ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Effentora 100 micrograms buccal tablets
Each buccal tablet contains 100 micrograms fentanyl (as citrate).
Excipient with known effect: Each tablet contains 10 mg of sodium.

Effentora 200 micrograms buccal tablets
Each buccal tablet contains 200 micrograms fentanyl (as citrate).
Excipient with known effect: Each tablet contains 20 mg of sodium.

Effentora 400 micrograms buccal tablets
Each buccal tablet contains 400 micrograms fentanyl (as citrate).
Excipient with known effect: Each tablet contains 20 mg of sodium.

Effentora 600 micrograms buccal tablets
Each buccal tablet contains 600 micrograms fentanyl (as citrate).
Excipient with known effect: Each tablet contains 20 mg of sodium.

Effentora 800 micrograms buccal tablets
Each buccal tablet contains 800 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.

Effentora 100 micrograms buccal tablets
Flat-faced, white, round bevelled-edge tablet, embossed on one side with a “C” and on the other side with “1”.

Effentora 200 micrograms buccal tablets
Flat-faced, white, round bevelled-edge tablet, embossed on one side with a “C” and on the other side with “2”.

Effentora 400 micrograms buccal tablets
Flat-faced, white, round bevelled-edge tablet, embossed on one side with a “C” and on the other side with “4”.

Effentora 600 micrograms buccal tablets
Flat-faced, white, round bevelled-edge tablet, embossed on one side with a “C” and on the other side with “6”.

Effentora 800 micrograms buccal tablets
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.

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, physical dependence and psychological dependence may develop upon repeated administration of opioids. Fentanyl can be abused in a manner similar to other opioids and all patients treated with opioids require monitoring for signs of abuse and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with opioids; however, these patients will require additional monitoring for signs of misuse, abuse, or addiction.

Repeated use of Effentora may 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

Effentora 100 micrograms buccal tablets
This medicinal product contains 10 mg sodium per buccal tablet, equivalent to 0.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Effentora 200 micrograms buccal tablets
Effentora 400 micrograms buccal tablets
Effentora 600 micrograms buccal tablets
Effentora 800 micrograms buccal tablets
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 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 ulceration Tongue disorder Oesophagitis Chapped lips	Oral mucosal blistering Dry lip	

	Very common	Common	Uncommon	Rare	Not known
			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		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 national reporting system listed in Appendix V.

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).

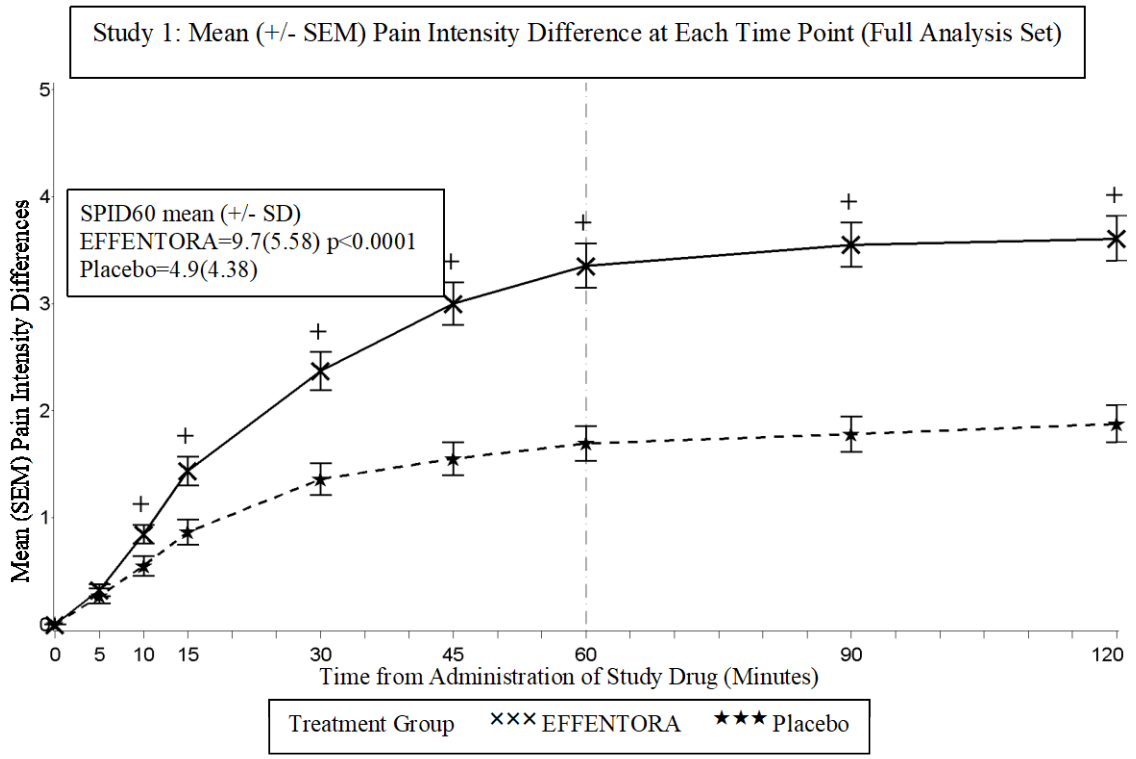
All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy as these patients will develop tolerance to respiratory depressant effects.

