SUMMARY OF PRODUCT CHARACTERISTICS

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 with known effect: Each tablet contains 20 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.

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.

In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Treatment duration and goals

Before initiating treatment with Effentora, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4). Effentora should not be used longer than necessary

Discontinuation of therapy

Effentora should be discontinued immediately if the patient no longer experiences breakthrough pain episodes. The treatment for the persistent background pain should be kept as prescribed.
If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor in order to manage the risk of abrupt withdrawal effects.

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 cannot 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 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
- Patients being treated with medicinal products containing sodium oxybate.

4.4 Special warnings and precautions for use

Because of the risks, including fatal outcome, associated with accidental exposure, misuse, and abuse, patients and their carers must be advised to keep Effentora in a safe and secure place, not accessible by others.

Accidental use in children

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.

Monitoring

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.

Maintenance opioid treatment

It is important that the maintenance 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 maintenance opioid treatment whilst taking Effentora. The product must not be given to patients without maintenance opioid therapy as there is an increased risk of respiratory depression and death.

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.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Alcohol
The concomitant use of alcohol with fentanyl can produce increased depressant effects which may result in a fatal outcome (see section 4.5).

Risks of concomitant administration with benzodiazepines or related drugs
Concomitant use of opioids, including Effentora, with benzodiazepines or related drugs may result in profound sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of opioids and benzodiazepines or related drugs should be made only in patients for whom alternative treatment options are inadequate.
If a decision is made to prescribe Effentora concomitantly with benzodiazepines or related drugs, the lowest effective dosages and minimum durations of concomitant use should be chosen. Patients should be closely monitored for signs and symptoms of respiratory depression and sedation (see section 4.5).

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.

Bradyarrhythmias
Fentanyl may produce bradycardia. Fentanyl should be used with caution in patients with previous or pre-existing bradyarrythmias.

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.

Serotonin Syndrome

Caution is advised when Effentora is co-administered with drugs that affect the serotoninergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose.

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, treatment with Effentora should be discontinued.

Tolerance and opioid use disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as Effentora.

Repeated use of Effentora can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment, can increase the risk of developing OUD. Abuse or intentional misuse of Effentora may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Effentora and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. Patients should be advised to contact their physician if these signs occur.

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Endocrine effects
Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decrease in plasma cortisol and testosterone. Clinical signs and symptoms may manifest from these hormonal changes.

Hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of fentanyl, the possibility of opioid-induced hyperalgesia should be considered. A fentanyl dose reduction or discontinuation of fentanyl treatment or treatment review may be indicated.

Anaphylaxis and hypersensitivity
Anaphylaxis and hypersensitivity have been reported in association with the use of oral transmucosal fentanyl products (see Section 4.8).

Excipient(s)

Sodium

This medicinal product contains 20 mg sodium per per buccal tablet, equivalent to 1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Agents that affect CYP3A4 activity
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.

CYP3A4 inducers
Co-administration with agents that induce 3A4 activity may reduce the efficacy of Effentora.

CYP3A4 inhibitors
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.

Agents that can increase CNS depressant effects
Co-administration of fentanyl with other central nervous system depressants, including other opioids, sedatives or hypnotics, (including benzodiazepines), general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines, gabapentinoids (gabapentin and pregabalin) and alcohol can produce additive depressant effects which may result in respiratory depression, hypotension, profound sedation, coma or a fatal outcome (see section 4.4).

Sedative medicines such as benzodiazepines or related drugs
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Partial opioid agonists/antagonists
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.

Serotoninergic agents
Co-administration of fentanyl with a serotoninergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition. Effentora is not recommended for use in patients who have received MAOIs within 14 days because severe and unpredictable potentiation by MAOIs has been reported with opioid analgesics.

Sodium oxybate
Concomitant use of medicinal products containing sodium oxybate and fentanyl is contraindicated (see section 4.3). The treatment with sodium oxybate should be discontinued before start of treatment with Effentora.

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.

With long-term use of fentanyl during pregnancy, there is a risk of neonatal opioid withdrawal syndrome which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see section 4.8).

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 5 days 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 and/or other fentanyl-containing compounds 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		
Immune system disorders				Hypersensitivity*	
Endocrine disorders				Hypogonadism	Adrenal insufficiency, Androgen deficiency
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 Disorientation		Drug dependence (addiction)* Drug abuse (see section 4.4), Delirium
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* Convulsion
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	Nausea	Constipation	Ileus Mouth	Oral mucosal	Dysphagia

	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
disorders	Vomiting	Stomatitis Dry mouth Diarrhoea Abdominal pain Gastro-oesophageal reflux disease Stomach discomfort Dyspepsia Toothache	ulceration Oral hypoaesthesia Oral discomfort Oral mucosal discolouration Oral soft tissue disorder Glossodynia Tongue blistering Gingival pain Tongue ulceration Tongue disorder Oesophagitis Chapped lips Tooth disorder	blistering Dry lip	
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		

	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
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		Pyrexia Neonatal withdrawal syndrome (see section 4.6) Drug tolerance
Investigations		Weight decreased	Platelet count decreased Heart rate increased Haematocrit decreased Haemoglobin decreased		
Injury, poisoning and procedural complications		Fall			
* See section Description of selected adverse reactions					

Description of selected adverse reactions

Tolerance
Tolerance can develop on repeated use.

