ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 50 micrograms/dose nasal spray, solution
Instanyl 100 micrograms/dose nasal spray, solution
Instanyl 200 micrograms/dose nasal spray, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Instanyl 50 micrograms/dose nasal spray, solution
Each ml of solution contains fentanyl citrate equivalent to 500 micrograms fentanyl.
1 dose (100 microlitres) contains 50 micrograms fentanyl.

Instanyl 100 micrograms/dose nasal spray, solution
Each ml of solution contains fentanyl citrate equivalent to 1,000 micrograms fentanyl.
1 dose (100 microlitres) contains 100 micrograms fentanyl.

Instanyl 200 micrograms/dose nasal spray, solution
Each ml of solution contains fentanyl citrate equivalent to 2,000 micrograms fentanyl.
1 dose (100 microlitres) contains 200 micrograms fentanyl.

For the 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, 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).

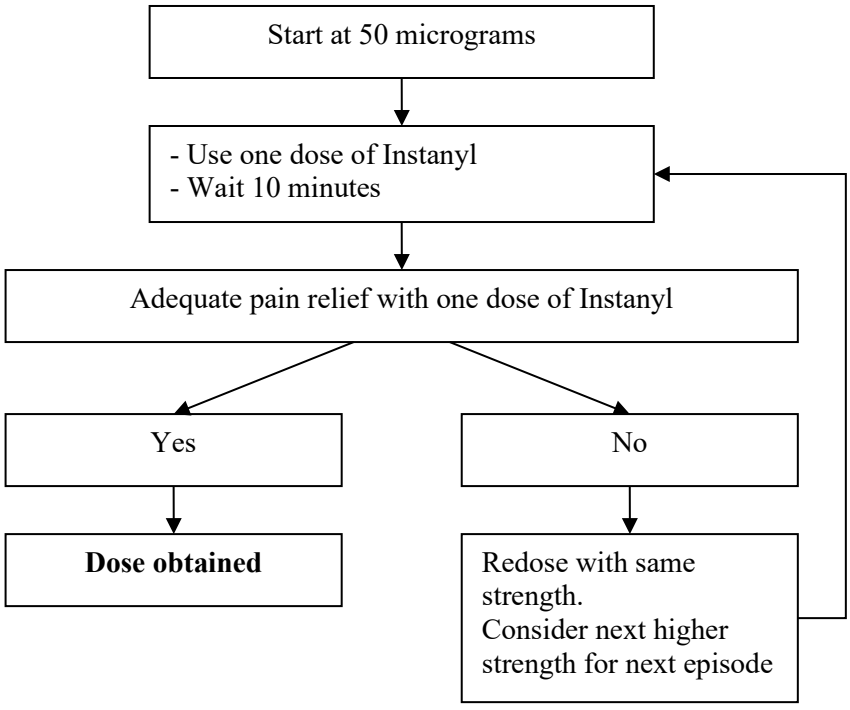
The dose of Instanyl for treatment of breakthrough pain was independent of the daily maintenance dose of opioid in the clinical studies (see section 5.1).

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 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.

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.

Precautions to be taken before handling or administering the medicinal product
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 for a period of more than 7 days, the nasal spray must be primed again by actuating once before the next dose is taken.

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

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.

Opioid use disorder (abuse 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 known to occur in the treatment of cancer related pain.

Repeated use of Instanyl may lead to Opioid Use Disorder (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).

Patients will require monitoring for signs of drug-seeking behaviour (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
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

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 appropriate 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

3 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:

Instanyl 50 micrograms/dose nasal spray, solution
1.8 ml containing 0.90 mg fentanyl ensuring the delivery of 10 doses of 50 micrograms
2.9 ml containing 1.45 mg fentanyl ensuring the delivery of 20 doses of 50 micrograms
5.0 ml containing 2.50 mg fentanyl ensuring the delivery of 40 doses of 50 micrograms

Instanyl 100 micrograms/dose nasal spray, solution
1.8 ml containing 1.80 mg fentanyl ensuring the delivery of 10 doses of 100 micrograms
2.9 ml containing 2.90 mg fentanyl ensuring the delivery of 20 doses of 100 micrograms
5.0 ml containing 5.00 mg fentanyl ensuring the delivery of 40 doses of 100 micrograms

Instanyl 200 micrograms/dose nasal spray, solution
1.8 ml containing 3.60 mg fentanyl ensuring the delivery of 10 doses of 200 micrograms
2.9 ml containing 5.80 mg fentanyl ensuring the delivery of 20 doses of 200 micrograms
5.0 ml containing 10.00 mg fentanyl ensuring the delivery of 40 doses of 200 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, the used and unused nasal spray solutions must be returned systematically and suitably in the child-resistant outer box and disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

Instanyl 50 micrograms/dose nasal spray, solution
EU/1/09/531/001-003

Instanyl 100 micrograms/dose nasal spray, solution
EU/1/09/531/004-006

Instanyl 200 micrograms/dose nasal spray, solution
EU/1/09/531/007-009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 July 2009
Date of latest renewal: 01 July 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 50 micrograms nasal spray, solution in single-dose container
Instanyl 100 micrograms nasal spray, solution in single-dose container
Instanyl 200 micrograms nasal spray, solution in single-dose container

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Instanyl 50 micrograms nasal spray, solution in single-dose container
Each single-dose container contains one dose (100 microlitres) of fentanyl citrate equivalent to 50 micrograms fentanyl.

Instanyl 100 micrograms nasal spray, solution in single-dose container
Each single-dose container contains one dose (100 microlitres) of fentanyl citrate equivalent to 100 micrograms fentanyl.

Instanyl 200 micrograms nasal spray, solution in single-dose container
Each single-dose container contains one dose (100 microlitres) of fentanyl citrate equivalent to 200 micrograms fentanyl.

For the 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, 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).

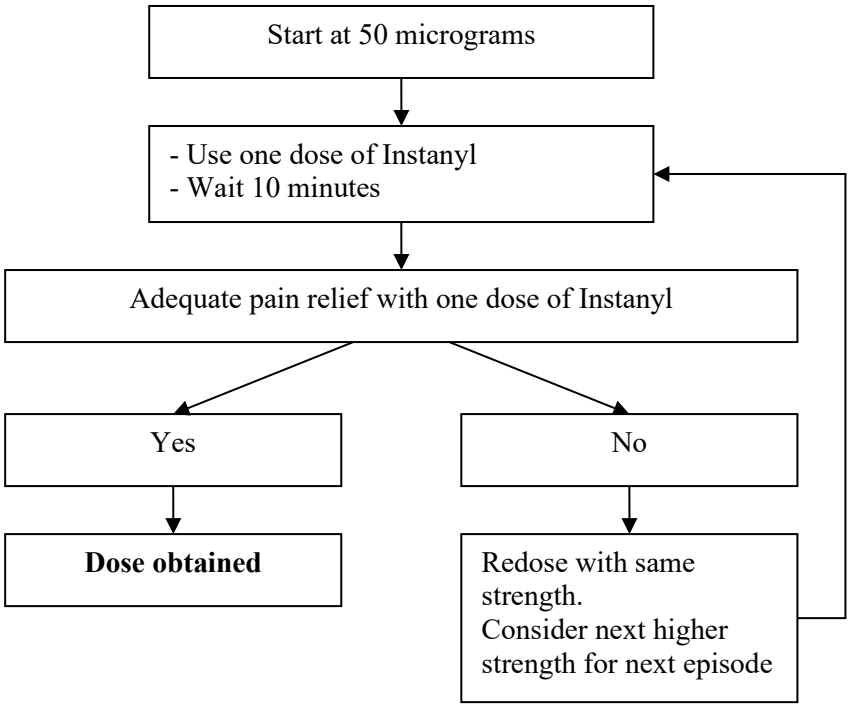
The dose of Instanyl for treatment of breakthrough pain was independent of the daily maintenance dose of opioid in the clinical studies (see section 5.1).

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 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.

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's head is in upright position when administrating Instanyl.

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

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.

Opioid use disorder (abuse 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 known to occur in the treatment of cancer related pain.

Repeated use of Instanyl may lead to Opioid Use Disorder (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).

