

1. NAME OF THE MEDICINAL PRODUCT

Effentora[®] ▼ 100, 200, 400, 600 and 800 micrograms buccal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each buccal tablet contains 100, 200, 400, 600 and 800 micrograms fentanyl (as citrate).

Excipient(s): Each 100 micrograms tablet contains 8 mg of sodium. Each 200 micrograms tablet contains 16 mg of sodium. Each 400 micrograms tablet contains 16 mg of sodium. Each 600 micrograms tablet contains 16 mg of sodium. Each 800 micrograms tablet contains 16 mg of sodium. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Buccal tablet.

Flat-faced, white, round bevelled-edge tablet, embossed on one side with a “C” and on the other side with “1” for 100 micrograms tablet, “2” for 200 micrograms tablet, “4” for 400 micrograms tablet, “6” for 600 micrograms tablet and “8” for 800 micrograms tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

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.

4.2 Posology and method of administration

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

Dose titration

Effentora should be individually titrated to an “effective” dose that provides adequate analgesia and minimises undesirable effects. In clinical studies, the effective dose of Effentora for BTP was not predictable from the daily maintenance dose of opioid.

Patients should be carefully monitored until an effective dose is reached.

Titration in patients not switching from other fentanyl containing products

The initial dose of Effentora should be 100 micrograms, titrating upwards as necessary through the range of available tablets strengths (100, 200, 400, 600, 800 micrograms).

Titration in patients switching from other fentanyl containing products

Due to different absorption profiles, switching must not be done at a 1:1 ratio. If switching from another oral fentanyl citrate product, independent dose titration with Effentora is required as bioavailability between products differs significantly. However, in these patients, a starting dose higher than 100 micrograms may be considered.

Method of titration

During titration, if adequate analgesia is not obtained within 30 minutes after the start of administration of a single tablet, a second Effentora tablet of the same strength may be used.

If treatment of a BTP episode requires more than one tablet, an increase in dose to the next higher available strength should be considered to treat the next BTP episode.

During titration, multiple tablets may be used: up to four 100 micrograms or up to four 200 micrograms tablets may be used to treat a single episode of BTP during dose titration according to the following schedule:

- If the initial 100 micrograms tablet is not efficacious, the patient can be instructed to treat the next episode of BTP with two 100 micrograms tablets. It is recommended that one tablet should be placed in each side of the mouth. If this dose is considered to be the effective dose, treatment of successive episodes of BTP may be continued with a single 200 micrograms tablet of Effentora.
- If a single 200 micrograms tablet of Effentora (or two 100 micrograms tablets) is not considered to be efficacious the patient can be instructed to use two 200 micrograms tablets (or four 100 micrograms tablets) to treat the next episode of BTP. It is recommended that two tablets should be placed in each side of the mouth. If this dose is considered to be the effective dose, treatment of successive episodes of BTP may be continued with a single 400 micrograms tablet of Effentora.
- For titration to 600 micrograms and 800 micrograms, tablets of 200 micrograms should be used.

Doses above 800 micrograms were not evaluated in clinical studies.

No more than two tablets should be used to treat any individual BTP episode, except when titrating using up to four tablets as described above.

Patients should wait at least 4 hours before treating another BTP episode with Effentora during titration.

Maintenance therapy

Once an effective dose has been established during titration, patients should continue to take this dose as a single tablet of that given strength.

Patients should wait at least 4 hours before treating another BTP episode with Effentora during maintenance therapy.

Dose readjustment

Generally, the maintenance dose of Effentora should be increased when a patient requires more than one dose per BTP episode for several consecutive BTP episodes.

Dose readjustment of Effentora and/or of the background opioid therapy may be required if patients consistently present with more than four BTP episodes per 24 hours.

Discontinuation of therapy

Effentora should be immediately discontinued if no longer required.

Use in children and adolescents:

Effentora is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

Use in the elderly (older than 65 years):

In clinical studies patients older than 65 years tended to titrate to a lower effective dose than younger patients. It is recommended that increased caution should be exercised in titrating the dose of Effentora in elderly patients.