Drug dependence

Repeated use of Effentora can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Opioid withdrawal symptoms such as nausea, vomiting, diarrhoea, anxiety, chills, tremor and sweating have been observed with transmucosal fentanyl.

Loss of consciousness and respiratory arrest have been observed in the context of overdose (see section 4.9).

Hypersensitivity reactions have been reported in post-marketing experience, including rash, erythema, lip and face swelling, and urticaria (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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, coma, hypotension, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death. Cases of Cheyne Stokes respiration have been observed in case of fentanyl overdose, particularly in patients with history of heart failure.

Toxic leukoencephalopathy has also been observed with fentanyl overdose.

Management

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.

Overdose (accidental ingestion) in the opioid-naive person
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.

Overdose in opioid-maintained patients
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.

Mechanism of action and pharmacodynamic effects
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.

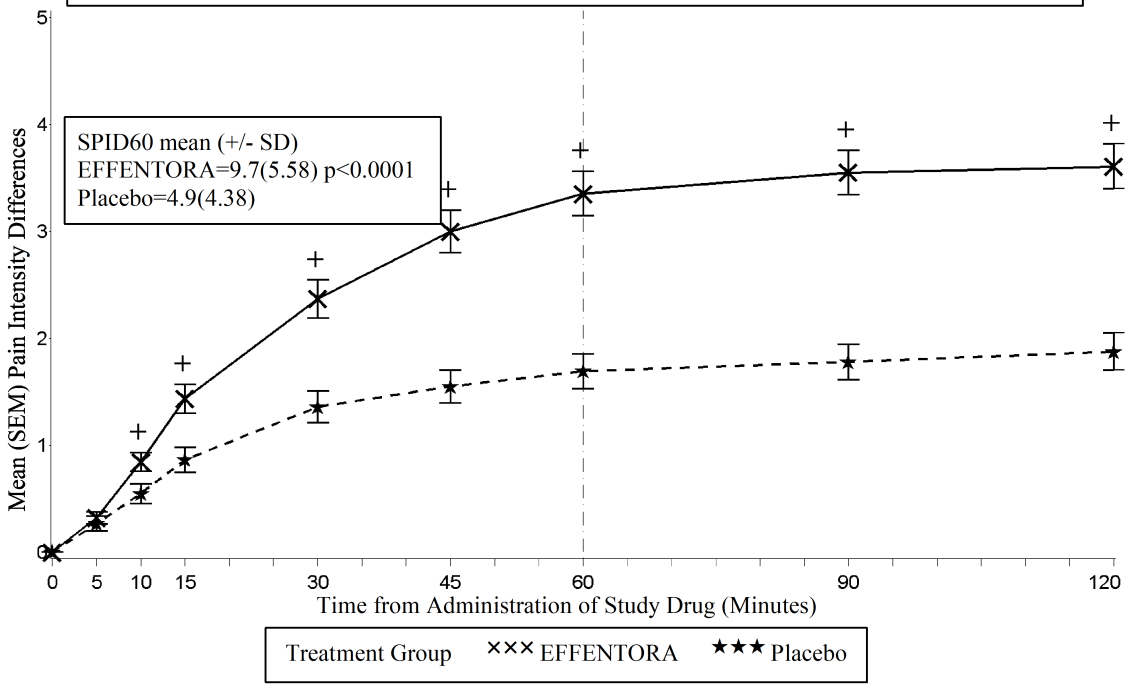
Opioids may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes (see also section 4.8).

Clinical efficacy and safety
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.