Patients will require monitoring for signs of drug-seeking behaviour (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	

System organ class	Common	Uncommon	Not known
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
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

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 appropriate 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
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Instanyl 50 micrograms nasal spray, solution in single-dose container
23 months

Instanyl 100 micrograms nasal spray, solution in single-dose container
3 years

Instanyl 200 micrograms nasal spray, solution in single-dose container
42 months

6.4 Special precautions for storage

Store below 30 °C.
Keep the blister in the outer carton. Keep stored upright.

6.5 Nature and contents of container

Single-dose container consisting of a vial (clear type I glass) integrated in a polypropylene spray container, packed in child-resistant blister.

Pack sizes: 2, 6, 8 and 10 single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Each single-dose container contains only one dose. The single-dose container should not be tested before use.

Because of the possible misuse of fentanyl unused nasal spray single-dose containers must be returned systematically and suitably in the child-resistant blister and disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

Instanyl 50 micrograms nasal spray, solution in single-dose container
EU/1/09/531/010-013

Instanyl 100 micrograms nasal spray, solution in single-dose container
EU/1/09/531/014-017

Instanyl 200 micrograms nasal spray, solution in single-dose container
EU/1/09/531/018-021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 July 2009
Date of latest renewal: 01 July 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 50 micrograms/dose nasal spray, solution
Instanyl 100 micrograms/dose nasal spray, solution
Instanyl 200 micrograms/dose nasal spray, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Instanyl 50 micrograms/dose nasal spray, solution
Each ml of solution contains fentanyl citrate equivalent to 500 micrograms fentanyl.
1 dose (100 microlitres) contains 50 micrograms fentanyl.

Instanyl 100 micrograms/dose nasal spray, solution
Each ml of solution contains fentanyl citrate equivalent to 1,000 micrograms fentanyl.
1 dose (100 microlitres) contains 100 micrograms fentanyl.

Instanyl 200 micrograms/dose nasal spray, solution
Each ml of solution contains fentanyl citrate equivalent to 2,000 micrograms fentanyl.
1 dose (100 microlitres) contains 200 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).

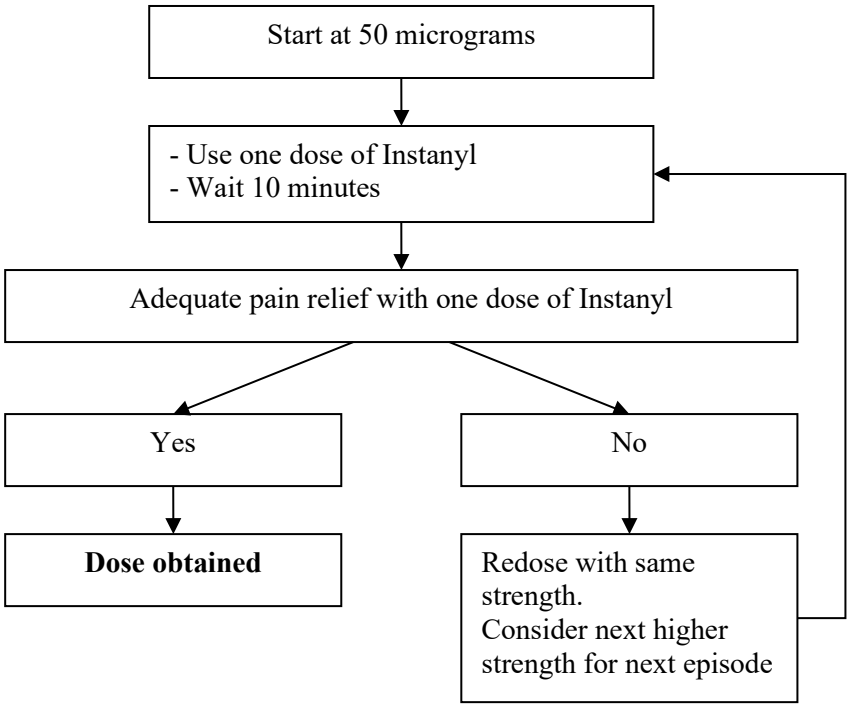
The dose of Instanyl for treatment of breakthrough pain was independent of the daily maintenance dose of opioid in the clinical studies (see section 5.1).

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.

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

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.

Opioid use disorder (abuse 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 known to occur in the treatment of cancer related pain.

Repeated use of Instanyl may lead to Opioid Use Disorder (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).

Patients will require monitoring for signs of drug-seeking behaviour (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
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

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 appropriate 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:

Instanyl 50 micrograms/dose nasal spray, solution. DoseGuard
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

Instanyl 100 micrograms/dose nasal spray, solution. DoseGuard
3.2 ml containing 3.20 mg fentanyl ensuring the delivery of 20 doses of 100 micrograms
4.3 ml containing 4.30 mg fentanyl ensuring the delivery of 30 doses of 100 micrograms
5.3 ml containing 5.30 mg fentanyl ensuring the delivery of 40 doses of 100 micrograms

Instanyl 200 micrograms/dose nasal spray, solution. DoseGuard
3.2 ml containing 6.40 mg fentanyl ensuring the delivery of 20 doses of 200 micrograms
4.3 ml containing 8.60 mg fentanyl ensuring the delivery of 30 doses of 200 micrograms
5.3 ml containing 10.60 mg fentanyl ensuring the delivery of 40 doses of 200 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

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

Instanyl 50 micrograms/dose nasal spray, solution
EU/1/09/531/023-025

Instanyl 100 micrograms/dose nasal spray, solution
EU/1/09/531/027-029

Instanyl 200 micrograms/dose nasal spray, solution
EU/1/09/531/031-033

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 July 2009
Date of latest renewal: 01 July 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Curida AS
Solbærvegen 5
NO-2409 Elverum
Norway

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to special and restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of (PSURs) for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of the multi-dose and single-dose product in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, all physicians, pharmacists and patients expected to prescribe/dispense/use Instanyl are provided with educational material regarding the correct and safe use of the product.

Educational material for the patients will contain the following:

- Patient information leaflet
- A patient/carer guide
- Enhanced digital access information

Patient/carer guide

- Instanyl to be used only if patients/carers have received the proper information regarding the use of the device and the safety precautions.
- Explanation of the indication.
- Explanation of Breakthrough Pain, Patients perception of pain and its treatment.
- Explanation of off label use, misuse, abuse, medication error, overdose, death and addiction.
- Definition of a patient at risk of overdose, abuse, misuse, dependence and addiction in order to inform prescribers/ pharmacists.
- Not to use Instanyl to treat any other short-term pain or pain status and/or for treatment of more than 4 breakthrough cancer pain episodes a day (section 3 PIL).
- Formulations are not interchangeable.
- Need for reference to prescriber/ pharmacists in case of any question.

How to use Instanyl

- Instructions for use of the nasal spray device.
- Instructions for opening and closing of the child-resistant box (for the multi-dose nasal spray), the child resistant cap (for the multi-dose nasal spray DoseGuard) or blister (for the single-dose nasal spray).
- For the multi-dose nasal spray and the multi-dose nasal spray DoseGuard: information about the dose counting scheme.
- For the multi-dose nasal spray or the multi-dose nasal spray DoseGuard, all unused devices or empty containers should be returned systematically according to the local regulation.
- For the single-dose nasal spray all unused devices should be returned systematically according to the local regulation.
- Advice on how to find digital information and instructional videos.

Educational material for the physicians will contain the following:

- The Summary of Product Characteristics and Package leaflet
- Guide for Physicians
- Prescribing checklist
- Enhanced digital access information

Guide for Physicians

- Treatment to be initiated/supervised by a physician experienced in the management of opioid therapy in cancer patients, in particularly regarding transition from hospital to home.
- Explanation of off label uses (i.e: indication, age) and the serious risks of misuse, abuse, medication error, overdose, death and addiction.
- Need for communication to patients/carers:
    - Treatment management and risks of abuse and dependence.
    - Need of periodic review by prescribers.
    - Encouragement for reporting of any issue with the management of the treatment.
- Identification *and* monitoring of patients at risk of abuse and misuse before and during the treatment to identify the key features of opioid use disorder (OUD): distinguishing features of opioid related side effects and opioid use disorder.
- Importance of reporting off-label use, misuse, abuse, addiction and overdose.
- Need for tailoring therapy if OUD is recognized.

