

Physician's Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

PecFent 100

PecFent 400

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each bottle contains: 1.55 ml (1,550 micrograms fentanyl)

PecFent 400 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 propyl parahydroxybenzoate (E216).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, solution.

A clear to practically clear colourless aqueous solution.

Patient safety information card

The marketing of PecFent is subject to a Risk management plan (RMP) including a 'patient safety information card'. The 'patient safety information card', emphasizes important safety information that the patient should be aware of before and during the treatment. Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Special warnings and precautions for use (4.4)]

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

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 (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 background pain should be kept as prescribed.

If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor as gradual downward opioid titration 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.

Method of administration

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).

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 CO₂ 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 serotonergic 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 propyl parahydroxybenzoate (E216). Propyl parahydroxybenzoate 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).

Serotonergic medicinal products:

Coadministration of fentanyl with a serotonergic 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.

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.

4.6 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.

4.7 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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	
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

	Common	Uncommon	Unknown
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
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	Hyperhidrosis Urticaria	
Musculoskeletal and connective tissue disorders		Arthralgia Muscle twitching	
Renal and urinary disorders		Anuria Dysuria Proteinuria Urinary hesitation	

	Common	Uncommon	Unknown
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form Healthcare professionals are asked to report <https://sideeffects.health.gov.il/>

4.8 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

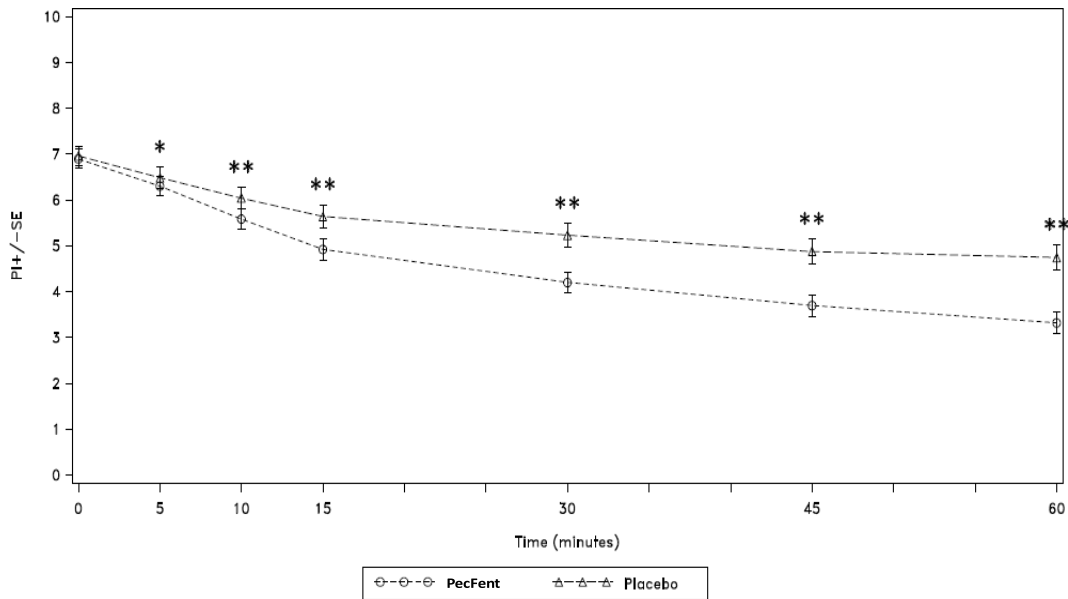
A double-blind, randomised, placebo-controlled crossover study has been conducted in which 114 patients who experienced on average 1 to 4 episodes of breakthrough pain (BTP) per day while taking maintenance opioid therapy were entered into an initial open-label titration phase in order to identify an 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 (SPID₃₀), 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 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).