Hepatic or renal impairment:

Effentora should be administered with caution to patients with moderate or severe hepatic or renal impairment (see section 4.4).

Patients with xerostomia:

Patients experiencing xerostomia are advised to drink water to moisten the buccal cavity prior to administration of Effentora. If this recommendation does not result in an appropriate effervescence, then a switch of therapy may be advised.

Method of administration:

Effentora tablet once exposed to moisture utilises an effervescent reaction to deliver the active substance. Therefore patients should be instructed not to open the blister until ready to place the tablet in the buccal cavity.

Opening the blister package

Patients should be instructed NOT to attempt to push the tablet through the blister because this could damage the buccal tablet. The correct method of releasing the tablet from the blister is: One of the blister units should be separated from the blister card by tearing it apart at the perforations. The blister unit should then be flexed along the line printed on the backing foil where indicated. The backing foil should be peeled back to expose the tablet. Patients should be instructed not to attempt to crush or split the tablet.

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.

Tablet administration

Patients should remove the tablet from the blister unit and immediately place the entire Effentora tablet in the upper portion of the buccal cavity (above an upper rear molar between the cheek and gum).

Effentora should be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet which usually takes approximately 14-25 minutes.

The Effentora tablet should not be sucked, chewed or swallowed, as this will result in lower plasma concentrations than when taken as directed.

After 30 minutes, if remnants from the Effentora tablet remain, they may be swallowed with a glass of water.

The length of time that the tablet takes to fully disintegrate following oromucosal administration does not appear to affect early systemic exposure to fentanyl.

Patients should not consume any food and drink when a tablet is in the buccal cavity. In case of buccal mucosa irritation, a change in tablet placement within the buccal cavity should be recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients without maintenance opioid therapy (see section 4.1) as there is an increased risk of respiratory depression.

Severe respiratory depression or severe obstructive lung conditions.

4.4 Special warnings and precautions for use

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.

In order to minimise the risks of opioid-related undesirable effects and to identify the effective dose, it is imperative that patients be monitored closely by health professionals during the titration process.

It is important that the long acting opioid treatment used to treat the patient's persistent pain has been stabilised before Effentora therapy begins.

As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of fentanyl. Particular caution should be used when titrating Effentora in patients with non-severe chronic obstructive pulmonary disease or other medical conditions predisposing them to respiratory depression, as even normally therapeutic doses of Effentora may further decrease respiratory drive to the point of respiratory failure.

Effentora should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO₂ retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

Intravenous fentanyl may produce bradycardia. In clinical trials with Effentora, no clear evidence for bradycardia was observed. However, Effentora should be used with caution in patients with pre-existing bradyarrhythmias.

In addition, Effentora should be administered with caution to patients with hepatic or renal impairment. The influence of hepatic and renal impairment on the pharmacokinetics of the medicinal product has not been evaluated, however, when administered intravenously the clearance of fentanyl has been shown to be altered in hepatic and renal impairment due to alterations in metabolic clearance and plasma proteins. After administration of Effentora, impaired hepatic and renal function may both increase the bioavailability of swallowed fentanyl and decrease its systemic clearance, which could lead to increased and prolonged opioid effects. Therefore, special care should be taken during the titration process in patients with moderate or severe hepatic or renal impairment.

Careful consideration should be given to patients with hypovolaemia and hypotension.

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.

This medicinal product contains
8 mg sodium per 100 micrograms tablet. 16 mg sodium per 200 micrograms tablet. 16 mg sodium per 400 micrograms tablet. 16 mg sodium per 600 micrograms tablet. 16 mg sodium per 800 micrograms tablet. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Fentanyl is metabolised mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore potential interactions may occur when Effentora is given concurrently with agents that affect CYP3A4 activity. Coadministration with agents that induce 3A4 activity may reduce the efficacy of Effentora. The concomitant use of Effentora with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, and nelfinavir) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug reactions including fatal respiratory depression. Patients receiving Effentora concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done with caution.

