ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Effentora 100 micrograms buccal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each buccal tablet contains 100 micrograms fentanyl (as citrate).

Excipient(s) with known effect: Each tablet contains 8 mg of sodium.
For the 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”.

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. Patients should be instructed not to use two different formulations of fentanyl concurrently for the treatment of breakthrough pain, and to dispose of any fentanyl product prescribed for BTP when switching to Effentora. The number of tablet strengths available to the patients at any time should be minimised to prevent confusion and potential overdose.

<u>Posology</u>

Dose titration

Effentora should be individually titrated to an “effective” dose that provides adequate analgesia and minimises adverse reactions. 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.

<u>Titration in patients not switching from other fentanyl containing products</u>
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. Breakthrough pain episodes may vary in intensity and the required Effentora dose might increase over time due to progression of the underlying cancer disease. In these cases, a second tablet of the same strength may be used. If a second tablet of Effentora was required for several consecutive times, the usual maintenance dose is to be readjusted (see below). Patients should wait at least 4 hours before treating another BTP episode with Effentora during maintenance therapy.

Dose readjustment

The maintenance dose of Effentora should be increased when a patient requires more than one tablet per BTP episode for several consecutive BTP episodes. For dose-readjustment the same principles apply as outlined for *dose titration* (see above).
Dose readjustment 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.

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.

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.

Paediatric population:

The safety and efficacy of Effentora in children aged 0 to 18 years have not been established. No data are available.

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 buccal cavity (near a molar between the cheek and gum).

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

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.
Alternatively, the tablet could be placed sublingually (see section 5.2).

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 listed in section 6.1.

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.

Treatment of acute pain other than breakthrough pain (e.g. postoperative pain, headache, migraine).

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, especially to a child. Therefore they must keep all tablets out of the sight and reach 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 and that the patient continues to be treated with the long acting opioid treatment whilst taking Effentora.

Respiratory depression
As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of fentanyl. Improper patient selection (e.g., use in patients without maintenance opioid therapy) and/or improper dosing have resulted in fatal outcome with Effentora as well as with other fentanyl products.
Effentora should only be used for conditions specified in section 4.1.

Chronic obstructive pulmonary disease
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.

Increased intracranial pressure, impaired consciousness
Effentora should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 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.

Cardiac disease
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.

Hepatic or renal impairment

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, dependence
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.

Controlled sodium diet
This medicinal product contains 8 mg sodium per 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 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should not be used by breastfeeding women and breastfeeding should not be restarted until at least 48 hours after the last administration of fentanyl.

Fertility
There are no human data on fertility available. In animal studies, male fertility was impaired (See Section 5.3).

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

Summary of the safety profile
Typical opioid adverse reactions 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.

Tabulated list of adverse reactions
The following adverse reactions have been reported with Effentora during clinical studies and post marketing experience. Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency (frequencies are defined as: very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to <1/100, rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data); within each frequency group, undesirable effects are presented in order of decreasing seriousness:

	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Oral candidiasis	Pharyngitis	Oral pustule	
Blood and lymphatic system disorders		Anaemia Neutropenia	Thrombocyto-penia		
Endocrine disorders				Hypogonadism	
Metabolism and nutrition disorders		Anorexia			

	Very common	Common	Uncommon	Rare	Not known
Psychiatric disorders		Depression Anxiety Confusional state Insomnia	Euphoric mood Nervousness Hallucination Visual hallucination Mental status changes Drug dependence (addiction) Disorientation		
Nervous system disorders	Dizziness Headache	Dysgeusia Somnolence Lethargy Tremor Sedation Hypoaesthesia Migraine	Depressed level of consciousness Disturbance in attention Balance disorder Dysarthria	Cognitive disorder Motor dysfunction	Loss of consciousness
Eye disorders			Visual disturbance Ocular hyperaemia Blurred vision Visual acuity reduced	Abnormal sensation in eye Photopsia	
Ear and labyrinth disorders			Vertigo Tinnitus Ear discomfort		
Cardiac disorders		Tachycardia	Bradycardia		
Vascular disorders		Hypotension Hypertension	Flushing Hot flush		
Respiratory, thoracic and mediastinal disorders		Dyspnoea Pharyngolaryn-geal pain	Respiratory depression Sleep apnoea syndrome		Respiratory arrest
Gastro-intestinal disorders	Nausea Vomiting	Constipation Stomatitis Dry mouth Diarrhoea Abdominal pain Gastro-oesophageal reflux disease Stomach discomfort Dyspepsia Toothache	Ileus Mouth ulceration Oral hypoaesthesia Oral discomfort Oral mucosal discolouration Oral soft tissue disorder Glossodynia Tongue blistering Gingival pain Tongue	Oral mucosal blistering Dry lip	

	Very common	Common	Uncommon	Rare	Not known
			ulceration Tongue disorder Oesophagitis Chapped lips Tooth disorder		
Hepatobiliary disorders			Biliary dilatation		
Skin and subcutaneous tissue disorders		Pruritus Hyperhidrosis Rash	Cold sweat Facial swelling Generalised pruritus Alopecia	Onychorrhexis	
Musculoskeletal and connective tissue disorders		Myalgia Back pain	Muscle twitching Muscular weakness		
Renal and urinary disorders			Urinary retention		
General disorders and administration site conditions	Application site reactions including bleeding, pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles	Peripheral oedema Fatigue Asthenia Drug withdrawal syndrome Chills	Malaise Sluggishness Chest discomfort Feeling abnormal Feeling jittery Thirst Feeling cold Feeling hot		
Investigations		Weight decreased	Platelet count decreased Heart rate increased Haematocrit decreased Haemoglobin decreased		
Injury, poisoning and procedural complications		Fall			

Description of selected adverse reactions

Tolerance, physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl.

Opioid withdrawal symptoms such as nausea, vomiting, diarrhoea, anxiety and shivering have been observed in studies with Effentora.

Loss of consciousness and respiratory arrest have been observed in the context of overdose.

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 effects being altered mental status, loss of consciousness, hypotension, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.

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; 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).

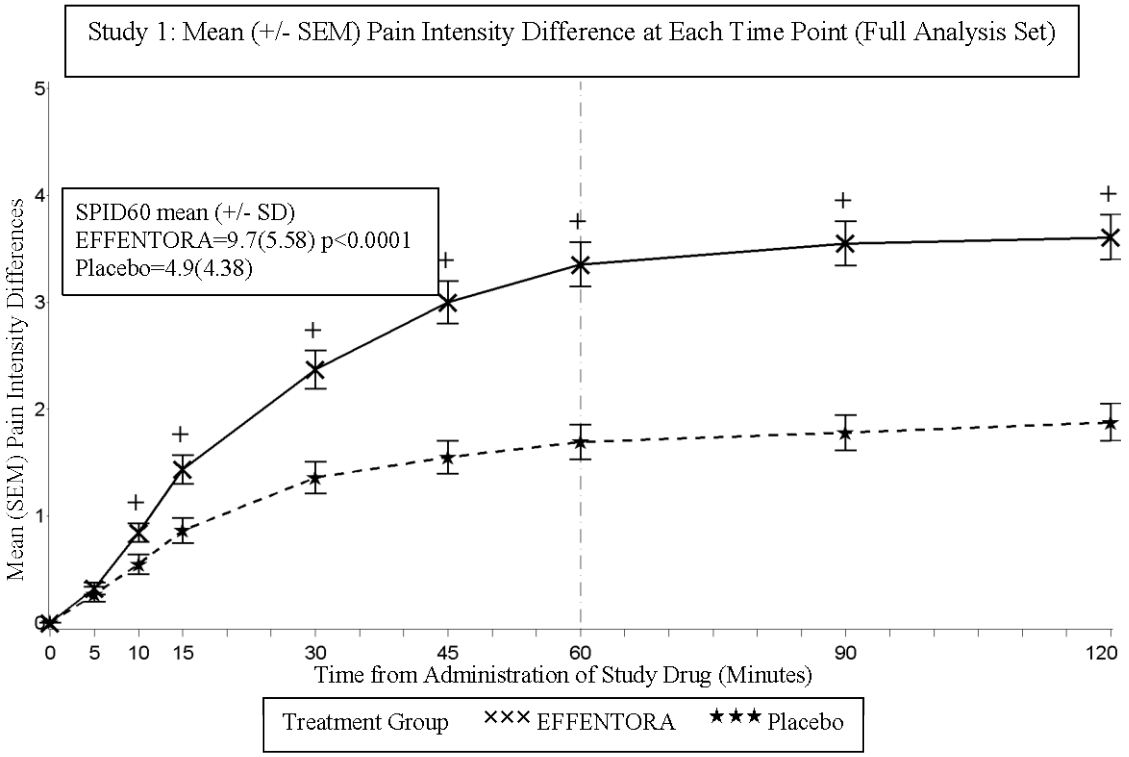
All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy as these patients will develop tolerance to respiratory depressant effects.

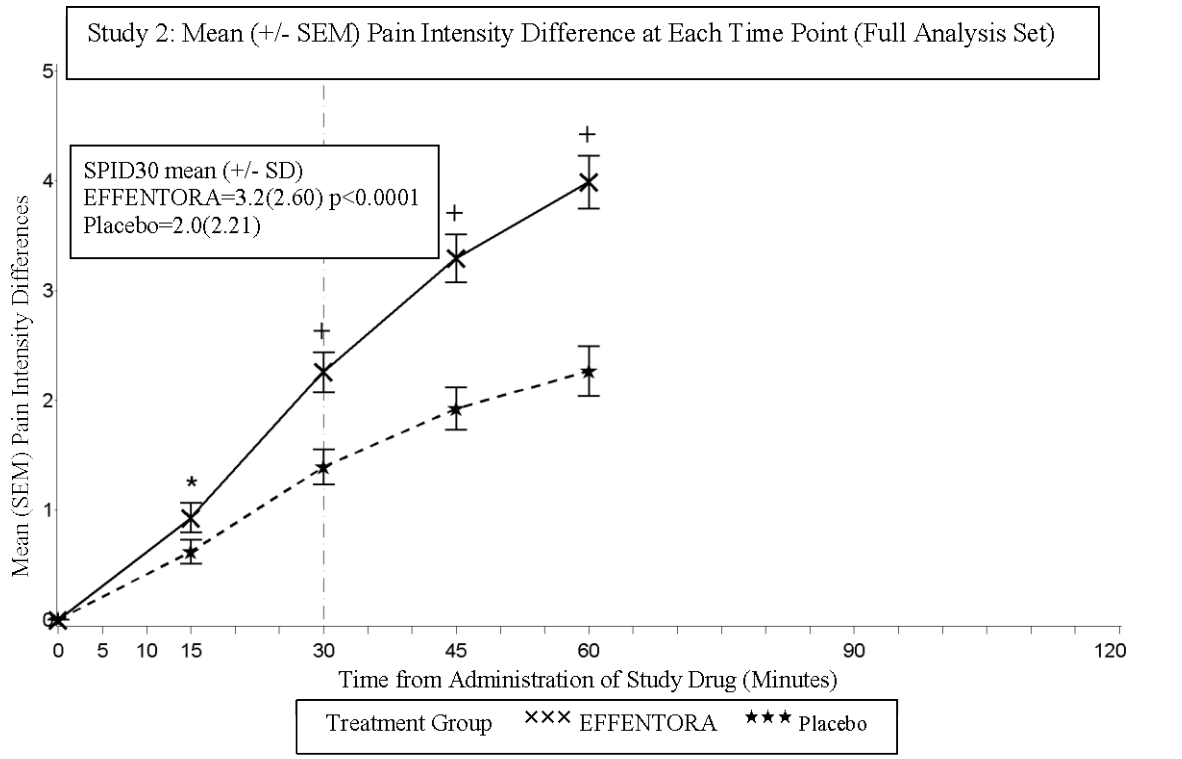
The safety and efficacy of Effentora have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Pre-emptive use of Effentora for predictable pain episodes was not investigated in the clinical trials. Two double-blind, randomized, placebo-controlled crossover studies 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. A comparison study between one 400 mcg Effentora tablet administered either buccally (i.e., between the cheek and the gum) or sublingually met the criteria of bioequivalence.

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.