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).

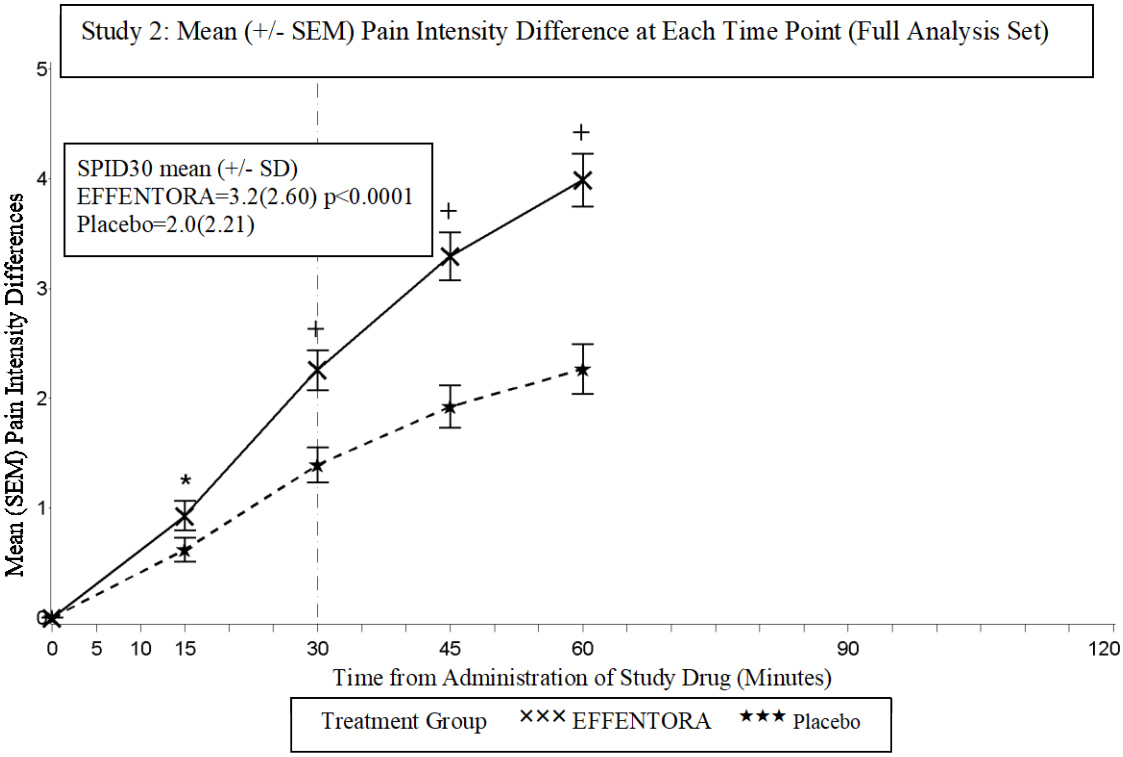
Clinical efficacy and safety
The safety and efficacy of Effentora have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Pre-emptive use of Effentora for predictable pain episodes was not investigated in the clinical trials. Two double-blind, randomized, placebo-controlled 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 ($p<0.0001$).



