

## **1. NAME OF THE MEDICINAL PRODUCT**

Instanyl<sup>®</sup> ▼ 50, 100 and 200 micrograms/dose nasal spray, solution

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml of solution contains fentanyl citrate equivalent to 500, 1,000 or 2,000 micrograms fentanyl. 1 dose (100 microliters) contains 50, 100 or 200 micrograms fentanyl.

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Nasal spray, solution (nasal spray)  
Clear, colourless solution.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Instanyl is indicated for the management of breakthrough pain in adults 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 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 of abuse of fentanyl.

Patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions. Patients must be carefully monitored during the titration process.

Titration to a higher dose necessitates contact with the health care professional.

The dose of Instanyl for treatment of breakthrough pain was independent of the daily maintenance dose of opioid in the clinical studies (see section 5.1).

Maximum daily dose: Treatment of up to four breakthrough pain episodes, each with no more than two doses separated by at least 10 minutes.

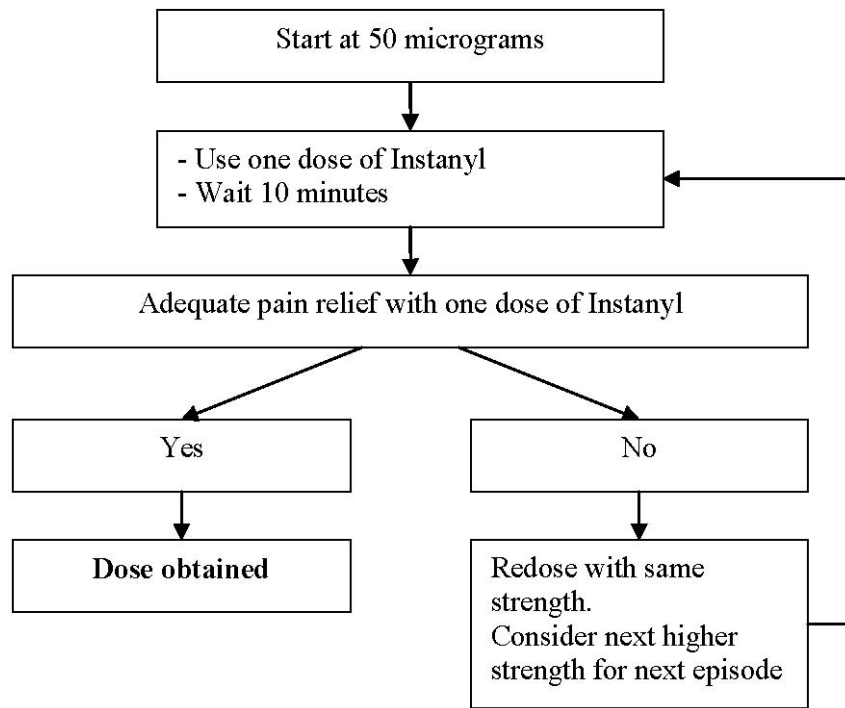
Patient should wait at least 4 hours before treating another breakthrough pain episode with Instanyl during both titration and maintenance therapy.

#### Dose titration

Before patients are titrated with Instanyl, it is expected that their background persistent pain is controlled by use of chronic opioid therapy and that they are experiencing no more than four episodes of breakthrough pain per day.

#### *Method of titration*

The initial strength should be one dose of 50 micrograms in one nostril, titrating upwards as necessary through the range of available strengths (50, 100, and 200 micrograms). If adequate analgesia is not obtained redosing of the same strength may be administered at the earliest after 10 minutes. Each titration step (dose strength) should be evaluated in several episodes.



#### Maintenance therapy

Once the dose has been established according to the steps described above, the patient should be maintained on this strength of Instanyl. If the patient has insufficient pain relief, redosing with same strength can be done at the earliest after 10 minutes.

#### Dose adjustment

Generally, the maintenance strength of Instanyl should be increased when a patient requires more than one dose per breakthrough pain episode for several consecutive episodes.

Dose adjustment of the background opioid therapy may be required if the patient consistently present with more than four breakthrough pain episodes per 24 hours.

If adverse reactions are intolerable or persistent, the strength should be reduced or treatment with Instanyl replaced by other analgesics.

#### Discontinuation of therapy

Instanyl should be discontinued immediately if the patient no longer experience breakthrough pain episodes. The treatment for the persistent background pain should be kept as prescribed.

If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor as gradual downward opioid titration is necessary in order to avoid the possibility of abrupt withdrawal effects.