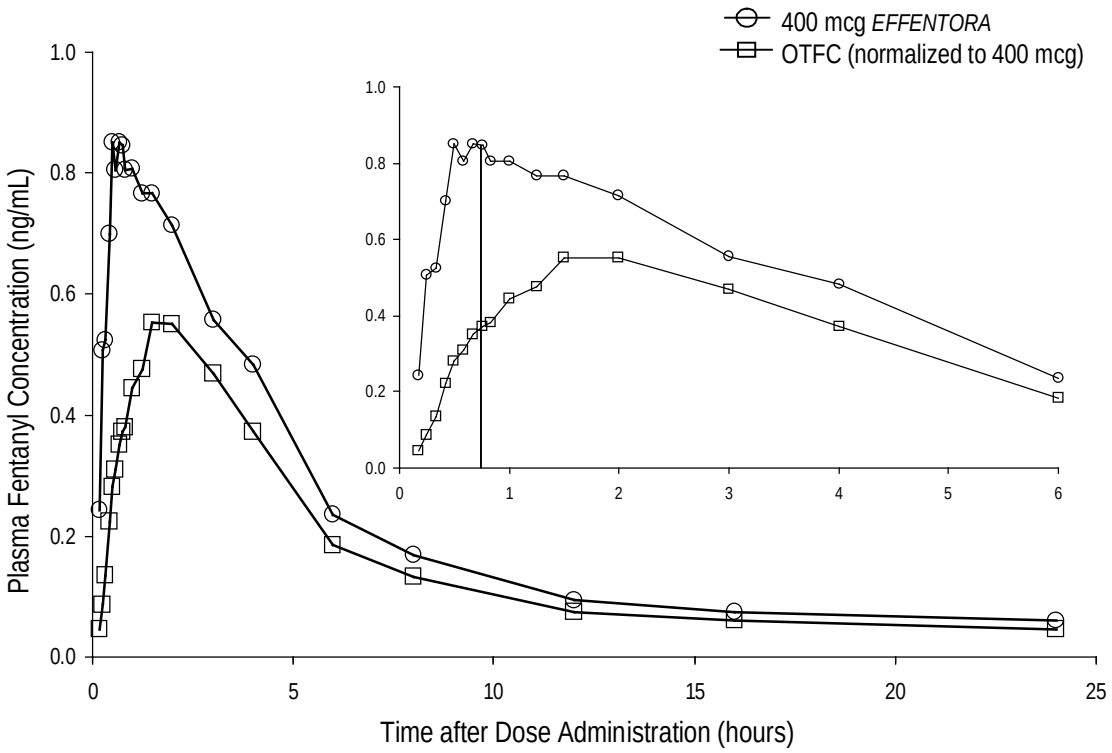
Pharmacokinetic Parameters in Adult Subjects Receiving Effentora*

Pharmacokinetic parameter (mean)	Effentora **400 micrograms**
Absolute bioavailability	**65%** (±20%)
Fraction absorbed transmucosally	**48%** (±31.8%)
T_{max} (minute) **	**46.8** (20-240)
C_{max} (ng/ml)	**1.02** (± 0.42)
$AUC_{0\text{-}tmax}$ (ng.hr/ml)	**0.40** (± 0.18)
$AUC_{0\text{-}inf}$ (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 Cmax were approximately 20% and 30% higher than plasma AUC and Cmax, 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, genotoxicity and carcinogenicity.

Embryo-foetal developmental toxicity studies conducted in rats and rabbits revealed no compound-induced malformations or developmental variations when administered during the period of organogenesis.

In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 mcg/kg/day, s.c.) and is considered secondary to the sedative effects of fentanyl in animal studies.
In studies on pre and postnatal development in rats the survival rate of offspring was significantly reduced at doses causing severe maternal toxicity. Further findings at maternally toxic doses in F1 pups were delayed physical development, sensory functions, reflexes and behaviour. These effects could either be indirect effects due to altered maternal care and/or decreased lactation rate or a direct effect of fentanyl on the pups.

Carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) did not reveal any findings indicative of oncogenic potential.

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

3 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10
3542DR Utrecht
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 April 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Effentora 200 micrograms buccal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each buccal tablet contains 200 micrograms fentanyl (as citrate).

Excipient(s) with known effect: Each tablet contains 16 mg of sodium.
For the 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 “2”.

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. Patients should be instructed not to use two different formulations of fentanyl concurrently for the treatment of breakthrough pain, and to dispose of any fentanyl product prescribed for BTP when switching to Effentora. The number of tablet strengths available to the patients at any time should be minimised to prevent confusion and potential overdose.

<u>Posology</u>

Dose titration

Effentora should be individually titrated to an “effective” dose that provides adequate analgesia and minimises adverse reactions. 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.

<u>Titration in patients not switching from other fentanyl containing products</u>
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. Breakthrough pain episodes may vary in intensity and the required Effentora dose might increase over time due to progression of the underlying cancer disease. In these cases, a second tablet of the same strength may be used. If a second tablet of Effentora was required for several consecutive times, the usual maintenance dose is to be readjusted (see below). Patients should wait at least 4 hours before treating another BTP episode with Effentora during maintenance therapy.

Dose readjustment

The maintenance dose of Effentora should be increased when a patient requires more than one tablet per BTP episode for several consecutive BTP episodes. For dose-readjustment the same principles apply as outlined for *dose titration* (see above).
Dose readjustment 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.

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.

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.

Paediatric population:

The safety and efficacy of Effentora in children aged 0 to 18 years have not been established. No data are available.

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 buccal cavity (near a molar between the cheek and gum).

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

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.
Alternatively, the tablet could be placed sublingually (see section 5.2).

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 listed in section 6.1.

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.

Treatment of acute pain other than breakthrough pain (e.g. postoperative pain, headache, migraine).

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, especially to a child. Therefore they must keep all tablets out of the sight and reach 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 and that the patient continues to be treated with the long acting opioid treatment whilst taking Effentora.

Respiratory depression
As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of fentanyl. Improper patient selection (e.g., use in patients without maintenance opioid therapy) and/or improper dosing have resulted in fatal outcome with Effentora as well as with other fentanyl products.
Effentora should only be used for conditions specified in section 4.1.

Chronic obstructive pulmonary disease
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.

Increased intracranial pressure, impaired consciousness
Effentora should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 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.

Cardiac disease
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.

Hepatic or renal impairment
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, dependence
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.

Controlled sodium diet
This medicinal product contains 16 mg sodium per 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 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should not be used by breastfeeding women and breastfeeding should not be restarted until at least 48 hours after the last administration of fentanyl.

Fertility
There are no human data on fertility available. In animal studies, male fertility was impaired (See Section 5.3).

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

Summary of the safety profile
Typical opioid adverse reactions 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.

Tabulated list of adverse reactions
The following adverse reactions have been reported with Effentora during clinical studies and post marketing experience. Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency (frequencies are defined as: very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to <1/100, rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data); within each frequency group, undesirable effects are presented in order of decreasing seriousness:

	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Oral candidiasis	Pharyngitis	Oral pustule	
Blood and lymphatic system disorders		Anaemia Neutropenia	Thrombocyto-penia		
Endocrine disorders				Hypogonadism	
Metabolism and nutrition disorders		Anorexia			

	Very common	Common	Uncommon	Rare	Not known
Psychiatric disorders		Depression Anxiety Confusional state Insomnia	Euphoric mood Nervousness Hallucination Visual hallucination Mental status changes Drug dependence (addiction) Disorientation		
Nervous system disorders	Dizziness Headache	Dysgeusia Somnolence Lethargy Tremor Sedation Hypoaesthesia Migraine	Depressed level of consciousness Disturbance in attention Balance disorder Dysarthria	Cognitive disorder Motor dysfunction	Loss of consciousness
Eye disorders			Visual disturbance Ocular hyperaemia Blurred vision Visual acuity reduced	Abnormal sensation in eye Photopsia	
Ear and labyrinth disorders			Vertigo Tinnitus Ear discomfort		
Cardiac disorders		Tachycardia	Bradycardia		
Vascular disorders		Hypotension Hypertension	Flushing Hot flush		
Respiratory, thoracic and mediastinal disorders		Dyspnoea Pharyngolaryn-geal pain	Respiratory depression Sleep apnoea syndrome		Respiratory arrest
Gastro-intestinal disorders	Nausea Vomiting	Constipation Stomatitis Dry mouth Diarrhoea Abdominal pain Gastro-oesophageal reflux disease Stomach discomfort Dyspepsia Toothache	Ileus Mouth ulceration Oral hypoaesthesia Oral discomfort Oral mucosal discolouration Oral soft tissue disorder Glossodynia Tongue blistering Gingival pain Tongue	Oral mucosal blistering Dry lip	

	Very common	Common	Uncommon	Rare	Not known
			ulceration Tongue disorder Oesophagitis Chapped lips Tooth disorder		
Hepatobiliary disorders			Biliary dilatation		
Skin and subcutaneous tissue disorders		Pruritus Hyperhidrosis Rash	Cold sweat Facial swelling Generalised pruritus Alopecia	Onychorrhexis	
Musculoskeletal and connective tissue disorders		Myalgia Back pain	Muscle twitching Muscular weakness		
Renal and urinary disorders			Urinary retention		
General disorders and administration site conditions	Application site reactions including bleeding, pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles	Peripheral oedema Fatigue Asthenia Drug withdrawal syndrome Chills	Malaise Sluggishness Chest discomfort Feeling abnormal Feeling jittery Thirst Feeling cold Feeling hot		
Investigations		Weight decreased	Platelet count decreased Heart rate increased Haematocrit decreased Haemoglobin decreased		
Injury, poisoning and procedural complications		Fall			

Description of selected adverse reactions

Tolerance, physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl.

Opioid withdrawal symptoms such as nausea, vomiting, diarrhoea, anxiety and shivering have been observed in studies with Effentora.

Loss of consciousness and respiratory arrest have been observed in the context of overdose.

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 effects being altered mental status, loss of consciousness, hypotension, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.

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; 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).

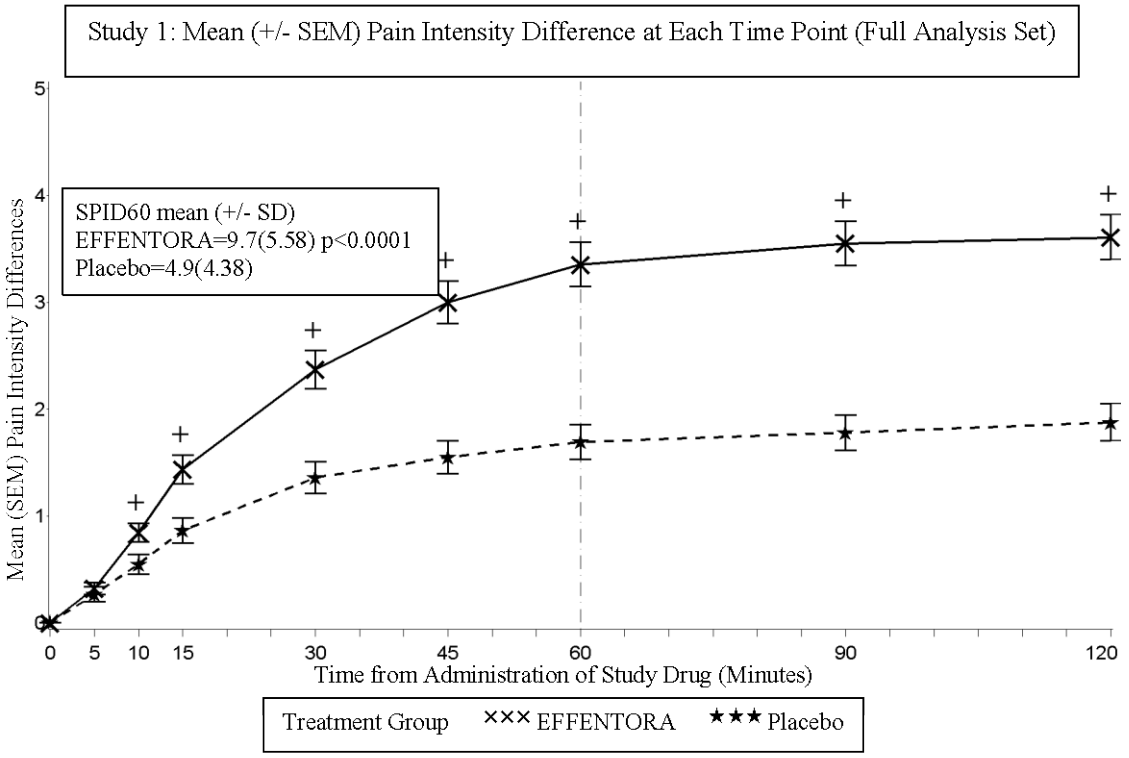
All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy as these patients will develop tolerance to respiratory depressant effects.