\+ 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



* 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.

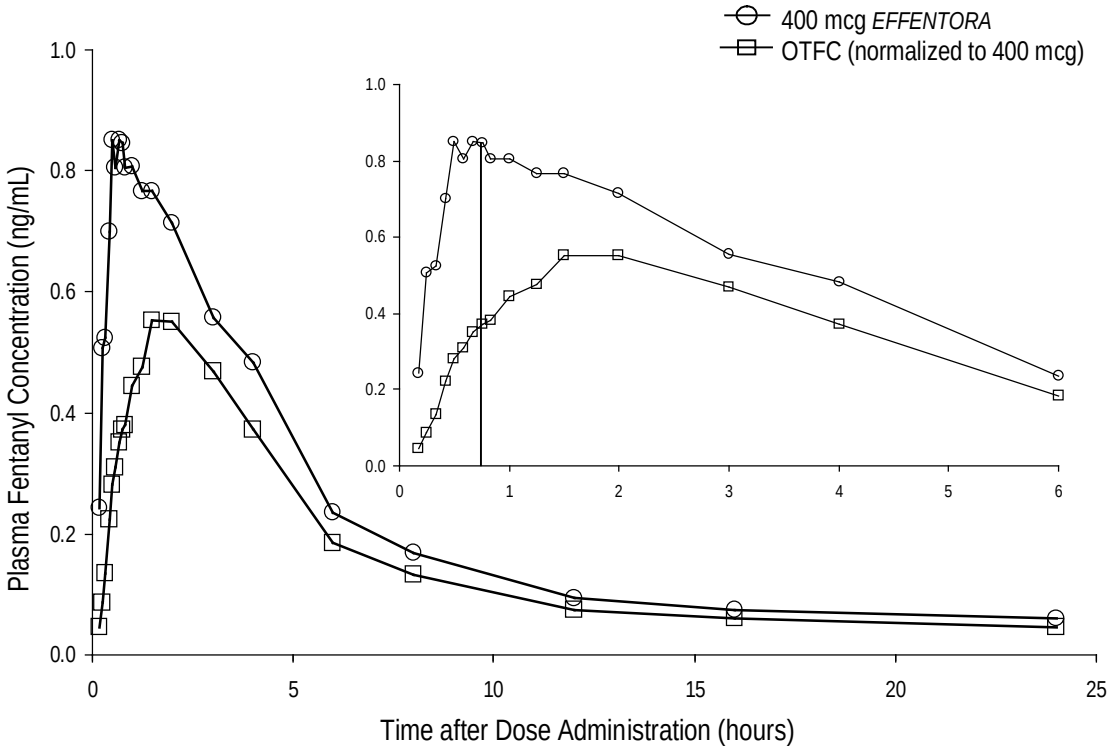
Pharmacokinetic Parameters in Adult Subjects Receiving Effentora*

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.

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) 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

TEVA B.V.
Swensweg 5
2031 GA Haarlem
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Effentora 100 micrograms buccal tablets
EU/1/08/441/001-002

Effentora 200 micrograms buccal tablets
EU/1/08/441/003-004

Effentora 400 micrograms buccal tablets
EU/1/08/441/005-006

Effentora 600 micrograms buccal tablets
EU/1/08/441/007-008

Effentora 800 micrograms buccal tablets
EU/1/08/441/009-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 April 2008

Date of latest renewal: 20 February 2013

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

Teva Pharmaceuticals Europe B.V.
Swensweg 5
2031 GA HAARLEM
Netherlands

Merckle GmbH
Ludwig-Merckle-Straße 3
89143 Blaubeuren
Germany

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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to the launch/use of Effentora in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that, all physicians, pharmacists and patients expected to prescribe/dispense/use Effentora are provided with educational material regarding the correct and safe use of the product.