The prescribers of Instanyl nasal spray must critically select the patients and counsel them on:

- Instructions for use of the nasal spray device.
- Instructions for opening and closing of the child-resistant box (for the multi-dose nasal spray), the child resistant cap (for the multi-dose nasal spray DoseGuard) or blister (for the single-dose nasal spray).

- Information about the dose counting scheme included in the labelling and the educational material for the multi-dose nasal spray.
- That for the multi-dose nasal spray and multi-dose nasal spray (DoseGuard) all unused devices or empty containers should be returned systematically according to the local regulation.
- That for the single-dose nasal spray all unused devices should be returned systematically according to the local regulation.
- Never sharing their medication or diverting the purpose of its use.
- Updated label information including hyperalgesia, use in pregnancy, drug interactions such as with benzodiazepines, iatrogenic addiction, withdrawal and dependence.
- The prescriber must make use of the checklist for prescribers.

Prescribing checklist

Required actions before prescribing Instanyl. Please complete all of the following before prescribing Instanyl single-dose or multi-dose nasal spray or multi-dose nasal spray DoseGuard:

- Ensure that all elements of the approved indication are fulfilled.
- Provide instructions for using the nasal spray to patient and/or carer.
- For single-dose nasal spray only: Advise the patient on the single use nature of the nasal spray (each nasal spray contains only one dose and the plunger should only be pressed once the spray tip is inserted into the nose, it should not be tested before use).
- Ensure the patient reads the package leaflet inside the Instanyl box.
- Supply the patient with the Instanyl patient brochure provided covering the below:
    - Cancer and Pain.
    - Instanyl. What is it? How do I use it?
    - Instanyl. Risks of misuse.
- Advise patient on how to open the child-resistant blister (for single-use Instanyl), the child-resistant box (for multi-dose Instanyl) or the child resistant cap (for multi-dose Instanyl DoseGuard) as described in the patient brochure 'Instanyl. What is it? How do I use it?'
- Explain the risks of using more than the recommended amount of Instanyl.
- Explain the use of the dose monitoring cards.
- Advise the patient on the signs of fentanyl overdose and the need for immediate medical assistance.
- Explain secure storage and the need to keep out of the reach and sight of children.
- Explain correct disposal of Instanyl single-dose or multi-dose nasal spray or multi-dose nasal spray DoseGuard.
- Remind the patient and/or caregiver that they should ask their doctor if they have any questions or concerns about how to use Instanyl or about the associated risks of misuse and abuse.

Educational material for the pharmacists will contain the following:

- The Summary of Product Characteristics and Package Leaflet
- Guide for Pharmacists
- Dispensing checklist
- Enhanced digital access information

Guide for Pharmacists

- Treatment to be initiated/supervised by a physician experienced in the management of opioid therapy in cancer patients, in particularly regarding transition from hospital to home.
- Explanation of off label uses (i.e: indication, age) and the serious risks of misuse, abuse, medication error, overdose, death and addiction.
- Need for communication to patients/carers:
    - Treatment management and risks of abuse and dependence.
    - Need of periodic review by prescribers.
    - Encouragement for reporting of any issue with the management of the treatment.

- Monitoring of patients at risk of abuse and misuse during the treatment to identify the key features of opioid use disorder (OUD): distinguishing features of opioid related side effects and opioid use disorder.
- Importance of reporting off-label use, misuse, abuse, addiction and overdose.
- Physician should be contacted if OUD recognized.
- Pharmacist must be familiar with the educational materials before is given to the patient.
- Instanyl nasal spray not interchangeable with other Fentanyl products.

The pharmacists dispensing Instanyl nasal spray must counsel the patients on:
- Instructions for use of the nasal spray device.
- Instructions for opening and closing of the child-resistant box (for the multi-dose nasal spray), the child resistant cap (for the multi-dose nasal spray DoseGuard) or blister (for the single-dose nasal spray).
- Information about dose counting scheme included in the labelling and the educational material for the multi-dose nasal spray or multi-dose nasal spray DoseGuard.
- The pharmacist must inform the patients that in order to prevent theft and misuse of Instanyl nasal spray they have to keep it in a safe place to avoid misuse and diversion.
- For the multi-dose nasal spray or multi-dose nasal spray DoseGuard, all unused devices or empty containers should be returned systematically according to the local regulation.
- For the single-dose nasal spray all unused devices should be returned systematically according to the local regulation.
- The pharmacist must make use of the checklist for pharmacists.

Dispensing checklist

Required actions before supplying Instanyl. Please complete the following before Instanyl single-dose, multi-dose nasal spray or multi-dose nasal spray DoseGuard is supplied:
- Ensure that all elements of the approved indication are fulfilled.
- Provide instructions for using the nasal spray to patient and/or carer.
- For single-dose nasal spray only: Advise the patient on the single use nature of the nasal spray (each nasal spray contains only one dose and the plunger should only be pressed once the spray tip is inserted into the nose, it should not be tested before use).
- Ensure the patient reads the package leaflet inside the Instanyl single-dose, multi-dose or multi-dose DoseGuard carton box.
- Supply the patient with the Instanyl patient brochure provided covering the below:
    - Cancer and Pain.
    - Instanyl. What is it? How do I use it?
    - Instanyl. Risks of misuse.
- Advise patient on how to open the child-resistant blister (for single-use Instanyl), the child-resistant box (for multi-dose Instanyl) or the child resistant cap (for multi-dose Instanyl DoseGuard) as described in the patient brochure ‘Instanyl. What is it? How do I use it?
- Explain the risks of using more than the recommended amount of Instanyl.
- Explain the use of the dose monitoring cards.
- Advise the patient on the signs of fentanyl overdose and the need for immediate medical assistance.
- Explain secure storage and the need to keep out of the reach and sight of children.
- Explain correct disposal of Instanyl single-dose or multi-dose nasal spray or multi-dose nasal spray DoseGuard.

Digital access to educational material

Digital access to all education material updates will be enhanced. Prescriber (physician), pharmacist and patient educational materials will be accessible via a website, and will be available for download. Instructional videos on use of the product will be also be accessible via a website. Details of enhanced digital accessibility will be discussed with National Competent Authorities and EMA upon approval of this RMP, as appropriate.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CHILD-RESISTANT OUTER BOX (Multi dose)

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 50 micrograms/dose nasal spray, solution
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains fentanyl citrate equivalent to 500 micrograms fentanyl. 1 dose of 100 microlitres equals 50 micrograms fentanyl.

3. LIST OF EXCIPIENTS

Also contains: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, purified water

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution 1.8 ml
Nasal spray, solution 2.9 ml
Nasal spray, solution 5.0 ml

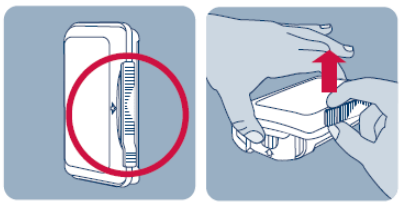
1.8 ml - 10 doses
2.9 ml - 20 doses
5.0 ml - 40 doses

5. METHOD AND ROUTE(S) OF ADMINISTRATION

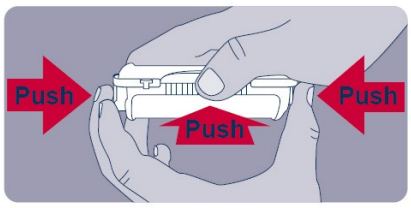
Read the package leaflet before use.
For nasal use

Instruction for opening and closing the box:

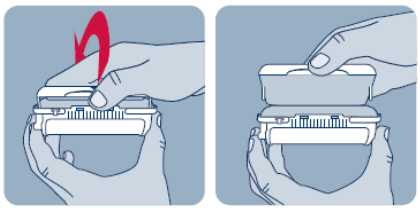
- Pick up the box



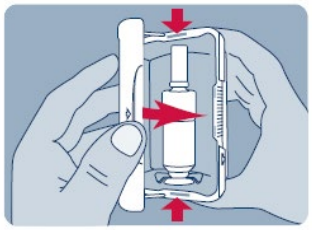
- Remove the tamper evidence the first time the box is opened
- Place a thumb and a middle finger on the side tabs