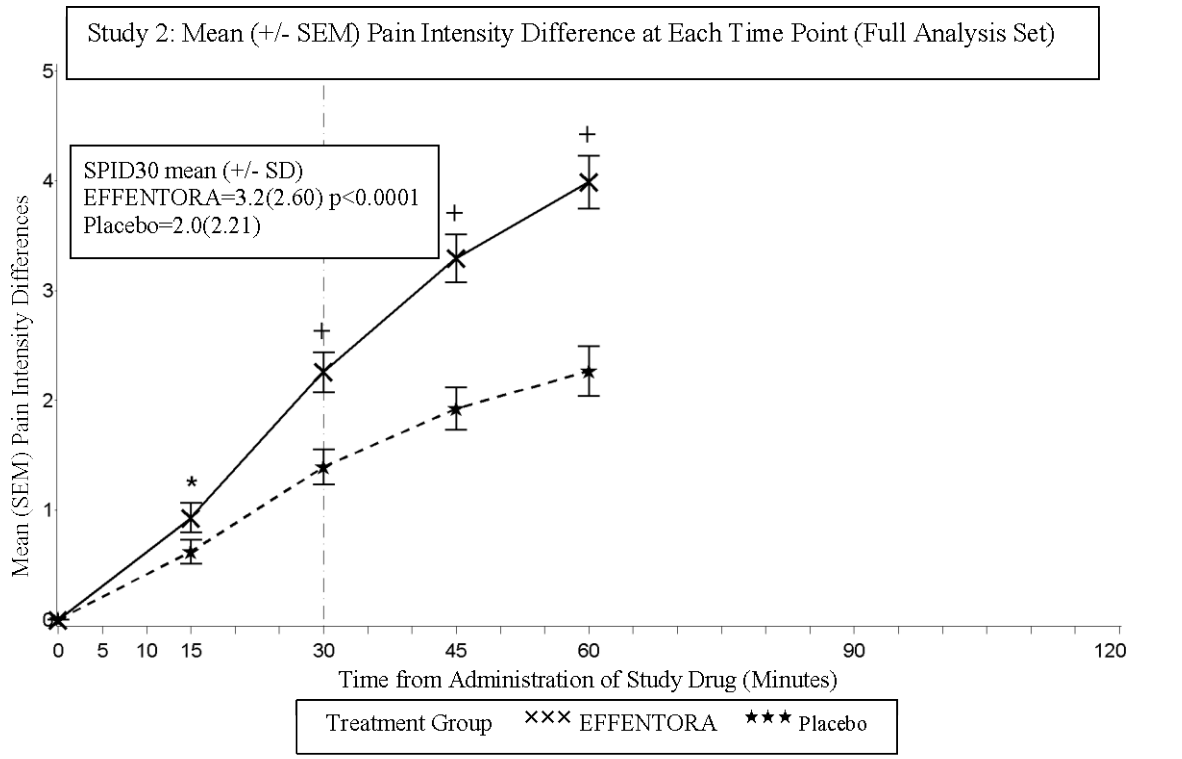
The safety and efficacy of Effentora have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Pre-emptive use of Effentora for predictable pain episodes was not investigated in the clinical trials. Two double-blind, randomized, placebo-controlled crossover studies 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. A comparison study between one 400 mcg Effentora tablet administered either buccally (i.e., between the cheek and the gum) or sublingually met the criteria of bioequivalence.

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.

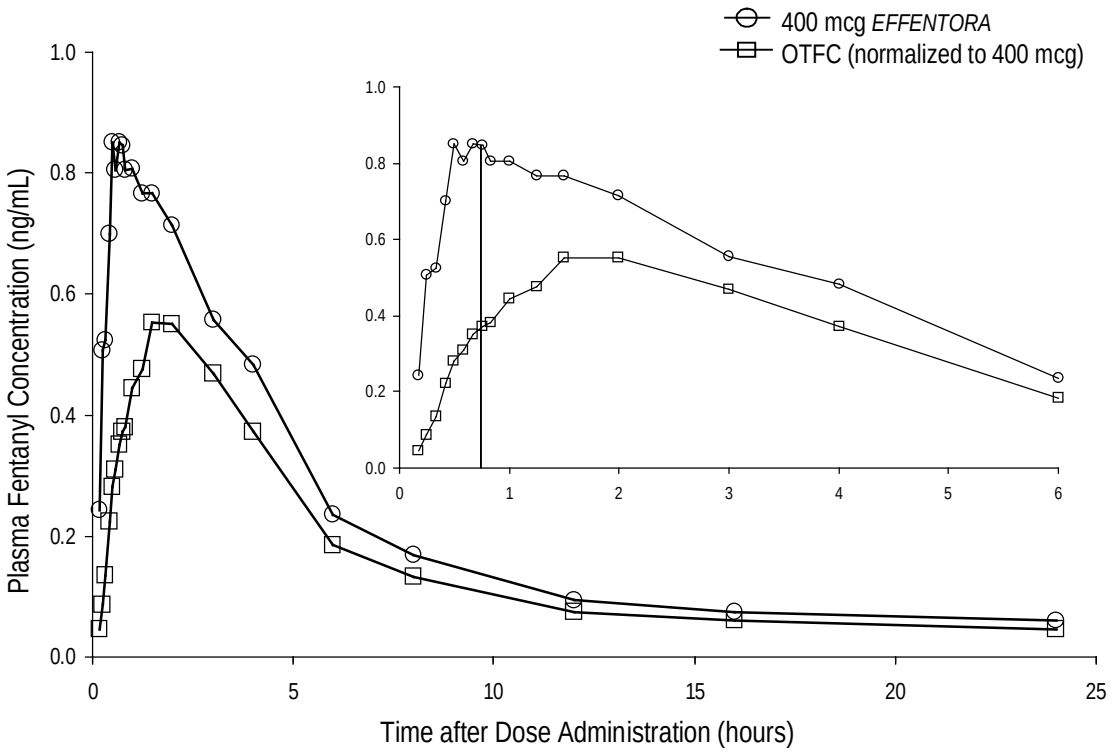
Pharmacokinetic Parameters in Adult Subjects Receiving Effentora*

Pharmacokinetic parameter (mean)	Effentora **400 micrograms**
Absolute bioavailability	**65%** (±20%)
Fraction absorbed transmucosally	**48%** (±31.8%)
T_{max} (minute) **	**46.8** (20-240)
C_{max} (ng/ml)	**1.02** (± 0.42)
$AUC_{0\text{-}tmax}$ (ng.hr/ml)	**0.40** (± 0.18)
$AUC_{0\text{-}inf}$ (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 Cmax were approximately 20% and 30% higher than plasma AUC and Cmax, 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, genotoxicity and carcinogenicity.

Embryo-foetal developmental toxicity studies conducted in rats and rabbits revealed no compound-induced malformations or developmental variations when administered during the period of organogenesis.

In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 mcg/kg/day, s.c.) and is considered secondary to the sedative effects of fentanyl in animal studies.
In studies on pre and postnatal development in rats the survival rate of offspring was significantly reduced at doses causing severe maternal toxicity. Further findings at maternally toxic doses in F1 pups were delayed physical development, sensory functions, reflexes and behaviour. These effects could either be indirect effects due to altered maternal care and/or decreased lactation rate or a direct effect of fentanyl on the pups.

Carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) did not reveal any findings indicative of oncogenic potential.

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

3 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10
3542DR Utrecht
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/003-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 April 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Effentora 400 micrograms buccal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each buccal tablet contains 400 micrograms fentanyl (as citrate).

Excipient(s) with known effect: Each tablet contains 16 mg of sodium.
For the 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 “4”.

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. Patients should be instructed not to use two different formulations of fentanyl concurrently for the treatment of breakthrough pain, and to dispose of any fentanyl product prescribed for BTP when switching to Effentora. The number of tablet strengths available to the patients at any time should be minimised to prevent confusion and potential overdose.

<u>Posology</u>

Dose titration

Effentora should be individually titrated to an “effective” dose that provides adequate analgesia and minimises adverse reactions. 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.

<u>Titration in patients not switching from other fentanyl containing products</u>
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. Breakthrough pain episodes may vary in intensity and the required Effentora dose might increase over time due to progression of the underlying cancer disease. In these cases, a second tablet of the same strength may be used. If a second tablet of Effentora was required for several consecutive times, the usual maintenance dose is to be readjusted (see below). Patients should wait at least 4 hours before treating another BTP episode with Effentora during maintenance therapy.

Dose readjustment

The maintenance dose of Effentora should be increased when a patient requires more than one tablet per BTP episode for several consecutive BTP episodes. For dose-readjustment the same principles apply as outlined for *dose titration* (see above).
Dose readjustment 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.

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.

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.

Paediatric population:

The safety and efficacy of Effentora in children aged 0 to18 years have not been established. No data are available.

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 buccal cavity (near a molar between the cheek and gum).

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

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.
Alternatively, the tablet could be placed sublingually (see section 5.2).

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 listed in section 6.1.

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.

Treatment of acute pain other than breakthrough pain (e.g. postoperative pain, headache, migraine).

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, especially to a child. Therefore they must keep all tablets out of the sight and reach 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 and that the patient continues to be treated with the long acting opioid treatment whilst taking Effentora.

Respiratory depression
As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of fentanyl. Improper patient selection (e.g., use in patients without maintenance opioid therapy) and/or improper dosing have resulted in fatal outcome with Effentora as well as with other fentanyl products.
Effentora should only be used for conditions specified in section 4.1.

Chronic obstructive pulmonary disease
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.

Increased intracranial pressure, impaired consciousness
Effentora should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 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.

Cardiac disease
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.

Hepatic or renal impairment
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, dependence
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.

Controlled sodium diet
This medicinal product contains 16 mg sodium per 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 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding

Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should not be used by breastfeeding women and breastfeeding should not be restarted until at least 48 hours after the last administration of fentanyl.

Fertility
There are no human data on fertility available. In animal studies, male fertility was impaired (See Section 5.3).

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

Summary of safety profile
Typical opioid adverse ractions 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.

Tabulated list of adverse reactions
The following adverse reactions have been reported with Effentora during clinical studies and post marketing experience. Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency (frequencies are defined as: very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to <1/100, rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data); within each frequency group, undesirable effects are presented in order of decreasing seriousness:

	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Oral candidiasis	Pharyngitis	Oral pustule	
Blood and lymphatic system disorders		Anaemia Neutropenia	Thrombocyto-penia		
Endocrine disorders				Hypogonadism	
Metabolism and nutrition disorders		Anorexia			

	Very common	Common	Uncommon	Rare	Not known
Psychiatric disorders		Depression Anxiety Confusional state Insomnia	Euphoric mood Nervousness Hallucination Visual hallucination Mental status changes Drug dependence (addiction) Disorientation		
Nervous system disorders	Dizziness Headache	Dysgeusia Somnolence Lethargy Tremor Sedation Hypoaesthesia Migraine	Depressed level of consciousness Disturbance in attention Balance disorder Dysarthria	Cognitive disorder Motor dysfunction	Loss of consciousness
Eye disorders			Visual disturbance Ocular hyperaemia Blurred vision Visual acuity reduced	Abnormal sensation in eye Photopsia	
Ear and labyrinth disorders			Vertigo Tinnitus Ear discomfort		
Cardiac disorders		Tachycardia	Bradycardia		
Vascular disorders		Hypotension Hypertension	Flushing Hot flush		
Respiratory, thoracic and mediastinal disorders		Dyspnoea Pharyngolaryn-geal pain	Respiratory depression Sleep apnoea syndrome		Respiratory arrest
Gastro-intestinal disorders	Nausea Vomiting	Constipation Stomatitis Dry mouth Diarrhoea Abdominal pain Gastro-oesophageal reflux disease Stomach discomfort Dyspepsia Toothache	Ileus Mouth ulceration Oral hypoaesthesia Oral discomfort Oral mucosal discolouration Oral soft tissue disorder Glossodynia Tongue blistering Gingival pain Tongue	Oral mucosal blistering Dry lip	

	Very common	Common	Uncommon	Rare	Not known
			ulceration Tongue disorder Oesophagitis Chapped lips Tooth disorder		
Hepatobiliary disorders			Biliary dilatation		
Skin and subcutaneous tissue disorders		Pruritus Hyperhidrosis Rash	Cold sweat Facial swelling Generalised pruritus Alopecia	Onychorrhexis	
Musculoskeletal and connective tissue disorders		Myalgia Back pain	Muscle twitching Muscular weakness		
Renal and urinary disorders			Urinary retention		
General disorders and administration site conditions	Application site reactions including bleeding, pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles	Peripheral oedema Fatigue Asthenia Drug withdrawal syndrome Chills	Malaise Sluggishness Chest discomfort Feeling abnormal Feeling jittery Thirst Feeling cold Feeling hot		
Investigations		Weight decreased	Platelet count decreased Heart rate increased Haematocrit decreased Haemoglobin decreased		
Injury, poisoning and procedural complications		Fall			

Description of selected adverse reactions

Tolerance, physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl.