Educational material for the patients will contain the following:

- Patient information leaflet
- A patient/carer guide
- Enhanced digital access information

Patient/carer guide

- EFFENTORA to be used only if patients/carers have received the proper information regarding the use of the drug and the safety precautions.
- Explanation of the indication.
- Explanation of Breakthrough Pain, Patients perception of pain and its treatment.
- Explanation of off label use, misuse, abuse, medication error, overdose, death and addiction.
- Definition of a patient at risk of overdose, abuse, misuse, dependence and addiction in order to inform prescribers/ pharmacists.
- Not to use EFFENTORA to treat any other short term pain or pain status and/or for treatment of more than 4 breakthrough cancer pain episodes a day (section 3 PIL).
- Formulations are not interchangeable.
- Need for reference to prescriber/ pharmacists in case of any question.
- How to use EFFENTORA

Educational material for the physicians will contain the following:

- The Summary of Product Characteristics and Package leaflet
- Guide for Physicians
- Prescribing checklist
- Enhanced digital access information

Guide for Physicians

- Treatment to be initiated/supervised by a physician experienced in the management of opioid therapy in cancer patients, in particularly regarding transition from hospital to home.
- Explanation of off label uses (i.e: indication, age) and the serious risks of misuse, abuse, medication error, overdose, death and addiction.
- Need for communication to patients/carers:
    - Treatment management and risks of abuse and dependence.
    - Need of periodic review by prescribers.
    - Encouragement for reporting of any issue with the management of the treatment.

- Identification and monitoring of patients at risk of abuse and misuse before and during the treatment to identify the key features of opioid use disorder (OUD): distinguishing features of opioid related side effects and opioid use disorder.
- Importance of reporting off label use, misuse, abuse, addiction and overdose.
- Need for tailoring therapy if OUD is recognized.

The prescribers of EFFENTORA must critically select the patients and counsel them on:

- Instructions for use of EFFENTORA
- Never sharing their medication or diverting the purpose of its use.
- Updated label information including hyperalgesia, use in pregnancy, drug interactions such as with benzodiazepines, iatrogenic addiction, withdrawal and dependence.
- The prescriber must make use of the checklist for prescribers.

Prescribing checklist
Required actions before prescribing EFFENTORA. Please complete all of the following before prescribing EFFENTORA:

- Ensure that all elements of the approved indication are fulfilled.
- Provide instructions for using EFFENTORA to patient and/or carer.
- Ensure the patient reads the package leaflet inside the EFFENTORA box.
- Supply the patient with the EFFENTORA patient brochure provided covering the below:
  - Cancer and Pain.
  - EFFENTORA. What is it? How do I use it?
  - EFFENTORA. Risks of misuse.
- Explain the risks of using more than the recommended amount of EFFENTORA.
- Explain the use of the dose monitoring cards.
- Advise the patient on the signs of fentanyl overdose and the need for immediate medical assistance.
- Explain secure storage and the need to keep out of the reach and sight of children.
- Remind the patient and/or caregiver that they should ask their doctor if they have any questions or concerns about how to use EFFENTORA or about the associated risks of misuse and abuse.

Educational material for the pharmacists will contain the following:

- The Summary of Product Characteristics and Package Leaflet
- Guide for Pharmacists
- Dispensing checklist
- Enhanced digital access information

Guide for Pharmacists

- Treatment to be initiated/supervised by a physician experienced in the management of opioid therapy in cancer patients, in particularly regarding transition from hospital to home.
- Explanation of off label uses (i.e: indication, age) and the serious risks of misuse, abuse, medication error, overdose, death and addiction.
- Need for communication to patients/carers:
    - Treatment management and risks of abuse and dependence.
    - Need of periodic review by prescribers.
    - Encouragement for reporting of any issue with the management of the treatment.
- Monitoring of patients at risk of abuse and misuse during the treatment to identify the key features of opioid use disorder (OUD): distinguishing features of opioid related side effects and opioid use disorder.
- Importance of reporting off label use, misuse, abuse, addiction and overdose.
- Physician should be contacted if OUD recognized.
- Pharmacist must be familiar with the educational materials before is given to the patient.
- EFFENTORA is not interchangeable with other Fentanyl products.

