

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vellofent 67 micrograms, sublingual tablets
Vellofent 133 micrograms, sublingual tablets
Vellofent 267 micrograms, sublingual tablets
Vellofent 400 micrograms, sublingual tablets
Vellofent 533 micrograms, sublingual tablets
Vellofent 800 micrograms, sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vellofent 67 micrograms sublingual tablets:
Each tablet contains 110 micrograms of fentanyl citrate, equivalent to 67 micrograms of fentanyl.

Vellofent 133 micrograms sublingual tablets:
Each tablet contains 210 micrograms of fentanyl citrate, equivalent to 133 micrograms of fentanyl.

Vellofent 267 micrograms sublingual tablets:
Each tablet contains 420 micrograms of fentanyl citrate, equivalent to 267 micrograms of fentanyl.

Vellofent 400 micrograms sublingual tablets:
Each tablet contains 630 micrograms of fentanyl citrate, equivalent to 400 micrograms of fentanyl.

Vellofent 533 micrograms sublingual tablets:
Each tablet contains 840 micrograms of fentanyl citrate, equivalent to 533 micrograms of fentanyl.

Vellofent 800 micrograms sublingual tablets:
Each tablet contains 1260 micrograms of fentanyl citrate, equivalent to 800 micrograms of fentanyl.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet

Vellofent 67 micrograms sublingual tablets:
This medicine is presented in the form of a white, convex, triangular tablet, height of 5.6 mm, printed with '0' in black ink on one face.

Vellofent 133 micrograms sublingual tablets:
This medicine is presented in the form of a white, convex, triangular tablet, height of 5.6 mm, printed with '1' in black ink on one face.

Vellofent 267 micrograms sublingual tablets:
This medicine is presented in the form of a white, convex, triangular tablet, height of 5.6 mm, printed with '2' in black ink on one face.

Vellofent 400 micrograms sublingual tablets:
This medicine is presented in the form of a white, convex, triangular tablet, height of 5.6 mm, printed with '4' in black ink on one face.

Vellofent 533 micrograms sublingual tablets:

This medicine is presented in the form of a white, convex, triangular tablet, height of 5.6 mm, printed with '5' in black ink on one face.

Vellofent 800 micrograms sublingual tablets:

This medicine is presented in the form of a white, convex, triangular tablet, height of 5.6 mm, printed with '8' in black ink on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vellofent is indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

BTP is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.

Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

4.2 Posology and method of administration

Posology

Treatment should be initiated by and remain under the guidance of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential of abuse of fentanyl. Patients should be instructed not to use two different formulations of fentanyl concurrently for the treatment of breakthrough pain, and to dispose of any fentanyl product prescribed for BTP when switching to Vellofent. The number of tablet strengths available to the patients at any time should be minimised to prevent confusion and potential overdose.

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

Dose Titration

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

The object of dose titration is to identify an optimal maintenance dose for ongoing treatment of breakthrough pain episodes. This optimal dose should provide adequate analgesia with an acceptable level of adverse reactions.

The optimal dose of Vellofent will be determined by upward titration, on an individual patient basis. Several doses are available for use during the dose titration phase. The initial dose of Vellofent used should be 133 micrograms, titrating upwards as necessary through the range of available dosage strengths.