Opioid withdrawal symptoms such as nausea, vomiting, diarrhoea, anxiety and shivering have been observed in studies with Effentora.

Loss of consciousness and respiratory arrest have been observed in the context of overdose.

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 effects being altered mental status, loss of consciousness, hypotension, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.

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;; 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).

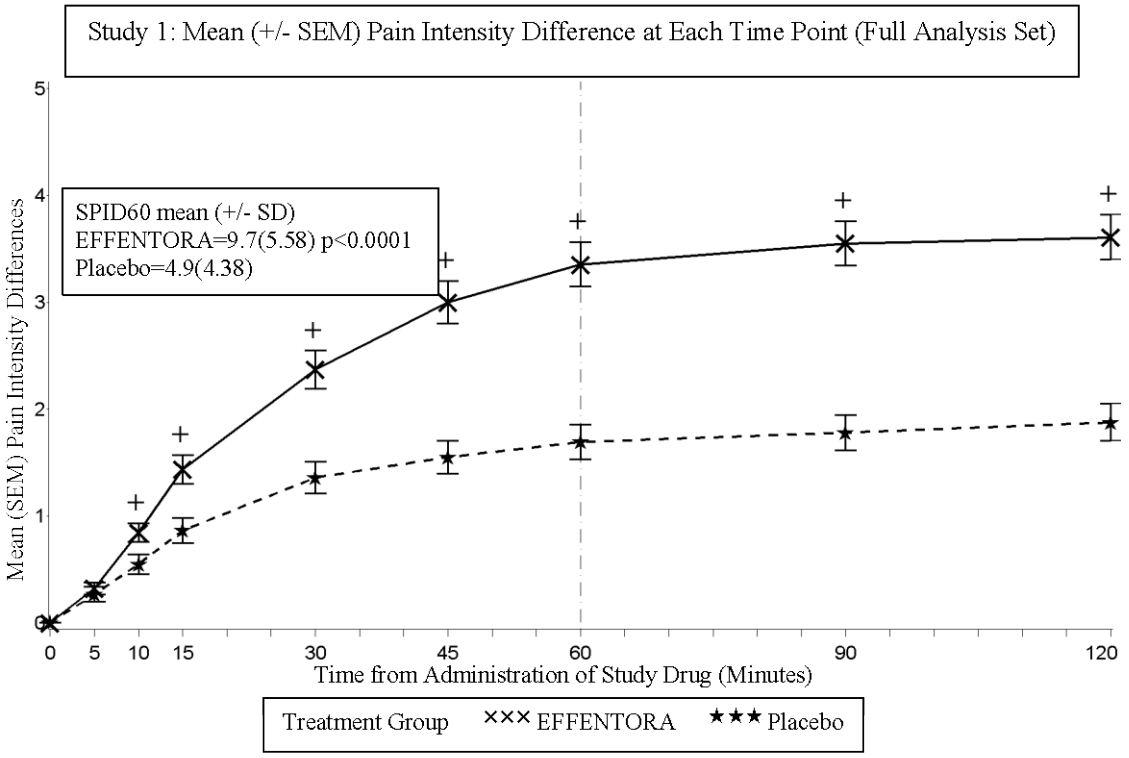
All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy as these patients will develop tolerance to respiratory depressant effects.

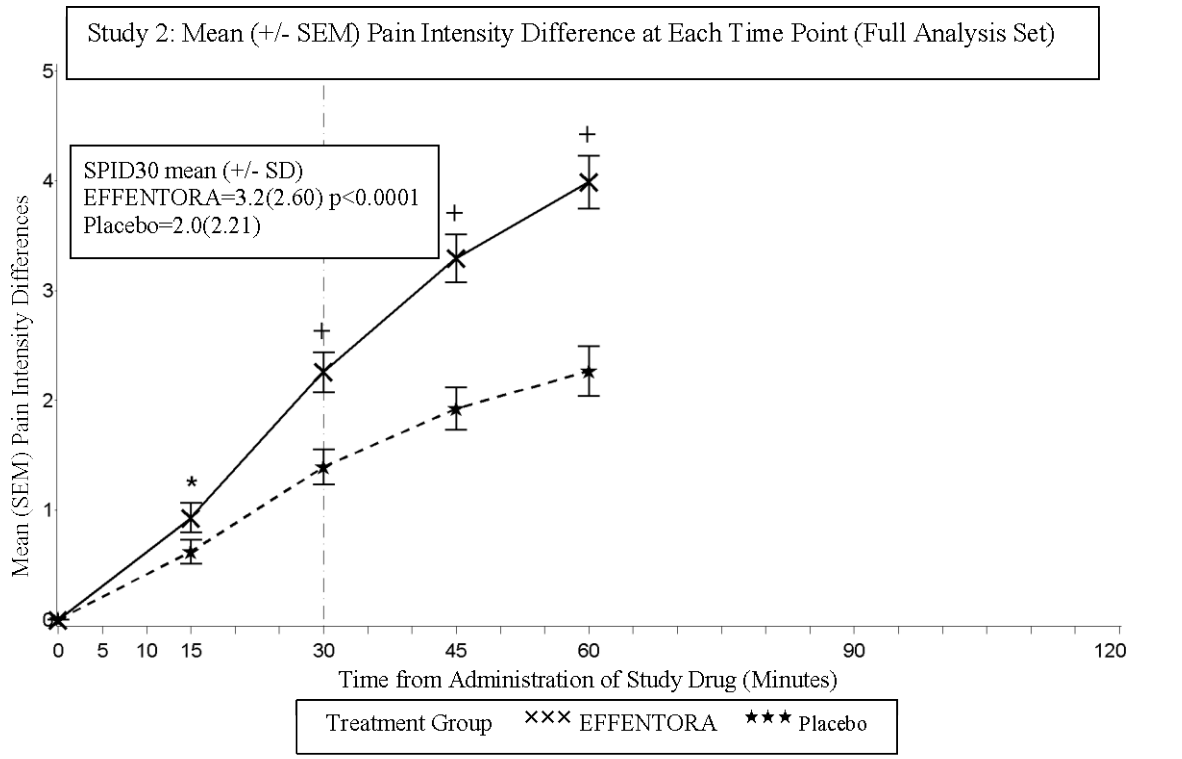
The safety and efficacy of Effentora have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Pre-emptive use of Effentora for predictable pain episodes was not investigated in the clinical trials. Two double-blind, randomized, placebo-controlled crossover studies 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. A comparison study between one 400 mcg Effentora tablet administered either buccally (i.e., between the cheek and the gum) or sublingually met the criteria of bioequivalence.

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.

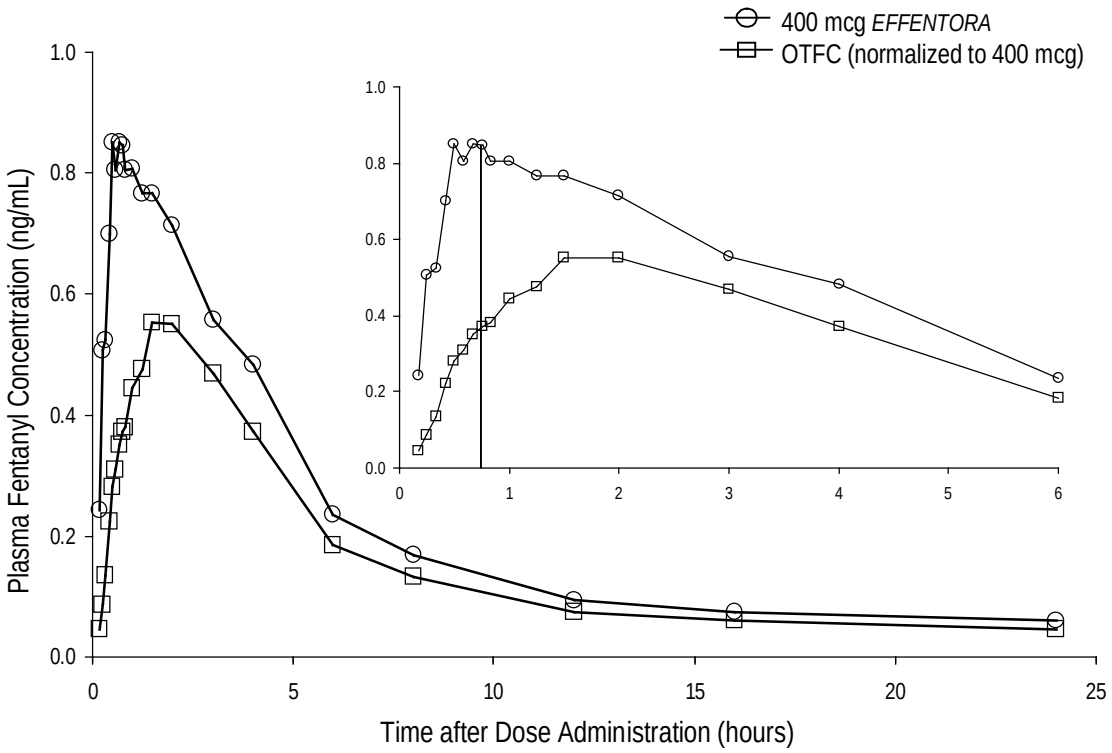
Pharmacokinetic Parameters in Adult Subjects Receiving Effentora*

Pharmacokinetic parameter (mean)	Effentora **400 micrograms**
Absolute bioavailability	**65%** (±20%)
Fraction absorbed transmucosally	**48%** (±31.8%)
T_{max} (minute) **	**46.8** (20-240)
C_{max} (ng/ml)	**1.02** (± 0.42)
$AUC_{0\text{-}tmax}$ (ng.hr/ml)	**0.40** (± 0.18)
$AUC_{0\text{-}inf}$ (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 Cmax were approximately 20% and 30% higher than plasma AUC and Cmax, 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, genotoxicity and carcinogenicity.

Embryo-foetal developmental toxicity studies conducted in rats and rabbits revealed no compound-induced malformations or developmental variations when administered during the period of organogenesis.

In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 mcg/kg/day, s.c.) and is considered secondary to the sedative effects of fentanyl in animal studies.
In studies on pre and postnatal development in rats the survival rate of offspring was significantly reduced at doses causing severe maternal toxicity. Further findings at maternally toxic doses in F1 pups were delayed physical development, sensory functions, reflexes and behaviour. These effects could either be indirect effects due to altered maternal care and/or decreased lactation rate or a direct effect of fentanyl on the pups.

Carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) did not reveal any findings indicative of oncogenic potential.

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

3 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10
3542DR Utrecht
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/005-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 April 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Effentora 600 micrograms buccal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each buccal tablet contains 600 micrograms fentanyl (as citrate).

Excipient(s) with known effect: Each tablet contains 16 mg of sodium.
For the 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 “6”.

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. Patients should be instructed not to use two different formulations of fentanyl concurrently for the treatment of breakthrough pain, and to dispose of any fentanyl product prescribed for BTP when switching to Effentora. The number of tablet strengths available to the patients at any time should be minimised to prevent confusion and potential overdose.

Posology

Dose titration

Effentora should be individually titrated to an “effective” dose that provides adequate analgesia and minimises adverse reactions. 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. Breakthrough pain episodes may vary in intensity and the required Effentora dose might increase over time due to progression of the underlying cancer disease. In these cases, a second tablet of the same strength may be used. If a second tablet of Effentora was required for several consecutive times, the usual maintenance dose is to be readjusted (see below). Patients should wait at least 4 hours before treating another BTP episode with Effentora during maintenance therapy.

