SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fentanyl Qube 200 microgram zuigtabletten met integrale applicator voor oromucosaal gebruik
Fentanyl Qube 400 microgram zuigtabletten met integrale applicator voor oromucosaal gebruik
Fentanyl Qube 600 microgram zuigtabletten met integrale applicator voor oromucosaal gebruik
Fentanyl Qube 800 microgram zuigtabletten met integrale applicator voor oromucosaal gebruik
Fentanyl Qube 1200 microgram zuigtabletten met integrale applicator voor oromucosaal gebruik
Fentanyl Qube 1600 microgram zuigtabletten met integrale applicator voor oromucosaal gebruik

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fentanyl Qube 200 microgram compressed lozenges One compressed lozenge contains 200 micrograms fentanyl (as citrate)

Fentanyl Qube 400 microgram compressed lozenges One compressed lozenge contains 400 micrograms fentanyl (as citrate)

Fentanyl Qube 600 microgram compressed lozenges One compressed lozenge contains 600 micrograms fentanyl (as citrate)

Fentanyl Qube 800 microgram compressed lozenges One compressed lozenge contains 800 micrograms fentanyl (as citrate)

Fentanyl Qube 1200 microgram compressed lozenges One compressed lozenge contains 1200 micrograms fentanyl (as citrate)

Fentanyl Qube 1600 microgram compressed lozenges One compressed lozenge contains 1600 micrograms fentanyl (as citrate)

Excipients with known effect
One compressed lozenge contains 1.89g of glucose (as hydrated dextrates) For

the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Compressed lozenge.

<Product name > is a white or slightly yellowish cylindrical lozenge of 17 – 20 mm of thickness and 11 – 12 mm of diameter, on which its respective dosage strength is printed, attached to a plastic handle at the opposite end also labelled with the dosage strength. The lozenges may develop brownish spots during storage.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Product name > is indicated for management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of pain that occurs on a background of persistent pain controlled by other means.

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

Posology

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

<Product name > is not interchangeable on a mcg to mcg basis with other short-acting fentanyl products that are indicated for the use of breakthrough cancer pain, as the pharmacokinetic profiles and/or dosing schedules of these products are significantly different. Patients should be instructed not to use more than one short-acting fentanyl product concurrently for the treatment of breakthrough cancer pain, and to dispose of any fentanyl product prescribed for breakthrough pain (BTP) when switching to <Product name >. The number of <Product name > strengths available to the patient at any time should be minimised to prevent confusion and potential overdose.

Any unused <Product name > units that the patient no longer requires must be disposed of properly. Patients must be reminded of the requirements to keep <Product name > stored in a location away from children.

Adults

Dose titration and maintenance therapy

<Product name> should be individually titrated to a "successful" dose that provides adequate analgesia and minimises adverse reaction. In clinical trials the successful dose of <Product name> for breakthrough pain was not predicted from the daily maintenance dose of opioid.

a) Titration

Before patients are titrated with <Product name>, it is expected that their background persistent pain will be controlled by use of opioid therapy and that they are typically experiencing no more than 4 episodes of breakthrough pain per day.

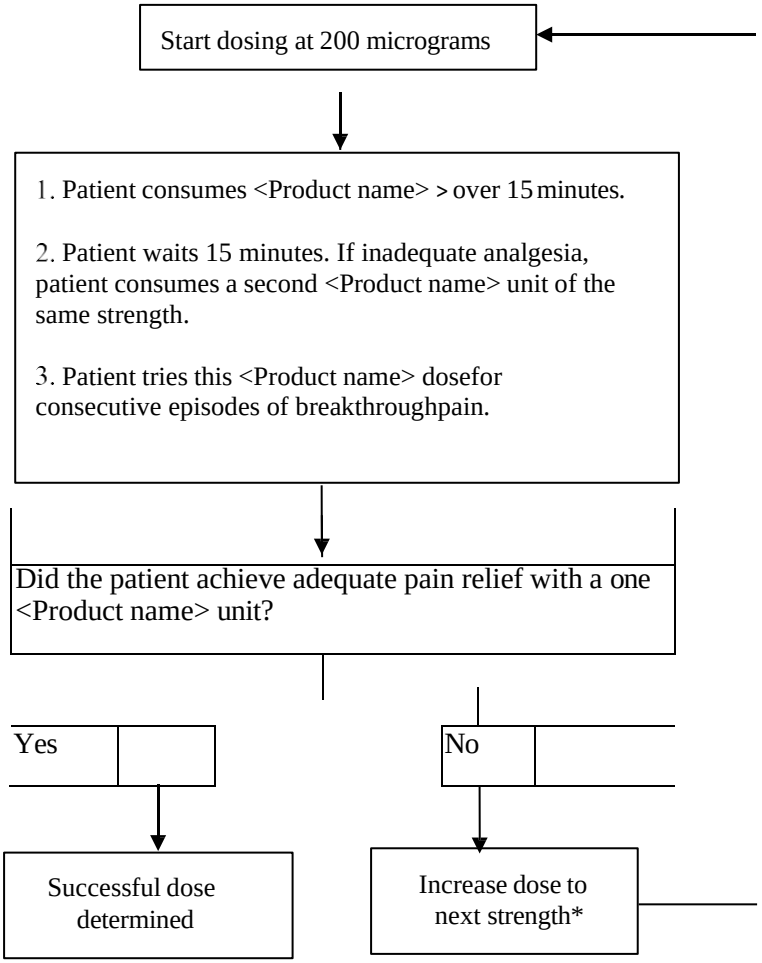
The initial dose of <Product name> used should be 200 micrograms, titrating upwards as necessary through the range of available dosage strengths (200, 400, 600, 800, 1200 and 1600 micrograms). Patients should be carefully monitored until a dose is reached that provides adequate analgesia with acceptable adverse reaction using a single dosage unit per episode of breakthrough pain. This is defined as the successful dose.

During titration, if adequate analgesia is not obtained within 30 minutes after starting the first unit (i.e. 15 minutes after the patient completes consumption of a single <Product name> unit), a second <Product name> unit of the same strength may be consumed. No more than two <Product name>

units should be used to treat any individual pain episode. At 1600 micrograms, a second dose is only likely to be required by a minority of patients.

If treatment of consecutive breakthrough pain episodes requires more than one dosage unit per episode, an increase in dose to the next higher available strength should be considered.

<Product name> Titration process



*Dose concentrations available are 200, 400, 600, 800, 1200 and 1600 micrograms.

b) Maintenance

Once a successful dose has been established (i.e., on average, an episode is effectively treated with a single unit), patients should be maintained on this dose and should limit consumption to a maximum of four <Product name> units per day.

Patients should be monitored by a health professional to ensure that the maximum consumption of four units of <Product name> per day is not exceeded.

Dose re-adjustment

The maintenance dose of <Product name> should be increased when an episode is not effectively treated with a single unit for several consecutive BTP episodes. For dose- readjustment the same principles apply as outlined for dose titration (see above).

If more than four episodes of breakthrough pain are experienced per day the dose of the long acting opioid used for persistent pain should be re-evaluated. If the dose of the long acting opioid is increased, the dose of <Product name> to treat breakthrough pain may need to be reviewed.

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

It is imperative that any dose re-titration of any analgesic is monitored by a health professional.

Discontinuation of therapy

<Product name> 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 as gradual downward opioid titration is necessary in order to avoid the possibility of abrupt withdrawal effects.

Use in the elderly

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously. Therefore dose titration needs to be approached with particular care. In the elderly, elimination of fentanyl is slower and the terminal elimination half-life is longer, which may result in accumulation of the active substance and to a greater risk of undesirable effects.

Formal clinical trials with <Product name> have not been conducted in the elderly population. It has been observed, however, in clinical trials that patients over 65 years of age required lower doses of <Product name> for successful relief of breakthrough pain.

Use in patients with hepatic or renal impairment
Special care should be taken during the titration process in patients with kidney or liver dysfunction (see section 4.4).

Paediatric population

Adolescents aged 16 years and above:
Follow adult dosage

Children aged 2 to 16 years old:
There is limited clinical trial experience of the use of <Product name> in paediatric patients already receiving maintenance opioid therapy (see sections 5.1 and 5.2). Safety and efficacy in paediatric patients below the age of 16 years have not been established; use in this patient population is therefore not recommended.

Method of administration

<Product name> is intended for oromucosal administration, and therefore should be placed in the mouth against the cheek and should be moved around the mouth using the applicator, with the aim of maximising the amount of mucosal exposure to the product. The <Product name> unit should be sucked, not chewed, as absorption of fentanyl via the buccal mucosa is rapid in comparison with systemic absorption via the gastrointestinal tract. Water may be used to moisten the buccal mucosa in patients with a dry mouth.

The <Product name> unit should be consumed over a 15- minute period. If signs of excessive

opioid effects appear before the <Product name> unit is fullyconsumed it should be immediately removed, and consideration given to decreasing future dosages

4.3 Contraindications

-Hypersensitivity to fentanyl or to any of the excipients listed in section 6.1.
-Patients without maintenance opioid therapy (see section 4.4) as there is an increased risk of respiratory depression.
-Treatment of acute pain other than breakthrough pain (e.g. postoperative pain, headache, migraine).
-Simultaneous use with monoamine oxidase inhibitors (MAOIs), or within 2 weeks after cessation of the use of MAOIs inhibitors (see sections 4.4 and 4.5).
-Severe respiratory depression or severe obstructive lung conditions.
- Patients being treated with medicinal products containing sodium oxybate.

4.4 Special warnings and precautions for use

Accidental use in children
Patients and their carers must be instructed that <Product name> contains an active substance in an amount that can be fatal to a child. Death has been reported in children who have accidentally ingested <Product name>.
Patients and their carers must be instructed to keep all units out of the reach and sight of children and to discard open and unopened units appropriately. An evaluation of each out-patient concerning possible accidental child exposures should be undertaken.

Maintenance opioid therapy
The product should not be given to patients without maintenance opioid therapy as there is an increased risk of respiratory depression and death. It is important that the maintenance opioid therapy used to treat the patient's persistent pain has been stabilized before <Product name> therapy begins and that the patient continues to be treated with the maintenance opioid therapy whilst taking <Product name>.

Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. Iatrogenic addiction following therapeutic use of opioids is known to occur.
Repeated use of <Product name> may lead to Opioid Use Disorder (OUD). Abuse or intentional misuse of [fentanyl-containing product] 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).
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.

Adrenal insufficiency
Cases of adrenal insufficiency have been reported with opioid use including fentanyl lozenges, more often following greater than one month of use. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers (see section 4.8).

Respiratory depression
As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of <Product name>. <Product name> patients should be monitored accordingly. Particular caution should be used when titrating <Product name> in patients with non-severe chronic obstructive pulmonary disease or other medical conditions predisposing them to respiratory depression, as even normally therapeutic doses of <Product name> 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).

Intracranial effects of CO2 retention, impaired consciousness, head injury
<Product name> 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
Intravenous fentanyl may produce bradycardia. Therefore, <Product name> should be used with caution in patients with previous or pre-existing bradyarrhythmias.

Hepatic or renal impairment
In addition, <Product name> should be administered with caution to patients with liver or kidney dysfunction. The influence of liver 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 disease due to alterations in metabolic clearance and plasma proteins. After administration of <Product name>, impaired liver 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 renaldisease.

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

Diabetic patients
Diabetic patients should be advised that the medicine product contains dextrates (dextrates are composed of 93% dextrose monohydrate and 7% maltodextrin. The total glucose load per dosage unit is approximately 1.89 grams per dose).

Dental decay
Normal oral hygiene is recommended to reduce any potential harm to the teeth. Because <Product name> contains approximately 2 grams of sugar, frequent consumption increases the risk of dental decay. The occurrence of dry mouth associated with the use of opioid medications may add to this risk. During treatment with <Product name>, regular dental visits are advised.

Serotonin syndrome
Caution is advised when <Product name> is co-administered with medicinal products that affect the serotoninergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic medicinal products such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with medicinal products 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 <Product name> should be discontinued.

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

Concomitant use of sedative medicines
Concomitant use of <product name> and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe <Product name> concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Paediatric population
<Product name> is not recommended for use in children and adolescents below 16 years due to lack of data on safety and efficacy (see sections 5.1 and 5.2).

Excipient
This medicine contains less than 1mmol sodium (23 mg) per compressed lozenge, that is to say essentially 'sodium-free

This medicine contains glucose (as hydrated dextrates) Patients with rare glucose-galactose malabsorption should not take this medicine. May be harmful to teeth.

4.5 Interaction with other medicinal products and other forms of interaction

Agents that affect CYP3A4 activity

CYP3A4 inhibitors
Fentanyl is metabolized by the CYP3A4 isoenzyme in the liver and intestinal mucosa. Potent inhibitors of CYP3A4 such as macrolide antibiotics (e.g. erythromycin), azole antifungals (e.g. ketoconazole, itraconazole, and fluconazole) and certain protease inhibitors (e.g. ritonavir), may increase the bioavailability of swallowed fentanyl and may also decrease its systemic clearance which may result in increased or prolonged opioid effects. Similar effects could be seen after concurrent ingestion of grapefruit juice, which is known to inhibit CYP3A4. Hence caution is advised if fentanyl is given concomitantly with CYP3A4 inhibitors.

CYP3A4 inducers
Co-administration with agents that induce 3A4 activity may reduce the efficacy of <Product name>.

Agents that can increase CNS depressants effects
The concomitant use of other CNS depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcohol may produce additive depressant effects which may result in a fatal outcome (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.

Serotonergic agents

Co-administration of fentanyl with a serotonergic agent, such as a Selective Serotonin Reuptake Inhibitor (SSRI) or a Serotonin Norepinephrine Reuptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition (see section 4.3).

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).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited of amount 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. <Product name> 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 <Product name> is administered, an antidote for the child should be readily available.

Breastfeeding
Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should not be used by breast-feeding women and breast-feeding 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 may 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, blurred or double vision while taking <Product name>.

4.8 Undesirable effects

Typical opioid side effects are to be expected with <Product name>. Frequently, these will cease or decrease in intensity with continued use of the product, as the patient is titrated to the most appropriate dose. However, the most serious adverse events are respiratory depression (potentially leading to apnoea or respiratory arrest), circulatory depression, hypotension and shock and all patients should be closely monitored for these.

Application site reactions, including gum bleeding, irritation, pain and ulcer have been reported in post-marketing use.

Because the clinical trials of <Product name> were designed to evaluate safety and efficacy in treating breakthrough pain, all patients were also taking concomitant opioids, such as sustained-release morphine or transdermal fentanyl, for their persistent pain. Thus it is not possible to definitively separate the effects of <Product name> alone.

The following adverse reactions have been reported with <Product name> 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, not known (cannot be estimated from the available data) :

System organ class	Very common	Common	Uncommon	Not known
Immune system disorders				anaphylactic reaction, tongue oedema, lip oedema
Endocrine disorders				adrenal insufficiency, androgen deficiency
Metabolism and nutrition disorders		anorexia		
Psychiatric disorders		confusion, anxiety, hallucinations, depression, emotional lability	abnormal dreams, depersonalisation, abnormal thinking, euphoria	insomnia, delirium
Nervous system disorders	somnolence, dizziness, headache	loss of consciousness, convulsion, vertigo, myoclonus, sedation, parathesia (including hyperaesthesia/circumoral parathesia), abnormal gait/incoordination, taste perversion	coma, slurred speech	
Eye disorders		abnormal vision (blurred, double vision)		

System organ class	Very common	Common	Uncommon	Not known
Vascular disorders			vasodilatation	flushing, hot flush
Respiratory, thoracic and mediastinal disorders	dyspnoea			pharyangeal oedema, respiratory depression
Gastrointestinal disorders	nausea, vomiting, constipation, abdominal pain	dry mouth, dyspepsia, stomatitis, tongue disorder (for example, burning sensation, ulcers), flatulence, abdomen enlarged	ileus, mouth ulcers, dental caries, gingival bleeding	tooth loss, gingival recession, gingivitis, diarrhoea
Skin and subcutaneous tissue disorders		pruritis, sweating, rash	urticaria	
Renal and urinary disorders		urinary retention		
General disorders and administration site conditions	asthenia	application site reactions including irritation, pain and ulcer, malaise		fatigue, peripheral oedema, pyrexia, withdrawal syndrome*, neonatal withdrawal syndrome, drug dependence (addiction), drug abuse bleeding at the site of application
Investigations		weight decreased		
Injury, poisoning and procedural complications		accidental injury (for example, falls)		

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

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 [To be completed nationally].

4.9 Overdose

Symptoms

The symptoms of fentanyl overdosage 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, cardiorespiratory arrest, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.

Cases of Cheynes Stokes respiration have been observed in case of fentanyl overdose, particularly in patients with history of heart failure.

Management
Immediate management of opioid overdose includes removal of the <Product name> unit via the applicator, 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 naïve 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 <Product name>, 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: Opioid analgesic, phenylpiperidone derivative. ATC code N02A BO3.

Mechanism of action
Fentanyl, a pure opioid agonist, acts primarily through interaction with mu-opioid receptors located in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). The most clinically useful pharmacological effect of the interaction of fentanyl with mu-opioid receptors is analgesia. The analgesic effects of fentanyl are related to the blood level of the active substance if proper allowance is made for the delay into and out of the CNS (a process with a 3-5minute half-life). In opioid-naïve individuals, analgesia occurs at blood levels of 1 to 2 ng/ml, while blood levels of 10-20 ng/ml would produce surgical anaesthesia and profound respiratory depression.

In patients with chronic cancer pain on stable doses of regularly scheduled opioids to control their persistent pain, fentanyl produced significantly more breakthrough pain relief compared with placebo at 15, 30, 45, and 60 minutes following administration.

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.

Pharmacodynamic effects

Other secondary actions include increase in the tone and decrease in the contractions of the gastrointestinal smooth muscle, which results in prolongation of gastrointestinal transit time and may be responsible for the constipatory effect of opioids.

While opioids generally increase the tone of urinary tract smooth muscle, the overall effect tends to vary, in some cases producing urinary urgency, in others difficulty in urination.

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients with pain and those receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. In non-tolerant subjects, typically peak respiratory effects are seen 15 to 30 minutes following the administration of fentanyl and may persist for several hours.

Additional secondary pharmacological effect includes miosis.

Paediatric population
There is limited experience of the use of <Product name> in paediatric patients, below the age of 16. In a clinical study, 15 (out of 38) paediatric patients, ranging in age from 5 to 15 years, already receiving maintenance opioid therapy and with breakthrough pain were treated with a similar product. The study was too small to allow conclusions on safety and efficacy in this patient population.

5.2 Pharmacokinetic properties General introduction

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.

Absorption

The absorption pharmacokinetics of fentanyl from <Product name> are a combination of rapid oromucosal absorption and slower gastrointestinal absorption of swallowed fentanyl. Approximately 25% of the total dose of <Product name> is rapidly absorbed from the buccal mucosa. The remaining 75% of the dose is swallowed and slowly absorbed from the gastrointestinal tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Absolute bioavailability is about 50% compared to intravenous fentanyl, divided equally between rapid oromucosal and slower gastrointestinal absorption. Cmax ranges from 0.39 to 2.51 ng/ml after consumption of <Product name> (200 micrograms to 1600 micrograms). Tmax is around 20 to 40 minutes after consumption of an <Product name> unit (range 20 – 480 minutes).

Distribution

Animal data show that fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. 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. The mean volume of distribution at steady state (V_{ss}) is 4 l/kg.

Biotransformation

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

Less than 7% of the 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. The total plasma clearance of fentanyl is 0.5 l/hr/kg (range 0.3-0.7 l/hr/kg). The terminal elimination half-life after <Product name> administration is about 7 hours.

Linearity/non-linearity

Dose proportionality across the available range of dosages (200 micrograms to 1600 micrograms) of <Product name> has been demonstrated.

Paediatric population

In a clinical study, 15 paediatric patients, ranging in age from 5 to 15 years, already receiving maintenance opioid therapy and with breakthrough pain were treated with a similar product at doses ranging from 200 mcg to 600 mcg. Area under the curve values based on observed concentrations were 2-fold higher in younger children than adolescents (5.25 versus 2.65 ng.hr/mL, respectively) and 4-fold higher in the younger children as compared to adults (5.25 versus 1.20 ng.hr/mL). On a weight adjusted basis, clearance and volume of distribution values were similar across the age range.

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 consistent with the sedative effects of fentanyl in animal studies. In studies on pre and postnatal development in rats the survival rate of offspring was significantly reduced at doses causing severe maternal toxicity. Further findings at maternally toxic doses in F1 pups were delayed physical development, sensory functions, reflexes and behaviour. These effects could either be indirect effects due to altered maternal care and/or decreased lactation rate or a direct effect of fentanyl on the pups.

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

Compressed Lozenge:

Dextrates hydrated Citric acid, anhydrous, Disodium phosphate, anhydrous Magnesium stearate
Artificial berry flavour (main components Tapioca starch, Arabic gum (E-414) and Triacetine)

Edible glue used to attach the lozenge to the handle:
Dextrates hydrated, Maize starch Water, purified

Printing ink
Ethanol,Water, Purified Shellac (E904), Acetone, FD&C Blue No. 1 (E133 Briliant Blue FCF) Ammonium Hydroxide (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Each <Product name> dosage unit is contained in a child-resistance and opaque PVC-PCTFE-PVdC-PVC/Al blisters, supplied in cartons of 1 , 3, 15 or 30 individual units.

Not all pack size may be marketed.

6.6 Special precautions for disposal

Lozenges with residual active substance should at no time be discarded or misplaced.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Proteus Pharma S.L.
Camino Labiano 45B- Bajo derecha
31192 Mutilva
(Navarra)
Spain

8. MARKETING AUTHORISATION NUMBER(S)

Fentanyl Qube 200 microgram RVG 121061
Fentanyl Qube 400 microgram RVG 121062
Fentanyl Qube 600 microgram RVG 121063
Fentanyl Qube 800 microgram RVG 121064
Fentanyl Qube 1200 microgram RVG 121065
Fentanyl Qube 1600 microgram RVG 121066

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 3 juni 2019
Datum van laatste verlenging: 10 januari 2024

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 9: 4 september 2023