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

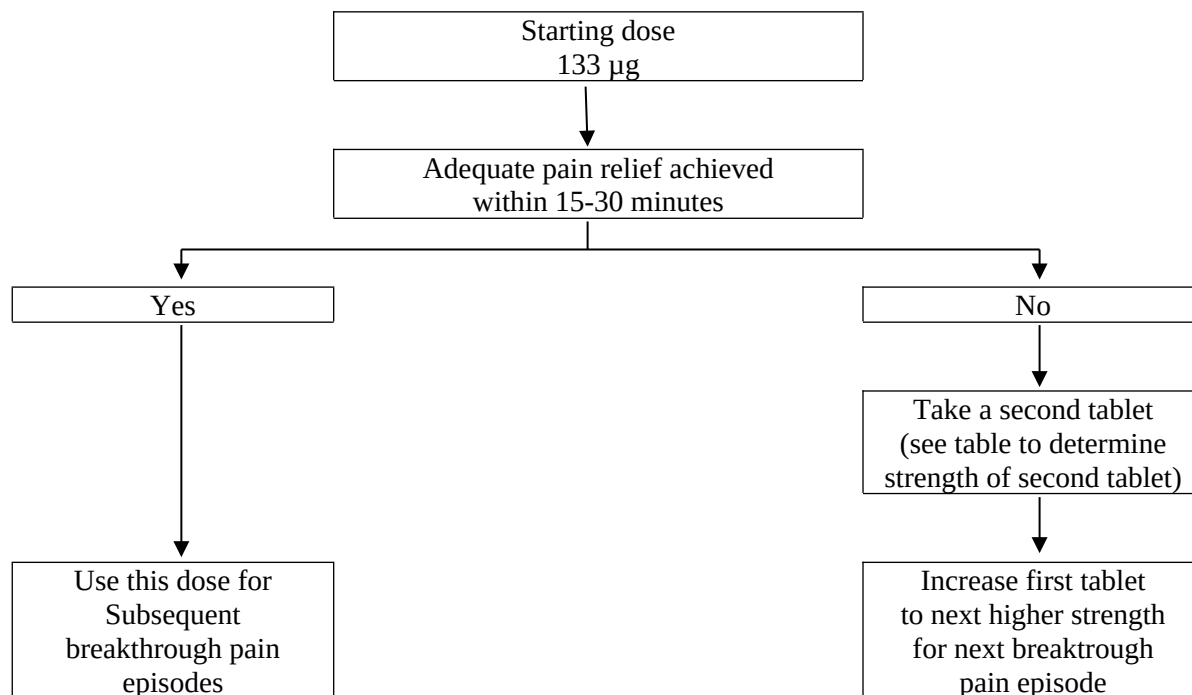
Switching from other fentanyl containing products to Vellofent must not occur at a 1:1 ratio because of different absorption profiles. If patients are switched from another fentanyl containing product, a new dose titration with Vellofent is required.

The following dose regimen is recommended for titration, although in all cases the physician should take into account the clinical need of the patient, age and concomitant illness.

All patients must start therapy with a single 133 micrograms sublingual tablet. If adequate analgesia is not obtained within 15-30 minutes of administration of a single tablet, a supplemental (second) 133 micrograms tablet may be administered. If treatment of a breakthrough pain episode requires more than one dosage unit,

an increase in dose to the next higher available strength should be considered (Refer to figure below). Dose escalation should continue in a stepwise manner until adequate analgesia is achieved. The dose strength for the supplemental (second) tablet should be increased from 133 to 267 micrograms at doses of 533 micrograms. This is illustrated in the schedule below. No more than two (2) tablets should be administered for a single episode of breakthrough pain during this titration phase.

VELLOFENT TITRATION PROCESS



Strength (micrograms) of first tablet per episode of breakthrough pain	Strength (micrograms) of supplemental (second) tablet to be taken 15-30 minutes after first tablet, if required
133	133
267	133
400	133
533	267
800	-

If adequate analgesia is achieved at the higher dose, but undesirable effects are considered unacceptable, an intermediate dose may be administered (using the 67 micrograms or 133 micrograms tablet).

Doses higher than 800 micrograms have not been evaluated in clinical studies.

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

Maintenance therapy

Once an appropriate dose has been established, which may be more than one tablet, patients should be maintained on this dose and should limit consumption to a maximum of four Vellofent doses per day.

Dose re-adjustment

If the response (analgesia or adverse reactions) to the titrated Vellofent dose markedly changes, an adjustment of dose may be necessary to ensure that an optimal dose is maintained.

If more than four episodes of breakthrough pain are consistently experienced per day, then the dose of the long acting opioid used for persistent pain should be re-evaluated. If the long acting opioid or dose of long acting

opioid is changed, the Vellofent dose should be re-evaluated and re-titrated as necessary to ensure the patient is on an optimal dose.

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

Treatment duration and goals

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

Discontinuation of therapy

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

Elderly

Dose titration needs to be approached with particular care and patients observed carefully for signs of fentanyl toxicity (see section 4.4).

Renal and hepatic impairment

Patients with kidney or liver dysfunction should be carefully observed for signs of fentanyl toxicity during the Vellofent titration phase (see section 4.4).

Paediatric population

The safety and efficacy of Vellofent in paediatric population (below 18 years) have not been established. No data are available.

Method of administration

Vellofent should be administered directly under the tongue at the deepest part.

Vellofent should not be swallowed, but allowed to completely dissolve in the sublingual cavity without chewing or sucking. Patients should be advised not to eat or drink anything until the sublingual tablet is completely dissolved.

After 30 minutes, if remnants from the Vellofent tablet remain, they may be swallowed.

In patients who have a dry mouth, water may be used to moisten the buccal mucosa before taking Vellofent.