Dose readjustment

The maintenance dose of Effentora should be increased when a patient requires more than one tablet per BTP episode for several consecutive BTP episodes. For dose-readjustment the same principles apply as outlined for *dose titration* (see above).
Dose readjustment 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.

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.

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.

Paediatric population:
The safety and efficacy of Effentora in children aged 0 to 18 years have not been established. No data are available.

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 buccal cavity (near a molar between the cheek and gum).

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

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.
Alternatively, the tablet could be placed sublingually (see section 5.2).

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 listed in section 6.1.

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.

Treatment of acute pain other than breakthrough pain (e.g. postoperative pain, headache, migraine).

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, especially to a child. Therefore they must keep all tablets out of the sight and reach 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 and that the patient continues to be treated with the long acting opioid treatment whilst taking Effentora.

Respiratory depression
As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of fentanyl. Improper patient selection (e.g., use in patients without maintenance opioid therapy) and/or improper dosing have resulted in fatal outcome with Effentora as well as with other fentanyl products.
Effentora should only be used for conditions specified in section 4.1.

Chronic obstructive pulmonary disease
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.

Increased intracranial pressure, impaired consciousness
Effentora should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 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.

Cardiac disease
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.

Hepatic or renal impairment
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, dependence
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.

Controlled sodium diet
This medicinal product contains 16 mg sodium per 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 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding

Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should not be used by breastfeeding women and breastfeeding should not be restarted until at least 48 hours after the last administration of fentanyl.

Fertility
There are no human data on fertility available. In animal studies, male fertility was impaired (See Section 5.3).

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

Summary of the safety profile
Typical opioid 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.

Tabulated list of adverse reactions
The following adverse reactions have been reported with Effentora during clinical studies and post marketing experience. Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency (frequencies are defined as: very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to <1/100, rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data); within each frequency group, undesirable effects are presented in order of decreasing seriousness:

	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Oral candidiasis	Pharyngitis	Oral pustule	
Blood and lymphatic system disorders		Anaemia Neutropenia	Thrombocyto-penia		
Endocrine disorders				Hypogonadism	
Metabolism and nutrition disorders		Anorexia			

	Very common	Common	Uncommon	Rare	Not known
Psychiatric disorders		Depression Anxiety Confusional state Insomnia	Euphoric mood Nervousness Hallucination Visual hallucination Mental status changes Drug dependence (addiction) Disorientation		
Nervous system disorders	Dizziness Headache	Dysgeusia Somnolence Lethargy Tremor Sedation Hypoaesthesia Migraine	Depressed level of consciousness Disturbance in attention Balance disorder Dysarthria	Cognitive disorder Motor dysfunction	Loss of consciousness
Eye disorders			Visual disturbance Ocular hyperaemia Blurred vision Visual acuity reduced	Abnormal sensation in eye Photopsia	
Ear and labyrinth disorders			Vertigo Tinnitus Ear discomfort		
Cardiac disorders		Tachycardia	Bradycardia		
Vascular disorders		Hypotension Hypertension	Flushing Hot flush		
Respiratory, thoracic and mediastinal disorders		Dyspnoea Pharyngolaryn-geal pain	Respiratory depression Sleep apnoea syndrome		Respiratory arrest
Gastro-intestinal disorders	Nausea Vomiting	Constipation Stomatitis Dry mouth Diarrhoea Abdominal pain Gastro-oesophageal reflux disease Stomach discomfort Dyspepsia Toothache	Ileus Mouth ulceration Oral hypoaesthesia Oral discomfort Oral mucosal discolouration Oral soft tissue disorder Glossodynia Tongue blistering Gingival pain Tongue	Oral mucosal blistering Dry lip	

	Very common	Common	Uncommon	Rare	Not known
			ulceration Tongue disorder Oesophagitis Chapped lips Tooth disorder		
Hepatobiliary disorders			Biliary dilatation		
Skin and subcutaneous tissue disorders		Pruritus Hyperhidrosis Rash	Cold sweat Facial swelling Generalised pruritus Alopecia	Onychorrhexis	
Musculoskeletal and connective tissue disorders		Myalgia Back pain	Muscle twitching Muscular weakness		
Renal and urinary disorders			Urinary retention		
General disorders and administration site conditions	Application site reactions including bleeding, pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles	Peripheral oedema Fatigue Asthenia Drug withdrawal syndrome Chills	Malaise Sluggishness Chest discomfort Feeling abnormal Feeling jittery Thirst Feeling cold Feeling hot		
Investigations		Weight decreased	Platelet count decreased Heart rate increased Haematocrit decreased Haemoglobin decreased		
Injury, poisoning and procedural complications		Fall			

Description of selected adverse reactions

Tolerance, physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl.

Opioid withdrawal symptoms such as nausea, vomiting, diarrhoea, anxiety and shivering have been observed in studies with Effentora.

Loss of consciousness and respiratory arrest have been observed in the context of overdose.

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 effects being altered mental status, loss of consciousness, hypotension, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.

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; 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).

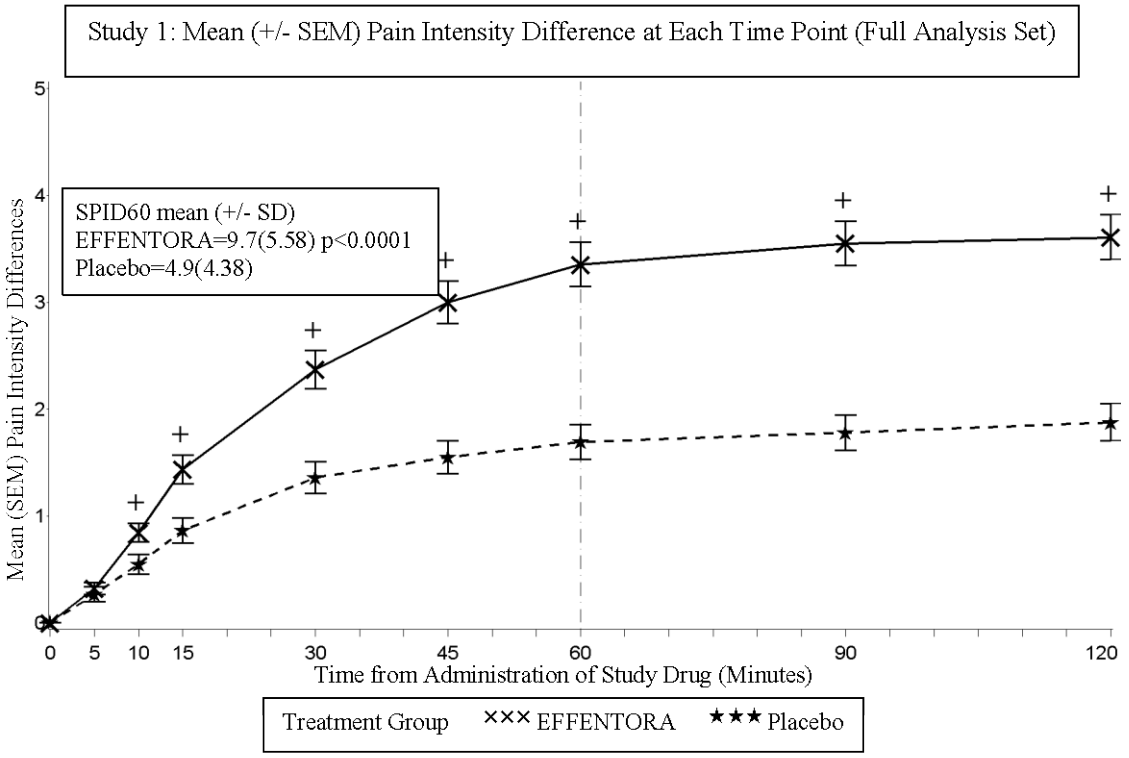
All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy as these patients will develop tolerance to respiratory depressant effects.

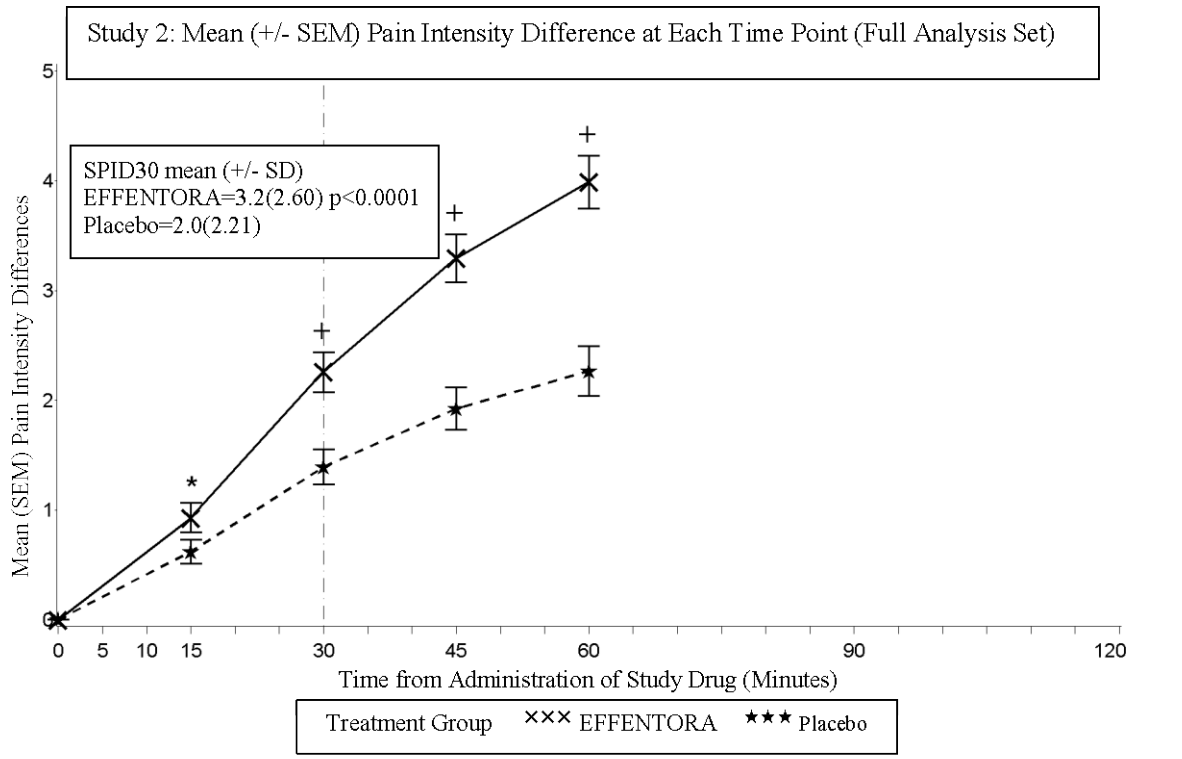
The safety and efficacy of Effentora have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Pre-emptive use of Effentora for predictable pain episodes was not investigated in the clinical trials. Two double-blind, randomized, placebo-controlled crossover studies 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. A comparison study between one 400 mcg Effentora tablet administered either buccally (i.e., between the cheek and the gum) or sublingually met the criteria of bioequivalence.

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.