The pharmacists dispensing EFFENTORA must counsel the patients on:

- Instructions for use of EFFENTORA.
- The pharmacist must inform the patients that in order to prevent theft and misuse of EFFENTORA they have to keep it in a safe place to avoid misuse and diversion.
- The pharmacist must make use of the checklist for pharmacists.

Dispensing checklist

Required actions before supplying EFFENTORA. Please complete the following before EFFENTORA is supplied:

- Ensure that all elements of the approved indication are fulfilled.
- Provide instructions for using EFFENTORA to patient and/or carer.
- Ensure the patient reads the package leaflet inside EFFENTORA carton box.
- Supply the patient with the EFFENTORA patient brochure provided covering the below:
    - Cancer and Pain.
    - EFFENTORA. What is it? How do I use it?
    - EFFENTORA. Risks of misuse.
- Explain the risks of using more than the recommended amount of EFFENTORA.
- Explain the use of the dose monitoring cards.
- Advise the patient on the signs of fentanyl overdose and the need for immediate medical assistance.
- Explain secure storage and the need to keep out of the reach and sight of children.

Digital access to educational material

Digital access to all education material updates will be enhanced. Prescriber (physician), pharmacist and patient educational materials will be accessible via a website, and will be available for download. Details of enhanced digital accessibility will be discussed with National Competent Authorities and EMA, as appropriate.

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. See leaflet for further information.

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 must only be used by patients already receiving maintenance opioid therapy for chronic cancer pain. Read enclosed leaflet for important warnings and directions.

Accidental use can cause serious harm and be fatal.

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 B.V. Swensweg 5 2031 GA Haarlem 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

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 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. See leaflet for further information.

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 must only be used by patients already receiving maintenance opioid therapy for chronic cancer pain. Read enclosed leaflet for important warnings and directions.

Accidental use can cause serious harm and be fatal.

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 B.V. Swensweg 5 2031 GA Haarlem 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

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 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. See leaflet for further information.

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 must only be used by patients already receiving maintenance opioid therapy for chronic cancer pain. Read enclosed leaflet for important warnings and directions**.**

Accidental use can cause serious harm and be fatal.

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 B.V. Swensweg 5 2031 GA Haarlem 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

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 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. See leaflet for further information.

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 must only be used by patients already receiving maintenance opioid therapy for chronic cancer pain. Read enclosed leaflet for important warnings and directions.

Accidental use can cause serious harm and be fatal.

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 B.V. Swensweg 5 2031 GA Haarlem Netherlands

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

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 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. See leaflet for further information.

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 must only be used by patients already receiving maintenance opioid therapy for chronic cancer pain. Read enclosed leaflet for important warnings and directions.

Accidental use can cause serious harm and be fatal.

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 B.V. Swensweg 5 2031 GA Haarlem 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

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 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. See section 4.

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 are not regularly using a prescribed opioid medicine (e.g codeine, fentanyl, hydromorphone, morphine, oxycodone, pethidine), 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
- If you are taking a medicine which contains sodium oxybate.

Warnings and precautions
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.

Store this medicine in a safe and secure place, where other people cannot access it (see section *5. How to store Effentora* for more information).