For instructions on how to open the blister, see section 6.6.

The tablet should not be stored once removed from the blister package as the tablet integrity can not be guaranteed and a risk of accidental exposure to a tablet can occur (see also section 4.4 for warnings in children).

Patients should be advised to keep Vellofent in a locked storage space.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients without maintenance opioid therapy (see section 4.1) as there is an increased risk of respiratory depression.

- Simultaneous use of monoamine-oxidase (MAO) inhibitors, or within 2 weeks after the cessation of the use of MAO inhibitors.
- 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 Vellofent in a safe and secure place, not accessible by others.

Patients and their carers must be instructed that Vellofent contains an active substance in an amount that can be fatal to a child, and therefore to keep all tablets out of the reach and sight of children and non-patients at all times.

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

It is important that the long acting opioid treatment used to treat the patient's persistent pain has been established before Vellofent therapy begins and that the patient continues to be treated with the long acting opioid treatment whilst taking Vellofent.

As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of fentanyl. Particular caution should be used when titrating Vellofent in patients with non-severe chronic obstructive pulmonary disease or other medical conditions predisposing them to respiratory depression, as even normally therapeutic doses of Vellofent may further decrease respiratory drive to the point of respiratory failure.

Sleep-related breathing disorders

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

Vellofent 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 a patient with a head injury and should be used only if clinically warranted.

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.

Cardiac disease

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

In addition, Vellofent should be administered with caution to patients with hepatic or renal impairment. The influence of hepatic and renal impairment on the pharmacokinetics of the medicinal product has not been evaluated, however, when administered intravenously the clearance of fentanyl has been shown to be altered in hepatic and renal impairment due to alterations in metabolic clearance and plasma proteins. After administration of Vellofent, impaired hepatic and renal function may both increase the bioavailability of swallowed fentanyl and decrease its systemic clearance, which could lead to increased and prolonged opioid effects. Therefore, special care should be taken during the titration process in patients with moderate or severe hepatic or renal impairment.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Vellofent 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 Vellofent 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).

Serotonin Syndrome

Caution is advised when Vellofent is co-administered with drugs that affect the serotonergic neurotransmitter systems.

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

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). If serotonin syndrome is suspected, treatment with Vellofent should be discontinued.

Vellofent has not been studied in patients with mouth wounds or mucositis. There may be a risk of increased systemic drug exposure in such patients and therefore extra caution is recommended during dose titration.

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 Vellofent 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 Vellofent 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 Vellofent 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Vellofent is contraindicated for use in patients who have received monoamine oxidase (MAO) inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Fentanyl is metabolized by the CYP3A4 isoenzyme in the liver and intestinal mucosa. Inhibitors of CYP3A4 such as

- macrolide antibiotics (e.g. erythromycin, clarithromycin, telithromycin),
- azole antifungals (e.g. ketoconazole, itraconazole, and fluconazole),
- certain protease inhibitors (e.g. ritonavir, indinavir, nelfinavir, saquinavir),
- calcium channel blockers (e.g. diltiazem or verapamil),
- anti-emetics (e.g. aprepitant or dronabinol),
- antidepressants (e.g. fluoxetine),
- antacids (e.g. cimetidine)

or alcohol may increase the bioavailability of swallowed fentanyl and may also decrease its systemic clearance which may result in increased or prolonged opioid effects and may cause potentially fatal respiratory depression. Similar effects could be seen after concurrent ingestion of grapefruit juice, which is known to inhibit CYP3A4. Hence caution is advised if fentanyl is given concomitantly with CYP3A4 inhibitors. Patients receiving Vellofent who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time.

The concomitant use of Vellofent with potent CYP3A4 inducers such as

- barbiturates and other sedatives (e.g. phenobarbital),
- anti-epileptics (e.g. carbamazepine, phenytoin, oxcarbazepine),
- certain antivirals (e.g. efavirenz, nevirapine),
- anti-inflammatory or immunosuppressive agents (e.g. glucocorticoids),
- anti-diabetics (e.g. pioglitazone),
- antibiotics for tuberculosis treatment (e.g. rifabutin, rifampin),
- psychotropic substances (e.g. modafinil),
- antidepressants (e.g. St. John's wort),

may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of Vellofent. Patients receiving Vellofent who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased Vellofent activity, or toxicity, and the dose of Vellofent should be adjusted accordingly.

The concomitant use of other central nervous system depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines, alcohol **and gabapentinoids (gabapentin and pregabalin)** may produce additive depressant effects.

