, hepatic, renal and endocrine systems.

Cardiovascular system

A cardiovascular safety evaluation study was performed to evaluate the potential effects of fentanyl citrate on arterial blood pressure, heart rate and electrocardiography, including the appropriate intervals, following subcutaneous dosing at doses of 0 (vehicle), 0.001, 0.01, or 0.05 mg/kg in conscious unrestrained beagle dogs. Measurements of arterial blood pressure, heart rate or lead II ECG parameters were determined continuously from 30 minutes prior to until 6 hours following administration

At 0.001 mg/kg, there were no significant effects on blood pressure, heart rate or ECG. At 0.01 mg/kg, heart rates were significantly lower with corresponding changes in ECG intervals. At 0.05 mg/kg there was an increase in systolic arterial blood pressure whereas diastolic pressure remained relatively unchanged. The observed decrease in heart rate produced a corresponding increase in RR, PR, QT and QRS duration. Although corrected for heart rate, the QTc interval obtained at 120 minutes was significantly increased when compared to time-matched vehicle control and pre-dose values, suggesting that the increase in QTc may be drug-related. An increase in the number of escape complexes within the first 30 minutes post-dosing in three of four dogs were considered to be associated with the decreased heart rate.

Effects of fentanyl on HERG channels and cardiac purkinje fibres have already been described in the literature. It is reported that fentanyl inhibits HERG channel with an IC_{50} of 1.8 μM (Katchman et al., 2002). Following application of the highest strength of FEPT (800 μg) mean C_{max} was quantified in clinical studies to be below 3 ng/ml (8.9 nM). This concentration is far below (approximately 200-fold) of the IC_{50} of HERG channel. Therefore, this finding seems not to be of clinical relevance. Fentanyl has also been tested for effects on action potential duration (APD) in canine cardiac purkinje fibers at concentrations of 0.095, 0.19 and 0.95 μM (Blair et al., 1989).

Nervous system

Male Sprague-Dawley rats were administered a single sc dose of fentanyl citrate at 0 (vehicle control) -0.003-0.03-0.3 mg/kg, and assessed in the Irwin.

Transient and dose-related effects were apparent in the mid and high dose groups. At 0.3 mg/kg the animals showed apparent CNS depression (flattened posture, decreased alertness, increased ease of handling and removal from cage, decreased touch response, decreased fearfulness, decreased body tone, exophthalmus, decreased corneal reflex, salivation, piloerection, decreased locomotor activity, slowed respiration, decreased startle response, catalepsy, passivity, and decreased righting reflex). The CNS depression was transient, with total recovery within 24 h.

Respiratory system

Male Sprague-Dawley rats were administered a single sc dose of fentanyl citrate at 0 (vehicle)-0.003-0.03-0.3 mg/kg, or a single iv dose of morphine at 20 mg/kg (reference control).

No significant differences in respiration rate or tidal volume were observed in rats treated with fentanyl citrate at doses of 0.003 and 0.03 mg/kg. In the high-dose group there was a significant decrease in respiration rate (at 30 minutes and 5 h) and a significant decrease in tidal volume at 30 minutes. Morphine produced a depression in respiration rate and tidal volume at 30 minutes post-dosing, consistent with its pharmacological classification as a respiratory depressant.

In summary, secondary pharmacological effects are respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria.

- **Pharmacodynamic drug interactions**

An overview of the literature has been submitted mainly on PD interactions with benzodiazepines, calcium and potassium ion channels activity and with some anesthetics. No new studies have been performed by the applicant.

Pharmacokinetics

The applicant has presented an overview of the pharmacokinetic properties of fentanyl, based on literature references.

In support of the formulation of Effentora, the applicant has submitted original studies related to the pH dependent transmucosal absorption of fentanyl in anaesthetised dogs. In addition, a study on human metabolism *in vitro* has been submitted.

Two methods of analysis have been used. A previously validated, commercially available RIA was used to determine plasma fentanyl concentrations in the submitted absorption study. The lower limit of quantification for fentanyl was 0.2 ng/ml.

GC-MS methods were developed for identification and quantification of various fentanyl metabolites. The limits of detection for norfentanyl, despropionylfentanyl and hydroxyfentanyl were 5, 2.5 and 2.5 ng/ml, respectively.

Absorption

A bioequivalence study comparing another OTFC product and this product (compressed powder formulation) was performed in anaesthetised dogs, looking at the pH dependence of transbuccal absorption of fentanyl. The values of both C_{max} and $AUC_{0-6\text{ hr}}$ following transmucosal fentanyl administration were pH-dependent; increasing with pH over the range 5.03-7.11. The profile for the compressed powder formulation buffered to pH 6.49 was most similar to that of the OTFC, with bioavailabilities of 21.3% and 19.4%, respectively. Absorption parameters have been further studied in humans (see clinical part).

Distribution

After distribution, the concentrations of fentanyl in umbilical vein perfusate in rabbits were approximately 25% of those in maternal arterial blood, and fetal plasma levels in sheep were approximately 40% of those in maternal plasma.

Fentanyl crosses the placental barrier in animals and humans and may affect the unborn. SPC and PIL have been labelled accordingly.

Fentanyl is excreted into human breast milk; therefore women should not breast-feed while taking Effentora because of the possibility of sedation and/or respiratory depression in their infants. SPC and PIL have been labelled accordingly.

Metabolism and excretion

With few exceptions, published literature indicates that fentanyl is extensively metabolised in all species studied, with dealkylation to norfentanyl as a major metabolic pathway.

Biotransformation of fentanyl by human microsomes (from livers and duodenum) have been studied *in vitro*. The metabolism *in vitro* is mainly by CYP3A4 as demonstrated by the applicant. Guitton et al (1997a) have reported that 5 different CYP enzymes (CYP1A1, CYP2C9, CYP3A4, CYP3A5 and CYP2D6) exhibited substantial capacity to decrease fentanyl content in single recombinant enzyme preparations. This suggests that CYP enzymes other than CYP3A4 may also be involved in human metabolism of fentanyl *in vitro*.

Toxicology

In substitute for conventional single dose, repeat dose and reproductive toxicity studies, the applicant has provided an overview based on published literature. Although many of the referred studies are performed more than 30 years ago and are not GLP-compliant, this is acceptable considering that the toxicity profile of fentanyl is well known.

- **Single dose toxicity**

Single dose toxicity described in the literature in several species and multiple routes of administration have been submitted. The toxic signs elicited by fentanyl administration in mice were generally similar to those exhibited by morphine and included increased spontaneous activity, circling, increased sensitivity to touch, Straub tail, increased muscle tone, respiratory depression and convulsions. After IV administration the LD50 was 0.03 mg/kg in monkeys, 2-6 mg/kg in rats, 11 mg/kg in mice and 15 mg/kg in mice. After oral administration the LD50 was 120 mg/kg in mice. After sub-cutaneous or intra-peritoneal administration, the LD50 varied from 1 to 60 mg/kg depending on the species.

- **Repeat dose toxicity**

A number of repeat-dosing studies using fentanyl by the oral, transmucosal and parenteral (IV, IM, SC) routes in rats, rabbits and dogs have been reported in the literature.

As the level of experimental detail in these studies is generally sparse, it does not permit a full scientific evaluation.

In rats, deaths occurred following oral doses of 10 mg/kg/day or more and following IM doses of 0.1 to 0.4 mg/kg/day. The main findings in these studies were weight loss or reductions in weight gain. There was no clear-cut evidence of target organ toxicity, although the data are limited, and the cause of death was considered to be associated with respiratory depression.

In rabbits, fentanyl was well-tolerated when administered by the transcutaneous route for up to 90 days at a dose of 0.66 mg/kg/day.

In dogs, IM administration of fentanyl at doses of 0.1 and 0.4 mg/kg/day for 30 days produced weight loss and/or no weight gain over the 30 day test period. Intravenous administration of 0.1, 0.3 and 1.0 mg/kg fentanyl to dogs for 30 days again produced a decrease in body weight at the highest dose, with dose-related clinical signs of sedation and convulsions. All dogs survived both the 30 day IM and IV dosing periods.

- Genotoxicity

Fentanyl citrate was evaluated in a standard battery of genotoxicity studies: an *in vitro* bacterial reverse mutation assay, an *in vitro* mammalian cell (L5178Y mouse lymphoma cells) mutagenicity assay, and an *in vivo* mouse micronucleus assay.

In one of two mouse lymphoma assay cultures, fentanyl caused a significant increase in mutation frequencies at the highest evaluated dose (500 µg/ml) following metabolic activation. Similar results have also been reported in previous genotoxicity studies with fentanyl. However, due to negative results in the second culture, and negative results in both Ames test *in vitro* and in the micronucleus test *in vivo*, the equivocal results are considered not clinically relevant. Fentanyl is not considered to be genotoxic.

- Carcinogenicity

Long-term carcinogenicity studies have not been performed with fentanyl. Although the carcinogenic potential of fentanyl citrate is unknown, the lack of carcinogenicity studies is considered acceptable in view of the sought indication, as for other approved fentanyl containing products with similar indications

- Reproduction Toxicity

Studies with female rats revealed reduced fertility and enhanced embryonal mortality. More recent studies showed that effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed. Teratogenic effects have not been demonstrated.

- Local tolerance

A study of local tolerance was performed as part of the pharmacokinetic dog study on different buccal formulations of fentanyl. No visual irritation was observed for any of the test formulations in any dog. Although this study is of limited relevance (off-target species, single dose administration), the difficulties inherent to the realisation of a repeat-dose local tolerance in animals and the experience in patients justifies the absence of further studies.

- Other toxicity studies

Studies on impurities

Qualifying genotoxicity studies have been performed with three potentially genotoxic arylamine impurities in the drug substance and/or the drug product; 4-(N-phenylamino)piperidine (Impurity A), N-1-(2-phenylethyl)-4-(N-phenylamino)piperidine (Impurity B) and 1-(N-benzyl)-4-N-phenylaminopiperidine (Impurity FC1003). The studies were performed in accordance with current regulations, and were validated with concordant positive controls. In the chromosomal aberration tests, the impurity concentrations were limited by excessive cytotoxicity.

The results of these genotoxicity studies do not indicate mutagenic or clastogenic effects of the three arylamine impurities.

Impurity B is listed in the Ph.Eur monograph, and is considered qualified up to the suggested specifications of 0.25% (designated as impurity D in the Ph.Eur). Proposed specifications for impurities A and FC1003 are below the level of qualification for both drug substance (0.15%) and drug product (1%), and further testing is therefore not required.

Ecotoxicity/environmental risk assessment

A phase I environmental risk assessment has been performed. Because the log K_{ow} is below 4.5, screening for persistence, bioaccumulation and toxicity was not considered necessary.

For the calculation of the Predicted Environmental Concentration (PEC) the default penetration factor (F_{pen}) of 0.01 has been refined to 0.001 based on published data on the target patient population (number of cancer patients suffering from breakthrough pain) and commercial experience. This was considered to be acceptable.

Using these estimates, the calculated PEC value is well below the threshold for a phase II assessment of 0.01 µg/l.

It is therefore concluded that Effentora is unlikely to represent a risk for the environment following the suggested usage in patients.

Discussion on the non-clinical aspects

Fentanyl is a well-known selective opioid agonist interacting primarily at µ opioid receptors located within the central nervous system. Fentanyl possesses analgesic activity with a potency 80-fold higher than morphine, but with shorter duration of action as well as sedative effects.

The safety pharmacology studies confirm the previously known effects of fentanyl on cardiovascular parameters (increased systolic blood pressure, reduced heart rate, ECG-changes including slight QTc-prolongation), CNS (depression) and respiratory system (depression).

The transmucosal absorption of fentanyl is pH dependant (between pH 5 to 7) and its profile has been characterised mainly in humans. Fentanyl is extensively metabolised in all species studied, with dealkylation to norfentanyl as a major metabolic pathway mediated by the CYP3A4.

In acute and repeat dose studies, there was no identified target organ of toxicity and toxic findings were mainly related to the expected respiratory depression.

Fentanyl is not considered to be genotoxic in the standard battery and the carcinogenic potential has not been studied, which is acceptable considering the clinical indication in cancer patients.

Fentanyl is potentially toxic to the reproduction, affecting the embryofoetal survival and fertility in animal studies. Teratogenic effects have not been observed.

The local tolerance is considered to be acceptable.

No negative impact on the environment is expected under the therapeutic use of this medicinal product.

1.4 Clinical aspects

Introduction

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The pharmacokinetic profile of fentanyl is well known and has been extensively characterized (Mather and Gourlay 1991). Therefore, only studies designed to characterize those aspects of the pharmacokinetics of FEFT that were expected to be unique for this novel formulation have been conducted for the purpose of this MAA. Overall, eleven pharmacokinetic (PK) studies have been carried out with the “generation III” formulation of Effentora that is proposed for marketing. They are summarised in the table below:

Study ID	Study start, location Design	Study objective	No of subjects enrolled (completed)	Dose FEBT	Inclusion criteria
099-11	2003, USA Randomized, open-label, 2-way crossover	Bioavailability, dose proportionality, bioequivalence	42 (39)	270-1300 µg single dose	Healthy volunteers 19-55 years
099-18	2003, USA Randomized, open-label, 4-treatment, 4-period, crossover	Dose proportionality	28 (25)	200-1080 µg single dose	Healthy volunteers 19-55 years
C25608/1026/BE/US	2005, USA Randomized, open-label, crossover	Bioequivalence (4 x 100 µg tablets vs. 1 x 400 µg)	30 (17)	400 µg single dose	Healthy volunteers 19-45 years
C25608/1027/PK/US	2005, USA Randomized, open-label, crossover	Dose proportionality	32 (31)	100-800 µg single dose	Healthy volunteers 18-44 years
C25608/1028/BA/US	2005, USA Randomized, open-label, crossover	Bioavailability (buccal/ swallowed/i.v.)	32 (26)	400 µg 800 µg single dose	Healthy volunteers 18-45 years
C25608/1029/PK/US	2005, USA Nonrandomized, open-label,	PK (single/multiple dose)	24 (21)	400 µg single dose, 400 µg x 4 for 5 days	Healthy volunteers 18-45 years
C25608/1037/PK/US	2006, USA Randomized, open-label, 4-period, crossover	PK, dose proportionality	30 (23)	600-1200 µg single dose	Healthy volunteers 18-45 years
099-19	2004, USA Randomized, open-label, 4-period, crossover	PK, dose proportionality	25 (19)	100-800 µg single dose	Healthy Japanese volunteers 19-55 years
099-20	2005, USA Open-label	PK (multiple dose)	14 (13)	400 µg x 4 for 2.5 days	Healthy Japanese volunteers 20-55 years
099-21	2005, USA Randomized, open-label, 3-period, crossover	PK (single dose) Bioequivalence (1 x 400 µg tablets vs. 2 x 200 µg)	29 (24)	400 µg single dose	Healthy Japanese volunteers 20-55 years
099-16	2005, USA Open-label	Safety/tolerability Opioid-tolerant cancer patients with or without mucositis	19 (16)	200 µg single dose	Opioid-tolerant cancer patients ≥ 18 years with or without mucositis

- Absorption

The fentanyl buccal tablet (FEBT) was designed as a buccal dosage form of fentanyl citrate that disintegrates in the buccal cavity using effervescence to facilitate transmucosal absorption. The theory underlying the idea of using effervescence as penetration enhancer was published by Pather et al. in 2001. Chemically, fentanyl reacts as a weak base with a pKa value of 7.3. At 1 pH unit below the pKa, the ratio of base to salt is 1:10, whereas at 1 pH unit above the pKa, this ratio is 10:1. Accordingly, solubility can be increased by lowering the pH value of the surrounding medium whereas absorption, which is dependent upon the un-ionized form of fentanyl, will increase with higher pH values. The effervescence obtained from the citric acid, sodium bicarbonate, and pH-adjusting ingredients of FEBT, is supposed to optimize solubility of fentanyl by initially creating a pH value of about 6.1 through the chemical reaction of water and carbon dioxide to form carbonic acid. Later, this unstable molecule disintegrates leaving carbon dioxide in the air and tissue which causes the pH to rise to 8.4 and thereby creates optimum conditions for the un-ionized fentanyl molecule to be transmucosally absorbed.

Fentanyl formulated as FEBT is readily absorbed, with an absolute bioavailability of 65% following buccal administration. The absorption profile of fentanyl formulated as FEBT is largely the result of an initial rapid absorption from the buccal mucosa, with peak plasma concentration attained at

approximately 50 to 53 minutes in the fasted state. Approximately 50% of the total dose administered is supposed to be absorbed across the buccal mucosa and rapidly becomes systemically available

The absolute and relative bioavailability of fentanyl formulated as FEBT is explored in **study 1028**. In this study transmucosal (buccal) FEBT (Oravescent fentanyl) (400 µg) was compared to oral (swallowed) FEBT (800 µg), transmucosal Actiq (800 µg), and intravenous fentanyl (400 µg). Absolute bioavailability of transmucosal and oral fentanyl formulated as FEBT was found to be 65 % and 31 %, respectively (see table below).

Table : Absolute bioavailability of fentanyl by treatment (table from study 1028)

Treatment	Mean±SD AUC _{0-inf} (N=26) ^a	Absolute bioavailability (N=25) ^b	95% CI
		Individual ratio (F)	
Transmucosal ORAVESCENT fentanyl (400 mcg)	6.48±2.98	0.65±0.20	0.51, 0.70
Oral ORAVESCENT fentanyl (800 mcg)	6.60±4.47	0.31±0.13	0.24, 0.33
Transmucosal ACTIQ (800 mcg)	9.58±3.91	0.47±0.11	0.40, 0.54
Intravenous fentanyl (400 mcg)	10.29±2.88	—	—

^a N=26 represents the full pharmacokinetic analysis set. For transmucosal ORAVESCENT fentanyl at 400 mcg, n=21; for oral ORAVESCENT fentanyl at 800 mcg, n=24; for ACTIQ at 800 mcg, n=26; and for intravenous fentanyl, n=25.

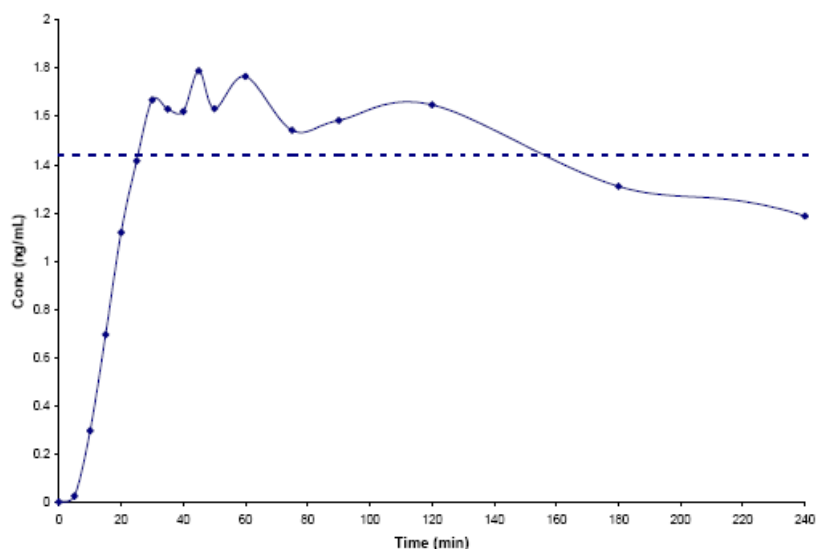
^b N=25 represents the number of subjects for whom absolute bioavailability could be calculated. For transmucosal ORAVESCENT fentanyl 400 mcg, n=20; for oral ORAVESCENT fentanyl, n=23; and for ACTIQ, n=25.

SD=standard deviation; CI=confidence interval; AUC_{0-inf}=area under the plasma concentration versus time curve (AUC) from zero to infinite time.

Pooled data from **studies 11, 18, 1026, 1027, 1028, 1029, and 1037** were used to characterize single-dose pharmacokinetic parameters, which were dose normalized to 100 µg across studies. A total of 199 subjects were included in the analysis of the single-dose pharmacokinetic profile.

Plasma concentrations following administration of FEBT typically reach approximately 80% of C_{max} (T80) within 25 minutes of administration and are maintained through 2 hours after administration (Figure 1 below).

Figure 1: Mean Plasma Concentration-Time Profile of Fentanyl Following a Single Dose of the Fentanyl Effervescent Buccal Tablet (n=199)



Pharmacokinetic parameters following the single-dose administration of fentanyl formulated as FEBT are summarized in Table below:

Table 3: Pharmacokinetic parameters of fentanyl following a single dose of FEBT in healthy subjects (dose-dependent parameters normalized to 100- μ g dose)

Fentanyl Effervescent Buccal Tablets	
Variable (unit)	(N=199)
C_{max} (ng/mL)	
n	199
Mean (SD)	0.247 (0.0954)
t_{max} (min)	
n	199
Median (range)	52.8 (19.8, 240.0)
$AUC_{0-\infty}$ (ng·h/mL)	
n	187
Mean (SD)	1.52 (0.646)
λ_z (1/h)	
n	187
Mean (SD)	0.0820 (0.0526)
$t_{1/2}$ (h)	
n	187
Median (range)	11.8 (2.33, 43.8)

Pooled data are from studies 11, 18, 1026, 1027, 1028, 1029, and 1037.

λ_z , apparent plasma/serum terminal elimination rate constant; AUC, area under the plasma/serum concentration by time curve; $AUC_{0-\infty}$, AUC from time zero to infinity; C_{max} , maximum observed plasma/serum concentration; n, number of subjects included in the analysis; SD, standard deviation; $t_{1/2}$, elimination half-life; t_{max} , time to maximum observed plasma/serum concentration.

The t_{max} values following a single dose of FEBT ranges from ca. 20 to 240 minutes. This wide range is explained by the combined transmucosal and gastrointestinal absorption and represent, for the majority of subjects, a high plasma concentration attained early and maintained over the first 2 hours after the start of administration of FEBT

- Distribution

Fentanyl is highly lipophilic and is well distributed beyond the vascular system, with a large apparent volume of distribution. After buccal administration of Effentora, fentanyl undergoes initial rapid distribution that represents an equilibration of fentanyl between plasma and the highly perfused tissues (brain, heart and lungs). Subsequently, fentanyl is redistributed between the deep tissue compartment (muscle and fat) and the plasma.

The plasma protein binding of fentanyl is 80% to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis.

- Elimination

Fentanyl is metabolised in the liver and in the intestinal mucosa to norfentanyl by CYP3A4 isoform. Norfentanyl is not pharmacologically active in animal studies. More than 90% of the administered dose of fentanyl is eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.

Following the intravenous administration of fentanyl, less than 7% of the administered dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the faeces. The metabolites are mainly excreted in the urine, while faecal excretion is less important.

Following the administration of Effentora, the terminal elimination phase of fentanyl is the result of the redistribution between plasma and a deep tissue compartment. This phase of elimination is slow, resulting in a terminal half-life $t_{1/2}$ of approximately 22 hours following buccal administration of the

formulation and approximately 18 hours following intravenous administration. The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h.

- Dose proportionality and time dependencies

In single dose studies, fentanyl from FEBT exhibits linear pharmacokinetics up to 1000 µg. Mean total systemic exposure ($AUC_{0-\infty}$) of fentanyl increased in a dose-proportional manner, while there was a tendency that C_{max} increased less than dose-dependent for the doses exceeding 1000 µg.

A slightly higher than expected accumulation after multiple-dose administration is postulated to be due to the larger contribution of a deep-tissue compartment to the area under the terminal portion of the profile following multiple-dose administration compared with a single dose.

- Special populations

The effect of renal or hepatic impairment on the pharmacokinetics of fentanyl formulated as FEBT has not been studied. Published experience from patients with renal and liver impairment is scarce. As stated in the SPC, special care should be taken in patients with severe hepatic or renal disease.

Differences in exposure with Effentora were observed in a clinical study with patients with grade 1 mucositis. C_{max} and AUC_{0-8} were 1% and 25% higher in patients with mucositis compared to those without mucositis, respectively. The differences observed are not considered to be clinically significant.

No studies have been performed specifically to explore dwell time and absorption of fentanyl formulated as FEBT in patients with xerostomia. These subjects are instructed to drink water prior to administration of FEBT 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. This is reflected in the SPC.

No formal clinical pharmacology studies were specifically conducted to study the effect of gender, weight, race, or age. Seven of 9 phase 1 single-dose studies with fentanyl formulated as FEBT are included in a pooled database. Pharmacokinetic parameters of fentanyl formulated as FEBT from this database showed that women had 21% higher mean dose-normalised $AUC_{0-\infty}$, and 29% higher mean C_{max} than men, probably largely attributable to differences in weight. From the same database, PK parameters showed that subjects with weight ≤ 73.5 kg had 10% higher mean dose-normalised $AUC_{0-\infty}$, and 12% higher mean C_{max} than subjects with weight > 73.5 kg.

- Pharmacokinetic interaction studies

No clinical or *in vitro* drug-drug interaction studies have been performed for FEBT. Fentanyl is primarily metabolized in the liver and intestinal mucosa by the cytochrome P450 (CYP) CYP3A4/5 isoforms to norfentanyl. Drugs that inhibit CYP3A4/5 activity may increase the bioavailability of swallowed fentanyl (by decreasing intestinal and hepatic first-pass metabolism) and may decrease the systemic clearance of fentanyl. Drugs that induce CYP3A4/5 activity may decrease the bioavailability and increase the systemic clearance of fentanyl. Patients who begin or end therapy with potent inhibitors of CYP3A4/5, such as macrolide antibiotics (eg, erythromycin), azole antifungal agents (eg, ketoconazole and itraconazole), and protease inhibitors (eg, ritonavir), or potent inducers of CYP3A4/5 (eg, rifampicin, carbamazepine, phenytoin) while receiving FEBT should be monitored for a change in opioid effects and, if warranted, the dose of FEBT should be adjusted accordingly. Concomitant use with MAO inhibitor can give unpredictable potentiation of opioid analgesics.

There are synergistic interactions between opioids and hypnotics with effects mainly on sedation, breathing and blood pressure. The interactions between benzodiazepines and opioids have been most thoroughly studied (not specifically for FEBT), although similar interactions may occur with non-benzodiazepine hypnotic drugs, sedating antihistamines and alcohol etc.

Pharmacodynamics

- Mechanism of action

Fentanyl has a high affinity and a strong agonist action on the μ -class opioid receptors. The effects on the κ -class opioid receptors are only evident in high doses, whereas the effects on the δ -class opioid receptors are questioned and, if existent, of little clinical relevance.

- Primary and Secondary pharmacology

Fentanyl is highly lipophilic and is rapidly transferred across the blood-brain barrier into the CNS. The μ - and κ -receptors in the brain and spinal cord are mostly responsible for the analgesic action of fentanyl. Side-effects as respiratory depression and constipation are thought to mainly be mediated through the μ -opioid receptors, located in the brainstem, spinal cord and in smooth muscle.

Clinical efficacy

The clinical study programme for the assessment of efficacy comprises three studies in patients with cancer and breakthrough pain (BTP). In addition, three studies in patients with BTP and painful conditions not related to cancer were also performed.

The sought indication was:

Effentora is indicated for the management of breakthrough pain (BTP) in patients with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

BTP is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.

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

In the approved indication, the 1st sentence has been amended as follows:

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

As fentanyl is a controlled opioid substance, this medicinal product will be subject to special medical prescription. In addition, in view of the indication and of the potential risk of serious adverse effects (respiratory depression) if not properly used, the treatment needs to be initiated by and to remain under the guidance of a physician experienced in the management of opioid therapy in cancer patients. These restrictions of use are reflected in the SPC section 4.2.

An overview of the submitted clinical studies is displayed in the table below:

Table : Studies contributing to clinical efficacy and safety data

Study number	Number of patients treated/ completed	Study design	Population	Study and control drugs Dose and regimen	Study objective	Primary efficacy endpoint	Secondary efficacy endpoints
Efficacy and safety (BTP in patients with cancer)							
099-14	Titration period 123/ 77 Double-blind period 77/68	Randomized, double-blind, placebo-controlled	Opioid-tolerant patients with cancer and BTP	- FEBT: 100, 200, 400, 600, or 800 mcg for 7 BTP episodes - Placebo: for 3 BTP episodes - Study drug (FEBT/placebo) given for 10 episodes in random order	Efficacy and safety	SPID ₃₀ calculated across each episode of BTP	- SPID ₁₅ , SPID ₄₅ , SPID ₆₀ - PID ₁₅ , PID ₃₀ , PID ₄₅ , PID ₆₀ - PR ₁₅ , PR ₃₀ , PR ₄₅ , PR ₆₀ - TOTPAR ₁₅ , TOTPAR ₃₀ , TOTPAR ₄₅ , TOTPAR ₆₀ - global medication performance assessment (30 and 60 minutes after study drug adm.) - proportion of BTP episodes for which rescue medication was used - relative risk of using rescue medication
C25608/3039/ BP/US	Titration period 125/87 Double-blind period 87/ 75	Randomized, double-blind, placebo-controlled	Opioid-tolerant patients with cancer and BTP	- FEBT: 100, 200, 400, 600, or 800 mcg for 7 BTP episodes - Placebo: for 3 BTP episodes - Study drug (FEBT/placebo) given for 10 episodes in random order	Efficacy and safety	SPID ₆₀ calculated across each episode of BTP	- SPID ₃₀ , SPID ₉₀ , SPID ₁₂₀ - PID ₅ , PID ₁₀ , PID ₁₅ , PID ₃₀ , PID ₄₅ , PID ₆₀ , PID ₉₀ , PID ₁₂₀ - PR ₅ , PR ₁₀ , PR ₁₅ , PR ₃₀ , PR ₄₅ , PR ₆₀ , PR ₉₀ , PR ₁₂₀ - TOTPAR ₆₀ , TOTPAR ₉₀ , TOTPAR ₁₂₀ - global medication performance assessment (60 and 120 minutes after study drug adm.) - proportion of BTP episodes for which rescue medication was used - time to meaningful PR - relative risk of using rescue medication - patient preference for BTP medication
099-15 ^a	214 (104 from study 14 and 3039, 110 de novo)/ 15 completed, 39 ongoing	Open-label, Long-Term	Opioid-tolerant patients with cancer and BTP	- FEBT-naïve patients: titration to successful dose (100-, 200-, 400-, 600- or 800 mcg) - All patients: FEBT 100, 200, 400, 600 or 800 mcg up to 12 months	Efficacy and safety	Safety was primary endpoint	Efficacy as measured by - Changes in FEBT dose - Patient's assessments of study medication - development of incremental tolerance
Supportive efficacy and safety (BTP in patients with other conditions than cancer-related pain)							
C25608/3041/ BP/US	Titration period 103/ 79 Double-blind period 79/77	Double-blind, randomized, placebo-controlled	Opioid-tolerant patients with chronic neuropathic pain and BTP	- FEBT: 100, 200, 400, 600, or 800 mcg for 6 BTP episodes - Placebo: for 3 BTP episodes	Efficacy and safety	SPID ₆₀	SPID at additional time points, PID, PR score, TOTPAR, time of meaningful PR, global medication performance assessments, use of rescue medication, and patient's assessment of study drug

				- Study drug (FEBT/placebo) given for 9 episodes in random order			
C25608/3042/ BP/US	Titration period 105/77 Double-blind period 77/ 75	Double- blind, randomized, placebo- controlled	Opioid-tolerant patients with chronic low back pain and BTP	- FEBT: 100, 200, 400, 600, or 800 mcg for 6 BTP episodes - Placebo: for 3 BTP episodes - Study drug (FEBT/placebo) given for 9 episodes in random order	Efficacy and safety	SPID ₆₀	SPID at additional time points, PID, PR score, TOTPAR, time of meaningful pain relief, global medication performance assessments, use of rescue medication, and patient's assessment of study drug
C25608/3040/ BP/US	633 (98 from study 3041 and 3042, 535 de novo)/ 0 completed, 409 ongoing	Open-label, Long-Term	Opioid-tolerant patients with chronic non- cancer pain and BTP	- FEBT-naïve patients: titration to successful dose (100-, 200-, 400-, 600- or 800 mcg) - All patients: FEBT 100, 200, 400, 600, or 800 mcg up to 18 months	Efficacy and safety	Safety was primary endpoint	Efficacy as measured by different efficacy parameters

- Dose response studies

Traditional dose-effect relationships have not been presented. However, the CHMP agrees that the pain conditions as well as the need for individual titration to successful doses, make dose-response estimates less meaningful, and the lack of such estimates is therefore considered acceptable.

The doses chosen for the titration scheme were based on pharmacokinetic comparison with a marketed OTFC fentanyl product. Accordingly, the start dose (100 mcg) and the other successive doses up to 800 mcg are considered suitable for the individual dose-response titration. Comparison of serum fentanyl PK following the administration of 1080 mcg FEBT and 1600 mcg OTFC showed that the average fentanyl exposure (AUC) was similar and the rate of absorption was faster for FEBT. However, responses to doses above 800 were not tested in cancer patients, even though sufficient analgesia was not achieved in all patients. However, it is important to note that the currently proposed dose range of 100 to 800 mcg has been proven to be effective for a large proportion of patients.

- Main studies

The dossier contains two main clinical efficacy / safety studies:

Study 099-14 (hereafter denoted 14):

«A Multicenter, Double-Blind, Placebo-Controlled Study of ORAVESCENT Fentanyl Citrate for the Treatment of Breakthrough Pain in Opioid-Tolerant Cancer Patients»

Study C25608/3039/BP/US (hereafter denoted 3039):

«A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of ORAVESCENT Fentanyl Citrate in Opioid-Tolerant Patients With Cancer and Breakthrough Pain»

In addition, a long-term open label safety study, study 099-15 (hereafter denoted 15) was conducted: «A Multicenter, Open_label Long-Term Study of ORAVESCENT Fentanyl Citrate for the Treatment of Breakthrough Pain in Opioid-Tolerant Cancer Patients»

This is an extension study where patients who completed one of the above mentioned studies and were eligible for this study, along with new patients who qualified for the study.

As no active comparator studies were submitted for efficacy and safety, the comparison with alternative treatments is largely confined to an indirect assessment based on comparative pharmacokinetic profiles between Effentora and the OTFC product.

METHODS

Study Participants

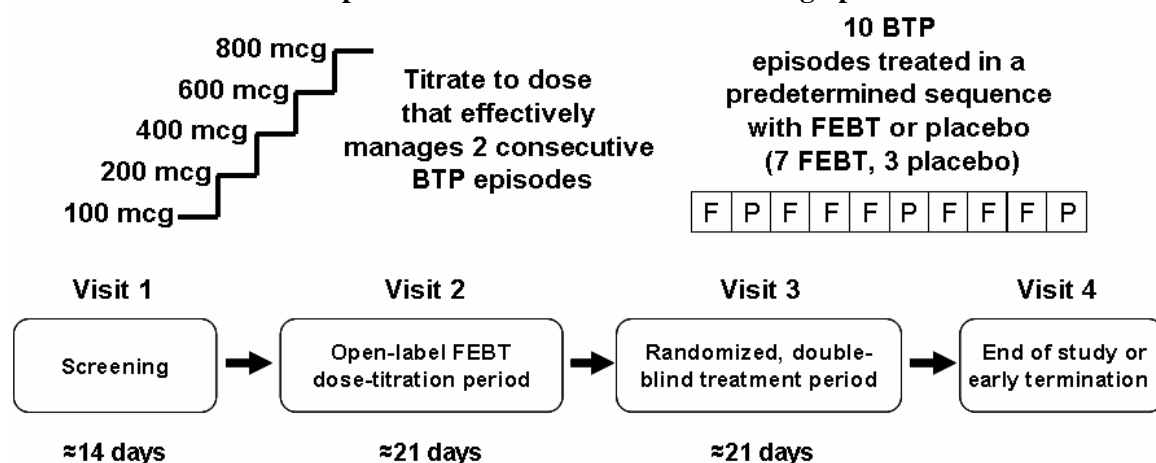
Both studies 14 and 3039 were multi-centre studies, each conducted at 30 centres in the United States.

The inclusion and exclusion criteria are acceptable and representative of the population likely to use the medication according to the proposed indication. These criteria do not differ markedly between the two studies, which are therefore described and discussed together. As the patients included are > 18 years of age, this precludes use in children and adolescents at this stage of clinical development.

Treatments

The study design of the two pivotal phase III studies are shown in the Figure below. It consisted of an open-label FEBT dose-titration period and a randomized, double-blind treatment period. The randomized, predetermined order of 7 FEBT tablets and 3 placebo tablets shown in the figure is 1 example of the 18 possible treatment sequences. This makes the individual patient his own placebo control.

Figure : Study design of study 14 and study 3039 of Fentanyl Buccal Tablets (FEBT) in patients with cancer and breakthrough pain



Note: Patients were not allowed to titrate above 800 mcg.

The purpose of the open-label dose titration period was to determine, for each patient individually, a successful dose. The patient’s successful dose was defined as the dose of FEBT, either 100, 200, 400, 600, or 800 mcg, that provided adequate analgesia (sufficient pain relief within 30 minutes after placing the tablet in the buccal cavity for 2 consecutive episodes of BTP that occurred at least 4 hours apart) without unacceptable adverse events.

Objectives

The objective of the studies was to determine the efficacy and safety of FEBT when used to relieve BTP in opioid-tolerant patients with cancer who were receiving maintenance opioids.

Outcomes/endpoints

Patients were asked to complete a series of assessments with each dose of study drug taken during the double-blind treatment period and record the information in a diary provided to them. These measures included pain intensity (PI), pain relief (PR), a global medication performance assessment, and the use of rescue medication.

The assessment of efficacy included the following measures for every episode of BTP for which study drug was used during the double-blind treatment period:

- PI assessment: An 11-point linear numerical rating scale was used by the patient to rate pain (0=no pain through 10=worst pain). Patients rated their pain immediately prior to the administration of study drug and at specified time points after the administration of study drug.
- PR assessment: A 5-point Likert scale was used to measure PR (0=none, 1=slight, 2=moderate, 3=a lot, and 4=complete). Patients rated their PR at specified time points after the administration of study drug.
- Global medication performance assessment: A 5-point categorical scale was used to rate how well study drug performed in controlling BTP (0=poor, 1=fair, 2=good, 3=very good, and 4=excellent). Patients rated global medication performance at specified time points after the administration of study drug.
- Use of rescue medication: Patients recorded any use of their standard rescue medication for BTP episodes for which study drug was used.

For integration of efficacy data from the 2 studies, SPID, PID, PR, and TOTPAR were calculated for the common time points in both studies at which PI was reported, ie, 15, 30, 45, and 60 minutes after the administration of study drug. Global medication performance assessment scores were integrated

for the common 60-minute time point. The proportion of BTP episodes for which rescue medication was used was integrated because it was not time dependent.

The pain intensity difference (PID) was derived from PI scores. PID is the change from PI score immediately prior to administration of study drug for each BTP episode to the PI assessment at each specified time point after administration of study drug.

The primary efficacy variable in both studies was the summed pain intensity difference (SPID). SPID was calculated as the sum of the PID at each specified interval after administration of study drug for each BTP episode.

The primary efficacy variable for study 14 was the sum of individual pain intensity differences through 30 minutes after the start of administration of study drug (SPID₃₀). SPID₃₀ was calculated for each BTP episode as the sum of PID at both 15 and 30 minutes after administration of study drug and is derived from PID as follows: $SPID_{30}=PID_{15}+PID_{30}$.

The primary efficacy variable for study 3039 was the SPID through 60 minutes after the start of administration of study drug (SPID₆₀).

Statistical methods

The primary efficacy variable in study 14 was SPID₃₀. This was compared between treatments by analysis of variance (ANOVA) with treatment and centre as fixed effects and patient as a random effect. This model was also used for secondary analyses of SPID and TOTPAR. Secondary efficacy variables PID, PR score, and global medication performance assessment were compared between treatments by the (one sample) Wilcoxon signed ranks test. The test was based on average scores for each patient per treatment.

In study 3039 the primary efficacy variable was SPID₆₀ which was compared between treatments by analysis of variance (ANOVA) with treatment as a fixed effect and patient as a random effect. This model was also used for the secondary variables of SPID, PID, and TOTPAR. A permutation test was performed on the primary variable to assess the robustness of the results. The secondary efficacy variables PID, PR score, and global medication performance assessment were compared between treatments by the (one sample) Wilcoxon signed ranks test.

RESULTS

Participant flow

A total of 248 patients entered the dose titration period for both studies. Of these, 150 patients entered the double-blind treatment period.

Baseline data

Patients' BTP pathophysiology at baseline was categorized as predominantly neuropathic, predominantly nociceptive, or mixed (about 50% neuropathic and 50% nociceptive). In the full analysis set for both studies combined, 20% of patients had predominantly neuropathic pain, 46% of patients had predominantly nociceptive pain, and 34% of patients had mixed pain. BTP pathophysiology at baseline for patients in the safety analysis set was generally comparable to those of the patients in the full analysis set.

At baseline, for the full analysis set, the median oral morphine equivalent dose per day taken as around-the-clock (ATC) medication overall was 160.0 mg (range 5.0 to 4800 mg). The mean oral morphine equivalent dose per day taken as rescue medication for BTP was 23.9 mg (range 1 to 480 mg) per episode. The data are summarised in the following table:

Variable Statistic	Study 14 (N=72)	Study 3039 (N=78)	Total (N=150)
ATC therapy (mg/day)			
n	69	78	147
Mean (SD)	241.8 (578.01)	225.0 (193.06)	232.9 (418.73)
Median	130.0	160.0	160.0
Min, max	5.0, 4800.0	60.0, 960.0	5.0, 4800.0
Rescue medication (mg/BTP episode)			
n	61	78	139
Mean (SD)	21.3 (23.91)	25.9 (53.28)	23.9 (42.87)
Median	16.0	18.0	16.0
Min, max	1.0, 160.0	6.0, 480.0	1.0, 480.0
Prior BTP therapy			
Oral transmucosal fentanyl citrate	1 (1)	8 (10)	9 (6)
Other	71 (99)	70 (90)	141 (94)

The average pain intensities associated with BTP episodes before the first dose of FEBT were similar in both studies (6.9 and 6.4 for studies 14 and 3039, respectively) as shown in the table below:

Table 2: Average Pain Intensity Pretreatment in Studies in Patients With Cancer (Full Efficacy Analysis Set)

Statistic	099-14		3039	
	FEBT (N=72)	Placebo (N=72)	FEBT (N=78)	Placebo (N=78)
Mean	6.9	6.9	6.4	6.4
SD	1.61	1.62	1.80	1.71
Range	3.1, 10.0	3.0, 10.0	2.2, 9.9	1.7, 9.7

SOURCE: [Summary 2.3](#).

FEBT=fentanyl effervescent buccal tablets; SD=standard deviation; N=number of patients.

Outcomes and estimation

A total of 167 (67%) patients identified a successful dose, and this dose was 100, 200, or 400 mcg for 31% (78 of 248) of patients and 600 or 800 mcg for 36% (89 of 248) of patients. During the dose titration period, the mean duration of exposure to treatment was 6.3 days (median 4.0 days, range 1 to 109 days).

Primary endpoint: Evaluation of Analgesic Efficacy Results (SPID)

The primary efficacy variable in study 14 was the SPID₃₀, and the primary efficacy variable in study 3039 was the SPID₆₀. The mean of the SPID_{time} is given for the 7 episodes of BTP with FEBT treatment compared with the mean for the 3 episodes with placebo, see next Table.

The primary efficacy variables of both studies showed a statistically significant difference between FEBT and placebo treatment in favour of FEBT. The treatment difference was 1.2 (95% CI [0.83, 1.62]) for study 14(SPID₃₀) and 4.8 (95% CI [3.87, 5.64]) for study 3039 (SPID₆₀).

Table : Summed Pain Intensity Difference at 30 and 60 minutes posttreatment (Full Analysis Set)

Variable Statistic	Study 14		Study 3039		Total	
	FEBT (N=72)	Placebo (N=72)	FEBT (N=78)	Placebo (N=78)	FEBT (N=150)	Placebo (N=150)
SPID 30 minutes posttreatment						
n	72	72	78	78	150	150
Mean (SD)	3.2 (2.60)	2.0 (2.21)	3.3 (2.23)	1.8 (1.92)	3.2 (2.41)	1.9 (2.06)
Median	2.6	1.3	2.7	1.3	2.7	1.3
Min, max	-1.0, 12.7	-1.7, 9.7	0.0, 9.6	-0.6, 9.8	-1.0, 12.7	-1.7, 9.8
p-value	<0.0001	—	<0.0001	—	—	—
95% CI (FEBT–placebo)	0.83, 1.62	—	1.07, 1.80	—	1.06, 1.60	—
SPID 60 minutes posttreatment						
n	72	72	78	78	150	150
Mean (SD)	10.5 (5.99)	6.2 (5.49)	9.7 (5.58)	4.9 (4.38)	10.1 (5.77)	5.5 (4.97)
Median	8.7	5.4	8.9	4.2	8.7	4.8
Min, max	-1.1, 27.6	-1.3, 23.0	0.0, 26.8	-0.9, 21.8	-1.1, 27.6	-1.3, 23.0
p-value	<0.0001	—	<0.0001	—	—	—
95% CI (FEBT–placebo)	3.42, 5.37	—	3.87, 5.64	—	3.92, 5.24	—

NOTE: The confidence interval, and p-value for the treatment comparison for study 14 are from an analysis of variance (ANOVA) with treatment and center as fixed factors and patient as a random factor. The confidence interval, and p-value for the treatment comparison for study 3039 are from an ANOVA with treatment as a fixed factor and patient as a random factor. The confidence interval for the treatment comparison for both studies combined are from an ANOVA with treatment and study as fixed factors and patient as a random factor.

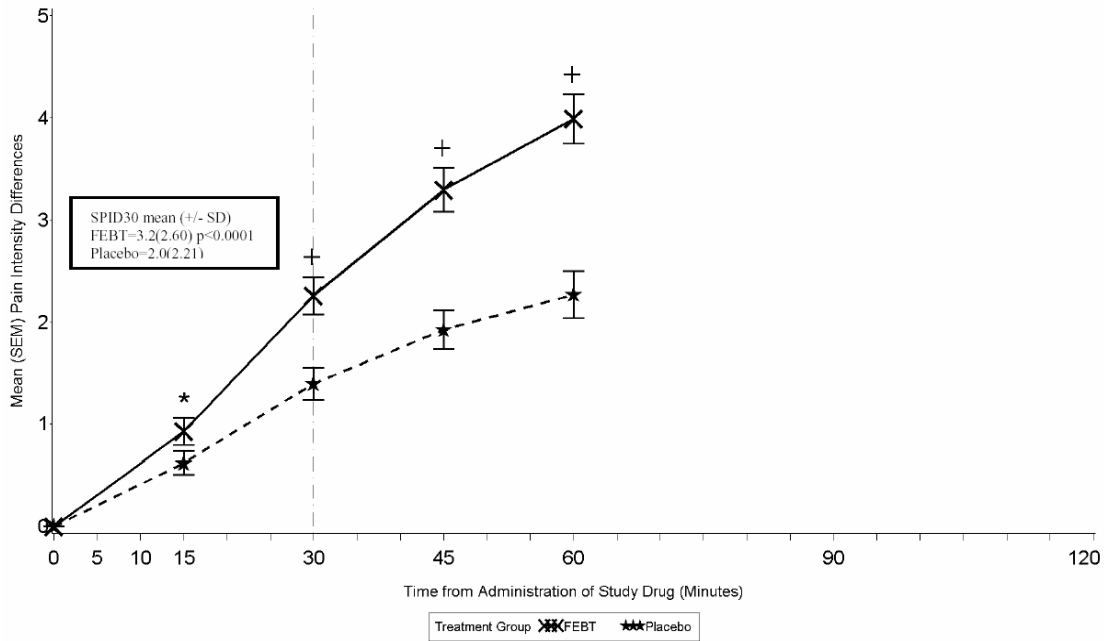
Secondary endpoints

The analyses of the secondary variables PID, PR, TOTPAR, global medication performance assessment at different time points and time to meaningful pain relief, suggest that FEBT provides better analgesia than placebo, also during the short period of BTP.

Evaluation of Analgesic Efficacy Results (PID)

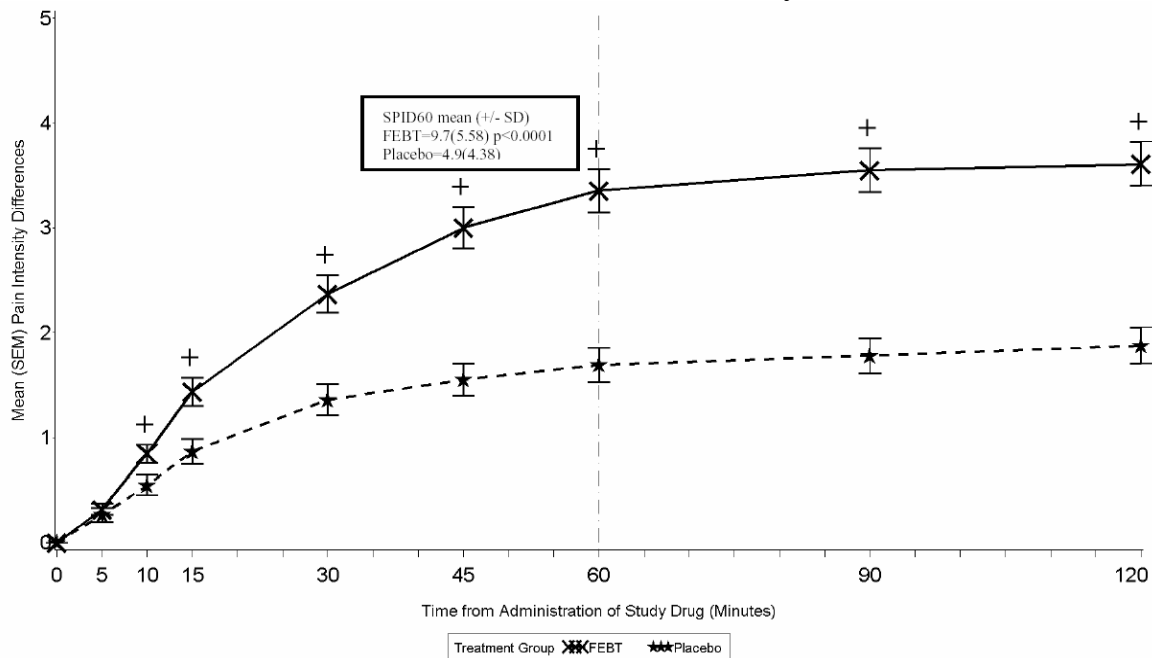
In study 14, the difference in favour of treatment with FEBT at every time point was statistically significant ($p < 0.01$ (* in Fig 4) at 15 minutes and $p < 0.0001$ (+ in Fig 4) at 30, 45, and 60 minutes), see Figure 4. The treatment difference between FEBT and placebo increased through the 60-minute observation period.

Figure 4: Mean (+/-SEM) Pain Intensity Difference in study 14 at each time point by treatment received (N=72) (Full Analysis Set)



In addition, for study 3039, mean PID at earlier (5 and 10 minutes) and at later (90 and 120 minutes) time points after administration of study drug were also secondary variables. At 10 minutes and at all time points through the end of the observation period (120 minutes), there was a statistically significant difference ($p < 0.0001$, ⁺ in Fig 5) in favour of treatment with FEBT (Figure 5).

Figure 5: Mean (+/-SEM) Pain Intensity Difference in study 3039 at each time point by treatment received (N=78) (Full Analysis Set)



The mean pain relief (PR) showed a statistically significant difference between FEBT and placebo treatment in favour of FEBT for both studies. Pain relief increased through 1 hour after the administration of study drug and was maintained through 2 hours.

Mean total pain relief (TOTPAR) showed a statistically significant ($p < 0.0001$) difference between FEBT and placebo treatment in favor of FEBT all time points. The difference in TOTPAR was maintained through 2 hours.

Global medication performance was assessed by patients 30 and 60 minutes after the administration of study drug in study 14, and 60 and 120 minutes after the administration of study drug in study 3039. The mean difference in performance between the FEBT and placebo was statistically significant ($p < 0.0001$) in favour of FEBT in both studies at 60 minutes, which is the only common time point for the 2 studies.

- Clinical studies in special populations

No studies have been performed in children and this is reflected in the SPC.

- Supportive studies

Study 15 was a long-term multicentre, open-label study designed to determine the tolerability and safety of FEBT when used as maintenance treatment to relieve BTP in opioid-tolerant patients with cancer. Secondary objectives were to assess the clinical efficacy of FEBT when used as maintenance treatment for BTP. The study included a screening period and an open-label dose titration period for new patients, and a maintenance treatment period for all patients.

The primary objective was to determine the tolerability and safety of FEBT when used long-term to relieve BTP in opioid-tolerant patients with cancer who are receiving ATC opioids. Clinical efficacy was assessed as a secondary objective.

197 patients fulfilled the criteria for long-term maintenance period, and were evaluable for efficacy. The mean exposure time was 181 days, 36 patients were treated ≥ 12 months. The median global medication performance ratings were 2.3 on a scale of 0 to 4 just prior to the start of maintenance treatment and 2.1 at endpoint. Of the 197 patients 69% had the same final dose at their final visit as their original successful dose.

In the other supportive studies (denoted 3040, 3041 and 3042) patients represent a separate patient population. However, the safety data for the studies are included in the safety analyses.

- Discussion on clinical efficacy

In the 2 pivotal, double-blind, placebo-controlled studies, the efficacy of FEBT was shown to be consistent, with significant (mostly highly significant) differences from placebo across the range of successful doses, across common time points (15, 30, 45, and 60 minutes after administration) and across all measures, including pain intensity (expressed as pain intensity difference and summed pain intensity difference), pain relief, rescue medication usage, and global medication performance. Patients receiving FEBT during the double-blind treatment phase were more than three times less likely to need rescue medication than patients receiving placebo.

However, the order of magnitude of the clinical response as effect size at the early time points is rather small (although highly significant): Summed pain intensity differences after 30 min (SPID₃₀) were 1.2 for study 14 and 1.5 for study 3039.

The effective dose was determined individually by using a titration regimen, in two consecutive BTP episodes. Accordingly, a dose-response relationship could not be determined because the design of the studies did not allow for a comparison across doses.

The titration regimen (starting at 100 mcg) was simple to follow, and the majority of patients (about 65%) achieved an effective dose. No linear or simple relationship between the daily maintenance dose and the effective dose of FEBT could be determined and there was considerable variability (see pharmacokinetic section).

It is known from the literature, that BTP usually has a rapid onset, and the median duration of a BTP episode has been estimated to 15-30 min (Svendsen et al. 2005). However, it is important to note that

the currently proposed dose range of 100 to 800 mcg has been proven to be effective for a large proportion of patients.

Indirect comparisons with alternative treatments may, however, indicate that the onset of action after administration of Effentora is more rapid than current alternatives like OTFC products and peroral opioids (see also Pharmacokinetic section).

On the other hand, the prolonged BTP episodes in some patients should also be taken into consideration, since such patients may well profit from a duration of action (up to 2 hours) that exceeds the average BTP periods. Even though Effentora has shortcomings regarding time-effect profile in the treatment of BTP, the product is nevertheless considered to be at least as efficient as current alternative oral treatments when taking into account the time-window of the transient BTP episodes.

Clinical safety

In addition to the 3 phase 3 studies in patients with cancer, and given the common mechanisms of BTP in patients with cancer and noncancer-related background pain, supportive safety data were also provided from 3 similarly designed studies, which included the same dosage regimen in patients with chronic non-cancer pain (neuropathic and musculoskeletal pain) and BTP. The safety analysis set comprises 358 patients for chronic cancer pain and 740 patients for non-cancer pain which is considered to be sufficiently large for safety evaluation.

- **Patient exposure**

A total of 1098 patients with BTP (both patients with cancer and patients with chronic non-cancer pain) received FEBT in six phase 3 studies. Of these patients, 358 were suffering from cancer (pain). An overall safety assessment was performed by pooling the safety data from all the studies in cancer (studies 14, 15, and 3039). In addition, the safety data obtained from all studies including patients with chronic non-cancer pain studies (3040, 3041, and 3042) were pooled. Furthermore, a total of 273 healthy men and women in 10 phase 1 studies and 16 opioid-tolerant patients with cancer (with and without oral mucositis) received one or more single doses of FEBT and were evaluated for safety.

Two study groupings were analysed in the overall safety assessment, and the main groups are described below.

The set of enrolled patients:

The set includes all patients who were enrolled (ie, were dispensed study drug) in any of the included studies, whether or not a patient took any study drug (FEBT or placebo). The set of enrolled patients was used for the summary of patient disposition.

The safety analysis set:

The set includes all patients in the set of enrolled patients who took at least 1 dose of study drug. The safety analysis set was used for all summaries of study drug exposure, demographic and baseline characteristics, and safety data.

Demographic characteristics of patients:

On average patients with cancer were older and tended to weigh less than patients with chronic non-cancer pain. There was a lower percentage of white people in the cancer patient group. The proportion of male and women was similar in the two groups of patients.

The BTP characteristics and opioid medications at baseline for patients are shown in the table below. ATC doses are expressed as oral morphine equivalent doses in mg. The ATC medication and rescue medication was higher for the patients with chronic non-cancer pain. The proportion of use of OTFC was similar between the two groups of patients.

Table 26: BTP characteristics and opioid medications at baseline (Safety Analysis Set)

Characteristic/therapy	Patients with cancer and BTP (N=358)	Patients with chronic noncancer pain and BTP (N=740)
Classification of BTP mechanism		
Predominantly neuropathic	62 (17)	117 (16)
Predominantly nociceptive	170 (47)	220 (30)
Mixed (about 50/50)	126 (35)	196 (26)
Not collected	-	207 (28)
Opioid usage at baseline		
Prior BTP therapy, n (%)		
OTFC	25 (7)	56 (8)
Other	333 (93)	684 (92)
ATC medication (mg/day)		
N	351	737
Mean	258.6	416.6
SD	386.15	2767.65
Median	160.0	160.0
Min, max	0.8, 4800.0	10.0, 70000.0
Rescue medication (mg/BTP episode)		
N	336	730
Mean	21.5	41.2
SD	30.57	151.80
Median	15.0	20.0
Min, max	1.0, 480.0	0.5, 3000.0

- Adverse events

In patients with cancer and BTP, the most frequently occurring adverse events ($\geq 10\%$ of patients by preferred term) in this patient population were the following: nausea, dizziness, vomiting, fatigue, headache, constipation, somnolence, anemia and peripheral edema. Adverse events related to the application site were reported for 31 (9%) patients. Common adverse events (those occurring in at least 5% of patients) are presented in the following Table:

Table: Treatment-emergent AEs occurring in at least 5% of patients with cancer and BTP overall (Safety Analysis Set)

System organ class MedDRA high-level term ^a MedDRA preferred term	Number (%) of patients with cancer and BTP (N=358)
Number of patients with posttreatment data	355 (100)
Number of patients with at least 1 adverse event	297 (84)
Blood and lymphatic system disorders	
Anemias NEC	38 (11)
Anemia	38 (11)
Neutropenias	17 (5)
Gastrointestinal disorders	
Nausea and vomiting symptoms	117 (33)
Nausea	104 (29)
Vomiting	62 (17)
Gastrointestinal atonic and hypomotility disorders NEC	50 (14)
Constipation	45 (13)
Gastrointestinal and abdominal pains (excl oral and throat)	38 (11)
Abdominal pain	25 (7)
Diarrhoea (excl infective)	27 (8)
Diarrhoea	27 (8)
Stomatitis and ulceration	19 (5)
General disorders and administration site conditions	
Asthenic conditions	81 (23)
Fatigue	56 (16)
Asthenia	31 (9)
Oedema NEC	43 (12)
Oedema peripheral	35 (10)
Application and instillation site reactions	31 (9)
Infections and infestations	
Lower respiratory tract and lung infections	29 (8)
Pneumonia	21 (6)
Upper respiratory tract infections	22 (6)
Candida infections	16 (5)
Investigations	
Physical examination procedures	28 (8)
Weight decreased	19 (5)
Metabolism and nutrition disorders	
Total fluid volume decreased	33 (9)
Dehydration	32 (9)
Appetite disorders	32 (9)
Anorexia	22 (6)
Potassium imbalance	18 (5)
Hypokalemia	18 (5)

Footnotes are presented at the end of the table

(continued)

Table: Treatment-emergent AEs occurring in at least 5% of patients with cancer and BTP overall (Safety Analysis Set) (Continued)

System organ class MedDRA high-level term ^a MedDRA preferred term	Number (%) of patients with cancer and BTP (N=358)
Musculoskeletal and connective tissue disorders	
Musculoskeletal and connective tissue signs and symptoms NEC	45 (13)
Back pain	17 (5)
Joint related signs and symptoms	18 (5)
Arthralgia	18 (5)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	
Oncologic complications and emergencies	17 (5)
Nervous system disorders	
Neurological signs and symptoms NEC	83 (23)
Dizziness	83 (23)
Disturbances in consciousness NEC	57 (16)
Somnolence	38 (11)
Headaches NEC	50 (14)
Headache	49 (14)
Paraesthesias and dysaesthesias	18 (5)
Tremor (excl. congenital)	16 (5)
Psychiatric disorders	
Confusion and disorientation	23 (6)
Confusional state	18 (5)
Depressive disorders	21 (6)
Depression	21 (6)
Anxiety symptoms	21 (6)
Anxiety	17 (5)
Respiratory, thoracic and mediastinal disorders	
Breathing abnormalities	30 (8)
Dyspnoea	21 (6)
Coughing and associated symptoms	28 (8)
Cough	20 (6)
Upper respiratory signs and symptoms	17 (5)
Skin and subcutaneous tissue disorders	
Apocrine and eccrine gland disorders	18 (5)
Pruritis NEC	18 (5)
Pruritis	16 (5)

^a High-level terms are sorted by descending order of incidence within system organ class. Patients may have reported more than 1 adverse event type, but are counted only once in each preferred term category and only once in each high-level term.

Adverse events related to the application site and oral mucosal examination findings.

For cancer patients, 31 (9%) had adverse events related to the application site. Twenty patients experienced events that were symptomatic, and 16 patients had physical findings related to the application site.

For non-cancer patients, 87 (12%) had adverse events related to the application site. Fifty-nine patients experienced events that were symptomatic, and 32 patients had physical findings related to the application site.

Overall, local tolerability does not appear to be of particular concern, since all of the events observed in healthy subjects were mild and resolved with no residual effects. Furthermore, these adverse events resolved without residual effect for the vast majority of patients. In section 4.2 of the SPC, a change in tablet placement within the buccal cavity is recommended in case of buccal mucosa irritation.

The incidence of adverse events related to the application site was not increase in patients with mucositis or dry mouth/xerostomia. It is recommended in the SPC (section 4.2) that patients experiencing xerostomia are advised to drink a glass of water to moisten the buccal cavity prior to administration of the product,

- Serious adverse event/deaths/other significant events

Deaths: A total of 75 patients died after enrolment into 1 of the Phase 3 studies of FEBT in patients with cancer and BTP. Twelve patients died of adverse events that started during the titration period and 63 patients died during or after the long-term maintenance treatment period. All deaths were due to the patients' underlying conditions and were considered not related or unlikely to be related to study drug.

Serious AEs: A total of 119 (34%) patients with cancer and BTP experienced 1 or more treatment-emergent serious adverse events (see following Table). The most frequently reported serious adverse events were pneumonia (14 [4%] patients) and dehydration (12 [3%] patients).

Five patients with cancer and BTP had adverse events of respiratory failure. In each case, the event was considered by the investigator to be related to the patient's underlying condition and not related to treatment with the study drug.

Adverse events of respiratory failure were reported for 2 patients with chronic non-cancer pain. One patient had pneumonia followed by respiratory failure. This was considered not related to study drug treatment. The other patient was reported as taking six 800-mcg tablets of FEBT over an 11-hour period in association with benzodiazepines and barbiturates. The patient was treated for poly-drug overdose. The events were considered possibly related to study drug treatment. The events resolved and the patient was withdrawn from the study. This case is a reminder of risks associated with overdose after repetitive frequent intake of fentanyl.

Overall, no unexpected trends in serious AEs are observed.

Table 31: Serious AEs in patients with cancer and BTP (Safety Analysis Set)

System organ class MedDRA preferred term	Number (%) of patients
	Total (N=358)
Number of patients with posttreatment data	355 (100)
Number of patients with at least 1 serious adverse event	119 (34)
Blood and lymphatic system disorders	9 (3)
Anaemia	5 (1)
Gastrointestinal disorders	16 (5)
Vomiting	7 (2)
Nausea	6 (2)
Abdominal pain	4 (1)
Diarrhoea	4 (1)
Infections and infestations	22 (6)
Pneumonia	14 (4)
Metabolism and nutrition disorders	17 (5)
Dehydration	12 (3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	71 (20)
Cancer pain	6 (2)
Colon cancer metastatic	5 (1)
Lung cancer metastatic	5 (1)
Breast cancer	4 (1)
Breast cancer metastatic	4 (1)
Colon cancer	4 (1)
Lung neoplasm malignant	4 (1)
Non-small cell lung cancer	4 (1)
Pancreatic carcinoma	4 (1)
Psychiatric disorders	9 (3)
Confusional state	5 (1)
Respiratory, thoracic and mediastinal disorders	15 (4)
Respiratory failure	4 (1)

- Laboratory findings

Clinically significant abnormal high serum chemistry values occurred for BUN, serum creatinine, uric acid, AST, ALT, alkaline phosphatase, and total bilirubin, and for the haematology values clinically significant abnormal high values occurred for WBC count, eosinophils, and platelet counts. The most frequently reported of these clinically significant hematology abnormalities were low hematocrit values (116 [38%] patients) and low hemoglobin values (76 [25%] patients).

- Safety in special populations

The safety in children and adolescents has not been studied. However, the risk of fatality in children is mentioned in the SPC.

It is known that the clearance of fentanyl after intravenous administration can be impaired in patients with hepatic or renal impairment. Therefore, caution is recommended in the SPC for such patients as well as for the elderly patients (> 65 years).

For all patients with cancer and BTP, the incidence of treatment-emergent adverse events was summarized for patient subgroups based on age group (≤ 65 years, > 65 years), BMI group ($<$ median [25.8 kg/m^2], \geq median), sex (men, women), and race group (white, nonwhite).

Taking extrinsic factors into consideration, for all patients with cancer and BTP, the incidence of adverse events was summarized for patient subgroups based on prior BTP therapy (OTFC, other), average daily dose, and average dose per BTP episode. The observed differences in adverse events were considered to be of minor clinical significance.

No studies have been conducted to evaluate the potential withdrawal and/or rebound effects of FEBT treatment. Adverse events of drug withdrawal syndrome or narcotic (opiate) withdrawal syndrome or symptoms were reported for 6 patients (1 patient with cancer pain and 5 patients with chronic non-cancer pain and BTP pain).

Overdose and drug abuse

Seven patients, all with chronic non-cancer pain and BTP, reported adverse events related to excessive opioid effects thought to be associated with opioid overdose. FEBT is a new formulation of fentanyl citrate designed for use by opioid-tolerant cancer patients with BTP. The abuse potential of fentanyl is well known and the same as other strong opioid analgesics. Because of the potential for abuse, a Risk Minimization Action Plan has been developed for FEBT. This plan includes tools designed to minimize the level of abuse and to minimize diversion of FEBT after it becomes commercially available.

- Safety related to drug-drug interactions and other interactions

The potential for drug-drug interaction (see pharmacokinetic section) is known in the scientific literature and adequately reflected in the SPC. In addition, the concomitant use with partial opioid agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) may induce withdrawal symptoms in opioid dependent patients. This is also reflected in the SPC.

- Discontinuation due to adverse events

For patients with cancer and BTP, a total of 103 (29%) withdrew from a study due adverse events. The most frequently reported adverse events leading to study withdrawal were nausea (4%) and vomiting (3%). Adverse events related to the application site led to the withdrawal of 6 (2%) patients. Application site ulcer led to the withdrawal of 1% of the patients, and application site erythema, irritation, edema, and pain each led to the withdrawal of 1 patient.

Most withdrawals due to adverse events in the cancer population were considered by the investigator not related or unlikely related to treatment with study drug. For cancer patients it is not unusual to be treated with a large number of different drugs concomitantly. Therefore it is almost impossible to judge which AE was caused by which drug, and hence which drug led to discontinuation.

- Post marketing experience

FEBT is currently marketed in the US only. Patient exposure to FEBT in the US is estimated at over a million patient treatment days.

A total of 120 ADRs were identified, of which 3 were serious up to the date of May 2007. Three additional reports with fatal outcome were received after this cut-off date.

Among the non-serious events, the most common reports were from the system order class of gastrointestinal disorders, with application site events reported more often than others.

All cases of death occurred as a result of improper patient selection (e.g. use in non-opioid tolerant patients), improper dosing, and/or improper product substitution. A safety warning to health care professionals has been issued to explain the dangers of this medicine when used improperly (available on the FDA website).

This is also reflected in the EU Product Information stating that patients experiencing multiple BTP episodes daily should wait at least 4 hours before treating another episode with Effentora, as recommended during clinical trials. In addition the warning on the risk of respiratory depression for non-opioid tolerant patients has been moved as a contra-indication (section 4.3 of the SPC). This is also reflected in the risk management plan as risk minimisation activities.

- Discussion on clinical safety

Fentanyl is a μ -receptor agonist with a profile of pharmacological activity similar to that of morphine, but with greater potency. It is primarily used as an intravenous analgesic, sedative, and anaesthetic before and during surgery, for the treatment of postoperative pain, for chronic pain (transdermal patches), and, finally, for management of breakthrough pain (BTP) in opioid-non-naïve patients with cancer (OTFC). Due to decades of widespread clinical use, the pharmacological / safety profile of the active substance is well established. The known adverse events associated with opioid use, are drug withdrawal syndrome, respiratory depression/failure, and pneumonia.

Therefore, the additional potential issues for the clinical safety of Effentora are whether this innovative administration technique using effervescence and the associated early time of maximum plasma concentration can cause an unexpectedly high incidence of AE typically observed in opioid therapy or of reactions at the application site.

Overall, the most common adverse events observed with FEBT treatment were characteristic of fentanyl-containing products, namely nausea, dizziness, constipation, fatigue, headache, and vomiting. The incidence and types of adverse events did not appear to be dose related which, most presumably, is to be explained by the fact that each patient was titrated to his individual need for analgesia. Furthermore, the rapid absorption of FEBT did not appear to affect the type or severity of adverse events observed in the context of these clinical trials.

Additionally, approximately 10% of patients experienced adverse events that could be considered related to tablet application site, e.g., application site pain, ulcer, or burning. In the majority of patients, these adverse events were mild to moderate and resolved without treatment interruption; women appeared to be at greater risk for application site adverse events. The incidence of application site reactions seen during clinical trials was confirmed by the first post-marketing data that are available from the US. Given the severity of the underlying illnesses of the patients included in the clinical studies, application site disorders are not to be regarded as major safety concerns.

1.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan which included a risk minimisation plan. However, in view of the restricted conditions of use (indication, experienced physicians) and of the well-known risks of fentanyl, the CHMP did not consider that the risk minimisation measures (educational material to healthcare professionals) proposed by the applicant should be mandatory at present.

The identified potential risks with Effentora in the RMP are:

- Misuse, abuse and diversion of Effentora
- Use of Effentora in patients who are not already receiving maintenance opioid therapy for chronic cancer pain
- Unintended (accidental) exposure to Effentora

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Misuse, abuse and diversion of Effentora	<p>Routine pharmacovigilance</p> <p>Expediting will address ADRs of special interest, including serious ADRs associated with suspected overdose, abuse, misuse or diversion.</p> <p>Additional activities</p> <p>Post Marketing Surveillance Plan monitoring the safety profile.</p> <p>Drug utilisation study.</p>	<p>Routine activities</p> <p>Product Information, in particular SPC:</p> <p>Section 4.2: “Physicians should keep in mind the potential of abuse of fentanyl.”</p> <p>Section 4.4: “Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. However, iatrogenic addiction following therapeutic use of opioids is rare.”</p> <p>Additional activities</p> <p>Information and educational program to prescribers</p>
Use of Effentora in patients who are not already receiving maintenance opioid therapy	<p>Routine pharmacovigilance</p> <p>Same as above</p> <p>Additional activities</p> <p>Same as above</p>	<p>Routine activities</p> <p>Section 4.1: “Effentora is indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.”</p> <p>And “Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.”</p> <p>Section 4.2: “Treatment should be initiated by and remain under the guidance of a physician experienced in the management of opioid therapy in cancer patients.”</p> <p>Section 4.3: Patients without maintenance opioid therapy (see section 4.1) as there is an increased risk of respiratory depression.</p> <p>Additional activities</p> <p>Communication to Health Care Professionals, to include information alerting to the potential risk of use in patients not already on opioid maintenance therapy.</p>
Unintended (accidental) exposure to Effentora	<p>Routine pharmacovigilance</p> <p>Same as above</p> <p>Additional activities</p> <p>Same as above</p>	<p>Routine activities</p> <p>Section 4.2: “The tablet should not be stored once removed from the blister package as the tablet integrity can not be guaranteed and a risk of accidental exposure to a tablet can occur.”</p> <p>Section 4.4: “Patients and their carers must be instructed that Effentora contains an active substance in an amount that can be fatal to a child, and therefore to keep all tablets out of the reach and sight of children.”</p> <p>Additional activities</p> <p>Communication to Health Care Professionals, to include information alerting to the potential risk of accidental exposure</p>

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

1.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

Generally, satisfactory documentation has been provided. The active substance is of compendial quality.

Regarding the finished product, the manufacturing process is adequately described and controlled. It should ensure a consistent quality for the product.

Non-clinical pharmacology and toxicology

Fentanyl is a well-known selective opioid agonist interacting primarily at μ opioid receptors located within the central nervous system. Fentanyl possesses analgesic activity with a potency 80-fold higher than morphine, but with shorter duration of action as well as sedative effects.

The safety pharmacology studies confirm the previously known effects of fentanyl on cardiovascular parameters (increased systolic blood pressure, reduced heart rate, ECG-changes including slight QTc-prolongation), CNS (depression) and respiratory system (depression).

The transmucosal absorption of fentanyl is pH dependant (between pH 5 to 7) and its profile has been characterised mainly in humans. Fentanyl is extensively metabolised in all species studied, with dealkylation to norfentanyl as a major metabolic pathway mediated by the CYP3A4.

In acute and repeat dose studies, there was no identified target organ of toxicity and toxic findings were mainly related to the expected respiratory depression.

Fentanyl is not considered to be genotoxic in the standard battery and the carcinogenic potential has not been studied, which is acceptable considering the clinical indication in cancer patients.

Fentanyl is potentially toxic to the reproduction, affecting the embryofoetal survival and fertility in animal studies. Teratogenic effects have not been observed.

The local tolerance is considered to be acceptable.

No negative impact on the environment is expected under the therapeutic use of this medicinal product.

Efficacy

In the 2 pivotal, double-blind, placebo-controlled studies, the efficacy of FEBT was shown to be consistent, with significant (mostly highly significant) differences from placebo across the range of successful doses, across common time points (15, 30, 45, and 60 minutes after administration) and across all measures, including pain intensity (expressed as pain intensity difference and summed pain intensity difference), pain relief, rescue medication usage, and global medication performance. Patients receiving FEBT during the double-blind treatment phase were more than three times less likely to need rescue medication than patients receiving placebo.

However, the order of magnitude of the clinical response as effect size at the early time points is rather small (although highly significant): Summed pain intensity differences after 30 min (SPID₃₀) were between 1.2 and 1.5.

Except for a small proportion of patients for which duration of BTP is very short, the currently proposed dose range of 100 to 800 mcg has been proven to be effective for a large proportion of patients. On the other hand, the prolonged BTP episodes in some patients should also be taken into consideration, since such patients may well profit from a duration of action (up to 2 hours) that exceeds the average BTP periods.

Overall, the product is nevertheless considered to be at least as efficient as current alternative oral treatments when taking into account the time-window of the transient BTP episodes.

Safety

The safety analysis set for chronic cancer pain comprises 358 patients, and that for noncancer pain comprises 740 patients which is considered to be sufficiently large for safety evaluation. Overall, the most common adverse events observed with FEBT treatment were characteristic of fentanyl products, namely nausea, dizziness, constipation, fatigue, headache, and vomiting. The incidence and types of adverse events did not appear to be dose related which, most presumably, is to be explained by the fact that each patient was titrated to his individual need for analgesia. Furthermore, the rapid absorption of FEBT did not appear to affect the type or severity of adverse events observed.

Approximately 10% of patients experienced adverse events that could be considered related to tablet application site, e.g., application site pain, ulcer, or burning. In the majority of patients, these adverse events were mild to moderate and resolved without treatment interruption; women appeared to be at greater risk for application site adverse events. The incidence of application site reactions seen during clinical trials was confirmed by the first post-marketing data that are available from the US. Given the severity of the underlying illnesses of the patients included in the clinical studies, application site disorders are not to be regarded as major safety concerns.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The most frequently occurring adverse events ($\geq 10\%$ of patients by preferred term) in this patient population were the following: nausea, dizziness, vomiting, fatigue, headache, constipation, somnolence, anemia and peripheral edema. Adverse events related to the application site were reported for 31 (9%) patients.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities adequately addressed these.

User consultation

Readability testing was conducted by in UK using the English version of the Patient Leaflet of the 100 mcg strength of Effentora. The protocol was laid out in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC as amended. The test was conducted with 20 volunteer adults between 18 and 66 years old with an equal split of males and females.

Acceptable answers to each question were found and understood by a minimum of 80% of subjects over two rounds of user testing. Therefore, the Patient Leaflet satisfies the obligations of the relevant legislation and guidelines.

Risk-benefit assessment

Efficacy of Effentora has been demonstrated in two phase III studies and one additional open-label continuation study in the treatment of breakthrough pain (BTP) in patients with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

The pharmacology of fentanyl and its associated efficacy and safety profile has been well established after decades of clinical use as intravenous or transdermal dosage forms. The particular absorption profile of the fentanyl effervescence buccal tablet technology with an estimated fraction of about 50% transmucosal absorption did not raise particular safety concerns during the clinical trials. No unexpected trends in serious AEs have been observed in these trials.

The overall benefit-risk assessment is therefore favourable. The applicant commits to perform a number of post authorisation follow-up measures with the objective to monitor the safety profile of Effentora and to report back to the CHMP within predefined timeframes.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns:
 - Misuse, abuse and diversion
 - Use in patients who are not already receiving maintenance opioid therapy for chronic cancer pain
 - Unintended (accidental) exposure to Effentora

These activities (see follow-up measures) include a Post Marketing Surveillance Plan monitoring the safety profile of Effentora (several studies) and a Drug utilisation study.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered 24 January 2008 that the risk-benefit balance of Effentora in the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain, was favourable and therefore recommended the granting of the marketing authorisation.