Talk to your doctor or pharmacist **BEFORE** using Effentora if:

- 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.
- You are over 65 years old - you may need a lower dose and any dose increase will be reviewed very carefully by your doctor.
- You have problems with your heart especially slow heart rate.
- You use benzodiazepines (see section 2 under "Other medicines and Effentora"). Using benzodiazepines can increase the chances of getting serious side effects including death
- You use antidepressants or antipsychotics (selective serotonin reuptake inhibitors [SSRIs], serotonin norepinephrine reuptake inhibitors [SNRIs], monoamine oxidase (MAO) inhibitors; see section 2 under "Do not use Effentora" and "Other medicines and Effentora")The use of these medicines with Effentora can lead to a **serotonin syndrome a potentially life-threatening condition** (see section 2 under "Other medicines and Effentora").
- You have ever developed adrenal insufficiency, a condition in which the adrenal glands do not produce enough hormones or lack of sex hormones (androgen deficiency) with opioid use (see section 4 under "Serious side effects").
- You have ever abused or been dependent on opioids or any other drug, alcohol or illegal drugs.
- You drink alcohol; please refer to section Effentora with food, drink and alcohol.

Consult your doctor **WHILE** using Effentora if:

- You experience pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of your medicine as prescribed by your doctor.
- You experience a combination of the following symptoms: nausea, vomiting, anorexia, fatigue, weakness, dizziness and low blood pressure. Together these symptoms may be a sign of a potentially life-threatening condition called adrenal insufficiency, a condition in which the adrenal glands do not produce enough hormones.
- Sleep-related breathing disorders: Effentora can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

Long-term use and tolerance

This medicine contains fentanyl which is an opioid medicine. Repeated use of opioid painkillers can result in the drug being less effective (you become accustomed to it, known as drug tolerance). You may also become more sensitive to pain while using Effentora. This is known as hyperalgesia. Increasing the dose of Effentora may help to further reduce your pain for a while, but it may also be harmful. If you notice that your medicine becomes less effective, talk to your doctor. Your doctor will decide whether it is better for you to increase the dose or to gradually decrease your use of Effentora.

Dependence and addiction

Repeated use of Effentora can also lead to dependence, abuse and addiction which may result in life-threatening overdose. The risk of these side effects can increase with a higher dose and longer duration of use. Dependence or addiction can make you feel that you are no longer in control of how much

medicine you need to use or how often you need to use it. You might feel that you need to carry on using your medicine, even when it doesn't help to relieve your pain.
The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent or addicted on Effentora if:

- You or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
- You are a smoker.
- You have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illness.

If you notice any of the following signs whilst using Effentora, it could be a sign that you have become dependent or addicted:

- You need to use the medicine for longer than advised by your doctor.
- You need to use more than the recommended dose.
- You are using the medicine for reasons other than prescribed, for instance, 'to stay calm' or 'help you sleep'.
- You have made repeated, unsuccessful attempts to quit or control the use of the medicine.
- When you stop taking the medicine you feel unwell (e.g. nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating), and you feel better once using the medicine again ('withdrawal effects').

If you notice any of these signs, speak to your doctor to discuss the best treatment pathway for you, including when it is appropriate to stop and how to stop safely.

Seek **URGENT** medical advice if:

- You experience symptoms such as difficulty in breathing or dizziness, swelling of the tongue, lip or throat while using Effentora. These might be early symptoms of a serious allergic reaction (anaphylaxis, hypersensitivity; see section 4 under "Serious side effects")

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 and adolescents below18 years of age.

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:

- Concomitant use of Effentora and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.

  However if your doctor does prescribe Effentora together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.

  Please tell your doctor about all sedative medicines you are taking (such as sleeping pills, medicines to treat anxiety, some medicines to treat allergic reactions (antihistamines), or tranquillisers) and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.
- Some muscle relaxants - such as baclofen, diazepam (see also section "Warnings and precautions".

- 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.
- Certain type of strong pain killers, called partial agonist/antagonists e.g. buprenorphine, nalbuphine and pentazocine (medicines for treatment of pain). You could experience symptoms of withdrawal syndrom (nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating) while using these medicines.
- Some painkillers for nerve pain (gabapentin and pregabalin).
- The risk of side effects increases if you are taking medicines such as certain antidepressants or antipsychotics. Effentora may interact with these medicines and you may experience mental status changes (e.g. agitation, hallucinations, coma), and other effects such as body temperature above 38°C, increase in heart rate, unstable blood pressure, and exaggeration of reflexes, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g nausea, vomiting, diarrhoea). Your doctor will tell you whether Effentora is suitable for you.