- Press side tabs inwards using your thumb and middle finger
- At the same time, place your other thumb on the front pressure pad and also press inwards
- Continue to apply pressure on all three points

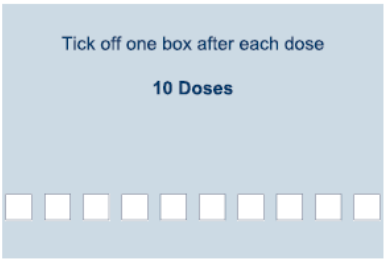


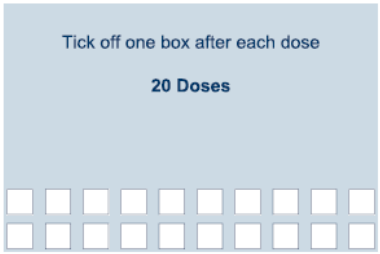
- Pull lid to open
- After use of Instanyl the nasal spray must be placed in the inner tray again and the box closed

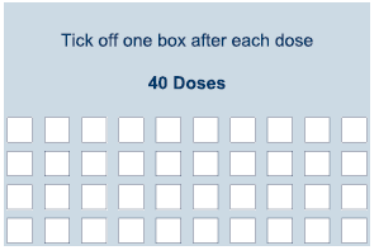


- When closing the box, make sure that the side tabs locate back into the slots
- Press down firmly until the side tabs click into position

Tick off one box after each dose
[*Tick boxes of 10, 20 or 40 tick boxes*]







Always place the nasal spray in the child-resistant box after use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only used for chronic cancer pain while taking other opioids.
Accidental use can be fatal.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Keep the bottle stored upright.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Refer to the package leaflet for information on disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/531/001
EU/1/09/531/002
EU/1/09/531/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Instanyl 50

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / BOTTLE (Multi dose)

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

Instanyl 50 micrograms/dose nasal spray
fentanyl

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.8 ml - 10 doses
2.9 ml - 20 doses
5.0 ml - 40 doses

6. OTHER

Accidental use can be fatal.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CHILD-RESISTANT OUTER BOX (Multi dose)

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 100 micrograms/dose nasal spray, solution
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains fentanyl citrate equivalent to 1,000 micrograms fentanyl. 1 dose of 100 microlitres equals 100 micrograms fentanyl.

3. LIST OF EXCIPIENTS

Also contains: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, purified water

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution 1.8 ml
Nasal spray, solution 2.9 ml
Nasal spray, solution 5.0 ml

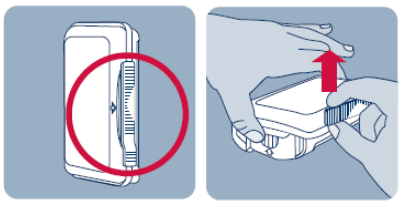
1.8 ml - 10 doses
2.9 ml - 20 doses
5.0 ml - 40 doses

5. METHOD AND ROUTE(S) OF ADMINISTRATION

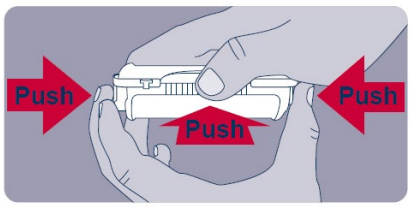
Read the package leaflet before use.
For nasal use

Instruction for opening and closing the box:

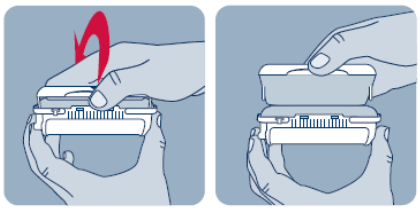
- Pick up the box



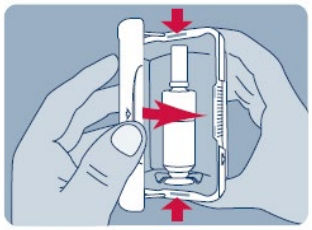
- Remove the tamper evidence the first time the box is opened
- Place a thumb and a middle finger on the side tabs



- Press side tabs inwards using your thumb and middle finger
- At the same time, place your other thumb on the front pressure pad and also press inwards
- Continue to apply pressure on all three points

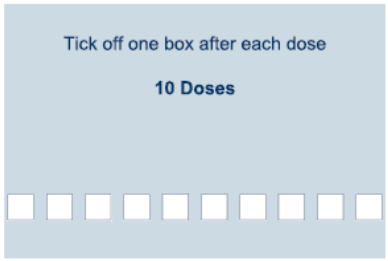


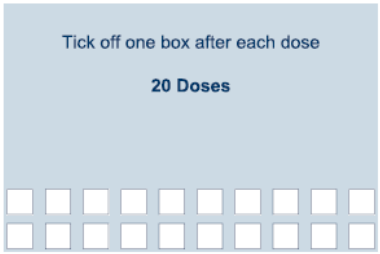
- Pull lid to open
- After use of Instanyl the nasal spray must be placed in the inner tray again and the box closed

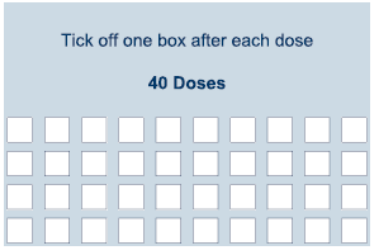


- When closing the box, make sure that the side tabs locate back into the slots
- Press down firmly until the side tabs click into position

Tick off one box after each dose
[*Tick boxes of 10, 20 or 40 tick boxes*]







Always place the nasal spray in the child-resistant box after use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only used for chronic cancer pain while taking other opioids.
Accidental use can be fatal.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Keep the bottle stored upright.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Refer to the package leaflet for information on disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/531/004
EU/1/09/531/005
EU/1/09/531/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Instanyl 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / BOTTLE (Multi dose)

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

Instanyl 100 micrograms/dose nasal spray
fentanyl

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.8 ml - 10 doses
2.9 ml - 20 doses
5.0 ml - 40 doses

6. OTHER

Accidental use can be fatal.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CHILD-RESISTANT OUTER BOX (Multi dose)

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 200 micrograms/dose nasal spray, solution
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains fentanyl citrate equivalent to 2,000 micrograms fentanyl. 1 dose of 100 microlitres equals 200 micrograms fentanyl.

3. LIST OF EXCIPIENTS

Also contains: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, purified water

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution 1.8 ml
Nasal spray, solution 2.9 ml
Nasal spray, solution 5.0 ml

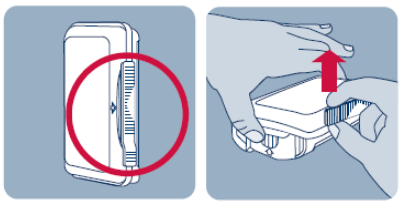
1.8 ml - 10 doses
2.9 ml - 20 doses
5.0 ml - 40 doses

5. METHOD AND ROUTE(S) OF ADMINISTRATION

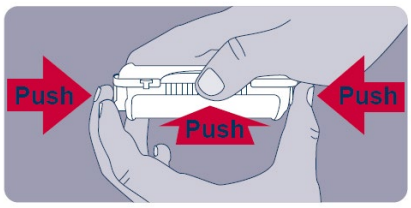
Read the package leaflet before use.
For nasal use

Instruction for opening and closing the box:

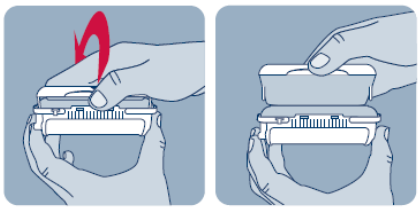
- Pick up the box



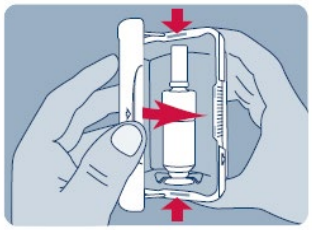
- Remove the tamper evidence the first time the box is opened
- Place a thumb and a middle finger on the side tabs



- Press side tabs inwards using your thumb and middle finger
- At the same time, place your other thumb on the front pressure pad and also press inwards
- Continue to apply pressure on all three points