#### Method of administration

Instanyl is intended for nasal use.

It is recommended that the patient sit or stand in upright position when administrating Instanyl.

Cleaning of the nasal spray tip is required after each use.

#### *Children and adolescents*

Instanyl is not recommended for use in children and adolescent below 18 years of age, due to lack of data on safety and efficacy.

#### *Elderly*

Limited data on pharmacokinetics, efficacy and safety are available for the use of Instanyl in patients above >65 years of age. Elderly patients may have a reduced clearance, a prolonged half-life and higher sensitivity to fentanyl than younger patients. Caution should therefore be taken in treatment of elderly, cachectic or debilitated patients.

In clinical trials elderly patients tend to titrate to a lower effective strength than patients less than 65 years of age. Particular caution should be exercised when titrating Instanyl in elderly patients.

#### *Hepatic impairment*

Instanyl should be administered with caution to patients with moderate to severe hepatic impairment (see section 4.4).

#### *Renal impairment*

Instanyl should be administered with caution to patients with moderate to severe renal impairment (see section 4.4).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Use in opioid-naïve patients.

Severe respiratory depression or severe obstructive lung conditions.

Previous facial radiotherapy.

Recurrent episodes of epistaxis (see section 4.4).

### **4.4 Special warnings and precautions for use**

#### *Respiratory depression*

As with all potent opioids clinical significant respiratory depression may occur with fentanyl, and patients must be observed for these effects. Patients with pain who receives 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 have more severe adverse reactions. In these patients, opioids may decrease respiratory drive and increase airway resistance.

#### *Impaired renal or hepatic function*

Fentanyl should be administered with caution to patients with moderate to severe hepatic or renal impairment. The influence of hepatic and renal impairment on the pharmacokinetics of Instanyl have not been evaluated; however, when administered intravenously the clearance of fentanyl has shown to be altered due to hepatic and renal impairment caused by alterations in metabolic clearance and plasma proteins.

#### *Increased intracranial pressure*

Fentanyl should be used with caution in patients with evidence of increased intracranial pressure, impaired consciousness or coma.

Instanyl should be used with caution in patients with cerebral tumour or head injury.

#### *Cardiac disease*

Fentanyl may produce bradycardia. Fentanyl should therefore be administered with caution to patients with bradyarrhythmias. Opioids may cause hypotonia, especially in patients with hypovolaemia. Instanyl should therefore be used with caution in patients with hypotonia and/or hypovolaemia.

#### *Nasal conditions*

If the patient experience recurrent episodes of epistaxis or nasal discomfort while taking Instanyl, an alternative administration form for treatment of breakthrough pain should be considered.

#### *Common cold*

The overall extent of fentanyl exposure in subjects with common cold without prior treatment with nasal vasoconstrictor is comparable to that in healthy subjects. For concomitant use of nasal vasoconstrictor see section 4.5.

#### *Abuse potential and dependence*

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. However, iatrogenic addiction following therapeutic use of opioids is rare in the treatment of cancer related pain.

### *Withdrawal symptoms*

Withdrawal symptoms may be precipitated through the administration of substances with opioid antagonist activity, e.g. naloxone, or mixed agonist/antagonist analgesic (e.g. pentazocine, butorphanol, buprenorphine, nalbuphine).

### *Treatment with other nasally administered medicinal products*

When initiating treatment with Instanyl, alternative administration forms should be considered for concurrent treatment of concomitant diseases that can be treated via nasal administration.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Instanyl is not recommended 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 metabolised mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore potential interactions may occur when Instanyl is given concurrently with agents that affect CYP3A4 activity. Co-administration with agents that induce 3A4 activity may reduce the efficacy of Instanyl. The concomitant use of Instanyl 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, and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug reactions including fatal respiratory depression. Patients receiving Instanyl concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dose increase should be done with caution.

In a pharmacokinetic interaction study it was found that the maximum plasma concentration of nasally applied fentanyl was reduced about 50% by the concomitant use of oxymetazoline, while the time to reach  $C_{max}$  ( $T_{max}$ ) was doubled. This may reduce the efficacy of Instanyl. It is recommended that concomitant use of nasal decongestants is avoided (see section 5.2)

The concomitant use of other central nervous system depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcohol 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 dependent patients

Concomitant use of Instanyl and other medicinal products (other than oxymetazoline) administered via the nose has not been evaluated in the clinical trials. It is recommended that alternative administration forms should be considered for concomitant treatment of concurrent diseases that can be treated via nasal administration.

