ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PecFent 100 micrograms/spray nasal spray, solution
PecFent 400 micrograms/spray nasal spray, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PecFent 100 micrograms/spray nasal spray, solution
Each ml of solution contains 1,000 micrograms fentanyl (as citrate)
1 spray (100 microlitres) contains 100 micrograms fentanyl (as citrate)

Bottles contain:
0.95 ml (950 micrograms fentanyl) - 2 spray bottle
or
1.55 ml (1,550 micrograms fentanyl) - 8 spray bottle

PecFent 400 micrograms/spray nasal spray, solution
Each ml of solution contains 4,000 micrograms fentanyl (as citrate)
1 spray (100 microlitres) contains 400 micrograms fentanyl (as citrate)

Each bottle contains 1.55 ml (6,200 micrograms fentanyl)

Excipients with known effect:
Each spray contains 0.02 mg propylparahydroxybenzoate (E216).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, solution (nasal spray).

A clear to practically clear colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PecFent is indicated for the management of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain 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 supervision of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential for abuse of fentanyl.

Posology

PecFent should be titrated to an "effective" dose that provides adequate analgesia and minimises adverse reactions without causing undue (or intolerable) adverse reactions, for two consecutively treated episodes of BTP. The efficacy of a given dose should be assessed over the ensuing 30 minute period.

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

PecFent is available in two strengths: 100 micrograms/spray and 400 micrograms/spray.

One dose of PecFent may include administration of 1 spray (100 microgram or 400 microgram doses) or 2 sprays (200 microgram or 800 microgram doses) of the same strength (either 100 microgram or 400 microgram strength).

Patients should not use more than 4 doses per day. Patients should wait at least 4 hours after a dose before treating another BTP episode with PecFent.

PecFent can deliver 100, 200, 400 and 800 microgram doses as follows:

Dose required (micrograms)	Product strength (micrograms)	Amount
100	100	One spray administered into one nostril
200	100	One spray administered into each nostril
400	400	One spray administered into one nostril
800	400	One spray administered into each nostril

Initial dose

- The initial dose of PecFent to treat episodes of BTP is always 100 micrograms (one spray), even in patients switching from other fentanyl containing products for their BTP.
- Patients must wait at least 4 hours before treating another episode of BTP with PecFent.

Method of titration

- Patients should be prescribed an initial titration supply of one bottle (2 sprays or 8 sprays) of PecFent 100 micrograms/spray.
- Patients whose initial dose is 100 micrograms and who need to titrate to a higher dose due to a lack of effect can be instructed to use two 100 microgram sprays (one in each nostril) for their next BTP episode. If this dose is not successful, the patient may be prescribed a bottle of PecFent 400 micrograms/spray and instructed to change to one 400 microgram spray for their next episode of pain. If this dose is not successful, the patient may be instructed to increase to two 400 microgram sprays (one in each nostril).
- From treatment initiation, patients should be closely followed and the dose titrated until an effective dose is reached and confirmed for two consecutively treated episodes of BTP.

Titration in patients switching between immediate-release fentanyl containing products

Substantial differences may exist in the pharmacokinetic profile of immediate-release fentanyl medicinal products, which result in clinically important differences in the rate and extent of absorption of fentanyl. Therefore, when switching between fentanyl containing medicinal products indicated for treatment of breakthrough pain, including intranasal formulations, it is essential that patients are again titrated with the new medicinal product, and not switched on a dose-for-dose (microgram-for-microgram) basis.

Maintenance therapy
Once an effective dose has been established during titration, patients should continue to take this dose up to a maximum of 4 doses per day.

Dose readjustment
Generally, the maintenance dose of PecFent should be increased only where the current dose fails to adequately treat the BTP for several consecutive episodes.

A review of the dose 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).

If adverse reactions are intolerable or persistent, the dose should be reduced or treatment with PecFent replaced by another analgesic.

Treatment duration and goals

Before initiating treatment with PecFent, 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). PecFent should not be used longer than necessary.

Discontinuation of therapy
PecFent should be discontinued immediately if the patient no longer experiences breakthrough pain episodes. The treatment for persistent backgound 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 therapy is necessary in order to avoid the possibility of abrupt withdrawal effects.

Special populations

Elderly (older than 65 years)
In the PecFent clinical trial programme, 104 (26.1%) of patients were over 60 years of age, 67 (16.8%) over 65 years and 15 (3.8%) over 75 years. There was no indication that older patients tended to titrate to lower doses or experience more adverse reactions. Nevertheless, in view of the importance of renal and hepatic function in the metabolism and clearance of fentanyl, additional care should be exercised in the use of PecFent in the elderly. No data on the pharmacokinetics of PecFent in elderly patients are available.

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

Paediatric population
The safety and efficacy of PecFent in children and adolescents aged below 18 years have not yet been established.

No data are available.

<u>Method of administration</u>
PecFent is for nasal use only.

The bottle should be removed from the child resistant container immediately prior to use and the protective cap removed. The bottle must be primed before first use by holding upright and simply pressing and releasing the finger grips either side of the nozzle until a green bar appears in the counting window (should occur after four sprays).

2 spray bottle:
The 2 spray bottle cannot be re-primed and once both doses are used, or if longer than 5 days since priming, the bottle and contents should be discarded as described in section 6.6.

8 spray bottle:
If the product has not been used for 5 days, it should be re-primed by spraying once.

The patient should be advised to write the date of first use in the space provided on the label of the child resistant container.

To administer PecFent the nozzle is placed a short distance (about 1 cm) into the nostril and pointed slightly towards the bridge of the nose. A spray is then administered by pressing and releasing the finger grips either side of the nozzle. An audible click will be heard and the number displayed on the counter will advance by one.

Patients must be advised that they may not feel the spray being administered, and that they should, therefore, rely on the audible click and the number on the counter advancing to confirm that a spray has been delivered.

The PecFent spray droplets form a gel in the nose. Patients should be advised not to blow their nose immediately after PecFent administration.

The protective cap should be replaced after each use and the bottle returned to the child resistant container for safe storage.

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 PecFent in a safe and secure place, not accessible by others.

Patients and their carers must be instructed that PecFent contains an active substance in an amount that can be fatal to a child.

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

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

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.

Respiratory depression
There is a risk of clinically significant respiratory depression associated with the use of fentanyl. Patients with pain who receive chronic opioid therapy develop tolerance to respiratory depression and hence the risk of respiratory depression in these patients is reduced. The use of concomitant central nervous system depressants may increase the risk of respiratory depression (see section 4.5).

Chronic pulmonary disease
In patients with chronic obstructive pulmonary diseases, fentanyl may cause more serious adverse reactions. In these patients, opioids may decrease respiratory drive and increase airway resistance.

Increased intracranial pressure
PecFent 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 patients with a head injury and should be used only if clinically warranted.

Cardiac disease
Fentanyl may produce bradycardia. PecFent should, therefore, be used with caution in patients with previous or pre-existing bradyarrhythmias.

Impaired hepatic or renal function
In addition, PecFent 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. Therefore, special care should be taken during the titration process in patients with moderate or severe hepatic or renal impairment.

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

Tolerance and Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl.

Repeated use of PecFent 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 PecFent 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 PecFent 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.

Athletes should be informed that treatment with fentanyl could lead to positive doping tests.

Serotonin Syndrome
Caution is advised when PecFent is coadministered 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 (see section 4.5).

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 PecFent should be discontinued.

Route of administration
PecFent is only intended for nasal use, and must not be administered by any other route. Due to physico-chemical properties of excipients included in the formulation, intravenous or intra-arterial injection must be avoided in particular.

Nasal conditions
If the patient experiences recurrent episodes of epistaxis or nasal discomfort while taking PecFent, an alternative method of administration for treatment of breakthrough pain should be considered.

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.

Concomitant use with sedatives
Concomitant use of PecFent 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 PecFent 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).

PecFent excipients
PecFent contains propylparahydroxybenzoate (E216). Propylparahydroxybenzoate may cause allergic reactions (possibly delayed) and, exceptionally, bronchospasm (if the medicinal product is not correctly administered).

4.5 Interaction with other medicinal products and other forms of interaction

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 PecFent.

Fentanyl is metabolised mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore potential interactions may occur when PecFent is given concurrently with medicinal products that affect CYP3A4 activity. Coadministration with medicinal products that induce 3A4 activity may reduce the efficacy of PecFent. The concomitant use of PecFent 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 PecFent concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dose increase should be undertaken with caution.

The concomitant use of other central nervous system depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, gabapentinoids (gabapentin and pregabalin) sedating antihistamines and alcohol may produce additive depressant effects. 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 lowest effective dose of sedative medicines should be used and duration of concomitant use should be limited (see section 4.4).

Serotoninergic medicinal products:
Coadministration of fentanyl with a serotoninergic medicinal product, 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.

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

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

Concomitant use of nasally administered oxymetazoline has been shown to decrease the absorption of PecFent (see section 5.2). The concomitant use of nasally administered vasoconstrictive decongestants during titration is, therefore, not recommended as this may lead to patients titrating to a dose that is higher than required. PecFent maintenance treatment may also be less effective in patients with rhinitis when administered concomitantly with a nasal vasoconstrictive decongestant. If this occurs, patients should be advised to discontinue their decongestant.

Concomitant use of PecFent and other medicinal products (other than oxymetazoline) administered via the nose has not been evaluated in the clinical trials. Other nasally administered treatments should be avoided within 15 minutes of dosing with PecFent.

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. PecFent should not be used during pregnancy unless clearly necessary.