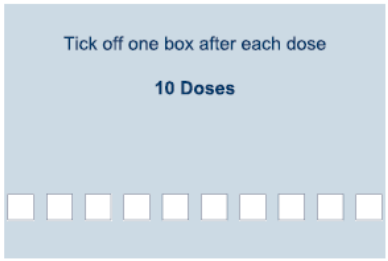


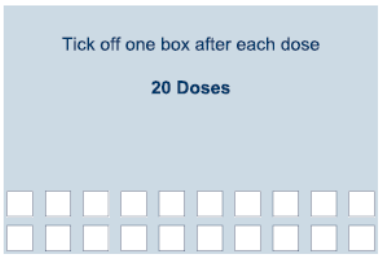
- Pull lid to open
- After use of Instanyl the nasal spray must be placed in the inner tray again and the box closed

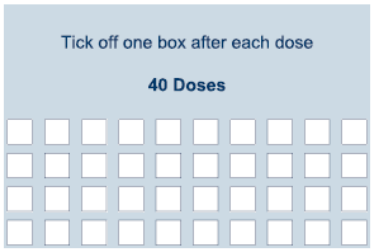


- When closing the box, make sure that the side tabs locate back into the slots
- Press down firmly until the side tabs click into position

Tick off one box after each dose
[*Tick boxes of 10, 20 or 40 tick boxes*]







Always place the nasal spray in the child-resistant box after use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only used for chronic cancer pain while taking other opioids.
Accidental use can be fatal.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Keep the bottle stored upright.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Refer to the package leaflet for information on disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/531/007
EU/1/09/531/008
EU/1/09/531/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Instanyl 200

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / BOTTLE (Multi-dose)

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

Instanyl 200 micrograms/dose nasal spray
fentanyl

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.8 ml - 10 doses
2.9 ml - 20 doses
5.0 ml - 40 doses

6. OTHER

Accidental use can be fatal.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX - CARTON (Single Dose)

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 50 micrograms nasal spray, solution in single-dose container
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (100 microlitres) contains fentanyl citrate equivalent to 50 micrograms (mcg) fentanyl

3. LIST OF EXCIPIENTS

Also contains: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution

2 single-dose containers
6 single-dose containers
8 single-dose containers
10 single-dose containers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For nasal use
The spray container contains only one dose. Do not test before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only used for chronic cancer pain while taking other opioids.
Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Keep the blister in the outer carton. Keep stored upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Refer to the package leaflet for information on disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/531/010
EU/1/09/531/011
EU/1/09/531/012
EU/1/09/531/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Instanyl 50, single-dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

INTERMEDIATE CHILD-RESISTANT BLISTER (Single dose)

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 50 micrograms nasal spray
fentanyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Nasal use
1 dose
Keep out of the sight and reach of children.
Accidental use can be fatal.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / SINGLE-DOSE NASAL SPRAY

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

Instanyl 50 mcg nasal spray
fentanyl
Nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX - CARTON (Single dose)

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 100 micrograms nasal spray, solution in single-dose container
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (100 microlitres) contains fentanyl citrate equivalent to 100 micrograms (mcg) fentanyl

3. LIST OF EXCIPIENTS

Also contains: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution

2 single-dose containers
6 single-dose containers
8 single-dose containers
10 single-dose containers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For nasal use
The spray container contains only one dose. Do not test before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only used for chronic cancer pain while taking other opioids.
Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Keep the blister in the outer carton. Keep stored upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Refer to the package leaflet for information on disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/531/014
EU/1/09/531/015
EU/1/09/531/016
EU/1/09/531/017

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Instanyl 100, single-dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

INTERMEDIATE CHILD-RESISTANT BLISTER (Single dose)

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 100 micrograms nasal spray
fentanyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Nasal use
1 dose
Keep out of the sight and reach of children.
Accidental use can be fatal.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / SINGLE-DOSE NASAL SPRAY

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

Instanyl 100 mcg nasal spray
fentanyl
Nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX - CARTON (Single dose)

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 200 micrograms nasal spray, solution in single-dose container
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (100 microlitres) contains fentanyl citrate equivalent to 200 micrograms (mcg) fentanyl

3. LIST OF EXCIPIENTS

Also contains: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, solution

2 single-dose containers
6 single-dose containers
8 single-dose containers
10 single-dose containers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For nasal use
The spray container contains only one dose. Do not test before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only used for chronic cancer pain while taking other opioids.
Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Keep the blister in the outer carton. Keep stored upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Refer to the package leaflet for information on disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/531/018
EU/1/09/531/019
EU/1/09/531/020
EU/1/09/531/021

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Instanyl 200, single-dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

INTERMEDIATE CHILD-RESISTANT BLISTER PACK (Single dose)

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 200 micrograms nasal spray
fentanyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Nasal use
1 dose
Keep out of the sight and reach of children.
Accidental use can be fatal.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / SINGLE-DOSE NASAL SPRAY

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

Instanyl 200 mcg nasal spray
fentanyl
Nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX – CARTON: DoseGuard

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 50 micrograms/dose nasal spray, solution
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains fentanyl citrate equivalent to 500 micrograms fentanyl. 1 dose of 100 microlitres equals 50 micrograms fentanyl.

3. LIST OF EXCIPIENTS

Also contains: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, purified water

4. PHARMACEUTICAL FORM AND CONTENTS

DoseGuard
Nasal spray, solution 3.2 ml
Nasal spray, solution 4.3 ml
Nasal spray, solution 5.3 ml

20 doses (3.2 ml)
30 doses (4.3 ml)
40 doses (5.3 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For nasal use

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

Keep out of the sight and reach of children.
Always close after use by putting the child-resistant cap back on to the nasal spray.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only used for chronic cancer pain while taking other opioids.
Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Do not freeze.
Keep stored upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Refer to the package leaflet for information on disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/531/023
EU/1/09/531/024
EU/1/09/531/025

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Instanyl 50

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / NASAL SPRAY DoseGuard

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

Instanyl 50 micrograms/dose nasal spray
fentanyl
Nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 doses (3.2 ml)
30 doses (4.3 ml)
40 doses (5.3 ml)

6. OTHER

Keep out of the sight and reach of children
Always close after use by putting the child-resistant cap back on to the nasal spray.
Accidental use can be fatal.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX – CARTON DoseGuard

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 100 micrograms/dose nasal spray, solution
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains fentanyl citrate equivalent to 1,000 micrograms fentanyl. 1 dose of 100 microlitres equals 100 micrograms fentanyl.

3. LIST OF EXCIPIENTS

Also contains: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, purified water

4. PHARMACEUTICAL FORM AND CONTENTS

DoseGuard
Nasal spray, solution 3.2 ml
Nasal spray, solution 4.3 ml
Nasal spray, solution 5.3 ml

20 doses (3.2 ml)
30 doses (4.3 ml)
40 doses (5.3 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For nasal use

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

Keep out of the sight and reach of children.
Always close after use by putting the child-resistant cap back on to the nasal spray.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only used for chronic cancer pain while taking other opioids.
Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Do not freeze.
Keep stored upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Refer to the package leaflet for information on disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/531/027
EU/1/09/531/028
EU/1/09/531/029

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Instanyl 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / NASAL SPRAY DoseGuard

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

Instanyl 100 micrograms/dose nasal spray
fentanyl
Nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 doses (3.2 ml)
30 doses (4.3 ml)
40 doses (5.3 ml)

6. OTHER

Keep out of the sight and reach of children
Always close after use by putting the child-resistant cap back on to the nasal spray.
Accidental use can be fatal.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX - CARTON DoseGuard

1. NAME OF THE MEDICINAL PRODUCT

Instanyl 200 micrograms/dose nasal spray, solution
fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains fentanyl citrate equivalent to 2,000 micrograms fentanyl. 1 dose of 100 microlitres equals 200 micrograms fentanyl.

3. LIST OF EXCIPIENTS

Also contains: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, purified water

4. PHARMACEUTICAL FORM AND CONTENTS

DoseGuard
Nasal spray, solution 3.2 ml
Nasal spray, solution 4.3 ml
Nasal spray, solution 5.3 ml

20 doses (3.2 ml)
30 doses (4.3 ml)
40 doses (5.3 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For nasal use

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

Keep out of the sight and reach of children.
Always close after use by putting the child-resistant cap back on to the nasal spray.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only used for chronic cancer pain while taking other opioids.
Accidental use can cause serious harm and be fatal.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Do not freeze.
Keep stored upright.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Refer to the package leaflet for information on disposal

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/531/031
EU/1/09/531/032
EU/1/09/531/033

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Instanyl 200

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / NASAL SPRAY DoseGuard

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

Instanyl 200 micrograms/dose nasal spray
fentanyl
Nasal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 doses (3.2 ml)
30 doses (4.3 ml)
40 doses (5.3 ml)

6. OTHER

Keep out of the sight and reach of children
Always close after use by putting the child-resistant cap back on to the nasal spray.
Accidental use can be fatal.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Instanyl 50 micrograms/dose nasal spray, solution
Instanyl 100 micrograms/dose nasal spray, solution
Instanyl 200 micrograms/dose nasal spray, solution
fentanyl

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Instanyl is and what it is used for

Instanyl contains the active substance fentanyl and belongs to a group of strong painkillers called opioids. Opioids act by blocking the pain signals to the brain.
Instanyl acts rapidly and is used for relieving breakthrough pain in adult cancer patients already treated with opioids for their usual pain. Breakthrough pain is an additional sudden pain that occurs despite you having taken your usual opioid pain relieving medicines.

2. What you need to know before you use Instanyl

Do not use Instanyl
- if you are allergic to fentanyl or any of the other ingredients of this medicine (listed in section 6).
- if you are not regularly using a prescribed opioid medicine (e.g codeine, fentanyl, hydromorphone, morphine, oxycodone, pethidine), every day on a regular schedule, for at least a week, to control your persistent pain. If you have not been using these medicines you must not use Instanyl, because it may increase the risk that breathing could become dangerously slow and/or shallow, or even stop.
- If you are taking a medicine which contains sodium oxybate.
- if you suffer from short-term pain other than breakthrough pain.
- if you have serious difficulties breathing or suffer from a serious obstructive lung disease.
- if you have previously received facial radiotherapy.
- if you suffer from recurrent episodes of nose bleeding.

Warnings and precautions
Talk to your doctor or pharmacist before using Instanyl, especially:
- if you suffer from a long-term obstructive lung disease, your breathing may be impaired by Instanyl.
- if you have problems with your heart especially slow heart rate, low blood pressure or low blood volume.

- if you have problems with your liver or kidneys.
- if you have problems with your brain function, e.g. due to a brain tumour, a head injury or increased intracranial pressure.
- if you have ever developed adrenal insufficiency or lack of sex hormones (androgen deficiency) with opioid use.
- if you or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
- if you are a smoker.
- if you have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.
- if you take sedative medicines such as benzodiazepines or related drugs (please also refer to the section 'Other medicines and Instanyl').
- if you take antidepressants or antipsychotics (please also refer to the section 'Other medicines and Instanyl').
- if you take medicines called partial agonist/antagonists e.g. buprenorphine, nalbuphine and pentazocine (medicines for treatment of pain) as you may experience symptoms of withdrawal syndrome. Please refer to the section 'Other medicines and Instanyl' for more information.
- if you use other nasal spray products, e.g. for common cold or allergy.

Sleep-related breathing disorders
Instanyl can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

If you experience difficulties breathing while being treated with Instanyl, it is very important that you contact your doctor or hospital immediately.

Consult your doctor while using Instanyl, if:
- you experience pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of your medicine as prescribed by your doctor.
- you experience a combination of the following symptoms: nausea, vomiting, anorexia, fatigue, weakness, dizziness and low blood pressure. Together these symptoms may be a sign of a potentially life-threatening condition called adrenal insufficiency, a condition in which the adrenal glands do not produce enough hormones.

If you experience recurrent nose bleeding or nasal discomfort whilst being treated with Instanyl, you must contact your doctor, who will consider alternative treatment for your breakthrough pain.

Repeated use of Instanyl may lead to dependence and abuse which may result in life-threatening overdose. If you think you are becoming dependent on Instanyl, it is important that you consult your doctor.

Children and adolescents
Instanyl should not be used in children and adolescents under 18 years of age.

Other medicines and Instanyl
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Instanyl may affect or be affected by other medicines.
Special care should be taken if you are treated with any of the following medicines:
- Other medicines for pain and some painkillers for nerve pain (such as gabapentin and pregabalin).
- any medicines which might normally make you sleepy (have a sedative effect) such as sleeping pills, sedative medicines such as benzodiazepines or related medicines, medicines to treat

anxiety, antihistamines, or tranquillisers, skeletal muscle relaxants and gabapentinoids (gabapentin and pregabalin). The use of such other medicines at the same time as Instanyl, may cause risk of drowsiness, deep sedation and affect your ability to breathe (respiratory depression), which may lead to coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.
However if your doctor does prescribe Instanyl together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.
Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

- any medicines that might have an effect on the way in which your body breaks down Instanyl, such as:
  - ritonavir, nelfinavir, amprenavir, and fosamprenavir (medicines that help control HIV infection);
  - CYP3A4 inhibitors such as ketoconazole, itraconazole, or fluconazole (used for treatment of fungal infections);
  - troleandomycin, clarithromycin, or erythromycin (medicines for treatment of bacterial infections);
  - aprepitant (used to treat severe nausea);
  - diltiazem and verapamil (medicines for treatment of high blood pressure or heart diseases).
- medicines called Monoamine Oxidase Inhibitors (MAOI) used for severe depression, even if you have been treated with one in the past 2 weeks.
- The risk of side effects increases if you are taking medicines such as certain antidepressants or antipsychotics. Instanyl may interact with these medicines and you may experience mental status changes (e.g. agitation, hallucinations, coma), and other effects such as body temperature above 38 °C, increase in heart rate, unstable blood pressure, and exaggeration of reflexes, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Your doctor will tell you whether Instanyl is suitable for you.
- medicines called partial agonist/antagonists e.g. buprenorphine, nalbuphine and pentazocine (medicines for treatment of pain). You could experience symptoms of withdrawal syndrome (nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating).
- other medicines taken via the nose, especially oxymetazoline, xylometazoline and similar medicines, which are used for relief of nose congestions.

Instanyl with food, drink and alcohol
Do not drink alcohol whilst being treated with Instanyl, as it can increase the risk of experiencing dangerous side effects.

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

Instanyl should not be used during pregnancy unless you have discussed this with your doctor.

Instanyl should not be used during childbirth because fentanyl may cause serious breathing problems in the new-born child.

Fentanyl can get into breast milk and may cause side effects in the breast-fed infant. Do not use Instanyl if you are breast-feeding. You should not start breast-feeding until at least 5 days after the last dose of Instanyl.

Driving and using machines
You should not drive or use machinery whilst being treated with Instanyl. Instanyl can cause dizziness, drowsiness and visual disturbances, which may affect your ability to drive or use machines.

3. How to use Instanyl

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

The dose of Instanyl is independent of your usual cancer pain treatment.

When you first start using Instanyl, your doctor will work with you to find the dose that will relieve your breakthrough pain.
The initial dose is one puff of 50 micrograms in one nostril each time you have an episode of breakthrough pain. During the determination of your right dose, your doctor may instruct you to change to a higher dose.

If your breakthrough pain is not relieved after 10 minutes, you may use only one puff more for this episode.
Generally you should wait 4 hours before treating another episode of breakthrough pain. On exceptional occasions where a new episode occurs earlier, you can use Instanyl to treat it but you must wait at least 2 hours before doing so. If you regularly have breakthrough pain episodes that are less than 4 hours apart, contact your doctor as your usual cancer pain treatment may have to be changed.

You can use Instanyl to treat up to four episodes of breakthrough pain per day.

If you experience more than four episodes of breakthrough pain per day, contact your doctor, as your usual cancer pain treatment may have to be changed.

In order to keep track of the number of doses of Instanyl used, you should use the tick-boxes in the booklet placed on top of the child-resistant outer box.

Do not change the dose of Instanyl or your other pain medicines on your own. Change in dose must be done together with your doctor.

Instanyl is for nasal use.

Please read the instruction for use at the end of this leaflet to learn how to use Instanyl.

If you use more Instanyl than you should or if you think someone has accidentally used Instanyl
You should contact your doctor, hospital or emergency room for assessment of the risk and for advice if you have taken more Instanyl than you should.

Symptoms of overdose are:
Sleepiness, drowiness, dizziness, reduced body temperature, slow heart beat, difficulties coordinating arms and legs.
In serious cases taking too much Instanyl may cause coma, sedation, convulsions or severe breathing difficulties (very slow or shallow breathing).
If you feel any of the above symptoms you should seek immediate medical assistance.

Note to carers
If you see the person taking Instanyl suddenly acting slowly, having difficulties breathing or if you have difficulties waking the person up:
- you should immediately call for emergency help.
- while waiting for the emergency help, you must try to keep the person awake by talking to or gently shaking the person every now and then.
- if the person has difficulty breathing, you should prompt the person to breathe in every 5-10 seconds.
- if the person has stopped breathing, you should attempt to resuscitate her/him until emergency help arrives.

If you think someone has accidentally taken Instanyl, please seek immediate medical assistance. Try to keep the person awake until emergency help arrives.
If someone has accidentally taken Instanyl, they may have the same symptoms as described above for overdose.

If you forget to use Instanyl
If the breakthrough pain is still ongoing, you may take Instanyl as prescribed by your doctor. If the breakthrough pain has stopped, do not take Instanyl until the next episode of breakthrough pain occurs.

If you stop using Instanyl
You should discontinue Instanyl when you no longer have any breakthrough pain. You should however continue to take your usual pain relieving medicine to treat your cancer pain. Contact your doctor to confirm the correct dose of your usual medicine if you are not sure.
You may experience withdrawal symptoms similar to the possible side effects of Instanyl when discontinuing Instanyl. If you experience withdrawal symptoms, you should contact your doctor. Your doctor will evaluate if you need medicine to reduce or eliminate the withdrawal symptoms.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The side effects will often stop or reduce in intensity with continued use of the product.

Discontinue the treatment and contact your doctor, hospital or emergency room immediately, if you:
- experience sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating or loss of consciousness.
- experience severe breathing difficulties.
- have a rattling sound when you breathe in.
- have convulsive pain.
- experience extreme dizziness.

These side effects can be very serious.

Other side effects reported after use of Instanyl:

Common (may affect up to 1 in 10 people):
Sleepiness, dizziness even with difficulties keeping balance, headache, irritation of the throat, nausea, vomiting, flushing, feeling very warm, excessive sweating.

Uncommon (may affect up to 1 in 100 people):
Sleeplessness, drowsiness, convulsive muscle contractions, abnormal sensation of the skin even unpleasant, change of taste, motion sickness, low blood pressure, severe breathing problems, nose bleeds, nasal ulcer, runny nose, constipation, inflammation of the mouth, dry mouth, skin pain, itching of the skin, fever.

Not known (frequency cannot be estimated from the available data)**:**
Allergic reaction, fall, diarrhoea, convulsions (fits), loss of consciousness, swelling of arms or legs, seeing or hearing things that are not really there (hallucinations), delirium (symptoms may include a combination of agitation, restlessness, disorientation, confusion, fear, seeing or hearing things that are not really there, sleep disturbance, nightmares), drug dependence (addiction), drug abuse, fatigue, malaise, withdrawal syndrome (may manifest by the occurrence of the following side effects nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating), shortness of breath.

There have also been reports of patients developing a hole in the septum of the nose – the structure, which separates the nostrils.

Prolonged treatment with fentanyl during pregnancy may cause withdrawal symptoms in the newborn which can be life-threatening (see section 2)

You should tell your doctor if you experience recurrent episodes of nose bleeding or nasal discomfort.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Instanyl

The pain-relieving medicine in Instanyl is very strong and can be life-threatening to children. Instanyl must be kept out of the sight and reach of children. Always place the nasal spray in the child-resistant box after use.
Do not use Instanyl after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of the month.
Store below 30 °C. Keep the nasal spray stored upright. Do not freeze. If Instanyl nasal spray is frozen the spray pump may crack. If uncertain of how the pump has been stored, you should check the spray pump before use.

Instanyl that has passed the expiry date or is no longer required, may still contain enough medicine to be harmful to other people, especially children. Do not throw away any medicines via wastewater or household waste. Any used or unused nasal spray should be returned systematically and suitably in the child-resistant outer box and discarded according to local requirements or returned to the pharmacy. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Instanyl contains
The active substance is fentanyl. The content is:
50 micrograms/dose: 1 ml contains fentanyl citrate equivalent to 500 micrograms fentanyl. 1 puff (100 microlitres) contains 50 micrograms fentanyl.
100 micrograms/dose: 1 ml contains fentanyl citrate equivalent to 1,000 micrograms fentanyl. 1 puff (100 microlitres) contains 100 micrograms fentanyl.
200 micrograms/dose: 1 ml contains fentanyl citrate equivalent to 2,000 micrograms fentanyl. 1 puff (100 microlitres) contains 200 micrograms fentanyl.

The other ingredients are sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, and purified water.

What Instanyl looks like and contents of the pack
Instanyl is a nasal spray, solution. The solution is clear and colourless. It is contained in a brown glass bottle with a metering pump.
The nasal spray is supplied in a child-resistant outer box and comes in three different pack sizes:
1.8 ml (equal to 10 doses), 2.9 ml (equal to 20 doses) and 5.0 ml (equal to 40 doses).
Not all pack sizes may be marketed.

The labelling of the three Instanyl strengths is differentiated by colour:
50 micrograms/dose labelling is orange.

100 micrograms/dose labelling is purple.
200 micrograms/dose labelling is greenish-blue.

Marketing Authorisation Holder
Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

Manufacturer
Curida AS
Solbærvegen 5
NO-2409 Elverum
Norway

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in {MM/YYYY}.

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

INSTRUCTIONS FOR USE OF INSTANYL NASAL SPRAY

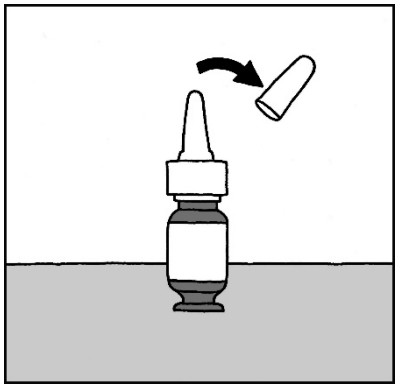
Please read the following instructions carefully to learn how to use Instanyl nasal spray:

Preparing Instanyl nasal spray for use:

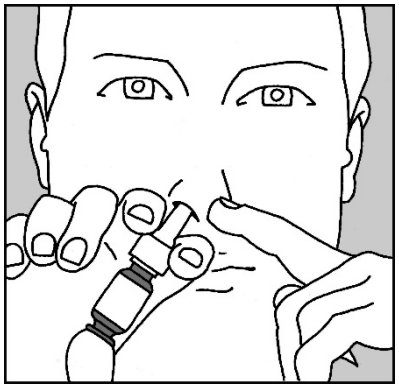
- Before using the nasal spray for the first time:
  - It must be pumped 3 or 4 times (primed) until a fine mist appears.
- **During this priming process medicine will be expelled. Therefore:**
  - **Priming should be performed in a well ventilated area.**
  - **Do not point the nasal spray in the direction of yourself and other people.**
  - **Do not point in the direction of surfaces and objects that could come into contact with other people, particularly children.**
- If you have not used Instanyl for more than 7 days the pump must be primed again by spraying once before the next dose is taken.

Instanyl nasal spray should be used in the following way:

1. Blow your nose if it feels blocked or you have a cold.
2. You should sit or stand in upright position.
3. Remove the protective cap from the spray.



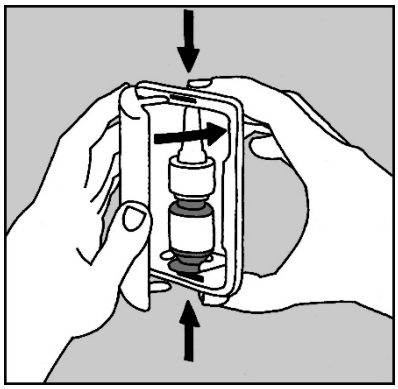
4. Hold the nasal spray upright.
5. Bend your head slightly forward.
6. Close one nostril by placing your finger against the side of your nose and insert the spray tip into the other nostril (approximately 1 cm). It does not matter which nostril you use. If you have to take a second dose after 10 minutes to get sufficient pain relief, this dose should be taken in the other nostril.