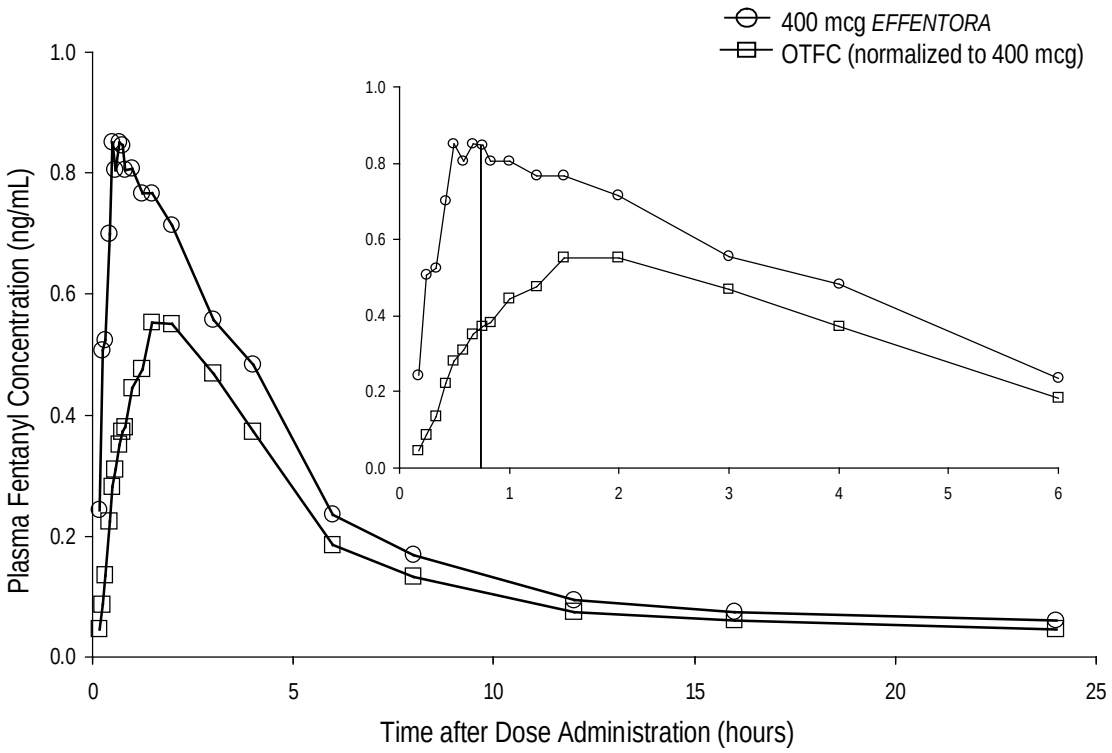
Pharmacokinetic Parameters in Adult Subjects Receiving Effentora*

Pharmacokinetic parameter (mean)	Effentora **400 micrograms**
Absolute bioavailability	**65%** (±20%)
Fraction absorbed transmucosally	**48%** (±31.8%)
T_{max} (minute) **	**46.8** (20-240)
C_{max} (ng/ml)	**1.02** (± 0.42)
$AUC_{0\text{-}tmax}$ (ng.hr/ml)	**0.40** (± 0.18)
$AUC_{0\text{-}inf}$ (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 Cmax were approximately 20% and 30% higher than plasma AUC and Cmax, 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, genotoxicity and carcinogenicity.

Embryo-foetal developmental toxicity studies conducted in rats and rabbits revealed no compound-induced malformations or developmental variations when administered during the period of organogenesis.

In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 mcg/kg/day, s.c.) and is considered secondary to the sedative effects of fentanyl in animal studies.
In studies on pre and postnatal development in rats the survival rate of offspring was significantly reduced at doses causing severe maternal toxicity. Further findings at maternally toxic doses in F1 pups were delayed physical development, sensory functions, reflexes and behaviour. These effects could either be indirect effects due to altered maternal care and/or decreased lactation rate or a direct effect of fentanyl on the pups.

Carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) did not reveal any findings indicative of oncogenic potential.

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

3 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10
3542DR Utrecht
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/007-008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 April 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Effentora 800 micrograms buccal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each buccal tablet contains 800 micrograms fentanyl (as citrate).

Excipient(s) with known effect: Each tablet contains 16 mg of sodium.
For the 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 “8”.

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. Patients should be instructed not to use two different formulations of fentanyl concurrently for the treatment of breakthrough pain, and to dispose of any fentanyl product prescribed for BTP when switching to Effentora. The number of tablet strengths available to the patients at any time should be minimised to prevent confusion and potential overdose.

<u>Posology</u>

<u>Dose titration</u>

Effentora should be individually titrated to an “effective” dose that provides adequate analgesia and minimises adverse reactions. 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.

<u>Titration in patients not switching from other fentanyl containing products</u>
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. Breakthrough pain episodes may vary in intensity and the required Effentora dose might increase over time due to progression of the underlying cancer disease. In these cases, a second tablet of the same strength may be used. If a second tablet of Effentora was required for several consecutive times, the usual maintenance dose is to be readjusted (see below). Patients should wait at least 4 hours before treating another BTP episode with Effentora during maintenance therapy.

Dose readjustment

The maintenance dose of Effentora should be increased when a patient requires more than one tablet per BTP episode for several consecutive BTP episodes. For dose-readjustment the same principles apply as outlined for *dose titration* (see above).
Dose readjustment 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.

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.
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.

Paediatric population:

The safety and efficacy of Effentora in children aged 0 to 18 years have not been established. No data are available.

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 buccal cavity (near a molar between the cheek and gum).

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

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.
Alternatively, the tablet could be placed sublingually (see section 5.2).

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 listed in section 6.1.

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.

Treatment of acute pain other than breakthrough pain (e.g. postoperative pain, headache, migraine).

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, especially to a child. Therefore they must keep all tablets out of the sight and reach 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 and that the patient continues to be treated with the long acting opioid treatment whilst taking Effentora.

Respiratory depression
As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of fentanyl. Improper patient selection (e.g., use in patients without maintenance opioid therapy) and/or improper dosing have resulted in fatal outcome with Effentora as well as with other fentanyl products.
Effentora should only be used for conditions specified in section 4.1.

Chronic obstructive pulmonary disease
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.

Increased intracranial pressure, impaired consciousness
Effentora should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 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.

Cardiac disease
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.

Hepatic or renal impairment
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, dependence
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.

Controlled sodium diet
This medicinal product contains 16 mg sodium per 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 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding

Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should not be used by breastfeeding women and breastfeeding should not be restarted until at least 48 hours after the last administration of fentanyl.

Fertility
There are no human data on fertility available. In animal studies, male fertility was impaired (See Section 5.3).

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

Summary of the safety profile
Typical opioid adverse reactions 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.

Tabulated list of adverse reactions
The following adverse reactions have been reported with Effentora during clinical studies and post marketing experience. Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency (frequencies are defined as: very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to <1/100, rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data); within each frequency group, undesirable effects are presented in order of decreasing seriousness:

	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Oral candidiasis	Pharyngitis	Oral pustule	
Blood and lymphatic system disorders		Anaemia Neutropenia	Thrombocyto-penia		
Endocrine disorders				Hypogonadism	
Metabolism and nutrition disorders		Anorexia			

	Very common	Common	Uncommon	Rare	Not known
Psychiatric disorders		Depression Anxiety Confusional state Insomnia	Euphoric mood Nervousness Hallucination Visual hallucination Mental status changes Drug dependence (addiction) Disorientation		
Nervous system disorders	Dizziness Headache	Dysgeusia Somnolence Lethargy Tremor Sedation Hypoaesthesia Migraine	Depressed level of consciousness Disturbance in attention Balance disorder Dysarthria	Cognitive disorder Motor dysfunction	Loss of consciousness
Eye disorders			Visual disturbance Ocular hyperaemia Blurred vision Visual acuity reduced	Abnormal sensation in eye Photopsia	
Ear and labyrinth disorders			Vertigo Tinnitus Ear discomfort		
Cardiac disorders		Tachycardia	Bradycardia		
Vascular disorders		Hypotension Hypertension	Flushing Hot flush		
Respiratory, thoracic and mediastinal disorders		Dyspnoea Pharyngolaryn-geal pain	Respiratory depression Sleep apnoea syndrome		Respiratory arrest
Gastro-intestinal disorders	Nausea Vomiting	Constipation Stomatitis Dry mouth Diarrhoea Abdominal pain Gastro-oesophageal reflux disease Stomach discomfort Dyspepsia Toothache	Ileus Mouth ulceration Oral hypoaesthesia Oral discomfort Oral mucosal discolouration Oral soft tissue disorder Glossodynia Tongue blistering Gingival pain Tongue	Oral mucosal blistering Dry lip	

	Very common	Common	Uncommon	Rare	Not known
			ulceration Tongue disorder Oesophagitis Chapped lips Tooth disorder		
Hepatobiliary disorders			Biliary dilatation		
Skin and subcutaneous tissue disorders		Pruritus Hyperhidrosis Rash	Cold sweat Facial swelling Generalised pruritus Alopecia	Onychorrhexis	
Musculoskeletal and connective tissue disorders		Myalgia Back pain	Muscle twitching Muscular weakness		
Renal and urinary disorders			Urinary retention		
General disorders and administration site conditions	Application site reactions including bleeding, pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles	Peripheral oedema Fatigue Asthenia Drug withdrawal syndrome Chills	Malaise Sluggishness Chest discomfort Feeling abnormal Feeling jittery Thirst Feeling cold Feeling hot		
Investigations		Weight decreased	Platelet count decreased Heart rate increased Haematocrit decreased Haemoglobin decreased		
Injury, poisoning and procedural complications		Fall			

Description of selected adverse reactions

Tolerance, physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl.

Opioid withdrawal symptoms such as nausea, vomiting, diarrhoea, anxiety and shivering have been observed in studies with Effentora.

Loss of consciousness and respiratory arrest have been observed in the context of overdose.

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 effects being altered mental status, loss of consciousness, hypotension, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.

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; 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).

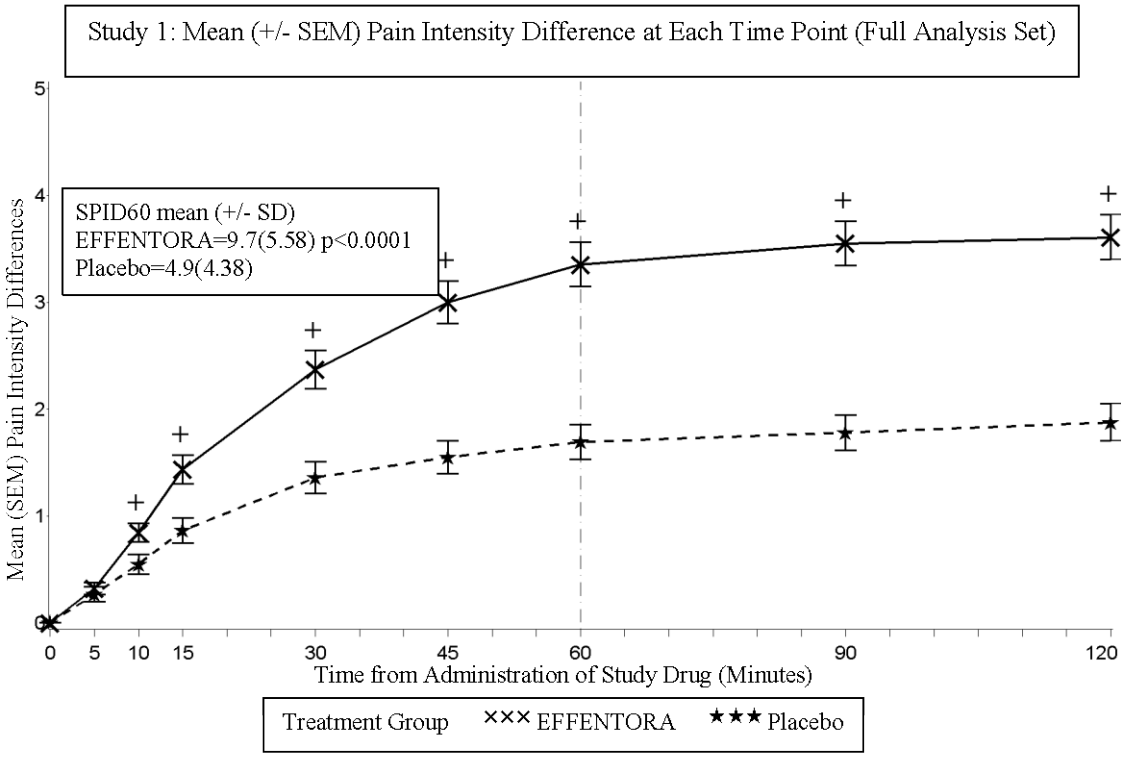
All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy as these patients will develop tolerance to respiratory depressant effects.