Following long-term treatment, fentanyl may cause withdrawal in the new-born infant. It is advised not to use fentanyl during labour and delivery (including caesarean section) because fentanyl passes through the placenta and may cause respiratory depression in the foetus. If PecFent 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 breastfeeding women and breast-feeding should not be restarted until at least 5 days after the last administration of fentanyl.

Fertility
There are no clinical data on the effects of fentanyl on fertility.

4.7 Effects on ability to drive and use machines

Opioid analgesics may impair the mental and/or physical ability required for driving or operating machinery.

Patients should be advised not to drive or operate machinery if they experience somnolence, dizziness, or visual disturbance or other adverse reactions which can impair their ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile
Typical opioid adverse reactions are to be expected with PecFent. 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 monitored for these.

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

Tabulated list of adverse reactions
The following adverse reactions have been reported with PecFent **and/or other fentanyl-containing compounds** during clinical studies and post marketing experience (frequencies 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); very rare (<1/10,000); unknown (cannot be estimated from available data)).

	Common	**Uncommon**	**Unknown**
Infections and infestations		Pneumonia Nasopharyngitis Pharyngitis Rhinitis	
Blood and lymphatic system disorders		Neutropenia	
Immune system disorders		Hypersensitivity	

	Common	Uncommon	Unknown
Metabolism and nutrition disorders		Dehydration Hyperglycaemia Decreased appetite Increased appetite	
Psychiatric disorders	Disorientation	Delirium Hallucination Confusional state Depression Attention deficit/hyperactivity disorder Anxiety Euphoric mood Nervousness	Insomnia Drug dependence (addiction) Drug abuse
Nervous system disorders	Dysgeusia Dizziness Somnolence Headache	Loss of consciousness Depressed level of consciousness Convulsion Ageusia Anosmia Memory impairment Parosmia Speech disorder Sedation Lethargy Tremor	
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Cyanosis	
Vascular disorders		Cardiovascular insufficiency Lymphoedema Hypotension Hot flush	Flushing
Respiratory, thoracic and mediastinal disorders	Epistaxis Rhinorrhoea Nasal discomfort (such as “nasal burning”)	Upper airway obstruction Pharyngolaryngeal pain Rhinalgia Nasal mucosal disorder Cough Dyspnoea Sneezing Upper respiratory tract congestion Nasal congestion Intranasal hypoaesthesia Throat irritation Postnasal drip Nasal dryness	Respiratory depression

	Common	Uncommon	Unknown
Gastrointestinal disorders	Vomiting Nausea Constipation	Intestinal perforation Peritonitis Oral hypoaesthesia Oral paraesthesia Diarrhoea Retching Abdominal pain Tongue disorder Mouth ulceration Dyspepsia Dry mouth	
Skin and subcutaneous tissue disorders	Pruritus	Hyperhydrosis Urticaria	
Musculoskeletal and connective tissue disorders		Arthralgia Muscle twitching	
Renal and urinary disorders		Anuria Dysuria Proteinuria Urinary hesitation	
Reproductive system and breast disorders		Vaginal haemorrhage	
General disorders and administration site conditions		Non-cardiac chest pain Asthenia Chills Face oedema Peripheral oedema Gait disturbance Pyrexia Fatigue Malaise Thirst	Withdrawal syndrome* Neonatal withdrawal syndrome Drug tolerance
Investigations		Platelet count decreased Weight increased	
Injury, poisoning and procedural complications		Fall Intentional drug misuse Medication error	

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

Description of selected adverse reactions

Tolerance
Tolerance can develop on repeated use.

Drug dependence
Repeated use of PecFent 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).

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

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

Immediate management of opioid overdose includes 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. Toxic leukoencephalopathy has also been observed with fentanyl overdose.

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. For details about such use the Summary of Product Characteristics of the individual opioid antagonist should be consulted.

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.

It should be noted that although statistically significant increases in C_{max} levels were seen following a second dose of PecFent given either one or two hours after the initial dose, this increase is not considered to be large enough to suggest that clinically concerning accumulation or over-exposure would occur, providing a wide safety margin for the recommended dose interval of four hours.

Although muscle rigidity interfering with respiration has not been seen following the use of PecFent, 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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
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.

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

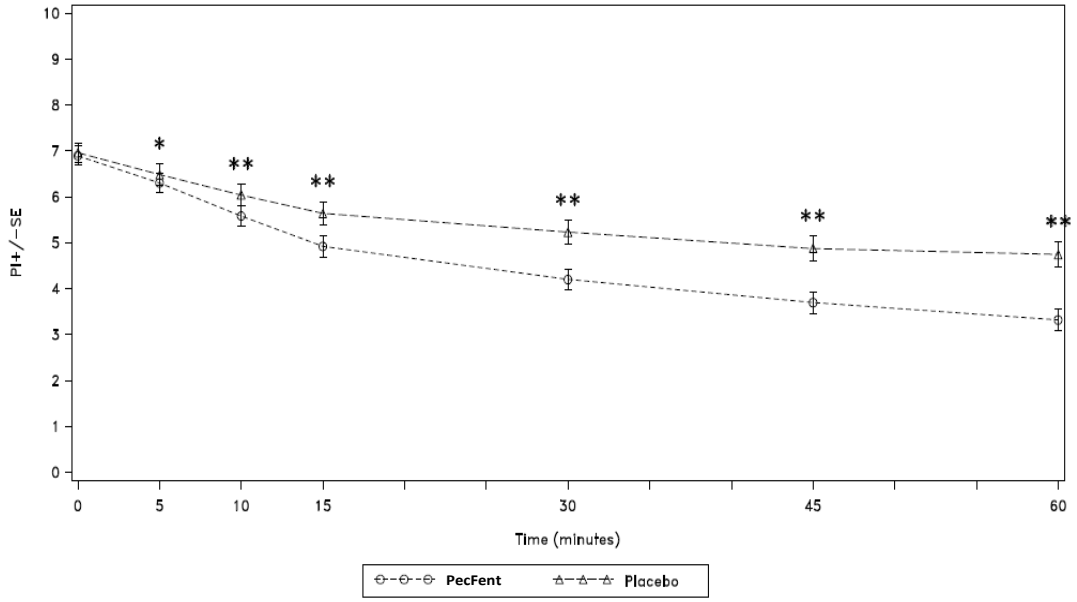
A double-blind, randomised, placebo-controlled crossover study has been conducted in which 114 patients who experienced on average 1 to 4 episodes of break through pain (BTP) per day while taking maintenance opioid therapy were entered into an initial open-label titration phase in order to identify an effective dose of PecFent (Study CP043). The patients entering the double-blind phase treated up to 10 episodes of BTP with either PecFent (7 episodes) or placebo (3 episodes) in a random order.

Of the patients entering the titration phase, only 7 (6.1 %) were unable to be titrated to an effective dose due to lack of efficacy and 6 (5.3 %) withdrew due to adverse events.

The primary endpoint was the comparison between the summed pain intensity difference at 30 minutes after dosing ($SPID_{30}$), which was 6.57 in the PecFent-treated episodes compared to 4.45 for placebo ($p<0.0001$). The SPID for PecFent-treated episodes was also significantly different to placebo at 10 15, 45 and 60 minutes after administration.

The mean pain intensity scores (73 patients) for all PecFent-treated episodes (459 episodes) compared to those treated with placebo (200 episodes) were significantly lower at 5, 10, 15, 30, 45 and 60 minutes following administration (see Figure 1).

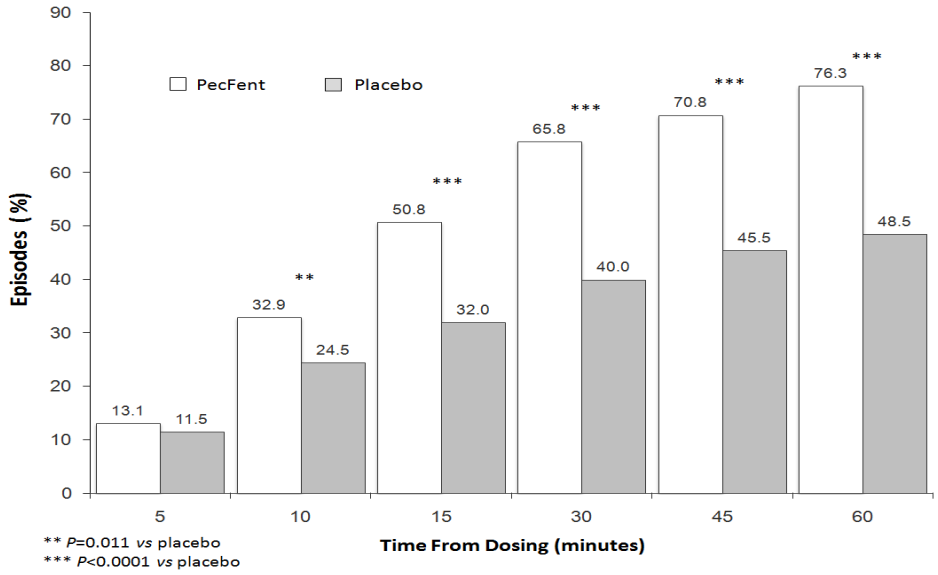
Figure 1: Mean (± SE) Pain Intensity Scores at Each Time Point (mITT Population)



Note: Pain Intensity Scores (mean of subject means) after **PecFent** and Placebo administration.
* Significant difference detected at the alpha<=0.05 level between **PecFent** and Placebo at that time point.
** Significant difference detected at the alpha<=0.01 level between **PecFent** and Placebo at that time point.

The superior efficacy of PecFent over placebo was supported by data from secondary endpoints including the number of BTP episodes with clinically meaningful pain relief, defined as a reduction in pain intensity score of at least 2 (Figure 2).