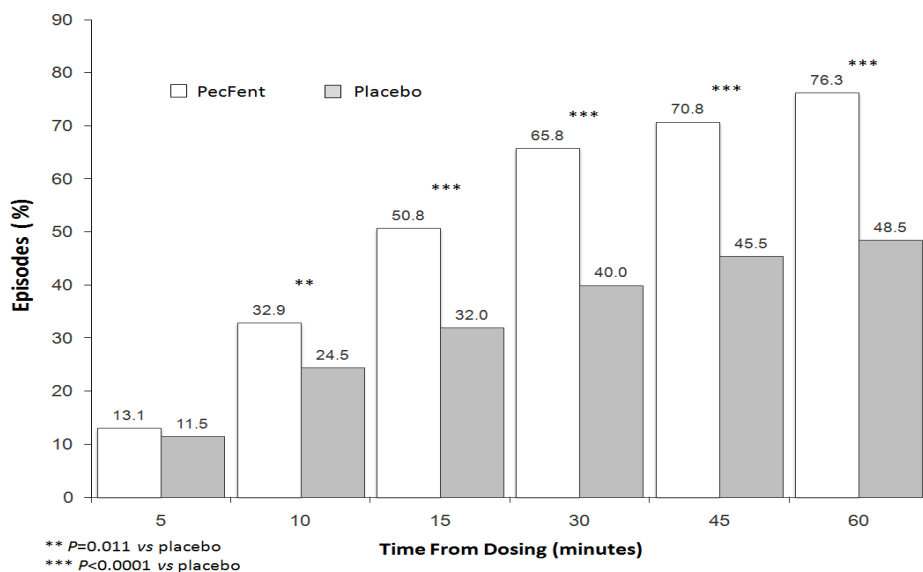
Figure 1: Mean (\pm SE) Pain Intensity Scores at Each Time Point (mITT Population)



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



** $P=0.011$ vs placebo
 *** $P<0.0001$ vs placebo

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.

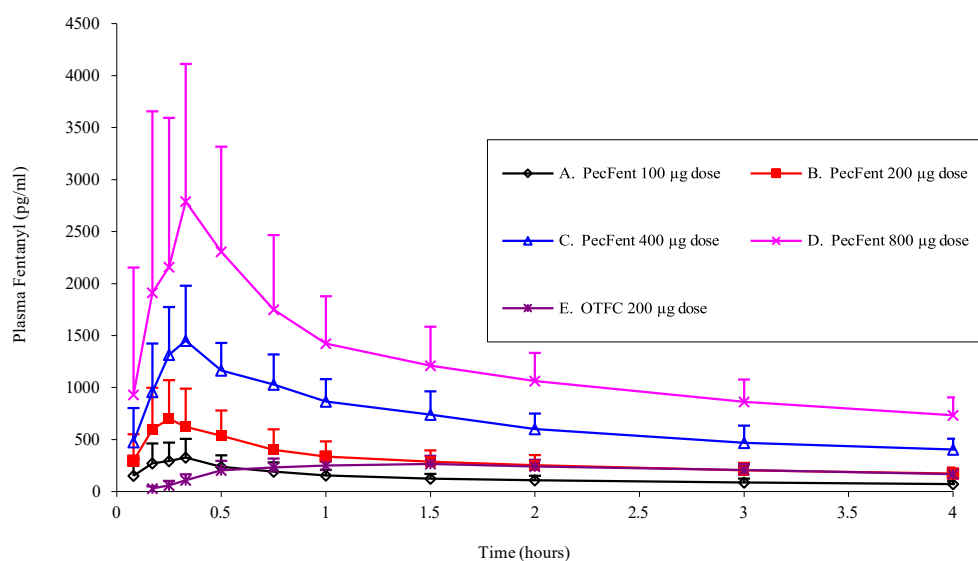
Pharmacokinetic parameters in adult subjects receiving PecFent and OTFC

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 carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The relevance of these findings to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Pectin
Sucrose
Propyl parahydroxybenzoate
Phenylethyl alcohol
Purified water
Hydrochloric acid or sodium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

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 (translucent cap for the 8 spray). In each case the product is packed in a clam-shell-like child resistant container.

Each bottle contains 1.55 ml ensuring delivery of 8 full sprays.

Bottles in their child resistant containers are supplied in cartons containing 1 or 4 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:
- 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. MANUFACTURER

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

8. IMPORTER AND LICENSE HOLDER

Medison Pharma Ltd.
POB 7090 Petach Tikva
Israel

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Registration No. PecFent 400: 152-60-33978

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