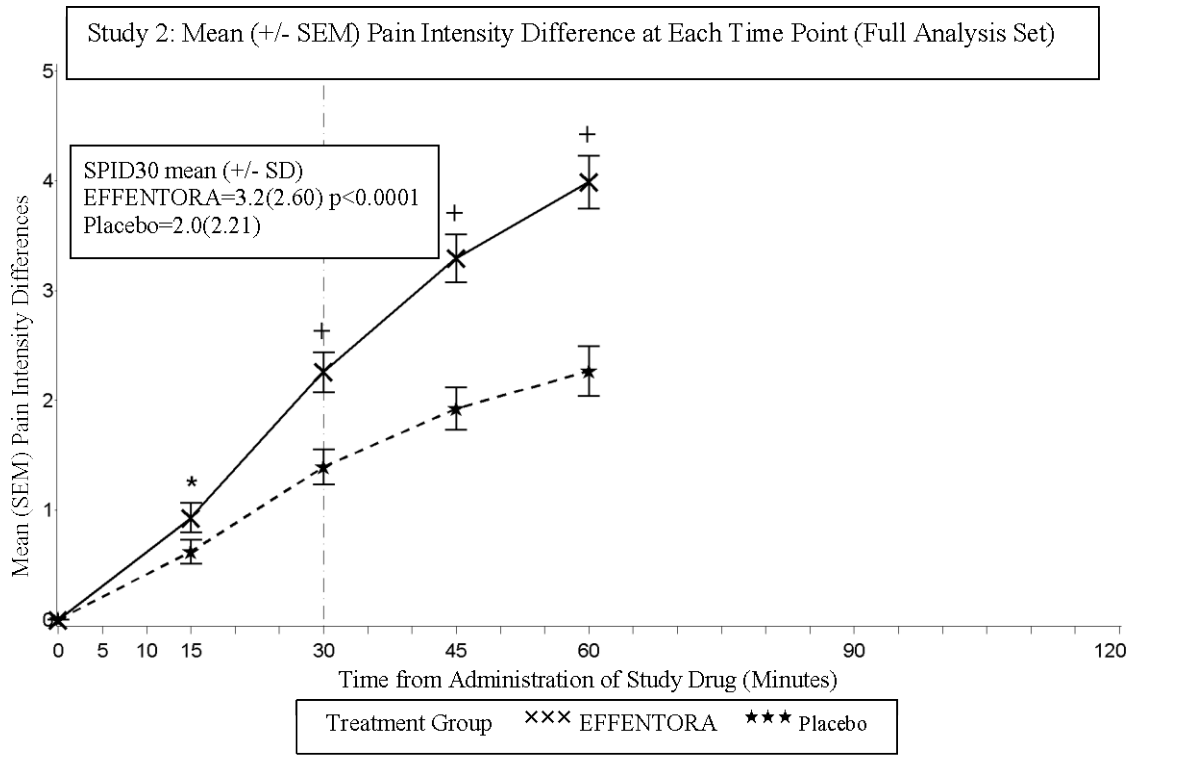
The safety and efficacy of Effentora have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Pre-emptive use of Effentora for predictable pain episodes was not investigated in the clinical trials. Two double-blind, randomized, placebo-controlled crossover studies 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. A comparison study between one 400 mcg Effentora tablet administered either buccally (i.e., between the cheek and the gum) or sublingually met the criteria of bioequivalence.

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.

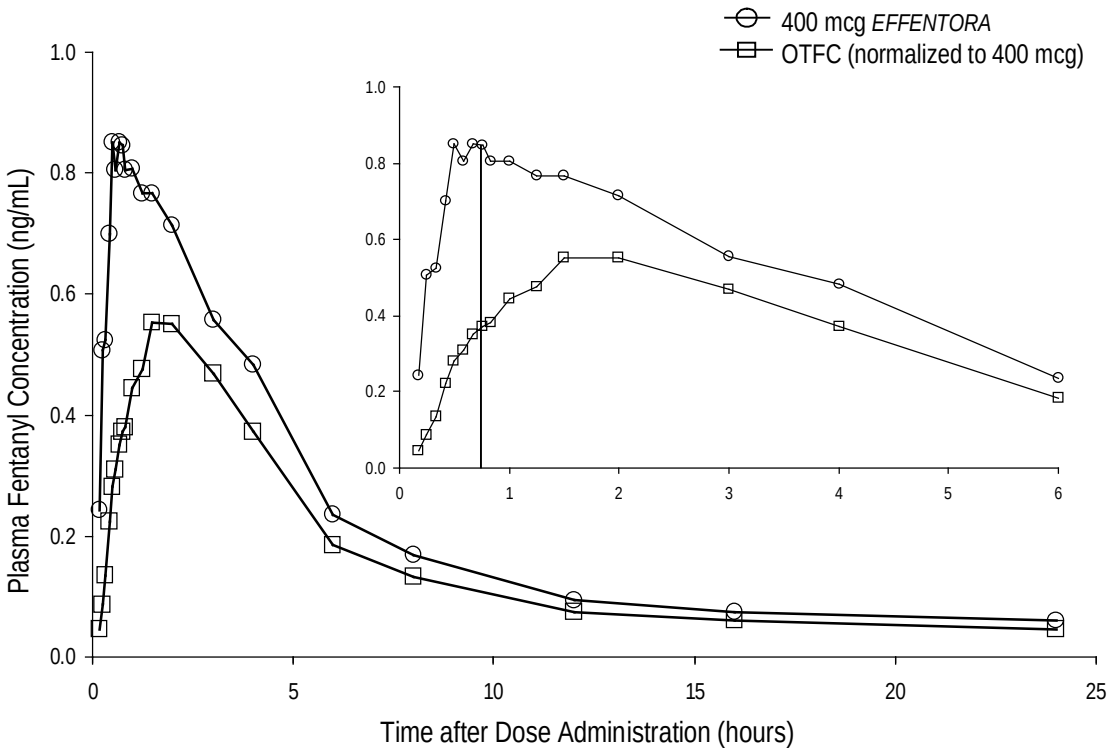
Pharmacokinetic Parameters in Adult Subjects Receiving Effentora*

Pharmacokinetic parameter (mean)	Effentora **400 micrograms**
Absolute bioavailability	**65%** (±20%)
Fraction absorbed transmucosally	**48%** (±31.8%)
T_{max} (minute) **	**46.8** (20-240)
C_{max} (ng/ml)	**1.02** (± 0.42)
$AUC_{0\text{-}tmax}$ (ng.hr/ml)	**0.40** (± 0.18)
$AUC_{0\text{-}inf}$ (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 Cmax were approximately 20% and 30% higher than plasma AUC and Cmax, 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, genotoxicity and carcinogenicity.

Embryo-foetal developmental toxicity studies conducted in rats and rabbits revealed no compound-induced malformations or developmental variations when administered during the period of organogenesis.

In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 mcg/kg/day, s.c.) and is considered secondary to the sedative effects of fentanyl in animal studies.
In studies on pre and postnatal development in rats the survival rate of offspring was significantly reduced at doses causing severe maternal toxicity. Further findings at maternally toxic doses in F1 pups were delayed physical development, sensory functions, reflexes and behaviour. These effects could either be indirect effects due to altered maternal care and/or decreased lactation rate or a direct effect of fentanyl on the pups.

Carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) did not reveal any findings indicative of oncogenic potential.

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

3 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.
Computerweg 10
3542DR Utrecht
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/009-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 April 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Cephalon France
20, rue Charles Martigny
94700 Maisons-Alfort
France

B. CONDITIONS OR RESTRICTION(S) REGARDING SUPPLY AND USE

Medicinal product subject to special and restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted every three years following the renewal of the marketing authorization .
When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

In each Member State where EFFENTORA is marketed the Marketing Authorisation Holder (MAH) shall agree an updated educational programme with the National Competent Authority. The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where EFFENTORA is marketed all healthcare professionals who are expected to prescribe EFFENTORA are provided with an information pack containing the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet

- Educational material for the healthcare professionals
- Educational material for the patients

The educational material for healthcare professionals shall consist of four items:

- Opioid prescribing guide
- Brochure on breakthrough pain
- EFFENTORA prescribing guide
- Titration guide tool

Key elements to be included in the educational material for healthcare professionals:

- Prescription of EFFENTORA only by physicians experienced in the management of opioid therapy in cancer patients
- Prescription of EFFENTORA only to critically selected patients with close following on
    - Instructions for use of fentanyl buccal tablet and how to place the tablet
    - Instructions on how to open the child-resistant blister
    - Information on the correct indication and the risk for abuse
    - Information on the titration process as indicated in the labelling
- Instructions on the safe use (to avoid the risk of overdosing), on storage (to avoid the risk of accidental exposure), and disposal of fentanyl buccal tablet
- Boxed statements as follows:

1. Effentora must not be prescribed in pain other than breakthrough cancer pain
2. Effentora must not be prescribed in patients with short term pain only
3. Effentora must not be prescribed in patients without around-the-clock opioid pain medication
4. Effentora must not be prescribed in patients below 18 years of age

The educational material for patients shall consist of the following three items:

1. A document explaining the titration process and the dosing recommendations after treatment initiation

2. A Q&A document, providing answers to potential questions on the following topics:

- What is Breakthrough pain?
- What is EFFENTORA for?
- How to use EFFENTORA (how to take it, how to reach the effective dose during the titration process)?
- Possible side effects (the most likely ones, how to recognise them and when to alert physicians)
- Risk of interactions with other medications
- Main precautions for use: How to prevent main risks (take the drug as prescribed; remain on maintenance opioid therapy; keep EFFENTORA out of the reach and the sight of children; prevent theft and misuse)
- Safe use, storage and disposal of EFFENTORA.

3. A Daily Pain Journal to record daily pain levels, providing patients and physicians with a follow-up tool for daily symptoms and treatment efficacy.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Effentora 100 micrograms buccal tablets
Fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each buccal tablet contains 100 micrograms fentanyl (as citrate)

3. LIST OF EXCIPIENTS

Contains sodium

4. PHARMACEUTICAL FORM AND CONTENTS

4 buccal tablets
28 buccal tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oromucosal use.
Place in buccal cavity. Not to be sucked, chewed or swallowed whole. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This product should only be used by patients already taking other opioids.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V. Computerweg 10, 3542DR Utrecht Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/001
EU/1/08/441/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Effentora 100

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 4 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Effentora 100 micrograms buccal tablets
Fentanyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

1. Tear
2. Bend
3. Peel

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Effentora 200 micrograms buccal tablets
Fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each buccal tablet contains 200 micrograms fentanyl (as citrate)

3. LIST OF EXCIPIENTS

Contains sodium

4. PHARMACEUTICAL FORM AND CONTENTS

4 buccal tablets
28 buccal tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oromucosal use.
Place in buccal cavity. Not to be sucked, chewed or swallowed whole. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This product should only be used by patients already taking other opioids.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V. Computerweg 10, 3542DR Utrecht Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/003
EU/1/08/441/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Effentora 200

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 4 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Effentora 200 micrograms buccal tablets
Fentanyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

1. Tear
2. Bend
3. Peel

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Effentora 400 micrograms buccal tablets
Fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each buccal tablet contains 400 micrograms fentanyl (as citrate)

3. LIST OF EXCIPIENTS

Contains sodium

4. PHARMACEUTICAL FORM AND CONTENTS

4 buccal tablets
28 buccal tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oromucosal use.
Place in buccal cavity. Not to be sucked, chewed or swallowed whole. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This product should only be used by patients already taking other opioids.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V. Computerweg 10, 3542DR Utrecht Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/005
EU/1/08/441/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Effentora 400

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 4 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Effentora 400 micrograms buccal tablets
Fentanyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

1. Tear
2. Bend
3. Peel

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Effentora 600 micrograms buccal tablets
Fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each buccal tablet contains 600 micrograms fentanyl (as citrate)

3. LIST OF EXCIPIENTS

Contains sodium

4. PHARMACEUTICAL FORM AND CONTENTS

4 buccal tablets
28 buccal tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oromucosal use.
Place in buccal cavity. Not to be sucked, chewed or swallowed whole. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This product should only be used by patients already taking other opioids.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/007
EU/1/08/441/008

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Effentora 600

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 4 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Effentora 600 micrograms buccal tablets
Fentanyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

1. Tear
2. Bend
3. Peel

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Effentora 800 micrograms buccal tablets
Fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each buccal tablet contains 800 micrograms fentanyl (as citrate)

3. LIST OF EXCIPIENTS

Contains sodium

4. PHARMACEUTICAL FORM AND CONTENTS

4 buccal tablets
28 buccal tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oromucosal use.
Place in buccal cavity. Not to be sucked, chewed or swallowed whole. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This product should only be used by patients already taking other opioids.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V. Computerweg 10, 3542DR Utrecht Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/441/009
EU/1/08/441/010

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Effentora 800

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 4 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Effentora 800 micrograms buccal tablets
Fentanyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

TEVA Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

1. Tear
2. Bend
3. Peel

B. PACKAGE LEAFLET

Package leaflet: Information for the user
Effentora 100 micrograms buccal tablets
Effentora 200 micrograms buccal tablets
Effentora 400 micrograms buccal tablets
Effentora 600 micrograms buccal tablets
Effentora 800 micrograms buccal tablets
Fentanyl

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet,.