Figure 2: Clinically Meaningful Pain Relief – PecFent *vs* placebo: % Patients' Episodes With ≥2 Point Reduction in Pain Intensity



In a double-blind, randomized comparator-controlled study (Study 044) of similar design to Study 043 conducted in opioid-tolerant patients with breakthrough cancer pain on stable doses of regularly scheduled opioids, PecFent was shown to be superior to immediate-release morphine sulfate (IRMS). Superiority was demonstrated by the primary endpoint, Pain Intensity Difference within 15 minutes, which was 3.02 in patients treated with PecFent compared to 2.69 in patients treated with IRMS (p=0.0396).

In a long-term, open-label, safety study (Study 045), 355 patients entered the 16-week treatment phase, during which 42,227 episodes of breakthrough cancer pain (BTP) were treated with PecFent. One hundred of these patients continued treatment for up to 26 months in an extension phase. Of the 355 patients treated in the open-label treatment phase, 90 % required no increase in dose.

In the randomised, placebo-controlled study (CP043) 9.4% of 459 PecFent-treated BTP episodes in 73 patients required use of any further (rescue) medicinal products within 60 minutes of dosing. During the longer-term, open-label study (CP045) this was 6.0 % of 42,227 episodes in 355 patients treated with PecFent during up to 159 days of treatment.

5.2 Pharmacokinetic properties

General introduction

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

PecFent utilises the PecSys nasal drug delivery system to modulate the delivery and absorption of fentanyl. The PecSys system allows the product to be sprayed into the front area of the nasal cavity as a fine mist of droplets, which gel on contact with the calcium ions present in the nasal mucosa. Fentanyl diffuses from the gel and is absorbed through the nasal mucosa; this gel-modulated absorption of fentanyl restrains the peak in plasma concentration (C_{max}) whilst allowing the attainment of an early time to that peak (T_{max}).

Absorption

In a pharmacokinetic study comparing PecFent (100, 200, 400 and 800 micrograms) with oral transmucosal fentanyl citrate (OTFC, 200 micrograms), fentanyl was shown to be rapidly absorbed following single dose intranasal administration of PecFent, with median T_{max} ranging from 15 to

21 minutes (T_{max} for OTFC was approximately 90 minutes). The variability of the pharmacokinetics of fentanyl was considerable following treatment with both PecFent and OTFC. Relative bioavailability of fentanyl from the PecFent treatment compared to the 200 microgram OTFC was approximately 120 %.

The main pharmacokinetic parameters are shown in the following table.

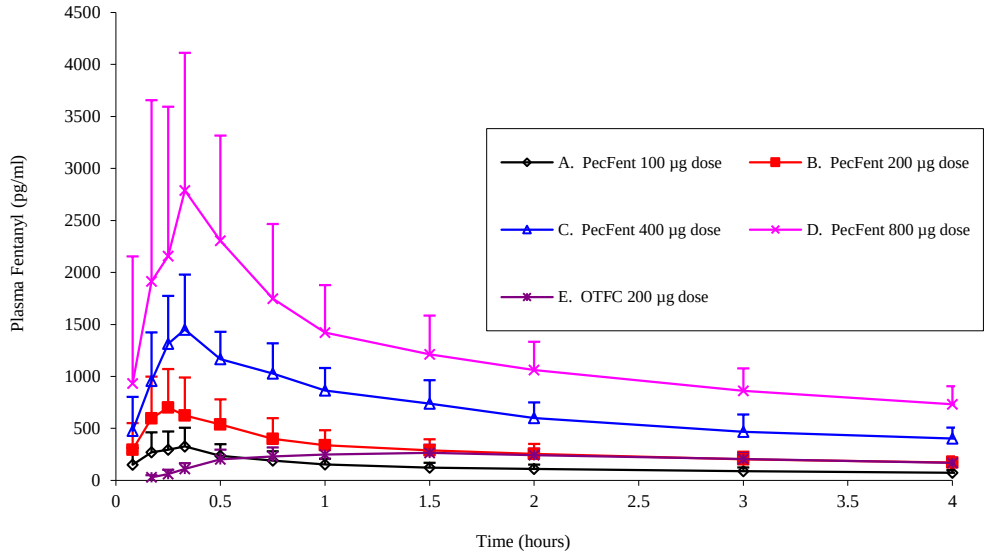
Pharmacokinetic parameters in adult subjects receiving PecFent and OTFC

Pharmacokinetic parameters (mean (%CV))	**PecFent**				**OTFC**
	100 micrograms	**200 micrograms**	**400 micrograms**	**800 micrograms**	**200 micrograms**
T_{max} (hours)*	0.33 (0.08-1.50)	0.25 (0.17-1.60)	0.35 (0.25-0.75)	0.34 (0.17-3.00)	1.50 (0.50 -8.00)
C_{max} (pg/ml)	351.5 (51.3)	780.8 (48.4)	1552.1 (26.2)	2844.0 (56.0)	317.4 (29.9)
AUC (pg.hour/ml)	2460.5 (17.9	4359.9 (29.8)	7513.4 (26.7)	17272 (48.9)	3735.0 (32.8)
$t_{1/2}$ (hour)	21.9 (13.6)	24.9 (51.3)	15.0 (24.7)	24.9 (92.5)	18.6 (31.4)

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

The curves for each dose level are similar in shape with increasing dose levels producing increasing plasma fentanyl levels. Dose-proportionality was demonstrated for C_{max} and area under the curve (AUC) in the dose range 100 micrograms to 800 micrograms (see Figure 3). If switching to PecFent from another fentanyl product for BTP, independent dose titration with PecFent is required as the bioavailability between products differs significantly.

Figure 3: Mean plasma fentanyl concentrations following single doses of PecFent and OTFC in healthy subjects



A pharmacokinetic study was conducted to evaluate the absorption and tolerability of a single dose of PecFent in patients with pollen-induced seasonal allergic rhinitis, comparing the un-challenged, acutely challenged (rhinitic) and acutely challenged and then treated with oxymetazoline, states.

There was no clinically significant effect of acute rhinitis on C_{max}, T_{max} or overall exposure to fentanyl, comparing the unchallenged with the acutely challenged states. Following treatment of the acute rhinitic state with oxymetazoline, there were reductions in C_{max} and exposure, and increases in T_{max} that were statistically, and possibly clinically, significant.

Distribution
Fentanyl is highly lipophilic and is well distributed beyond the vascular system, with a large apparent volume of distribution. Animal data have shown that, following absorption, 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.

Biotransformation
The metabolic pathways following nasal administration of PecFent have not been characterised in clinical studies. Fentanyl is metabolised in the liver to norfentanyl by cytochrome CYP3A4 isoform. Norfentanyl is not pharmacologically active in animal studies. It is more than 90 % eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.

Elimination
Disposition of fentanyl following intranasal administration of PecFent has not been characterised in a mass balance study. Less than 7 % of an administered dose of fentanyl 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 following intravenous administration is approximately 42 L/h.

Linearity/non-linearity
Dose-proportionality was demonstrated for C_{max} and AUC in the dose range 100 micrograms to 800 micrograms.
The effect of renal or hepatic impairment on the pharmacokinetics of PecFent has not been studied.

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) with fentanyl did not induce any findings indicative of oncogenic potential. Evaluation of brain slides from the carciogenicity 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

Pectin (E440)
Mannitol (E421)
Phenylethyl alcohol
Propylparahydroxybenzoate (E216)
Sucrose
Hydrochloric acid (0.36%) or sodium hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 spray bottle:
18 months
After priming, use within 5 days.

8 spray bottle:
3 years
After first use: 60 days

6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze.
Keep the bottle in the child resistant container in order to protect from light.
Store the bottle in the child resistant container at all times, even when finished.

6.5 Nature and contents of container

Bottle (clear Type I glass) with an attached metering pump incorporating an audible dose counter and a protective cap (solid white cap for the 2 spray and translucent cap for the 8 spray). In each case the product is packed in a clam-shell-like child resistant container.

Bottles contain:
0.95 ml ensuring delivery of 2 full sprays
or
1.55 ml ensuring delivery of 8 full sprays.

Bottles in their child resistant containers are supplied in cartons containing:
For 2 spray bottle: 1 bottle.
For 8 spray bottle: 1, 4 or 12 bottles.

Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal

Partially used PecFent bottles may contain enough medicine to be harmful or life-threatening to a child. Even if there is little or no medicine left in the bottle, PecFent must be disposed of properly, according to the following steps:

- Patients and caregivers must be instructed to properly dispose of all unused, partially used and used PecFent bottles. The patient should be instructed how to do this correctly.

- If there are any unwanted therapeutic sprays remaining in the bottle, the patient should be instructed to expel these as follows:

2 spray bottle:
- Aim the spray away from themselves (and any other people) and expel remaining spray until the red number "2" appears in the counting window and there are no more full therapeutic sprays obtainable from the bottle.
- After the counter has advanced to "2", the patient should continue to push down on the finger grips (there will be some increased resistance) a total of four times in order to expel any residual medicine from the bottle.
- After the 2 therapeutic sprays have been emitted, the patient will not hear a click and the counter will not advance beyond "2"; further sprays emitted will not be full sprays and should **not be** used therapeutically.

8 spray bottle:
- Aim the spray away from themselves (and any other people) and expel remaining spray until the red number "8" appears in the counting window and there are no more full therapeutic sprays obtainable from the bottle.
- After the counter has advanced to "8", the patient should continue to push down on the finger grips (there will be some increased resistance) a total of four times in order to expel any residual medicine from the bottle.
- After the 8 therapeutic sprays have been emitted, the patient will not hear a click and the counter will not advance beyond "8"; further sprays emitted will not be full sprays and should **not be** used therapeutically.

As soon as PecFent is no longer needed, patients and members of their household must be advised to systematically dispose of any bottles remaining from a prescription as soon as possible by returning them to their child-resistant container and discarding them, according to local requirements or by returning them to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2,
2132NP Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/644/007

EU/1/10/644/001
EU/1/10/644/002
EU/1/10/644/005

EU/1/10/644/003
EU/1/10/644/004
EU/1/10/644/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 August 2010
Date of latest renewal: 17 July 2015

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. MANUFACTURERRESPONSIBLE 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 RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
L. Molteni & C dei F. LLi Alitti Società di Esercizio S.p.A
Strada Statale 67
Tosco Romagnola
Fraz. Granatieri
IT-50018 Scandicci (FI)
Italy

B. CONDITIONS OR RESTRICTIONS 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

o Periodic safety update reports (PSURs)

The requirements for submission of PSURs 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

o Risk Management Plan (RMP)

The marketing authorisation holder (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 signficant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

o Additional risk minimisation measures

Prior to the launch or use of PecFent 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 PecFent 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

- PecFent to be used only if patients/carers have received the proper information regarding the use of the device and the safety precautions.
- Explanation of the indication.
- Explanation of Breakthrough Pain, patient's 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 PecFent 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 PecFent.

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 for periodic review by prescribers
    - Encouragement for reporting 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 recognised.

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

- Instructions for use of PecFent.
- 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 PecFent. Please complete all of the following before prescribing PecFent:

- Ensure that all elements of the approved indication are fulfilled.
- Provide instructions for using PecFent to patient and/or carer.
- Ensure the patient reads the package leaflet inside the PecFent box.
- Supply the patient with the PecFent patient brochure provided covering the below:
    - Cancer and Pain.
    - PecFent. What is it? How do I use it?
    - PecFent. Risk of misuse.
- Explain the risks of using more than the recommended amount of PecFent.
- Explain the use of the dose monitoring cards.
- Advise the patients 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 PecFent 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.
- PecFent is not interchangeable with other fentanyl products.

The pharmacist dispensing PecFent must counsel patients on:
- Instructions for use of PecFent.
- The pharmacist must inform the patients that in order to prevent theft and misuse of PecFent 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 PecFent. Please complete the following before PecFent is supplied:
- Ensure that all elements of the approved indication are fulfilled.
- Provide instructions for using PecFent to the patient and/or carer.
- Ensure the patient reads the package leaflet inside PecFent carton box.
- Supply the patient with the PecFent patient brochure provided covering the below:
    - Cancer and Pain.
    - PecFent. What is it? How do I use it?
    - PecFent. Risks of misuse.
- Explain the risks of using more than the recommended amount of PecFent.
- 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. Instructional videos on use of the product will also be accessible via a website. 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

PecFent 100 micrograms/spray nasal spray solution
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each spray contains 100 micrograms of fentanyl (as citrate)
Each ml of solution contains 1,000 micrograms fentanyl (as citrate)

3. LIST OF EXCIPIENTS

Also contains: pectin (E440), mannitol (E421), phenylethyl alcohol, propylparahydroxybenzoate (E216), sucrose, purified water and hydrochloric acid (0.36%) or sodium hydroxide for pH adjustment. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution

[2 spray bottle:]
1 bottle – 0.95 ml (2 sprays) per bottle

[8 spray bottle:]
1 bottle – 1.55 ml (8 sprays) per bottle
4 bottles – 1.55 ml (8 sprays) per bottle
12 bottles 1.55 ml (8 sprays) per bottle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Nasal use

[2 spray bottle:]
If the spray has not been used within 5 days after priming it should be discarded.

[8 spray bottle:]
If PecFent has not been used for 5 days, re-prime by spraying once.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only for use by people already taking other opioid medicines daily for constant cancer pain. Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

EXP

[2 spray bottle:]
After priming, use within 5 days.

[8 spray bottle:]
After first-use, use within 60 days

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not freeze.
Keep the bottle in the child resistant container in order to protect from light.
Store the PecFent bottle in the child resistant container at all times, even when finished.

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

Kyowa Kirin Holdings B.V.
Bloemlaan 2,
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/644/007 100 micrograms, 2 sprays, 1 bottle

EU/1/10/644/001 100 micrograms, 8 sprays, 1 bottle
EU/1/10/644/002 100 micrograms, 8 sprays, 4 bottles
EU/1/10/644/005 100 micrograms, 8 sprays, 12 bottles

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PecFent 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

PARTICULARS TO APPEAR ON THE CHILD RESISTANT CONTAINER (CRC)

1. NAME OF THE MEDICINAL PRODUCT

PecFent 100 micrograms/spray nasal spray
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each spray contains 100 micrograms of fentanyl (as citrate)

3. LIST OF EXCIPIENTS

Also contains: pectin (E440), mannitol (E421), phenylethyl alcohol, propylparahydroxybenzoate (E216), sucrose, purified water and hydrochloric acid (0.36%) or sodium hydroxide for pH adjustment. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Nasal use
Read the package leaflet before use.

[2 spray bottle:]
If the spray has not been used within 5 days after priming it should be discarded.

[8 spray bottle:]
If PecFent has not been used for 5 days, re-prime by spraying once.

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

[Pull-out label on the CRC] [Front cover]: Accidental use can be fatal.
[Base label]: Accidental use can be fatal.
[Inside of the label]: Only for use by people already taking other opioid medicines daily for constant cancer pain. Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

2 spray bottle:
After priming, use within 5 days.

Date of priming: …….

8 spray bottle:
After first-use, use within 60 days
Date of first use: …….

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not freeze.
Keep the bottle in the child resistant container in order to protect from light.
Store the PecFent bottle in the child resistant container at all times, even when finished.

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

Kyowa Kirin Holdings B.V.
Bloemlaan 2,
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PecFent 100 micrograms/spray nasal spray
fentanyl
Nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.95 ml – 2 sprays
1.55 ml - 8 sprays

6. OTHER

Accidental use can be fatal

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

PecFent 400 micrograms/spray nasal spray solution
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each spray contains 400 micrograms of fentanyl (as citrate)
Each ml of solution contains 4,000 micrograms fentanyl (as citrate)

3. LIST OF EXCIPIENTS

Also contains: pectin (E440), mannitol (E421), phenylethyl alcohol, propylparahydroxybenzoate (E216), sucrose, purified water and hydrochloric acid (0.36%) or sodium hydroxide for pH adjustment. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution
1 bottle – 1.55 ml (8 sprays) per bottle
4 bottles – 1.55 ml (8 sprays) per bottle
12 bottles – 1.55 ml (8 sprays) per bottle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Nasal use
If PecFent has not been used for 5 days, re-prime by spraying once.

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

Only for use by people already taking other opioid medicines daily for constant cancer pain. Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

EXP
After first-use, use within 60 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not freeze.
Keep the bottle in the child resistant container in order to protect from light.
Store the PecFent bottle in the child resistant container at all times, even when finished.

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

Kyowa Kirin Holdings B.V.
Bloemlaan 2,
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/644/003 400 micrograms, 8 sprays, 1 bottle
EU/1/10/644/004 400 micrograms, 8 sprays, 4 bottles
EU/1/10/644/006 400 micrograms, 8 sprays, 12 bottles

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PecFent 400

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN

PARTICULARS TO APPEAR ON THE CHILD RESISTANT CONTAINER (CRC)

1. NAME OF THE MEDICINAL PRODUCT

PecFent 400 micrograms/spray nasal spray
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each spray contains 400 micrograms of fentanyl (as citrate)

3. LIST OF EXCIPIENTS

Also contains: pectin (E440), mannitol (E421), phenylethyl alcohol, propylparahydroxybenzoate (E216), sucrose, purified water and hydrochloric acid (0.36%) or sodium hydroxide for pH adjustment. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Nasal use
Read the package leaflet before use.
If PecFent has not been used for 5 days, re-prime by spraying once.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[Pull-out label on the CRC] [Front cover]: Accidental use can be fatal.
[Base label]: Accidental use can be fatal.
[Inside of the label]: Only for use by people already taking other opioid medicines daily for constant cancer pain. Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

After first-use, use within 60 days
Date of first use: …….

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not freeze.
Keep the bottle in the child resistant container in order to protect from light.
Store the PecFent bottle in the child resistant container at all times, even when finished.

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

Kyowa Kirin Holdings B.V.
Bloemlaan 2,
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PecFent 400 micrograms/spray nasal spray
fentanyl
Nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.55 ml - 8 sprays

6. OTHER

Accidental use can be fatal

B. PACKAGE LEAFLET

Package leaflet: Information for the user

PecFent 100 micrograms/spray nasal spray, solution
PecFent 400 micrograms/spray nasal spray, solution
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 doctoror 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 PecFent is and what it is used for

What PecFent is
PecFent contains fentanyl, which is a strong pain-relieving medicine known as an opioid pain killer.

What PecFent is used for
PecFent is used in adults with cancer for a type of pain called 'breakthrough' pain.
- Breakthrough pain comes on suddenly.
- It comes on even though you have taken your usual opioid pain killer (such as morphine, fentanyl, oxycodone or hydromorphone) to control your constant background pain.

PecFent is only to be used by adults who are already taking other opioid medicines daily for their constant cancer pain.

How PecFent works
PecFent is a nasal spray, solution
- When you spray PecFent into your nose the very small spray droplets form a thin gel.
- Fentanyl is absorbed quickly through the lining of your nose and into the blood stream.
- This means the medicine gets into your system quickly to relieve your breakthrough pain.

2. What you need to know before you use PecFent

Do not use PecFent if:
- you are allergic to fentanyl or any of the other ingredients of this medicine (listed in Section 6).
- 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 PecFent, because it may increase the risk that breathing could become dangerously slow and/or shallow, or even stop.
- you suffer from short-term pain other than breakthrough pain.