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

Effentora with food, 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 serious side effects including death.

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 using this medicine.

Pregnancy
Effentora should not be used during pregnancy unless you have discussed this with your doctor.
If Effentora is used for a long time during pregnancy, there is also a risk of the new-born child having withdrawal symptoms which might be life-threatening if not recognized and treated by a doctor.

You should not use Effentora during childbirth because fentanyl may cause respiratory depression in the new-born child.

Breast-feeding
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 until at least 5 days 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

Effentora 100 micrograms
This medicine contains 10 mg sodium (main component of cooking/table salt) in each buccal tablet. This is equivalent to 0.5 % of the recommended maximum daily dietary intake of sodium for an adult.

Effentora 200 micrograms, Effentora 400 micrograms, Effentora 600 micrograms, Effentora 800 micrograms
This medicine contains 20 mg sodium (main component of cooking/table salt) in each buccal tablet. This is equivalent to 1 % of the recommended maximum daily dietary intake of sodium for an adult.

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.

Before starting treatment and regularly during treatment, your doctor will also discuss with you what you may expect from using Effentora, when and how long you need to take it, when to contact your doctor, and when you need to stop it (see also section 2).

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 a change may be required to your treatment regimen. Your doctor may change the treatment for your persistent pain; when your persistent pain is controlled, your doctor may need to change the dose of Effentora. If your doctor suspects Effentora-related increased sensitivity to pain (hyperalgesia), a reduction of your Effentora dose may be considered (see section 2 under “Warnings and precautions”). 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. In severe cases taking too much Effentora may also lead to coma. If you feel very dizzy, very sleepy or have slow or shallow breathing, please seek immediate medical assistance.
- An overdose may also result in a brain disorder known as toxic leukoencephalopathy.

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 you no longer have any breakthrough pain. You must however continue to take your usual opioid pain relieving medicine to treat your persistent cancer pain as advised by your doctor. You may experience withdrawal symptoms similar to the possible side effects of Effentora when discontinuing Effentora. If you experience withdrawal symptoms or if you are concerned about your pain relief, you should contact your doctor. Your doctor will evaluate if you need medicine to reduce or eliminate the withdrawal symptoms.

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 cause side effects, although not everybody gets them. If you notice any of these, contact your doctor.

Serious side effects

- **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.**

- **Contact your doctor immediately if you experience a combination of the following symptoms**
  - Nausea, vomiting, anorexia, fatigue, weakness, dizziness and low blood pressure

  Together these symptoms may be a sign of a potentially life-threatening condition called adrenal insufficiency. A condition in which the adrenal glands do not produce enough hormones.

Other side effects

Very common: 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: may affect up to 1 in 10 people
- feeling anxious or confused, depression, insomnia
- abnormal taste, weight decreased
- sleepiness, sedation, excessive tiredness, weakness, migraine, numbness, swelling of arms or legs, drug withdrawal syndrome (may manifest by the occurrence of the following side effects nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating), 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
- fatigue

Uncommon: 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 are not really there (hallucinations), reduced consciousness, change in mental state, 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, feeling very warm (hot flushes),
- severe 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
- malaise
- flushing

Rare: 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
- Allergic reactions such as rash, redness, swollen lip and face, hives

Not known: frequency cannot be estimated from the available data
- loss of consciousness, stop in breathing, convulsion (fits)
- lack of sex hormones (androgen deficiency)
- drug dependence (addiction) (see section 2)
- drug abuse (see section 2)
- drug tolerance (see section 2)
- delirium (symptoms may include a combination of agitation, restlessness, disorientation, confusion, fear, seeing or hearing things that are not really there, sleep disturbance, nightmares)
- prolonged treatment with fentanyl during pregnancy may cause withdrawal symptoms in the newborn which can be life-threatening (see section 2)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Effentora

Store this medicine in a safe and secure place, where other people cannot access it. It can cause serious harm and be fatal to people who may take this medicine by accident, or intentionally when it has not been prescribed for them.

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 which is stated on the blister package label and the carton. The expiry date refers to the last day of that month.
- 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, citric acid, 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.

Marketing Authorisation Holder
TEVA B.V.
Swensweg 5
2031 GA Haarlem
Netherlands

Manufacturer
Teva Pharmaceuticals Europe B.V.
Swensweg 5
2031 GA HAARLEM
Netherlands

Merckle GmbH
Ludwig-Merckle-Straße 3
89143 Blaubeuren
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder or call the following number:

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A./AG
Tel/Tél: +32 3 820 73 73

България
Тева Фарма ЕАД
Тел.: +359 2 489 95 85

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Danmark
Teva Denmark A/S
Tlf: +45 44 98 55 11

Deutschland
TEVA GmbH
Tel: +49 731 402 08

Eesti
UAB Teva Baltics Eesti filiaal
Tel: + 372 661 0801

Ελλάδα
Specifar A.B.E.E.
Τηλ: +30 2118805000

Lietuva
UAB Teva Baltics
Tel: +370 5 266 02 03

Luxembourg/Luxemburg
Teva Pharma Belgium N.V./S.A./AG.
Tél: +32 3 820 73 73

Magyarország
Teva Gyógyszergyár Zrt.
Tel.: (+ 36) 1 288 6400

Malta
Teva Pharmaceuticals Ireland
L-Irlanda
Tel: +44 (0) 207 540 7117

Nederland
Teva Nederland B.V.
Tel: +31 (0) 800 0228 400

Norge
Teva Norway AS
Tlf: +47 66 77 55 90

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
Tel: +43 197007 0

España
Teva Pharma, S.L.U.
Tel: + 34 91 387 32 80

France
Teva Santé
Tél: +33 1 55 91 78 00

Hrvatska
Pliva Hrvatska d.o.o
Tel: + 385 1 37 20 000

Ireland
Teva Pharmaceuticals Ireland
Tel: +44 (0) 207 540 7117

Ísland
Teva Pharma Iceland ehf.
Sími: +354 5503300

Italia
Teva Italia S.r.l.
Tel: +39 028917981

Κύπρος
Specifar A.B.E.E.
Τηλ: +30 2118805000

Latvija
UAB Teva Baltics filiāle Latvijā
Tel: +371 67 323 666

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +48 22 345 93 00

Portugal
Teva Pharma - Produtos Farmacêuticos, Lda.
Tel: +351 21 476 75 50

România
Teva Pharmaceuticals S.R.L.
Tel: +4021 230 65 24

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 1 58 90 390

Slovenská republika
TEVA Pharmaceuticals Slovakia s.r.o.
Tel: +421257267911

Suomi/Finland
Teva Finland Oy
Puh/Tel: +358 20 180 5900

Sverige
Teva Sweden AB
Tel: +46 (0)42 12 11 00

United Kingdom (Northern Ireland)
Teva Pharmaceuticals Ireland
Ireland
Tel: +44 (0) 207 540 7117

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

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for fentanyl (transmucosal route of administration), the scientific conclusions of PRAC are as follows:

In view of literature reports, spontaneous reports and previous actions taken for other opioid products (e.g. fentanyl transdermal patches, solution for injection), the PRAC considers that further information regarding Opioid Use Disorder (OUD) should be communicated to the prescribers and patients. The PRAC concluded that the product information of products containing fentanyl (transmucosal route of administration) should be amended accordingly.

In view of literature reports, spontaneous reports and previous actions taken for other opioid products (e.g. fentanyl transdermal patches, solution for injection), the PRAC considers that further information regarding the storage in a safe and secure place should be provided in the product information. The PRAC concluded that the product information of products containing fentanyl (transmucosal route of administration) should be amended accordingly.

In view of available data on toxic leukoencephalopathy in a context of overdose from the literature and spontaneous reports including cases with at least a reasonable possibility for a causal relationship with fentanyl overdose, the PRAC Rapporteur concluded that the product information of products containing fentanyl (transmucosal route of administration) should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for fentanyl (transmucosal route of administration) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing fentanyl (transmucosal route of administration) is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.