What is in this leaflet

1. What Effentora is and what it is used for

The active substance of Effentora is fentanyl citrate. Effentora is a pain-relieving medicine known as an opioid, which is used to treat breakthrough pain in adult patients with cancer who are already taking other opioid pain medicines for their persistent (around-the-clock) cancer pain.
Breakthrough pain is additional, sudden pain that occurs in spite of you having taken your usual opioid pain-relieving medicines.

2. What you need to know before you use Effentora

Do not use Effentora:
- If you have <u>not</u> been using a prescribed opioid pain medicine every day on a regular schedule, for at least a week, to control your persistent pain. If you have not been using these medicines you **must not** use Effentora, because it may increase the risk that breathing could become dangerously slow and/or shallow, or even stop.
- If you are allergic to fentanyl or any of the other ingredients of this medicine (listed in section 6).
- If you suffer from severe breathing problems or severe obstructive lung conditions.
- If you suffer from short-term pain other than breakthrough pain, such as pain from injuries or surgery, headaches or migraines.

Warnings and precautions
Talk to your doctor or pharmacist before using Effentora.
Keep using the opioid pain medicine you take for your persistent (around-the-clock) cancer pain during your Effentora treatment.
Whilst you are being treated with Effentora, do not use other fentanyl treatments previously prescribed for your breakthrough pain. If you still have some of these fentanyl treatments at home, contact your pharmacist to check how to dispose of them.

If you have any of the following, talk to your doctor or pharmacist before starting Effentora:
- Your other opioid pain medicine taken for your persistent (around-the-clock) cancer pain is not stabilised yet.
- You are suffering from any condition that has an effect on your breathing (such as asthma, wheezing, or shortness of breath).
- You have a head injury.
- You have an exceptionally slow heart rate or other heart problems.
- You have liver or kidney problems, as these organs have an effect on the way in which your system breaks down the medicine.
- You have low amount of fluid in the circulation or low blood pressure

What to do if someone accidentally takes Effentora
If you think someone has accidentally taken Effentora please seek immediate medical assistance. Try to keep the person awake until emergency help arrives.

If someone has accidentally taken Effentora, they may have the same side effects as described in the section 3 “If you use more Effentora than you should”.

Children and adolescents
Do not give this medicine to children between the ages of 0 and 18 years.

Other medicines and Effentora
Tell your doctor or pharmacist before starting Effentora if you are taking or have recently taken or might take any of the following medicines:
- Any medicines which might normally make you sleepy (have a sedative effect) such as sleeping pills, medicines to treat anxiety, antihistamines, or tranquillisers.
- Any medicines that might have an effect on the way in which your body breaks down Effentora, such as ritonavir, nelfinavir, amprenavir, and fosamprenavir (medicines that help control HIV infection) or other so-called CYP3A4 inhibitors such as ketoconazole, itraconazole, or fluconazole (used for treatment of fungal infections), troleandomycine, clarithromycine, or erythromycine (medicines for treatment of bacterial infections), aprepitant (used for severe nausea) and diltiazem and verapamil (medicines for treatment of high blood pressure or heart diseases).
- Medicines called monoamine-oxidase (MAO) inhibitors (used for severe depression) or have done so in the past 2 weeks.
- Medicines called partial opioid agonist/antagonists e.g. buprenorphine, nalbuphine and pentazocine (medicines for treatment of pain).

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Effentora with food and drink and alcohol
- Effentora may be used before or after, but not during, meals. You may drink some water before using Effentora to help moisten your mouth, but you should not drink or eat anything while taking the medicine.
- You should not drink grapefruit juice while using Effentora because it may affect the way your body breaks down Effentora.
- Do not drink alcohol while using Effentora. It can increase the risk of experiencing dangerous side effects.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Effentora should not be used during pregnancy unless you have discussed this with your doctor.
You should not use Effentora during childbirth because fentanyl may cause respiratory depression in the new-born child.
Fentanyl can get into breast milk and may cause side effects in the breast-fed infant. Do not use Effentora if you are breast-feeding. You should not start breast-feeding within 48 hours after the last dose of Effentora.

Driving and using machines
You should discuss with your doctor whether it is safe for you to drive, or operate machinery after taking Effentora. Do not drive or operate machinery if you: are feeling sleepy or dizzy; have blurred or double vision; or have difficulty in concentrating. It is important you know how you react to Effentora before driving or operating machinery.

Effentora contains sodium
Each tablet of Effentora 100 micrograms contains 8 mg of sodium. Each tablet of Effentora 200 micrograms, Effentora 400 micrograms, Effentora 600 micrograms and Effentora 800 micrograms contains 16 mg of sodium. You should take this into consideration if you are on a controlled sodium diet and seek advice from your doctor.

3. How to use Effentora

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Dosage and frequency
When you first start using Effentora, your doctor will work with you to find the dose that will relieve your breakthrough pain. It is very important that you use Effentora exactly as the doctor tells you The initial dose is 100 micrograms. During determination of your right dose, your doctor may instruct you to take more than one tablet per episode. If your breakthrough pain is not relieved after 30 minutes, use only 1 more tablet of Effentora during the titration period.

Once the right dose has been determined with your doctor, use 1 tablet for an episode of breakthrough pain as a general rule. In the further course of treatment your requirement for analgesic therapy may change. Higher doses may be necessary. If your breakthrough pain is not relieved after 30 minutes, use only 1 more tablet of Effentora during this dose-readjustment period.
Contact your doctor if your right dose of Effentora does not relieve your breakthrough pain. Your doctor will decide if your dose needs to be changed.

Wait at least 4 hours before treating another episode of breakthrough pain with Effentora.

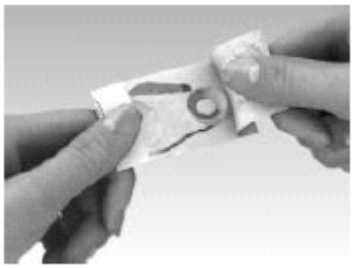
You must let your doctor know immediately if you are using Effentora more than four times per day, as he may change your medicine for your persistent pain. When your persistent pain is controlled again, your doctor may need to change your dose of Effentora. For the most effective relief, let your doctor know about your pain and how Effentora is working for you, so that the dose can be changed if needed.

Do not change doses of Effentora or your other pain medicines on your own. Any change in dosage must be prescribed and monitored by your doctor.

If you are not sure about the right dose, or if you have questions about taking this medicine, you should contact your doctor.

Method of administration
Effentora buccal tablets are for oromucosal use. When you place a tablet in your mouth, it dissolves and the medicine is absorbed through the lining of your mouth, into the blood system. Taking the medicine in this way allows it to be absorbed quickly to relieve your breakthrough pain.

Taking the medicine
- Open the blister only when you are ready to use the tablet. The tablet must be used immediately once removed from the blister.
- Separate one of the blister units from the blister card by tearing apart at the perforations.
- Bend the blister unit along the line where indicated.
- Peel the blister backing to expose the tablet. Do NOT attempt to push the tablet through the blister, because this can damage the tablet.



- Remove the tablet from the blister unit and **immediately** place the entire tablet near a molar tooth between the gum and the cheek (as shown in the picture). Sometimes, your doctor may tell you to place the tablet under your tongue instead.
- Do not attempt to crush or split the tablet.

- Do not bite, suck, chew, or swallow the tablet, as this will result in less pain relief than when taken as directed.
- The tablet should be left between the cheek and gum until dissolved, which usually takes approximately 14 to 25 minutes.
- You may feel a gentle bubbling sensation between your cheek and gum as the tablet dissolves.
- In case of irritation, you may change the placement of the tablet on the gum.
- After 30 minutes, if pieces of the tablet remain, they may be swallowed with a glass of water.

If you use more Effentora than you should
- The most common side effects are feeling sleepy, sick or dizzy. If you begin to feel very dizzy, or very sleepy before the tablet is completely dissolved, rinse your mouth with water and spit the remaining pieces of the tablet into a sink or toilet right away.
- A serious side effect of Effentora is slow and/or shallow breathing. This can occur if your dose of Effentora is too high or if you take too much Effentora. If this occurs, please seek immediate medical assistance.

If you forget to use Effentora
If the breakthrough pain is still ongoing, you may take Effentora as prescribed by your physician. If the breakthrough pain has stopped, do not take Effentora until the next breakthrough pain episode.

If you stop using Effentora

You should discontinue Effentora when no longer required. You should continue to take your usual opioid medicine to treat your persistent pain and you may contact your doctor to confirm its correct dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can have side effects, although not everybody gets them. If you notice any of these, contact your doctor.

The most serious side effects are shallow breathing, low blood pressure and shock. Effentora like other fentanyl products can cause very severe breathing problems which can lead to death. If you become very sleepy or have slow and/or shallow breathing, you or your carer should contact your doctor immediately and call for emergency help.

Very common side effects (may affect more than 1 in 10 people):
- Dizziness, headache
- feeling nauseous, vomiting
- at the site of tablet application: pain, ulcer, irritation, bleeding, numbness, loss of sensation, redness, swelling or spots

Common side effects (may affectup to 1 in 10 people):
- feeling anxious or confused, depression, difficulty in sleeping
- abnormal taste, weight decreased
- sleepiness, sedation, excessive tiredness, weakness, migraine, numbness, swelling of arms or legs, drug withdrawal syndrome, shaking, falls, chills
- constipation, inflammation of the mouth, dry mouth, diarrhoea, heartburn, loss of appetite, stomach pain, uncomfortable stomach, indigestion, toothache, oral thrush
- itching, excessive sweating, rash
- shortness of breath, painful throat
- decrease in white cells in the blood, decrease in red blood cells, decreased or raised blood pressure, unusually fast heart rate
- muscle pain, back pain

Uncommon side effects (may affect up to 1 in 100 people):
- sore throat
- decrease in cells that help the blood to clot,
- feeling elated, nervous, abnormal, jittery or slow; seeing or hearing things that aren't really there, reduced consciousness, change in mental state, dependence (reliance on the medicine, addiction), disorientation, lack of concentration, loss of balance, vertigo, problem with speaking, ringing in the ear, ear discomfort
- disturbed or blurred vision, red eye
- unusually low heart rate, hot flushes,
- breathing problems, trouble breathing during sleep,
- one or more of the following problems in the mouth: ulcer, loss of sensation, discomfort, unusual colour, soft tissue disorder, tongue disorder, painful or blistered or ulcerated tongue, gum pain, chapped lips, tooth disorder
- inflammation of the oesophagus, paralysis of the gut, gall bladder disorder
- cold sweat, swollen face, generalised itching, hair loss, muscle twitching, muscular weakness, feeling unwell, chest discomfort, thirst, feeling cold, feeling hot, difficulty passing urine

Rare side effects (may affect up to 1 in 1,000 people):
- disturbance in thinking, movements disturbance
- blisters in the mouth, dry lips, collection of pus under the skin in the mouth

- lack of testosterone, abnormal sensation in eye, observing flashes of light, brittle nails

Frequency not known:
- loss of consciousness, stop in breathing

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Effentora

The pain-relieving medicine in Effentora is very strong and could be life-threatening if taken accidentally by a child. This medicine must be kept out of the sight and reach of children.
- Do not use this medicine after the expiry/use before date shown on the blister package label and the carton.
- Store in the original package in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Effentora contains
The active substance is fentanyl. Each tablet contains either:
- 100 micrograms fentanyl (as citrate)
- 200 micrograms fentanyl (as citrate)
- 400 micrograms fentanyl (as citrate)
- 600 micrograms fentanyl (as citrate)
- 800 micrograms fentanyl (as citrate)

The other ingredients are mannitol, sodium starch glycolate type A, sodium hydrogen carbonate, sodium carbonate anhydrous, citric acid anhydrous, magnesium stearate.

What Effentora looks like and contents of the pack
The buccal tablets are flat-faced, round bevelled-edge tablet, embossed one side with a “C” and on the other side with “1” for Effentora 100 micrograms, with “2” for Effentora 200 micrograms, with “4” for Effentora 400 micrograms, with “6” for Effentora 600 micrograms, with “8” for Effentora 800 micrograms.

Each blister contains 4 buccal tablets, supplied in cartons of 4 or 28 buccal tablets.
Not all pack sizes may be marketed.

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TEVA Pharma B.V.
Computerweg 10
3542DR Utrecht
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Manufacturer
Cephalon France
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder or call the following number:

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu