SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Instanyl 50 micrograms/dose nasal spray, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains fentanyl citrate equivalent to 500 micrograms fentanyl.
1 dose (100 microlitres) contains 50 micrograms fentanyl.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, solution (nasal spray). DoseGuard
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, misuse, addiction and overdose of fentanyl (see section 4.4).

Posology

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

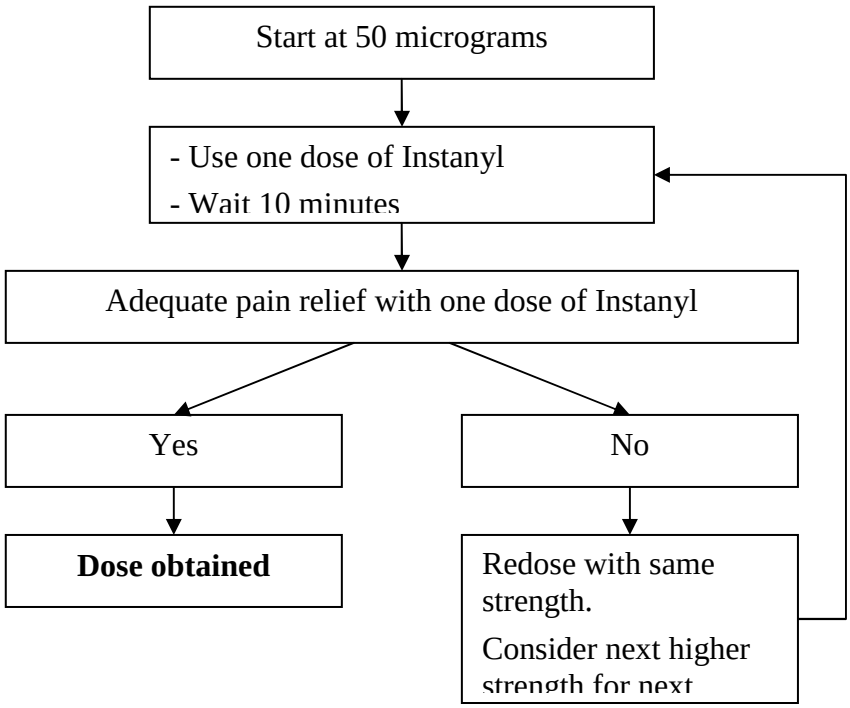
The dose of Instanyl for treatment of breakthrough pain was independent of the daily maintenance dose of opioid in the clinical studies (see section 5.1).

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

Patients should wait 4 hours before treating another breakthrough pain episode with Instanyl during both titration and maintenance therapy. On exceptional occasions where a new episode occurs earlier, patients can use Instanyl to treat it but they must wait at least 2 hours before doing so. Dose adjustment of the background opioid therapy following pain reassessment should be considered if the patient frequently presents with breakthrough pain episodes that are less than 4 hours apart or with more than four breakthrough pain episodes per 24 hours.

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 achieved, 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 the same strength can be undertaken 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 following pain reassessment should be considered if the patient frequently presents with breakthrough pain episodes that are less than 4 hours apart or 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 be replaced by other analgesics.

Treatment duration and goals
Before initiating treatment with Instanyl, 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). Instanyl should not be used longer than necessary.

Discontinuation of therapy
Instanyl 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 physician as gradual downward opioid titration is necessary in order to avoid the possibility of abrupt withdrawal effects.

Special populations

Elderly and Cachectic population
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. Limited data on pharmacokinetics are available for the use of fentanyl in cachectic (debilitated) patients. Cachectic patients may have reduced clearance of fentanyl. 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).

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

No data are available.

Method of administration

Instanyl is intended for nasal use only.

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.

Instanyl incorporates an electronic dose counter, and a lock out period between doses to minimise the risk of accidental overdose, misuse and abuse and to provide some reassurance to patients regarding these risks. Following administration of two doses within 60 minutes, Instanyl will lock for a period of 2 hours, from the first dose taken, before another dose can be administered.

Precautions to be taken before handling or administering the medicinal product
Before using Instanyl for the first time, the nasal spray must be primed. A priming sequence of 5 actuations of the nasal spray container is required, indicated by ‘P5’, ‘P4’, ‘P3’, ‘P2’ and ‘P1’ in the display.

If the product has not been used for a period of more than 7 days, the nasal spray must be primed again, by actuating once before the next dose is taken, this is indicated by ‘P’ in the display.

During the priming process product will be expelled. Therefore, the patient must be instructed that the priming should be conducted in a well ventilated area, pointing away from the patient and other people, and away from surfaces and objects that could come into contact with other people, particularly children.

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.

Treatment of acute pain other than breakthrough pain.

Patients being treated with medicinal products containing sodium oxybate.

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

Because of the risks, including fatal outcome, associated with accidental exposure, misuse, and abuse, patients and their carers must be advised to keep Instanyl in a safe and secure place, not accessible by others.

Respiratory depression

Clinically significant respiratory depression may occur with fentanyl, and patients must be observed for these effects. Patients with pain who receive chronic opioid therapy develop tolerance to respiratory depression and hence the risk of respiratory depression in these patients may be 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.

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

Concomitant use of Instanyl 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 Instanyl 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).

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 use may be associated with bradycardia. Fentanyl should therefore be used with caution in patients with previous or pre-existing bradyarrhythmias.
Opioids may cause hypotension, especially in patients with hypovolaemia. Instanyl should therefore be used with caution in patients with hypotension and/or hypovolaemia.

Serotonin syndrome

Caution is advised when Instanyl is coadministered with medicinal products that affect the serotoninergic neurotransmitter systems.

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

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 Instanyl should be discontinued.

Hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of fentanyl, the possibility of opioid-induced hyperalgesia should be considered. A fentanyl dose reduction or discontinuation of fentanyl treatment or treatment review may be indicated.

Nasal conditions

If the patient experiences 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.

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 Instanyl 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 Instanyl 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 Instanyl 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.

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).

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.

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).

Coadministration of fentanyl with a serotoninergic 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.

Instanyl is not recommended for use in patients who have received Monoamine Oxidase Inhibitors (MAOIs) within 14 days because severe and unpredictable potentiation by MAOIs 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 medicinal products that affect CYP3A4 activity. Coadministration with medicinal products 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 Instanyl with other central nervous system depressants, (including opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, tranquillisers, sedating antihistamines and alcohol), skeletal muscle relaxants and gabapentinoids (gabapentin and pregabalin) may produce additive depressant effects:
hypoventilation, hypotension, profound sedation, respiratory depression, coma or death may occur. Therefore, the use of any of these medicinal products concomitantly with Instanyl requires special patient care and observation.

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).

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 with 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 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. Instanyl should not be used in pregnancy unless clearly necessary and if the benefits outweigh the risks.

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 newborn (neonate). If Instanyl has been administered, an antidote for the child should be readily available.

Breast-feeding

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.

Fertility

There are no human data on fertility available. In animal studies, male and female fertility was impaired at sedative doses (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, opioid analgesics are known to impair the mental and/or physical ability required for driving or operating machinery. Patients undergoing treatment with Instanyl should be advised not to drive or operate machinery. Instanyl can cause somnolence, dizziness, visual disturbances or other adverse reactions which may affect their ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The following categories are used to rank the undesirable effects by frequency of occurrence: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 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.

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

System organ class	Common	Uncommon	Not known
Immune system disorders			Anaphylactic shock, anaphylactic reaction, hypersensitivity
Psychiatric disorders		Insomnia	Hallucination, delirium, drug dependence (addiction), drug abuse
Nervous system disorders	Somnolence, dizziness, headache	Sedation, myoclonus, paraesthesia, dysaesthesia, dysgeusia	Convulsions, loss of consciousness
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	Nasal septum perforation, dyspnoea
Gastrointestinal disorders	Nausea, vomiting	Constipation, stomatitis, dry mouth	Diarrhoea
Skin and subcutaneous tissue disorders	Hyperhidrosis	Pain of skin, pruritus	
General disorders and administration site conditions		Pyrexia	Fatigue, malaise peripheral oedema, withdrawal syndrome*, neonatal withdrawal syndrome, Drug tolerance
Injury, poisoning and procedural complications			Fall

*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 Instanyl 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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The signs and symptoms of fentanyl overdose are expected to be an extension of its pharmacological actions e.g. lethargy, coma and severe respiratory depression. Other signs may be hypothermia, decreased muscle tonus, bradycardia and hypotension. Signs of toxicity are deep sedation, ataxia, miosis, convulsions and respiratory depression, which is the main symptom. Toxic leukoencephalopathy has also been observed with fentanyl overdose. Cases of Cheyne Stokes respiration have been observed in case of fentanyl overdose, particularly in patients with history of heart failure.

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 appropiate parenteral fluid therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, opioids, ATC code: N02AB03

Mechanism of action

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

Clinical safety and efficacy

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 receiving low maintenance opioid dose tended to achieve effective pain relief with a lower strength of Instanyl compared to patients taking higher levels of maintenance opioid dose. This observation was most distinct for patients receiving Instanyl 50 micrograms.

In the clinical studies in cancer patients, the most frequent strengths used were 100 and 200 micrograms; however, patients should be titrated to the optimal dose of Instanyl for treating BTP in cancer (see section 4.2).

All three strengths of Instanyl demonstrated 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 ≥ 500 mg/day morphine or ≥ 200 micrograms/hour transdermal fentanyl is limited.

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

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.

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 approximately 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.

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).

Bioequivalence

A pharmacokinetic study has shown that Instanyl single-dose and multi-dose nasal spray are bioequivalent.

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.

In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 µg/kg/day, s.c.) and is consistent with the sedative effects of fentanyl in animal studies. Furthermore, studies in 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.

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

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

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 stored upright.

6.5 Nature and contents of container

A polypropylene (PP) nasal spray container consisting of a glass bottle (brown Type 1 glass) with metering pump. The nasal spray container has an electronic display, a dose counter, a lock-out mechanism and a child-resistant cap.

Available in the following presentations:

3.2 ml containing 1.60 mg fentanyl ensuring the delivery of 20 doses of 50 micrograms
4.3 ml containing 2.15 mg fentanyl ensuring the delivery of 30 doses of 50 micrograms
5.3 ml containing 2.65 mg fentanyl ensuring the delivery of 40 doses of 50 micrograms

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Because of the possible misuse of fentanyl and the possible amount of the solution left, any used and unused nasal spray must be returned systematically and appropriately disposed of in accordance with local requirements or returned to the pharmacy.

The nasal spray container contains batteries. The batteries cannot be replaced.

7 MARKETING AUTHORISATION HOLDER

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Via San Giuseppe Cottolengo 15
20143 Milan
Italy

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 59384/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

07/10/2024