## **4.6 Pregnancy and lactation**

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. Instanyl 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. If Instanyl is administered, an antidote for the child should be readily available.

Fentanyl is excreted into human milk and may cause sedation and respiratory depression in the breast-fed infant. Fentanyl should only be used by breastfeeding women if the benefits outweigh the potential risks for both mother and child.

#### 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 are known to impair the mental and/or physical ability required for driving or operating machinery. Patient should be advised not to drive or operate machinery if they experience somnolence, dizziness, visual disturbances or other adverse reaction which can impair their ability to drive and operate machinery.

#### 4.8 Undesirable effects

Typical opioid adverse reactions are to be expected with Instanyl. Frequently, most of these will cease or decrease in intensity with continued use of the medicinal product. The most serious adverse reactions are respiratory depression (potentially leading to apnoea or respiratory arrest), circulatory depression, hypotension and shock and all patients should be closely monitored for these.

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

The adverse reactions considered to be at least possibly related to treatment in the clinical trials of Instanyl are included in the table below.

The following categories are used to rank the undesirable effects by frequency of occurrence: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1000$ ); and very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Common	Uncommon
Psychiatric disorders		Dependence, insomnia
Nervous system disorders	Somnolence, dizziness, headache	Sedation, myoclonus, paraesthesia, dysaesthesia, dysgeusia
Ear and Labyrinth disorders	Vertigo	Motion sickness
Cardiac disorders		Hypotension
Vascular disorders	Flushing, hot flush	
Respiratory, thoracic and mediastinal disorders	Throat irritation	Respiratory depression, epistaxis, nasal ulcer, rhinorrhea
Gastrointestinal disorders	Nausea, vomiting	Constipation, stomatitis, dry mouth
Skin and subcutaneous tissue disorders	Hyperhidrosis	Pain of skin, pruritus
General disorders and administration site conditions		Pyrexia

#### 4.9 Overdose

##### *Symptoms*

The symptoms of fentanyl overdose are expected to be an extension of its pharmacological actions e.g. lethargy, coma and severe respiratory depression. Other symptoms may be hypothermia, decreased muscle tonus, bradycardia, hypotonia. Signs of toxicity are deep sedation, ataxia, miosis, convulsions and respiratory depression which is the main symptom.

##### *Treatment*

For management of respiratory depression immediate countermeasures should be started including physical or verbal stimulation of the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The half-life of the antagonist may be short, therefore repeated administration or continuous infusion

may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube and oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should be maintained.

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Phenylpiperidine derivates. ATC code: N02AB03

#### *Mechanism of action*

Fentanyl is an opioid analgesic interacting primarily with the opioid  $\mu$ -receptor as a pure agonist with low affinity for the  $\delta$ - and  $\kappa$ -opioid receptors. The primary therapeutic action is analgesia. The secondary pharmacological effects are respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria.

#### *Pharmacodynamic effects*

The efficacy and safety of Instanyl (50, 100 and 200 micrograms) have been assessed in two randomised, double-blind, cross-over, placebo-controlled pivotal studies in 279 opioid-tolerant adult cancer patients (age 32-86 years) with breakthrough pain (BTP). The patients had an average of 1 to 4 episodes per day while taking maintenance opioid therapy. Patients in the second pivotal study had earlier participated in the Instanyl pharmacokinetic study or in the first pivotal study.

The clinical studies demonstrated the efficacy and safety of Instanyl. No distinct correlation between the maintenance opioid dose and Instanyl doses have been established, however in the second pivotal study patients with low maintenance opioid dose tended to achieve effective pain relief with a correspondingly lower strength of Instanyl compared to patients taking higher levels of maintenance opioid dose. This was most distinct for patients ending on Instanyl 50 micrograms.

In the clinical studies in cancer patients, the most frequent strength used were 100 and 200 micrograms

All three strengths of Instanyl showed statistically significant ( $p < 0.001$ ) higher pain intensity difference at 10 minutes ( $PID_{10}$ ) compared with placebo. Furthermore Instanyl was significantly superior to placebo in BTP relief at 10, 20, 40, and 60 minutes following administration. The results of summary of PID at 60 minutes ( $SPID_{0-60}$ ) showed that all strengths of Instanyl had significantly higher mean  $SPID_{0-60}$  scores compared with placebo ( $p < 0.001$ ) demonstrating better pain relief of Instanyl compared to placebo during 60 minutes.

The safety and efficacy of Instanyl have been evaluated in patients taking the medicinal product at the onset of a breakthrough pain episode. Instanyl should not be used pre-emptively.