The concomitant use of other central nervous system depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcohol may produce additive depressant effects.

Effentora is not recommended for use in patients who have received monoamine oxidase (MAO) inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

The concomitant use of partial opioid agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependant patients.

4.6 Pregnancy and lactation

There are no adequate data from the use of fentanyl in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Effentora should not be used in pregnancy unless clearly necessary.

Following long-term treatment, fentanyl may cause withdrawal in the new-born infant. It is advised not to use fentanyl during labour and delivery (including caesarean section) because fentanyl passes through the placenta and may cause respiratory depression in the foetus. If Effentora is administered, an antidote for the child should be readily available.

Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should only be used by breastfeeding women if the benefits outweigh the potential risks for both mother and child.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients should be advised not to drive or operate machinery if they experience somnolence, dizziness, or visual disturbance while taking Effentora and not to drive or operate machinery until they know how they react.

4.8 Undesirable effects

Typical opioid undesirable effects are to be expected with Effentora. Frequently, these will cease or decrease in intensity with continued use of the medicinal product, as the patient is titrated to the most appropriate dose. However, the most serious adverse reactions are respiratory depression (potentially

leading to apnoea or respiratory arrest), circulatory depression, hypotension and shock and all patients should be closely monitored for these.

The clinical studies of Effentora were designed to evaluate safety and efficacy in treating BTP and all patients were also taking concomitant opioids, such as sustained-release morphine or transdermal fentanyl, for their persistent pain. Therefore it is not possible to definitively separate the effects of Effentora alone.

The adverse reactions considered to be at least possibly-related to treatment from clinical studies were as follows (frequencies defined as: very common $\geq 1/10$, common $\geq 1/100$ to $< 1/10$, uncommon $\geq 1/1,000$ to $< 1/100$; within each frequency grouping, undesirable effects are presented in order of decreasing seriousness):

	Very common	Common	Uncommon
Investigations			Platelet count decreased Heart rate increased Haematocrit decreased Haemoglobin decreased
Cardiac disorders			Tachycardia, Bradycardia
Blood and lymphatic system disorders			Anaemia Neutropenia Thrombocytopenia
Nervous system disorders	Dizziness	Dysgeusia Somnolence Lethargy Headache Tremor Sedation	Depressed level of consciousness Disturbance in attention Cognitive disorder Hypoaesthesia Balance disorder Migraine Motor dysfunction Dysarthria
Eye disorders			Visual disturbance Ocular hyperaemia Abnormal sensation in eye Photopsia Blurred vision Visual acuity reduced
Ear and labyrinth disorders			Vertigo Tinnitus Ear discomfort
Respiratory, thoracic and mediastinal disorders			Dyspnoea Pharyngolaryngeal pain

	Very common	Common	Uncommon
Gastrointestinal disorders	Nausea	Vomiting Constipation Stomatitis Dry mouth Diarrhoea	Mouth ulceration Oral hypoaesthesia Oral discomfort Oral mucosal blistering Oral mucosal discolouration Oral soft tissue disorder Glossodynia Tongue blistering Gingival pain Stomach discomfort Tongue ulceration Tongue disorder Dyspepsia Abdominal pain Oesophagitis Gastrooesophageal reflux disease Chapped lips Dry lip Tooth disorder Toothache
Renal and urinary disorders			Urinary retention
Skin and subcutaneous tissue disorders		Pruritis Hyperhidrosis	Cold sweat Facial swelling Rash Generalised pruritus Alopecia Onychorrhexis
Musculoskeletal and connective tissue disorders			Myalgia Muscle twitching Muscular weakness Back pain
Metabolism and nutrition disorders			Anorexia
Infections and infestations			Oral candidiasis Pharyngitis Oral pustule
Injury, poisoning and procedural complications			Fall
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Multiple myeloma
Vascular disorders			Flushing Hypertension Hot flush