- you have a serious breathing or lung problem.
- you are being treated with medicines contain sodium oxybate.

Do not use PecFent if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before using PecFent.

Warnings and precautions

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

Keeping PecFent safe from children
- You must keep PecFent in the child resistant storage container when you are not using it, even if you have used all 8 sprays. This is because PecFent could be life-threatening if taken by a child by accident.

Check with your doctor or pharmacist before using PecFent if:
- you have not been taking the same dose of your daily opioid medicine for your constant pain for some time
- you have breathing problems such as asthma, wheezing or shortness of breath
- you suffer a severe blow to the head
- you have problems with your heart especially slow heart rate
- you have low blood pressure or a low amount of fluid in your circulation
- you have liver or kidney problems. This is because it may affect the way in which your body breaks down the medicine.
- you take antidepressants or antipsychotics, please refer to the section '**Other medicines and PecFent'.**

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before using PecFent.
- If you are an athlete, using PecFent may result in positive doping-tests.

Consult your doctor while using PecFent if:
- you suffer from recurrent nose bleeding - he may advise an alternative treatment
- you feel that PecFent is becoming less effective in treating your episodes of breakthrough pain
- 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 think you are becoming dependent on PecFent
- 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
- you have ever developed adrenal insufficiency or lack of sex hormones (androgen deficiency) with opioid use

<u>Long-term use and tolerance</u>
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 PecFent. This is known as hyperalgesia. Increasing the dose of PecFent 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 PecFent.

Dependence and addiction

Repeated use of PecFent 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 PecFent 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 PecFent, 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.

Sleep-related breathing disorders

PecFent 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.

Children and adolescents

PecFent is not approved for use in children under 18 years of age.

Other medicines and PecFent

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular tell your doctor or pharmacist before using PecFent if you are taking or have recently taken any of the following medicines:

- medicines that might make you sleepy such as sleeping tablets, tranquilisers, muscle relaxants, medicines for anxiety such as benzodiazepines (e.g. diazepam), or medicines for allergies (anti-histamines). Use of PecFent at the same time as medicines that make you feel sleepy increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening**. Contact your doctor if you get any of these symptoms.** For this reason use of PecFent, together with sedatives, should only be considered when other treatment options are not possible. However, if your doctor does prescribe PecFent together with sedative medicines the dose and length of treatment should be limited by your doctor. **Tell your doctor about all sedative medicines you are taking, and follow your doctors dose instructions closely.** It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above.

- medicines for depression called ‘monoamine-oxidase inhibitors’ (MAOI). Tell your doctor or pharmacist if you have taken an MAOI medicine in the past 2 weeks before using PecFent. The risk of side effects increases if you are taking medicines such as certain antidepressants or antipsychotics. PecFent 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 PecFent is suitable for you.
- nasal sprays to treat a stuffy nose (containing a decongestant such as oxymetazoline)
- medicines that might have an effect on the way your body breaks down PecFent. These include:
    - medicines for HIV infection (such as ritonavir, nelfinavir, amprenavir or fosamprenavir)
    - medicines for fungal infections (such as ketoconazole, itraconazole or fluconazole)
    - medicines for bacterial infections (such as troleandomycin, clarithromycin or erythromycin)
    - ‘aprepitant’ - used to stop you feeling sick
    - ‘diltiazem’ and ‘verapamil’ - used for high blood pressure or heart problems.
    - other pain killers called partial agonist/antagonist like buprenorphine, nalbuphine, pentazocine. You could experience symptoms of withdrawal syndrome (nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating) while using these medicines.
    - some painkillers for nerve pain (gabapentin and pregabalin)

If any of the above applies to you (or you are not sure), talk to your doctor or pharmacist before using PecFent.

Don’t use any other kind of nasal spray for at least 15 minutes after using PecFent.

PecFent with food, drink and alcohol
- Do not drink alcohol while using PecFent. It can increase the risk of getting serious side effects.
- Do not drink grapefruit juice while using PecFent. It may affect the way your body breaks down PecFent.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Do not use PecFent if you are pregnant or might get pregnant, unless your doctor has told you to.
- Do not use PecFent during child birth. This is because it may cause breathing problems in your baby.
- Do not use PecFent if you are breast-feeding. This is because the medicine can get into your breast milk and may cause side effects in the breast-fed child.
- You should not start breast-feeding within 5 days after the last dose of PecFent.

Driving and using machines
- Talk to your doctor about whether it will be safe for you to drive or use tools or machines after using PecFent.
- You may feel sleepy, dizzy or have problems with your eyesight after using PecFent. If this happens, do not drive or use any tools or machines.
- Do not drive or use tools or machines until you know how this medicine makes you feel.

PecFent contains propylparahydroxybenzoate (E216).
May cause allergic reactions (possibly delayed), and exceptionally, bronchospasm (if you do not use the nasal spray correctly).

3. How to use PecFent

Before starting treatment and regularly during treatment, your doctor will also discuss with you what you may expect from using PecFent, 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).

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

PecFent comes in two different strengths: a 100 microgram per spray bottle and a 400 microgram per spray bottle. Make sure that you use the strength that your doctor has prescribed for you.

How much to use

- A dose to treat a breakthrough pain episode might be either 1 spray or 2 sprays (one in each nostril). Your doctor will tell you how many sprays (1 or 2) you should use to treat your breakthrough pain episode.
- **Do not use more than the dose your doctor prescribes for any single breakthrough pain episode.**
- Do not use PecFent more than 4 times daily
- Wait at least 4 hours to take the next dose of PecFent.

Starting dose

- The starting dose is 100 micrograms.
- This is a single spray into one nostril from the 100 microgram per spray bottle.
- See 'Using the PecFent bottle' for instructions on how to use a dose.

Finding the right dose

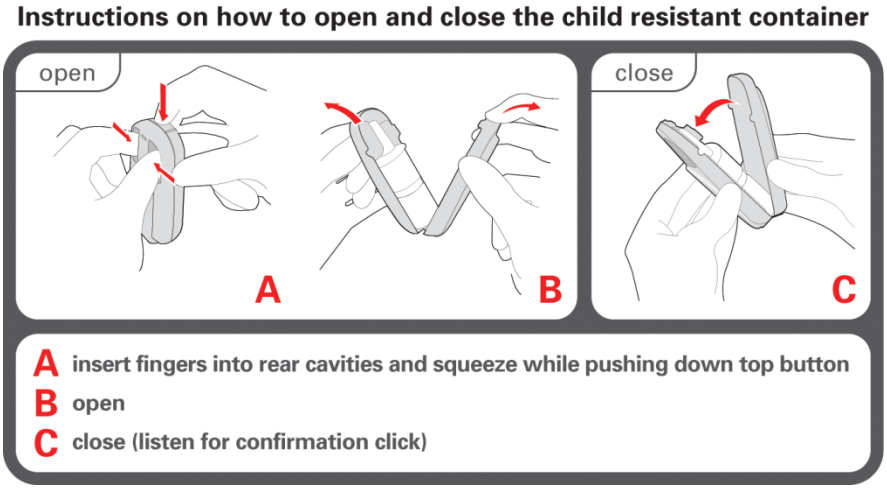
- Your doctor will then help you find the right dose to relieve your breakthrough pain. It is very important to follow your doctor's instructions.
- Tell your doctor about your pain and how PecFent is working. Your doctor will decide if your PecFent dose needs to be changed.
- Do not change the dose yourself.

Once you have found the right dose

- Tell your doctor if your dose of PecFent does not relieve your breakthrough pain. Your doctor will decide if your dose needs to be changed. **Do not change the dose of PecFent or your other pain medicines yourself.**
- Tell your doctor straight away if you have more than 4 episodes of breakthrough pain a day. Your doctor may change the medicine for your constant pain. Once your constant pain is controlled, your doctor may then change your dose of PecFent.

If you are not sure about the right dose or how much PecFent to use, ask your doctor.

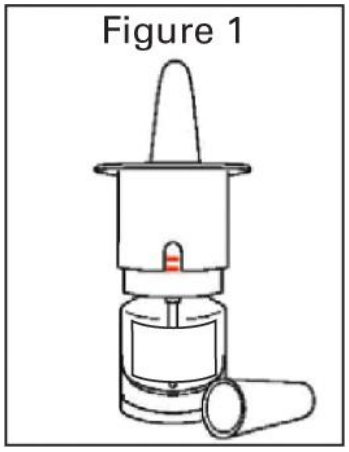
Using the PecFent bottle

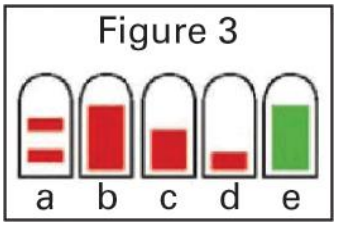


Preparing the PecFent bottle for use

Before you use a new bottle of PecFent you need to prepare it for use. This is called 'priming'.
To prime the bottle, please follow the instructions below:

1. A new bottle of PecFent will show two red lines in the counting window in the white plastic top on the bottle (Figure 1 and Figure 3a).
2. Take off the clear plastic protective cap from the nozzle (Figure 1).
3. Aim the nasal spray away from you (and any other people).
4. Hold the PecFent nasal spray upright with your thumb on the bottom of the bottle, and your first and middle fingers on the finger grips each side of the nozzle (Figure 2).
5. Firmly press down on the finger grips until a 'click' is heard and then let go of the grips (Figure 2). You will hear a second 'click' and there should now be a single large red bar in the counting window (Figure 3b).
6. Repeat step 5 three times. As you repeat step 5, the red bar will become smaller and smaller until you see a green bar in the counting window (Figure 3b-e). The green bar means the PecFent nasal spray is ready to use.
7. Wipe the nozzle with a tissue and flush the tissue down the toilet.
8. If you are not going to use your medicine straight away, put the protective cap back on. Then put the PecFent bottle in the child-resistant storage container. If PecFent has not been used for 5 days, re-prime by spraying once.





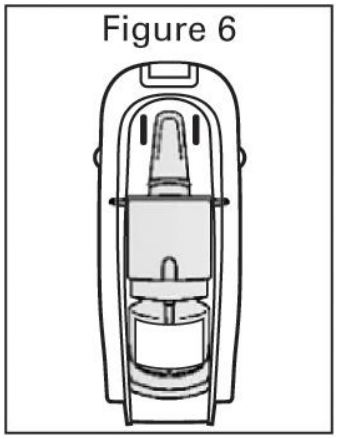
Using PecFent

PecFent is only to be used by spraying into your nostril.

1. Check that there is a green bar or a number showing in the counting window (Figure 4): this confirms that the PecFent bottle has been primed (see 'Preparing the PecFent bottle for use' above).
2. Blow your nose if you feel you need to.
3. Sit down with your head upright.
4. Take off the protective cap from the nozzle.
5. Hold the PecFent bottle with your thumb on the bottom of the bottle and your first and middle fingers on the finger grips (Figure 4).
6. Put the nozzle a short distance (about 1 cm) into your nostril. Point it inwards towards the wall of your nose. This will tilt the bottle slightly (Figure 5).
7. Close the other nostril with a finger from your other hand (Figure 5).
8. Firmly press down on the finger grips so that PecFent sprays into your nostril. When you hear a click let go of the grips. Note: You may not feel anything happen in your nose at all – do not trust this to mean the spray did not operate – rely on the click and number counter.
9. Breathe in gently through your nose and out through your mouth.
10. The number counter will move forward after each use and show how many sprays have been used.
11. If your doctor has prescribed a second spray, repeat steps 5 to 9, using the other nostril.

Do not use more than the dose that your doctor prescribes to treat any single pain episode.

12. Put the bottle back in the child-resistant container after each use. Keep out of the sight and reach of children (Figure 6)
13. Stay sitting for at least 1 minute after using the nasal spray.



Number of sprays in a PecFent bottle
There are 8 full sprays in each PecFent bottle.

- After the first spray, number 1 will appear in the counting window. This will go up each time the spray is used.
- When you see a red 8 in the counting window, the bottle is finished and you will no longer be able to get a full spray from it.

Disposal of unused PecFent
If you can see a number, other than 8 in the counting window, you have **NOT** used all 8 sprays in the bottle. There are still doses of PecFent left in the bottle.

You must empty the remaining doses of PecFent from the bottle by aiming the nasal spray away from you (and any other people) and pressing and releasing the grips until the red number "8" appears in the counting window.

When you see the number "8" in the counting window, there is still medicine in the bottle that you must empty.

- You will need to press down and release the finger grips 4 more times while aiming the nasal spray away from you (and any other people).
- You will feel some increased resistance when you press down and the finger grips will only move a small amount.
- You will **NOT** hear a click when you press down .
- The counter will stay on the number "8".
- Put the protective cap back on the spray bottle.
- Put the bottle back in the child resistant container.
- Speak to your local pharmacy about disposal of empty bottles (see '**How to store PecFent')**

If the PecFent nasal spray is blocked or does not spray properly

- If the spray is blocked, aim the spray away from you (and any other people) and push firmly down on the pump. This should clear any blockage.
- If your nasal spray is still not working properly, dispose of the faulty bottle and start a new one. Tell your doctor what happened. **Never try to fix the nasal spray yourself or take it apart.** This is because it may then give you the wrong dose.

Dispose of the PecFent bottle and start a new one if:

- It has been 60 days or more since you primed or used your bottle for the first time.

If you use more PecFent than you should

- You may feel sleepy, sick, dizzy or have slow or shallow breathing. In severe cases taking too much PecFent may also lead to coma. If you feel very dizzy, very sleepy or have slow or shallow breathing, call an ambulance or ask someone else to call one straight away.
- An overdose may also result in a brain disorder known as toxic leukoencephalopathy.

If you stop using PecFent

If you no longer have breakthrough pain, talk to your doctor before stopping PecFent and follow his/her advice. However, you should keep taking your other opioid medicine to treat your constant pain. Your doctor may need to check the dose.

You may experience withdrawal symptoms similar to the possible side effects of PecFent when discontinuing PecFent. If you experience withdrawal symptoms, 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.

Call an ambulance or ask someone else to call one straight away if you:

- feel very dizzy or faint
- feel very sleepy
- get slow or shallow breathing
- get cold clammy skin, look pale, have a weak pulse or other signs of shock.

If you or your carer notice any of the side effects above, call an ambulance straight away.

Common side effects (may affect up to 1 in 10 people):

- not knowing where you are (disorientated)

- change in taste
- feeling dizzy
- feeling or being sick
- feeling sleepy, headache
- nose bleed, discomfort in the nose (such as nasal burning), runny nose
- constipation
- itchy skin

Uncommon side effects: (may affect up to 1 in 100 people):
- chest infection
- painful, sore or inflamed throat or nose
- cough, sneezing, catarrh or cold, changes in the fluid produced by your nose
- allergic reaction, rash
- loss of or increase in appetite, weight increase
- dehydration, feeling thirsty
- misusing the medicine
- seeing or hearing things that are not really there (hallucinations/delirium), feeling confused
- feeling depressed, worried, slow or nervous
- a lack of concentration or increased activity
- memory loss
- feeling "high"
- being less aware or responsive, losing consciousness
- convulsion (fits)
- muscle convulsions or trembling
- loss of taste, loss or change in sense of smell
- difficulty in speaking
- blue skin colour
- vertigo, falling over, malaise
- heat and circulation not working properly, hot flush or fever, chills, excessive sweating
- swelling of the soft tissue
- low blood pressure
- blockage in the wind-pipe
- shortness of breath
- vaginal bleeding
- tear in the intestine or inflammation of the stomach lining
- numbness or tingling in the mouth, tongue, or nose, or other tongue problems, mouth ulcers, dry mouth
- diarrhoea
- retching, stomach pains, indigestion
- sore or painful joints
- difficulty in or inability to pass water
- chest pain
- feeling tired or weak, problems moving
- changes in blood cells (detected by laboratory tests)
- increased blood sugar
- protein in the urine

Other side effects (frequency not known (frequency cannot be estimated from the available data)**)**
- Severe breathing problems
- Flushing
- Insomnia
- Withdrawal syndrome (may manifest by the occurrence of the following side effects nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating)
- Drug tolerance, drug dependence (addiction), drug abuse (see section 2)

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 PecFent

Keep this medicine out of the sight and reach of children. PecFent could be life-threatening if taken by a child by accident.

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.

- Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.
- Do not store PecFent above 25°C.
- Do not freeze.
- Keep the bottle in its child resistant container in order to protect from light.
- Store the PecFent bottle in the child resistant container at all times, even when finished.
- Do not use for more than 60 days after first use (either priming or using to treat a breakthrough pain episode).
- PecFent that has passed the expiry date or is no longer required may still contain enough medicine to be harmful to other people, especially children. PecFent should not be disposed of via wastewater or household waste. Any unwanted PecFent should be disposed of as soon as possible following the instructions under ***Disposal of unused PecFent***. Any empty bottles should be returned to their child resistant container and discarded by taking them back to the pharmacy or according to local requirements.

6. Contents of the pack and other information

What PecFent contains

The active substance is fentanyl.
- *PecFent 100 micrograms/spray nasal spray, solution*
  Each ml of solution contains 1,000 micrograms fentanyl (as citrate).
  1 spray (100 microlitres) contains 100 micrograms fentanyl (as citrate).
- *PecFent 400 micrograms/spray nasal spray, solution*
  Each ml of solution contains 4,000 micrograms fentanyl (as citrate).
  1 spray (100 microlitres) contains 400 micrograms fentanyl (as citrate).

The other ingredients (excipients) are pectin (E440), mannitol (E421), phenylethyl alcohol, propylparahydroxybenzoate (E216), sucrose, purified water and hydrochloric acid or sodium hydroxide for pH adjustment.

What PecFent looks like and contents of the pack
The medicine is a clear to almost clear, colourless nasal spray, solution. It is contained in a clear glass bottle, fitted with a metering pump. The pump has a spray counter that clicks, so you can hear as well as see that the spray has been given and a protective cap. After the PecFent bottle has been primed

(prepared for use) it delivers 8 full sprays. Each PecFent bottle is supplied in a child resistant container.

PecFent bottles in their child resistant containers are supplied in cartons containing 1, 4 or 12 bottles. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Kyowa Kirin Holdings B.V.
Bloemlaan 2,
2132NP Hoofddorp
The Netherlands

Manufacturer

L. Molteni & C. dei F.lli Alitti Società di Esercizio S.p.A
Strada Statale 67 Tosco Romagnola,
Fraz. Granatieri – 50018 Scandicci (FI)
Italy

This leaflet was last revised

Other sources of information

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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

PecFent 100 micrograms/spray nasal spray, solution - two-spray bottle
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 doctoror 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 PecFent is and what it is used for

What PecFent is
PecFent contains fentanyl, which is a strong pain-relieving medicine known as an opioid pain killer.

What PecFent is used for
PecFent is used in adults with cancer for a type of pain called 'breakthrough' pain.
- Breakthrough pain comes on suddenly.
- It comes on even though you have taken your usual opioid pain killer (such as morphine, fentanyl, oxycodone or hydromorphone) to control your constant background pain.