The clinical experience with Instanyl in patients with background opioid treatment equivalent to  $\geq 500$  mg/day morphine or  $\geq 200$  micrograms/hour transdermal fentanyl is limited.

Instanyl in doses above 400 micrograms have not been evaluated in clinical trials.

### **5.2 Pharmacokinetic properties**

#### *Absorption*

Fentanyl is highly lipophilic. Fentanyl exhibits three compartment distribution kinetics. Animal data shows 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 approximately 80%. The absolute bioavailability of Instanyl is about 89%.

Clinical data show that fentanyl is absorbed very rapidly through the nasal mucosa. Administration of Instanyl in single doses ranging from 50 to 200 micrograms fentanyl per dose in opioid tolerant cancer patients produces a

rapid  $C_{max}$  level of 0.35 to 1.2 ng/ml. The corresponding median  $T_{max}$  are 12-15 minutes. However, higher values for  $T_{max}$  were observed in a dose-proportionality study in healthy volunteers.

#### *Distribution*

After intravenous administration of fentanyl the initial distribution half-life is approximately 6 minutes and a similar half-life is seen after the nasal administration of Instanyl. The elimination half-life is approximately 3-4 hours for Instanyl in cancer patients.

#### *Biotransformation*

Fentanyl is metabolised primarily in the liver via CYP3A4. The major metabolite, norfentanyl is inactive.

#### *Elimination*

About 75% of fentanyl is excreted into the urine, mostly as inactive metabolites, with less than 10% as unchanged active substance. About 9% of the dose is recovered in the faeces primarily as metabolites.

#### *Dose linearity*

Instanyl shows linear kinetics. Dose linearity from 50 micrograms to 400 micrograms of Instanyl has been demonstrated in healthy subjects.

A drug-drug-interaction study was performed with a nasal vasoconstrictor (oxymetazoline). Subjects with allergic rhinitis received oxymetazoline nasal spray one hour prior to Instanyl. Comparable bioavailability (AUC) of fentanyl was achieved with and without oxymetazoline, while fentanyl  $C_{max}$  decreased and  $T_{max}$  increased by a factor two when oxymetazoline was administered. The overall extent of fentanyl exposure in subjects with allergic rhinitis without prior treatment with nasal vasoconstrictor is comparable to that in healthy subjects. Concomitant use of nasal vasoconstrictor should be avoided (see section 4.5).

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Long-term carcinogenicity studies have not been performed.

Local tolerance studies with Instanyl in mini-pigs demonstrated that Instanyl administration was well tolerated.

Studies with female rats revealed reduced fertility and enhanced embryonal mortality. More recent studies showed that effects on the embryo were due to maternal toxicity and not to direct effects of the substances on the developing embryo. In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed. Teratogenic effects have not been demonstrated.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium dihydrogen phosphate dihydrate  
Disodium phosphate dihydrate  
Purified water

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years

#### **6.4 Special precautions for storage**

Store below 30°C.

Do not freeze.

Keep the bottle stored upright.

#### **6.5 Nature and contents of container**

Bottle (brown Type 1 glass) with metering pump and dust cap packed in a child-resistant outer box.

Available in the following presentations:

1.8 ml containing 0.90, 1.80 or 3.60 mg fentanyl ensuring the delivery of 10 doses of 50, 100 or 200 micrograms

2.9 ml containing 1.45, 2.50 or 5.00 mg fentanyl ensuring the delivery of 20 doses of 50, 100 or 200 micrograms

5.0 ml containing 2.50, 5.00 or 10.00 mg fentanyl ensuring the delivery of 40 doses of 50, 100 or 200 micrograms

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal and other handling**

Before using Instanyl for the first time, the nasal spray must be primed until a fine mist appears; 3 to 4 actuations of the nasal spray are usually required.

If the product has not been used during a period of more than seven days, the nasal spray must be actuated once to waste before the next dose is taken.

Because of the possible misuse of fentanyl and the possible amount of the solution left, the used and unused nasal spray solutions must be returned systematically and suitably in the child-resistant outer box according to local requirements or returned to the pharmacy.

### **7. MARKETING AUTHORISATION HOLDER**

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### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/09/531/001-009

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

20 July 2009

### **10. DATE OF REVISION OF THE TEXT**

### **11. LEGAL CATEGORY**

CD (Sch 2), POM

Detailed information on this product is available on the website of the European Medicines Agency (EMA)  
<http://www.ema.europa.eu>