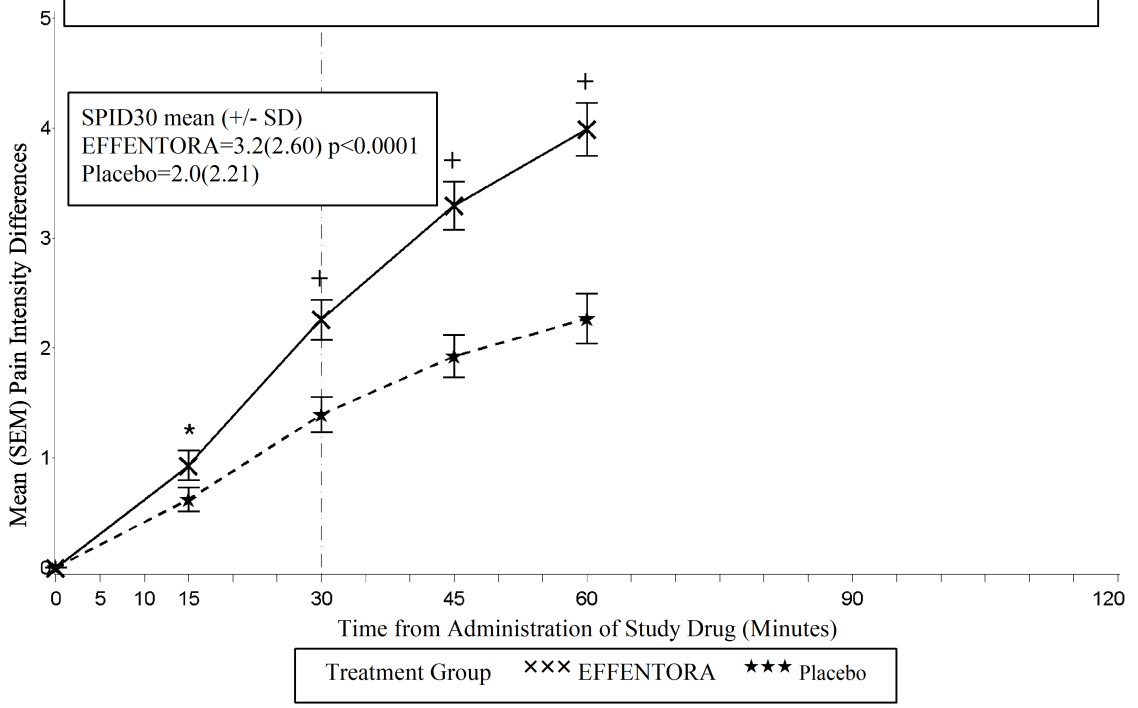
In the pivotal clinical study (study 1), the primary endpoint was the average sum of differences in pain intensity scores from dosing to 60 minutes, inclusive (SPID60), which was statistically significant compared to placebo ($p<0.0001$).

Study 1: Mean (+/- SEM) Pain Intensity Difference at Each Time Point (Full Analysis Set)



+ p<0.0001 EFFENTORA versus placebo, in favor of EFFENTORA, by an analysis of variance
PID=pain intensity difference; SEM=standard error of the mean

Study 2: Mean (+/- SEM) Pain Intensity Difference at Each Time Point (Full Analysis Set)



* 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.

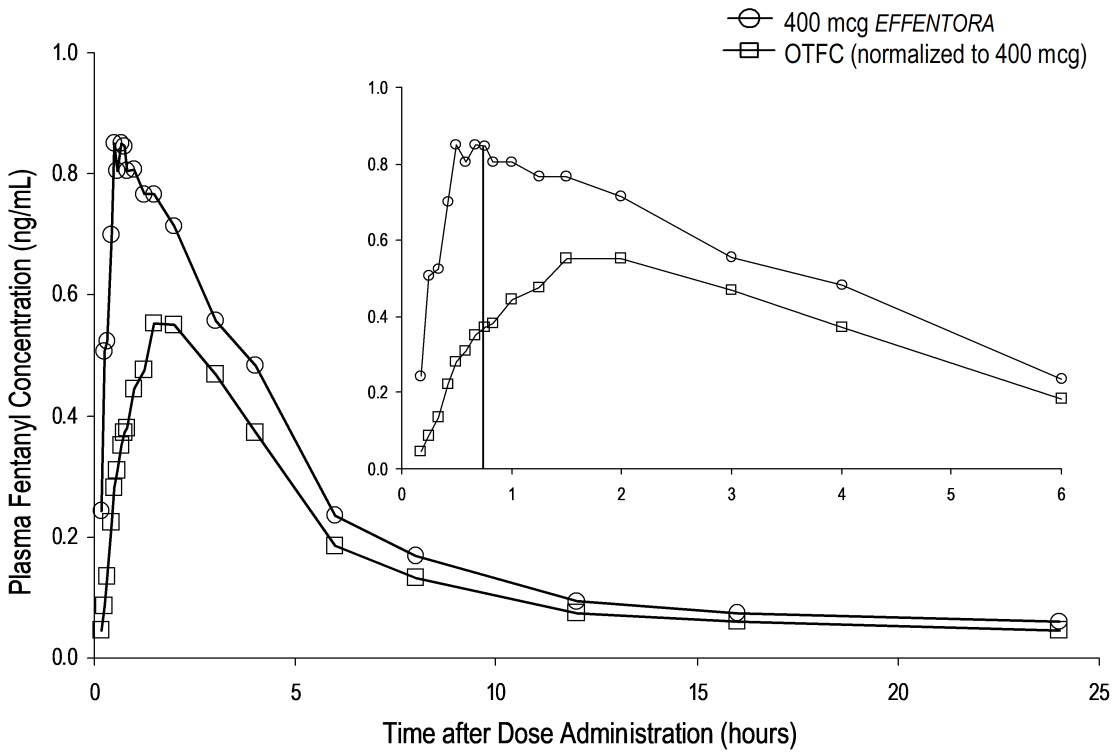
Pharmacokinetic Parameters in Adult Subjects Receiving Effentora*

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 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.



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) with fentanyl did not reveal any findings indicative of oncogenic potential. Evaluation of brain slides from the carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The relevance of these findings to humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium starch glycolate type A

Sodium hydrogen carbonate

Sodium carbonate

Citric acid

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

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