PecFent is only to be used by adults who are already taking other opioid medicines daily for their constant cancer pain.

How PecFent works
PecFent is a nasal spray, solution
- When you spray PecFent into your nose the very small spray droplets form a thin gel.
- Fentanyl is absorbed quickly through the lining of your nose and into the blood stream.
- This means the medicine gets into your system quickly to relieve your breakthrough pain.

2. What you need to know before you use PecFent

Do not use PecFent if:
- you are allergic to fentanyl or any of the other ingredients of this medicine (listed in Section 6).
- 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 PecFent, because it may increase the risk that breathing could become dangerously slow and/or shallow, or even stop.
- you suffer from short-term pain other than breakthrough pain.
- you have a serious breathing or lung problem.
- you are being treated with medicines contain sodium oxybate.

Do not use PecFent if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before using PecFent.

Warnings and precautions

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

Keeping PecFent safe from children

- You must keep PecFent in the child resistant storage container when you are not using it, even if you have used all **2** sprays. This is because PecFent could be life-threatening if taken by a child by accident.

Check with your doctor or pharmacist before using PecFent if:

- you have not been taking the same dose of your daily opioid medicine for your constant pain for some time
- you have breathing problems such as asthma, wheezing or shortness of breath
- you suffer a severe blow to the head
- you have problems with your heart especially slow heart rate
- you have low blood pressure or a low amount of fluid in your circulation
- you have liver or kidney problems. This is because it may affect the way in which your body breaks down the medicine.
- you take antidepressants or antipsychotics, please refer to the section '**Other medicines and PecFent'.**

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before using PecFent.

- If you are an athlete, using PecFent may result in positive doping-tests.

Consult your doctor while using PecFent if**:**

- you suffer from recurrent nose bleeding - he may advise an alternative treatment
- you feel that PecFent is becoming less effective in treating your episodes of breakthrough pain
- 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 think you are becoming dependent on PecFent
- 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
- you have ever developed adrenal insufficiency or lack of sex hormones (androgen deficiency) with opioid use

<u>Long-term use and tolerance</u>

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 PecFent. This is known as hyperalgesia. Increasing the dose of PecFent 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 PecFent.

<u>Dependence and addiction</u>

Repeated use of PecFent 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 PecFent 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 PecFent, 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.

Sleep-related breathing disorders
PecFent 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.

Children and adolescents
PecFent is not approved for use in children under 18 years of age.

Other medicines and PecFent
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular tell your doctor or pharmacist before using PecFent if you are taking or have recently taken any of the following medicines:
- medicines that might make you sleepy such as sleeping tablets, tranquilisers, muscle relaxants, medicines for anxiety such as benzodiazepines (e.g. diazepam), or medicines for allergies (anti-histamines). Use of PecFent at the same time as medicines that make you feel sleepy increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening**. Contact your doctor if you get any of these symptoms.** For this reason use of PecFent, together with sedatives, should only be considered when other treatment options are not possible. However, if your doctor does prescribe PecFent together with sedative medicines the dose and length of treatment should be limited by your doctor. **Tell your doctor about all sedative medicines you are taking, and follow your doctors dose instructions closely.** It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above.
- medicines for depression called 'monoamine-oxidase inhibitors' (MAOI). Tell your doctor or pharmacist if you have taken an MAOI medicine in the past 2 weeks before using PecFent.

The risk of side effects increases if you are taking medicines such as certain antidepressants or antipsychotics. PecFent 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 PecFent is suitable for you.

- nasal sprays to treat a stuffy nose (containing a decongestant such as oxymetazoline)
- medicines that might have an effect on the way your body breaks down PecFent. These include:
    - medicines for HIV infection (such as ritonavir, nelfinavir, amprenavir or fosamprenavir)
    - medicines for fungal infections (such as ketoconazole, itraconazole or fluconazole)
    - medicines for bacterial infections (such as troleandomycin, clarithromycin or erythromycin)
    - 'aprepitant' - used to stop you feeling sick
    - 'diltiazem' and 'verapamil' - used for high blood pressure or heart problems.
    - other pain killers called partial agonist/antagonist like buprenorphine, nalbuphine, pentazocine. You could experience symptoms of withdrawal syndrome (nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating) while using these medicines.
    - some painkillers for nerve pain (gabapentin and pregabalin)

If any of the above applies to you (or you are not sure), talk to your doctor or pharmacist before using PecFent.

Don't use any other kind of nasal spray for at least 15 minutes after using PecFent.

PecFent with food, drink and alcohol

- Do not drink alcohol while using PecFent. It can increase the risk of getting serious side effects.
- Do not drink grapefruit juice while using PecFent. It may affect the way your body breaks down PecFent.

Pregnancy, breast-feeding and fertility

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

- Do not use PecFent if you are pregnant or might get pregnant, unless your doctor has told you to.
- Do not use PecFent during child birth. This is because it may cause breathing problems in your baby.
- Do not use PecFent if you are breast-feeding. This is because the medicine can get into your breast milk and may cause side effects in the breast-fed child.
- You should not start breast-feeding within 5 days after the last dose of PecFent.

Driving and using machines

- Talk to your doctor about whether it will be safe for you to drive or use tools or machines after using PecFent.
- You may feel sleepy, dizzy or have problems with your eyesight after using PecFent. If this happens, do not drive or use any tools or machines.
- Do not drive or use tools or machines until you know how this medicine makes you feel.

PecFent contains propylparahydroxybenzoate (E216).

May cause allergic reactions (possibly delayed), and exceptionally, bronchospasm (if you do not use the nasal spray correctly).

3. How to use PecFent

Before starting treatment and regularly during treatment, your doctor will also discuss with you what you may expect from using PecFent, 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).

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

PecFent comes in two different strengths: a 100 microgram per spray bottle and a 400 microgram per spray bottle. Make sure that you use the strength that your doctor has prescribed for you.

How much to use

- A dose to treat a breakthrough pain episode might be either 1 spray or 2 sprays (one in each nostril). Your doctor will tell you how many sprays (1 or 2) you should use to treat your breakthrough pain episode.
- **Do not use more than the dose your doctor prescribes for any single breakthrough pain episode.**
- Do not use PecFent more than 4 times daily
- Wait at least 4 hours to take the next dose of PecFent.

Starting dose

- The starting dose is 100 micrograms.
- This is a single spray into one nostril from the 100 microgram per spray bottle.
- See 'Using the PecFent bottle' for instructions on how to use a dose.

Finding the right dose

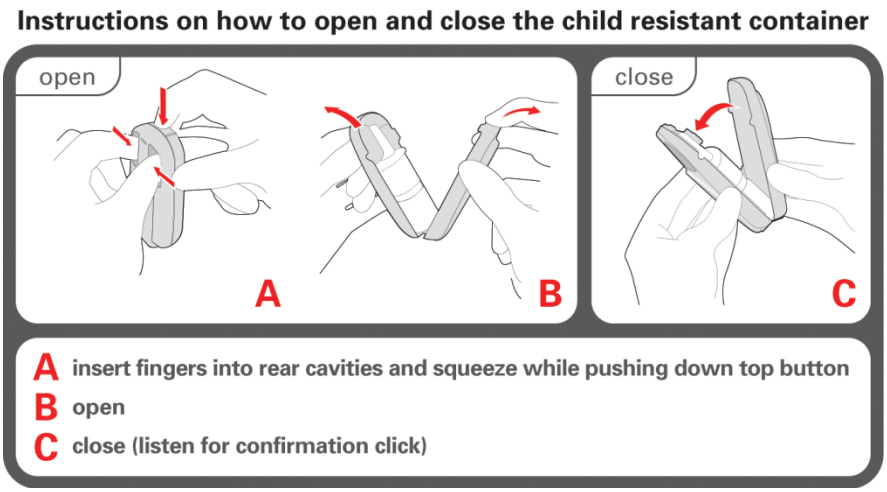
- Your doctor will then help you find the right dose to relieve your breakthrough pain. It is very important to follow your doctor's instructions.
- Tell your doctor about your pain and how PecFent is working. Your doctor will decide if your PecFent dose needs to be changed.
- Do not change the dose yourself.

Once you have found the right dose

- Tell your doctor if your dose of PecFent does not relieve your breakthrough pain. Your doctor will decide if your dose needs to be changed. **Do not change the dose of PecFent or your other pain medicines yourself.**
- Tell your doctor straight away if you have more than 4 episodes of breakthrough pain a day. Your doctor may change the medicine for your constant pain. Once your constant pain is controlled, your doctor may then change your dose of PecFent.

If you are not sure about the right dose or how much PecFent to use, ask your doctor.

Using the PecFent bottle



Preparing the PecFent bottle for use

Before you use a new bottle of PecFent you need to prepare it for use. This is called 'priming'. It is recommended that you prime the bottle immediately before use rather than in advance (Note: This 2 spray bottle cannot be re-primed. If the spray has not been used within 5 days after priming, the bottle should be discarded.)

To prime the bottle, please follow the instructions below:

1. A new bottle of PecFent will show two red lines in the counting window in the white plastic top on the bottle (Figure 1 and Figure 3a).
2. Take off the white plastic protective cap from the nozzle (Figure 1).
3. Aim the nasal spray away from you (and any other people).
4. Hold the PecFent nasal spray upright with your thumb on the bottom of the bottle, and your first and middle fingers on the finger grips each side of the nozzle (Figure 2).
5. Firmly press down on the finger grips until a 'click' is heard and then let go of the grips (Figure 2). You will hear a second 'click' and there should now be a single large red bar in the counting window (Figure 3b).
6. Repeat step 5 three times. As you repeat step 5, the red bar will become smaller and smaller until you see a green bar in the counting window (Figure 3b-e). The green bar means the PecFent nasal spray is ready to use.
7. Wipe the nozzle with a tissue and flush the tissue down the toilet.