	Very common	Common	Uncommon
General disorders and administration site conditions	Application site reactions including pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles	Fatigue	Asthenia Malaise Sluggishness Chest discomfort Feeling abnormal Feeling jittery Thirst Feeling cold Chills Feeling hot Drug withdrawal syndrome
Psychiatric disorders		Disorientation Euphoric mood	Anxiety Nervousness Hallucination Visual hallucination Insomnia Confusional state

4.9 Overdose

The symptoms of fentanyl overdose are expected to be similar in nature to those of intravenous fentanyl and other opioids, and are an extension of its pharmacological actions, with the most serious significant effect being respiratory depression.

Immediate management of opioid overdose includes removal of the Effentora buccal tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, assessment of the level of consciousness, ventilatory and circulatory status, and assisted ventilation (ventilatory support) if necessary.

For treatment of overdose (accidental ingestion) in the opioid-naive person, intravenous access should be obtained and naloxone or other opioid antagonists should be employed as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the Summary of Product Characteristics of the individual opioid antagonist for details about such use.

For treatment of overdose in opioid-maintained patients, intravenous access should be obtained. The judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

Although muscle rigidity interfering with respiration has not been seen following the use of Effentora, this is possible with fentanyl and other opioids. If it occurs, it should be managed by the use of assisted ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics; opioids; phenylpiperidine derivatives; ATC code N02AB03.

Fentanyl is an opioid analgesic, interacting predominantly with the opioid μ -receptor. Its primary therapeutic actions are analgesia and sedation. Secondary pharmacological effects are respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria.

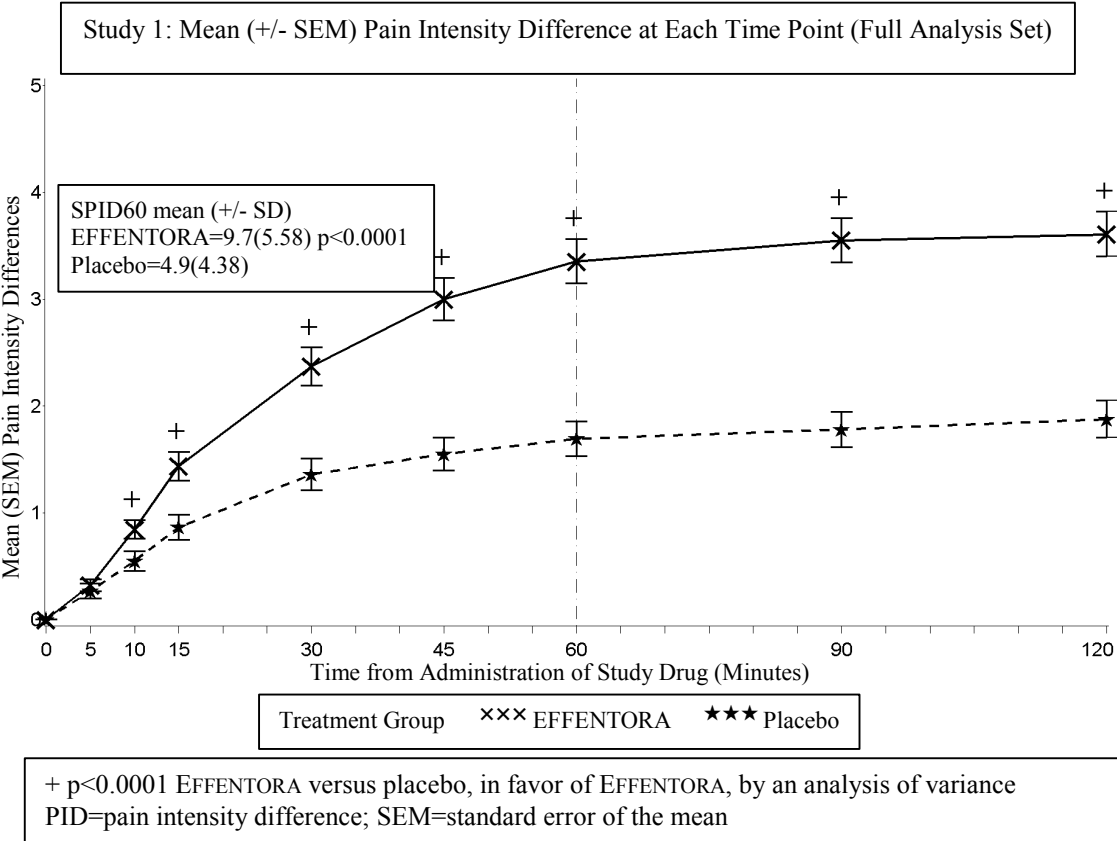
The analgesic effects of fentanyl are related to its plasma level. In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance to opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of Effentora should be individually titrated to achieve the desired effect (see section 4.2).

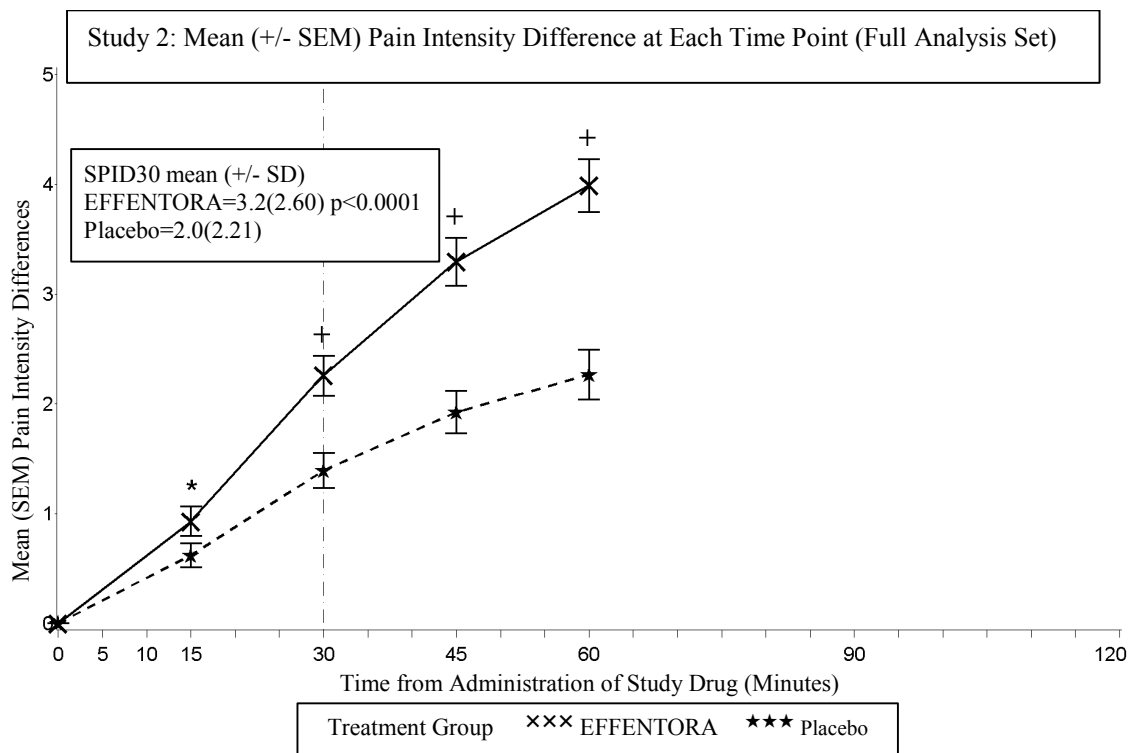
All opioid μ -receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy as these patients will develop tolerance to respiratory depressant effects.

The safety and efficacy of Effentora have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Pre-emptive use of Effentora for predictable pain episodes was not investigated in the clinical trials. Two double-blind, randomized, placebo-controlled crossover studies have been conducted involving a total of 248 patients with BTP and cancer who experienced on average 1 to 4 episodes of BTP per day while taking maintenance opioid therapy. During an initial open-label phase, patients were titrated to an effective dose of Effentora. Patients who identified an effective dose entered the double-blind phase of the study. The primary efficacy variable was the patient’s assessment of pain intensity. Patients assessed pain intensity on a 11-point scale. For each BTP episode, pain intensity was assessed prior to and at several time points after treatment.

Sixty-seven percent of the patients were able to be titrated to an effective dose.

In the pivotal clinical study (study 1), the primary endpoint was the average sum of differences in pain intensity scores from dosing to 60 minutes, inclusive (SPID60), which was statistically significant compared to placebo ($p < 0.0001$).





* p<0.01 EFFENTORA versus placebo, in favor of EFFENTORA, by one-sample Wilcoxon signed rank test
+ p<0.0001 EFFENTORA versus placebo, in favor of EFFENTORA, by one-sample Wilcoxon signed rank test
PID=pain intensity difference; SEM=standard error of the mean

In the second pivotal study (study 2), the primary endpoint was SPID30, which was also statistically significant compared to placebo (p<0.0001).

Statistically significant improvement in pain intensity difference was seen with Effentora versus placebo as early as 10 minutes in Study 1 and as early as 15 minutes (earliest time point measured) in Study 2. These differences continued to be significant at each subsequent time point in each individual study.

5.2 Pharmacokinetic properties

General introduction

Fentanyl is highly lipophilic and can be absorbed very rapidly through the oral mucosa and more slowly by the conventional gastrointestinal route. It is subject to first-pass hepatic and intestinal metabolism and the metabolites do not contribute to fentanyl's therapeutic effects.

Effentora employs a delivery technology which utilises an effervescent reaction which enhances the rate and extent of fentanyl absorbed through the buccal mucosa. Transient pH changes accompanying the effervescent reaction may optimise dissolution (at a lower pH) and membrane permeation (at a higher pH).

Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not affect early systemic exposure to fentanyl.

The effect of renal or hepatic impairment on the pharmacokinetics of Effentora has not been studied.

Absorption:

Following oromucosal administration of Effentora, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of Effentora is largely the result of an initial rapid

absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after oromucosal administration. Approximately 50% of the total dose administered is rapidly absorbed transmucosally and becomes systemically available. The remaining half of the total dose is swallowed and slowly absorbed from the gastrointestinal tract. About 30% of the amount swallowed (50% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available.

The main pharmacokinetic parameters are shown in the following table.

Pharmacokinetic Parameters* in Adult Subjects Receiving Effentora

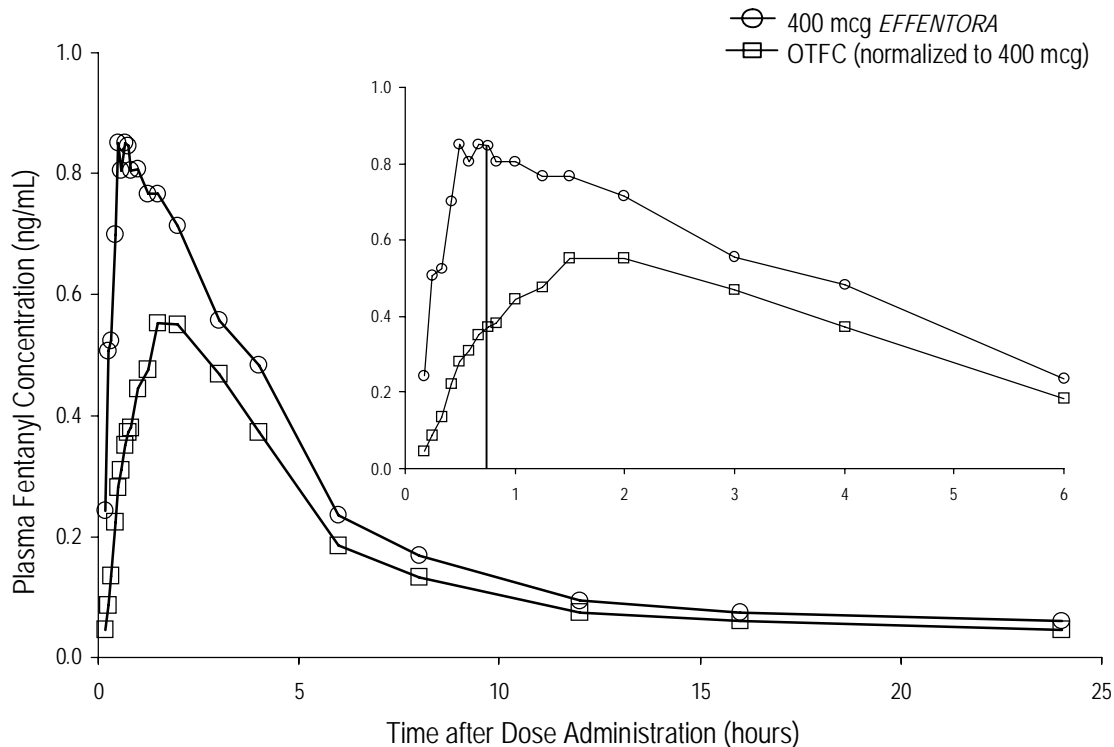
Pharmacokinetic parameter (mean)	Effentora 400 micrograms
Absolute bioavailability	65% ($\pm 20\%$)
Fraction absorbed transmucosally	48% ($\pm 31.8\%$)
T_{max} (minute) **	46.8 (20-240)
C_{max} (ng/ml)	1.02 (± 0.42)
AUC_{0-tmax} (ng.hr/ml)	0.40 (± 0.18)
AUC_{0-inf} (ng.hr/ml)	6.48 (± 2.98)

* Based on venous blood samples (plasma). Fentanyl citrate concentrations obtained in serum were higher than in plasma: Serum AUC and C_{max} were approximately 20% and 30% higher than plasma AUC and C_{max}, respectively. The reason of this difference is unknown.

** Data for T_{max} presented as median (range).

In pharmacokinetic studies that compared the absolute and relative bioavailability of Effentora and oral transmucosal fentanyl citrate (OTFC), the rate and extent of fentanyl absorption in Effentora demonstrated exposure that was between 30% to 50% greater than that for oral transmucosal fentanyl citrate. If switching from another oral fentanyl citrate product, independent dose titration with Effentora is required as bioavailability between products differs significantly. However, in these patients, a starting dose higher than 100 micrograms may be considered.

Mean Plasma Concentration Versus Time
Profiles Following Singles Doses of *EFFENTORA* and OTFC in Healthy Subjects



OTFC data was dose adjusted (800 mcg to 400 mcg)

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 were not clinically significant.

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.

Biotransformation

The metabolic pathways following buccal administration of Effentora have not been characterised in clinical studies. 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.

Elimination

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 median terminal elimination half-life $t_{1/2}$ of approximately 22 hours following buccal administration of the effervescent formulation and approximately 18 hours following intravenous administration. The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h.

Linearity/non-linearity

Dose proportionality from 100 micrograms to 1000 micrograms has been demonstrated.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

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.

Long term carcinogenicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium starch glycolate type A
Sodium hydrogen carbonate
Sodium carbonate anhydrous
Citric acid anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium laminated blister of PVC/Al foil/Polyamide/PVC with paper/polyester lidding.

Blister packs are supplied in cartons of 4 or 28 tablets. Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

Patients and carers must be advised to dispose of any unopened tablets remaining from a prescription as soon as they are no longer needed.

Any used or unused but no longer required product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Cephalon Europe
5 rue Charles Martigny
F-94700 Maisons-Alfort
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/001-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 April 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu>.