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

Serotonergic Drugs

Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Sedative medicines such as benzodiazepines or related drugs

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

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

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. Vellofent should not be used in 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 or in the new-born infant. If Vellofent 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 breastfeeding should not be restarted until at least 5 days after the last administration of fentanyl.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed.

However, opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients should be advised not to drive or operate machinery if they experience somnolence, dizziness, or visual disturbance while taking Vellofent and not to drive or operate machinery until they know how they react.

4.8 Undesirable effects

Typical opioid side effects are to be expected with Vellofent. Frequently, these will cease or decrease in intensity with continued use of the product, as the patient is titrated to the most appropriate dose. However, the most serious adverse reactions are respiratory depression (potentially leading to apnoea or respiratory arrest), circulatory depression, hypotension and shock and all patients should be closely monitored for these. The most frequently observed adverse reactions include: nausea, vomiting, constipation, headache, somnolence/fatigue and dizziness.

The following adverse reactions have been reported with Vellofent and/or other fentanyl-containing compounds during clinical studies and post marketing experience.

Due to the concomitant treatment with opioids, during clinical trials and in the clinical practice, it is not possible to definitively separate the effects of fentanyl alone

Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency (frequencies are 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 $<1/10,000$), not known (cannot be estimated from the available data):

MedDRA system organ class	Very common	Common	Uncommon	Not known
Metabolism and nutrition disorders			anorexia	
Psychiatric disorders		confusion, anxiety, hallucinations, abnormal thinking	abnormal dreams, depersonalisation, depression, emotional lability, euphoria	Insomnia, drug dependence (addiction), drug abuse, delirium.

MedDRA system organ class	Very common	Common	Uncommon	Not known
Nervous system disorders	somnolence, sedation, dizziness	loss of consciousness, vertigo, headache, myoclonus, taste perversion	coma, convulsion, paraesthesia (including hyperaesthesia/circumoral paraesthesia), abnormal gait/incoordination	
Eye disorders			abnormal vision (blurred, double vision)	
Vascular disorders		hypotension		flushing and hot flush
Respiratory, thoracic and mediastinal disorders			dyspnoea, respiratory depression	
Gastrointestinal disorders	nausea, constipation	vomiting, dry mouth, abdominal pain, dyspepsia,	ileus, flatulence, abdomen enlarged, dental caries	tooth loss, gingival recession, diarrhoea.
Skin and subcutaneous tissue disorders		pruritus, sweating	rash	
Renal and urinary disorders			urinary retention	
General disorders and administration site conditions		asthenia	malaise	fatigue, peripheral oedema, pyrexia, withdrawal syndrome*, neonatal withdrawal syndrome, drug tolerance
Injury, poisoning and procedural complications		accidental injury (for example, falls)		

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

Description of selected adverse reactions

Tolerance

Tolerance can develop on repeated use.

Drug dependence

Repeated use of Vellofent 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 [To be completed nationally]

4.9 Overdose

The symptoms of fentanyl overdosage are expected to be similar in nature to those of intravenous fentanyl and other opioids, and are an extension of its pharmacological actions, with the most serious significant effects being altered mental status, loss of consciousness, coma, cardiorespiratory arrest, respiratory depression, respiratory distress and respiratory failure, which have resulted in death. Cases of Cheynes Stokes respiration have been observed in case of fentanyl overdose, particularly in patients with history of heart failure. *Toxic leukoencephalopathy has also been observed with fentanyl overdose.*

Immediate management of opioid overdose includes removal of the Vellofent if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, assessment of the level of consciousness, ventilatory and circulatory status, and assisted ventilation (ventilatory support) if necessary.

For treatment of overdosage (accidental ingestion) in the opioid naïve person, intravenous access should be obtained, and naloxone or other opioid antagonists should be employed as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the Summary of Product Characteristics of the individual opioid antagonist for details about such use. 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.

If severe or persistent hypotension occurs, hypovolaemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

Muscle rigidity interfering with respiration has been reported with fentanyl and other opioids. In this situation, endotracheal intubation, assisted ventilation and administration of opioid antagonists as well as muscle relaxants may be requested.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: phenylpiperidine derivatives.

ATC code: N02AB03.

Mechanism of action

Fentanyl is an opioid analgesic, interacting predominantly with the opioid μ -receptor.

Pharmacodynamic effects

Primary therapeutic actions of fentanyl are analgesia and sedation. Secondary pharmacological effects are respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria.

The analgesic effects of fentanyl are related to its plasma level. In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance to opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of Vellofent should be individually titrated to achieve the desired effect (see section 4.2).

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

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

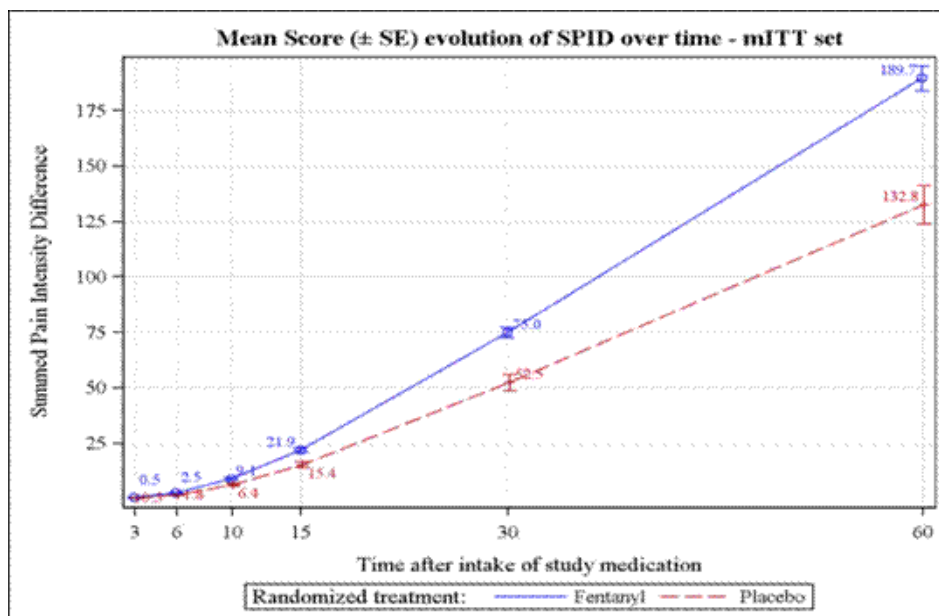
Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract leading to a prolongation in gastrointestinal transit time, which may be responsible for the constipating effect of fentanyl.

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.

Clinical efficacy and safety

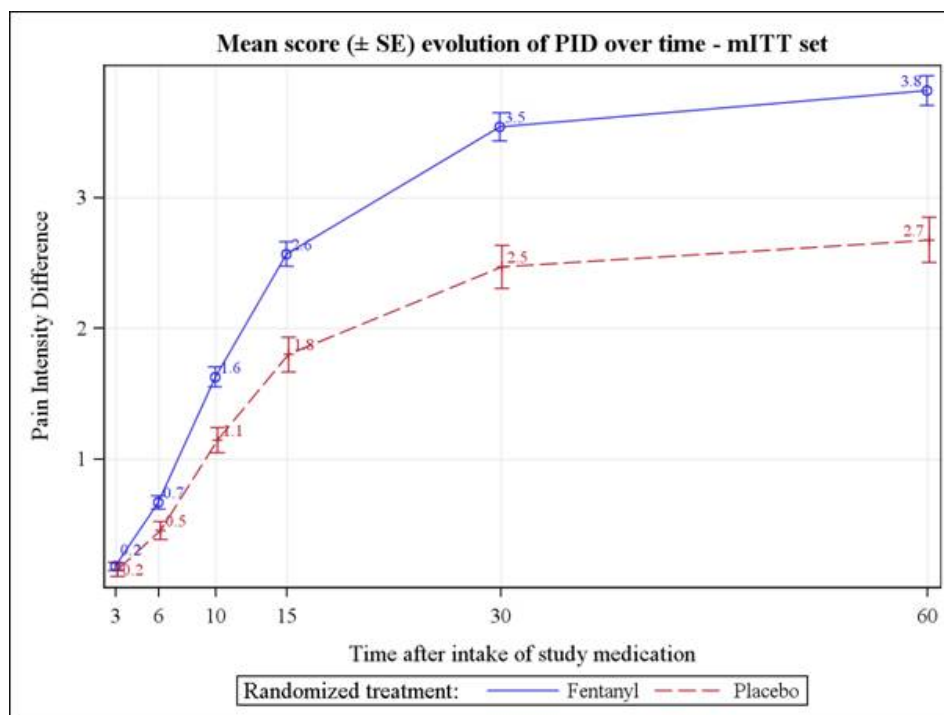
The efficacy and safety of Vellofent have been assessed in a double blind randomized, placebo-controlled, cross over study in 91 opioid-treated adult cancer patients who experienced 1 to 4 episodes of breakthrough pain (BTP) per day. The primary endpoint was the sum of pain intensity difference at 30 minutes (SPID30) after dosing which was statistically significant compared to placebo ($p < 0.0001$).