Figure 1

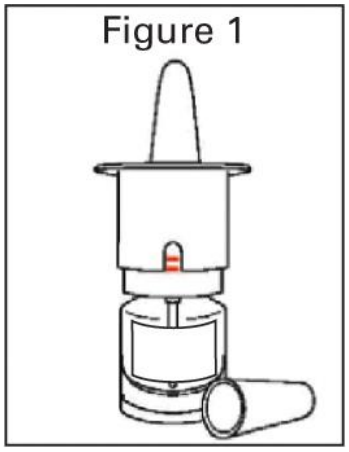
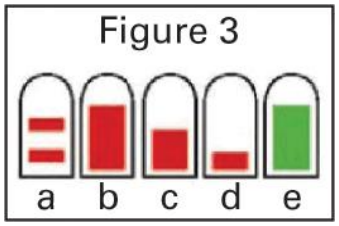


Figure 2

Figure 3



Using PecFent

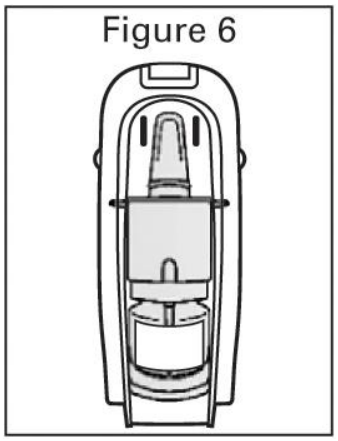
PecFent is only to be used by spraying into your nostril.

1. Check that there is a green bar or a number showing in the counting window (Figure 4): this confirms that the PecFent bottle has been primed (see 'Preparing the PecFent bottle for use' above).
2. Blow your nose if you feel you need to.
3. Sit down with your head upright.
4. Take off the protective cap from the nozzle.
5. Hold the PecFent bottle with your thumb on the bottom of the bottle and your first and middle fingers on the finger grips (Figure 4).
6. Put the nozzle a short distance (about 1 cm) into your nostril. Point it inwards towards the wall of your nose. This will tilt the bottle slightly (Figure 5).
7. Close the other nostril with a finger from your other hand (Figure 5).
8. Firmly press down on the finger grips so that PecFent sprays into your nostril. When you hear a click let go of the grips. Note: You may not feel anything happen in your nose at all – do not trust this to mean the spray did not operate – rely on the click and number counter.
9. Breathe in gently through your nose and out through your mouth.
10. The number counter will move forward after each use and show how many sprays have been used.

11. If your doctor has prescribed a second spray, repeat steps 5 to 9, using the other nostril.

Do not use more than the dose that your doctor prescribes to treat any single pain episode.

12. Put the bottle back in the child-resistant container after each use. Keep out of the sight and reach of children (Figure 6)
13. Stay sitting for at least 1 minute after using the nasal spray.



Number of sprays in this PecFent bottle
There are 2 full sprays in each PecFent bottle.

- After the first spray, number 1 will appear in the counting window. This will go up to the number 2 when the spray is used again.
- When you see the red 2 in the counting window, the bottle is finished and you will no longer be able to get a full spray from it.

Disposal of unused PecFent

- If you can see a number, other than 2 in the counting window, you have NOT used all 2 sprays in the bottle. There are still doses of PecFent left in the bottle.

- **You must empty this remaining dose of PecFent from the bottle** by aiming the nasal spray away from you (and any other people) and pressing and releasing the grips until the red number "2" appears in the counting window.

When you see the number "2" in the counting window, there is still medicine in the bottle that you must empty.

- You will need to press down and release the finger grips 4 more times while aiming the nasal spray away from you (and any other people).
- You will feel some increased resistance when you press down and the finger grips will only move a small amount.
- You will **NOT** hear a click when you press down .
- The counter will stay on the number "2".
- Put the protective cap back on the spray bottle.
- Put the bottle back in the child resistant container.
- Speak to your local pharmacy about disposal of empty bottles (see '**How to store PecFent')**

If the PecFent nasal spray is blocked or does not spray properly

- If the spray is blocked, aim the spray away from you (and any other people) and push firmly down on the pump. This should clear any blockage.
- If your nasal spray is still not working properly, dispose of the faulty bottle and start a new one. Tell your doctor what happened. **Never try to fix the nasal spray yourself or take it apart.** This is because it may then give you the wrong dose.

Dispose of the PecFent bottle and start a new one if:
- It is more than 5 days since you primed your bottle for the first time.

If you use more PecFent than you should
- You may feel sleepy, sick, dizzy or have slow or shallow breathing. In severe cases taking too much PecFent may also lead to coma. If you feel very dizzy, very sleepy or have slow or shallow breathing, call an ambulance or ask someone else to call one straight away.
- An overdose may also result in a brain disorder known as toxic leukoencephalopathy.

If you stop using PecFent
If you no longer have breakthrough pain, talk to your doctor before stopping PecFent and follow his/her advice. However, you should keep taking your other opioid medicine to treat your constant pain. Your doctor may need to check the dose.

You may experience withdrawal symptoms similar to the possible side effects of PecFent when discontinuing PecFent. If you experience withdrawal symptoms, 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.

Call an ambulance or ask someone else to call one straight away if you:
- feel very dizzy or faint
- feel very sleepy
- get slow or shallow breathing
- get cold clammy skin, look pale, have a weak pulse or other signs of shock.

If you or your carer notice any of the side effects above, call an ambulance straight away.

Common side effects (may affect up to 1 in 10 people):
- not knowing where you are (disorientated)
- change in taste
- feeling dizzy
- feeling or being sick
- feeling sleepy, headache
- nose bleed, discomfort in the nose (such as nasal burning), runny nose
- constipation
- itchy skin

Uncommon side effects: (may affect up to 1 in 100 people):
- chest infection
- painful, sore or inflamed throat or nose
- cough, sneezing, catarrh or cold, changes in the fluid produced by your nose
- allergic reaction, rash
- loss of or increase in appetite, weight increase
- dehydration, feeling thirsty
- misusing the medicine
- seeing or hearing things that are not really there (hallucinations/delirium), feeling confused
- feeling depressed, worried, slow or nervous
- a lack of concentration or increased activity
- memory loss

- feeling “high”
- being less aware or responsive, losing consciousness
- convulsion (fits)
- muscle convulsions or trembling
- loss of taste, loss or change in sense of smell
- difficulty in speaking
- blue skin colour
- vertigo, falling over, malaise
- heat and circulation not working properly, hot flush or fever, chills, excessive sweating
- swelling of the soft tissue
- low blood pressure
- blockage in the wind-pipe
- shortness of breath
- vaginal bleeding
- tear in the intestine or inflammation of the stomach lining
- numbness or tingling in the mouth , tongue, or nose, or other tongue problems, mouth ulcers, dry mouth
- diarrhoea
- retching, stomach pains, indigestion
- sore or painful joints
- difficulty in or inability to pass water
- chest pain
- feeling tired or weak, problems moving
- changes in blood cells (detected by laboratory tests)
- increased blood sugar
- protein in the urine

Other side effects (frequency not known (frequency cannot be estimated from the available data)**)**
- Severe breathing problems
- Flushing
- Insomnia
- Withdrawal syndrome (may manifest by the occurrence of the following side effects nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating)
- Drug tolerance, drug dependence (addiction), drug abuse (see section 2)

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 PecFent

Keep this medicine out of the sight and reach of children. PecFent could be life-threatening if taken by a child by accident.

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.

- Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.
- Do not store PecFent above 25°C.
- Do not freeze.
- Keep the bottle in its child resistant container in order to protect from light.
- Store the PecFent bottle in the child resistant container at all times, even when finished.
- Do not use for more than 5 days after first use (either priming or using to treat a breakthrough pain episode).
- PecFent that has passed the expiry date or is no longer required may still contain enough medicine to be harmful to other people, especially children. PecFent should not be disposed of via wastewater or household waste. Any unwanted PecFent should be disposed of as soon as possible following the instructions under ***Disposal of unused PecFent***. Any empty bottles should be returned to their child resistant container and discarded by taking them back to the pharmacy or according to local requirements.

6. Contents of the pack and other information

What PecFent contains

The active substance is fentanyl.

- *PecFent 100 micrograms/spray nasal spray, solution*
  Each ml of solution contains 1,000 micrograms fentanyl (as citrate).
  1 spray (100 microlitres) contains 100 micrograms fentanyl (as citrate).

The other ingredients (excipients) are pectin (E440), mannitol (E421), phenylethyl alcohol, propylparahydroxybenzoate (E216), sucrose, purified water and hydrochloric acid or sodium hydroxide for pH adjustment.

What PecFent looks like and contents of the pack
The medicine is a clear to almost clear, colourless nasal spray, solution. It is contained in a clear glass bottle, fitted with a metering pump and a protective cap. The pump has a spray counter that clicks, so you can hear as well as see that the spray has been given. After the PecFent bottle has been primed (prepared for use) it delivers 2 full sprays. Each PecFent bottle is supplied in a child resistant container.

PecFent 2 spray bottles in their child resistant containers are supplied in a carton containing 1 bottle.
Marketing Authorisation Holder
Kyowa Kirin Holdings B.V.
Bloemlaan 2,
2132NP Hoofddorp
The Netherlands

Manufacturer
L. Molteni & C. dei F.lli Alitti Società di Esercizio S.p.A
Strada Statale 67 Tosco Romagnola,
Fraz. Granatieri – 50018 Scandicci (FI)
Italy

This leaflet was last revised in

Other sources of information
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.