Sum of pain intensity difference from 6 minutes after dosing and up to 60 minutes was also significant compared to placebo (respectively $p=0.02$ after 6 minutes and $p<0.0001$ after 60 minutes) (see figure below).



The superior efficacy of Vellofent over placebo was supported by data from secondary endpoints:

- mean pain intensity difference (PID) was significantly higher for the BTP episodes treated with fentanyl than those treated with placebo from 6 minutes after dosing and up to 60 minutes (respectively $p=0.003$ and $p<0.0001$) (see figure below);



- mean pain relief (PR) was significantly higher for the BTP episodes treated with fentanyl than those treated with placebo from 6 minutes after dosing and up to 60 minutes (respectively $p=0.002$ and $p<0.0001$);
- episodes of BTP treated with Vellofent required the use of rescue medication significantly less often than episodes treated with placebo;
- significant improvement in pain scores ($\geq 33\%$ and $\geq 50\%$ reductions) was reported for BTP treated with Vellofent at 15 and 30 minutes.

Paediatric population

No data are available.

5.2 Pharmacokinetic properties

Fentanyl is highly lipophilic and can be absorbed very rapidly through the oral mucosa and more slowly through the gastrointestinal tract. Orally administered fentanyl undergoes pronounced hepatic and intestinal first pass effects and the metabolites do not contribute to fentanyl's therapeutic effects.

Vellofent employs a technology that allows rapid release of fentanyl and enhances the rate and extent of fentanyl absorbed through the oral mucosa. The absolute bioavailability of Vellofent has not been determined but is estimated to be about 70%.

Absorption

Mean maximal plasma concentrations range from 360 to 2070 pg/ml (after administration of 133 to 800 µg of Vellofent) and are reached within 50 and 90 minutes.

Distribution

Fentanyl is highly lipophilic and is well distributed beyond the vascular system, with a large apparent volume of distribution. After sublingual administration of Vellofent, fentanyl undergoes initial rapid distribution that represents an equilibration of fentanyl between plasma and the highly perfused tissues (brain, heart and lungs). Subsequently, fentanyl is redistributed between the deep tissue compartment (muscle and fat) and the plasma.

The plasma protein binding of fentanyl is 80% to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis.

Biotransformation and elimination

Fentanyl is metabolised in the liver and in the intestinal mucosa to norfentanyl by CYP3A4 isoform. Norfentanyl is not pharmacologically active in animal studies. More than 90% of the administered dose of fentanyl is eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.

Following the intravenous administration of fentanyl, less than 7% of the administered dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the faeces. The metabolites are mainly excreted in the urine, while faecal excretion is less important.

The terminal elimination phase of fentanyl is the result of the redistribution between plasma and a deep tissue compartment. Following the administration of Vellofent, the terminal elimination half-life is approximately 12 hours.

Linearity/non linearity

Dose proportionality from 133 micrograms to 800 micrograms has been demonstrated.

Renal/hepatic impairment

Impaired hepatic or renal function could cause increased serum concentrations. Elderly, cachectic or generally impaired patients may have a lower fentanyl clearance, which could cause a longer terminal half-life for the compound (see sections 4.2 and 4.4).

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 reveal any findings indicative of oncogenic potential. Evaluation of brain slides from the carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The relevance of these findings to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate anhydrous

Microcrystalline cellulose

Disodium phosphate anhydrous

Hypromellose

Macrogol

Magnesium stearate

Maltodextrin

Titanium dioxide (E171)

Triacetin

Printing ink [shellac, black iron oxide (E172)]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original blister package, in order to protect from light.

6.5 Nature and contents of container

Peelable, child resistant blister:

- Polyamide-Aluminium-PVC / Aluminium foil blister, contained in a cardboard outer carton.
- Polyamide-Aluminium-PVC / Aluminium-PET foil blister, contained in a cardboard outer carton.

Pack sizes: 3, 4, 15 or 30 sublingual tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The blister pack should be opened as shown on the blister foil, by peeling back the tab of the foil top on the blister and gently removing the sublingual tablet. The sublingual tablet should not be pushed through the foil.

Sublingual tablets with remaining active substance must not be disposed of in household waste. Waste material should be disposed of safely. Patients/carers should be encouraged to dispose any unused product in accordance with national and local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 October 2012

10. DATE OF REVISION OF THE TEXT

23-AUG-2024