7. Press the pump down quickly and completely with two fingers, once, while breathing in through your nose. You must make sure the pump is pressed all the way down. You may not feel the dose in your nose, but you have received it when you have pressed the pump.
8. Clean the nasal spray tip after use with a clean tissue, and then throw away the tissue afterwards.

If after 10 minutes you need a second dose of Instanyl to relieve your pain, repeat steps 1 to 8 in the other nostril.

Always place Instanyl in the child-resistant box after use. **Keep out of the sight and reach of children.**



Keep track of how many doses you have used and how many you have left in your nasal spray by using the dose-counting card provided with Instanyl nasal spray. Every time you use Instanyl nasal spray, make sure you or your carer fills in the information on the card.

If Instanyl nasal spray is blocked or does not spray properly:

- If it is blocked, aim the nasal spray away from you (and any other people) and push firmly down on the pump. This should clear any blockage.
- If your nasal spray is still not working properly, talk to your pharmacist. **Never try to fix the nasal spray yourself or take it apart**. This is because it may then give you the wrong dose.

Package leaflet: Information for the user

Instanyl 50 micrograms nasal spray, solution in single-dose container
Instanyl 100 micrograms nasal spray, solution in single-dose container
Instanyl 200 micrograms nasal spray, solution in single-dose container
fentanyl

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Instanyl is and what it is used for

Instanyl contains the active substance fentanyl and belongs to a group of strong painkillers called opioids. Opioids act by blocking the pain signals to the brain.
Instanyl acts rapidly and is used for relieving breakthrough pain in adult cancer patients already treated with opioids for their usual pain. Breakthrough pain is an additional sudden pain that occurs despite you having taken your usual opioid pain relieving medicines.

2. What you need to know before you use Instanyl

Do not use Instanyl
- if you are allergic to fentanyl or any of the other ingredients of this medicine (listed in section 6).
- if you are not regularly using a prescribed opioid medicine (e.g codeine, fentanyl, hydromorphone, morphine, oxycodone, pethidine), every day on a regular schedule, for at least a week, to control your persistent pain. If you have not been using these medicines you must not use Instanyl, because it may increase the risk that breathing could become dangerously slow and/or shallow, or even stop.
- if you are taking a medicine which contains sodium oxybate.
- if you suffer from short-term pain other than breakthrough pain.
- if you have serious difficulties breathing or suffer from a serious obstructive lung disease.
- if you have previously received facial radiotherapy.
- if you suffer from recurrent episodes of nose bleeding.

Warnings and precautions
Talk to your doctor or pharmacist before using Instanyl, especially:
- if you suffer from a long-term obstructive lung disease, your breathing may be impaired by Instanyl.
- if you have problems with your heart especially slow heart rate, low blood pressure or low blood volume.

- if you have problems with your liver or kidneys.
- if you have problems with your brain function, e.g. due to a brain tumour, a head injury or increased intracranial pressure.
- if you have ever developed adrenal insufficiency or lack of sex hormones (androgen deficiency) with opioid use.
- if you or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
- if you are a smoker.
- if you have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.
- if you take sedative medicines such as benzodiazepines or related drugs (please also refer to the section 'Other medicines and Instanyl').
- if you take antidepressants or antipsychotics (please also refer to the section 'Other medicines and Instanyl').
- if you take medicines called partial agonist/antagonists e.g. buprenorphine, nalbuphine and pentazocine (medicines for treatment of pain) as you may experience symptoms of withdrawal syndrome. Please refer to the section 'Other medicines and Instanyl' for more information.
- if you use other nasal spray products, e.g. for common cold or allergy.

Sleep-related breathing disorders
Instanyl can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

If you experience difficulties breathing while being treated with Instanyl, it is very important that you contact your doctor or hospital immediately.

Consult your doctor while using Instanyl, if:
- you experience pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of your medicine as prescribed by your doctor.
- you experience a combination of the following symptoms: nausea, vomiting, anorexia, fatigue, weakness, dizziness and low blood pressure. Together these symptoms may be a sign of a potentially life-threatening condition called adrenal insufficiency, a condition in which the adrenal glands do not produce enough hormones.

If you experience recurrent nose bleeding or nasal discomfort whilst being treated with Instanyl, you must contact your doctor, who will consider alternative treatment for your breakthrough pain.

Repeated use of Instanyl may lead to dependence and abuse which may result in life-threatening overdose. If you think you are becoming dependent on Instanyl, it is important that you consult your doctor.

Children and adolescents
Instanyl should not be used in children and adolescents under 18 years of age.

Other medicines and Instanyl
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Instanyl may affect or be affected by other medicines.
Special care should be taken if you are treated with any of the following medicines:
- Other medicines for pain and some painkillers for nerve pain (such as gabapentin and pregabalin).
- any medicines which might normally make you sleepy (have a sedative effect) such as sleeping pills, sedative medicines such as benzodiazepines or related medicines, medicines to treat

anxiety, antihistamines, or tranquillisers, skeletal muscle relaxants and gabapentinoids (gabapentin and pregabalin). The use of such other medicines at the same time as Instanyl, may cause risk of drowsiness, deep sedation and affect your ability to breathe (respiratory depression), which may lead to coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.
However if your doctor does prescribe Instanyl together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.
Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

- any medicines that might have an effect on the way in which your body breaks down Instanyl, such as:
  - ritonavir, nelfinavir, amprenavir, and fosamprenavir (medicines that help control HIV infection);
  - CYP3A4 inhibitors such as ketoconazole, itraconazole, or fluconazole (used for treatment of fungal infections);
  - troleandomycin, clarithromycin, or erythromycin (medicines for treatment of bacterial infections);
  - aprepitant (used to treat severe nausea);
  - diltiazem and verapamil (medicines for treatment of high blood pressure or heart diseases).
- medicines called Monoamine Oxidase Inhibitors (MAOI) used for severe depression, even if you have been treated with one in the past 2 weeks.
- The risk of side effects increases if you are taking medicines such as certain antidepressants or antipsychotics. Instanyl may interact with these medicines and you may experience mental status changes (e.g. agitation, hallucinations, coma), and other effects such as body temperature above 38 °C, increase in heart rate, unstable blood pressure, and exaggeration of reflexes, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Your doctor will tell you whether Instanyl is suitable for you.
- medicines called partial agonist/antagonists e.g. buprenorphine, nalbuphine and pentazocine (medicines for treatment of pain). You could experience symptoms of withdrawal syndrome (nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating).
- other medicines taken via the nose, especially oxymetazoline, xylometazoline and similar medicines, which are used for relief of nose congestions.

Instanyl with food, drink and alcohol
Do not drink alcohol whilst being treated with Instanyl, as it can increase the risk of experiencing dangerous side effects.

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

Instanyl should not be used during pregnancy unless you have discussed this with your doctor.

Instanyl should not be used during childbirth because fentanyl may cause serious breathing problems in the new-born child.

Fentanyl can get into breast milk and may cause side effects in the breast-fed infant. Do not use Instanyl if you are breast-feeding. You should not start breast-feeding until at least 5 days after the last dose of Instanyl.

Driving and using machines
You should not drive or use machinery whilst being treated with Instanyl. Instanyl can cause dizziness, drowsiness and visual disturbances, which may affect your ability to drive or use machines.

3. How to use Instanyl

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

The dose of Instanyl is independent of your usual cancer pain treatment.

When you first start using Instanyl, your doctor will work with you to find the dose that will relieve your breakthrough pain.
The initial dose is one puff of 50 micrograms in one nostril each time you have an episode of breakthrough pain. During the determination of your right dose, your doctor may instruct you to change to a higher dose.

If your breakthrough pain is not relieved after 10 minutes, you may use only one puff more for this episode.
Generally you should wait 4 hours before treating another episode of breakthrough pain. On exceptional occasions where a new episode occurs earlier, you can use Instanyl to treat it but you must wait at least 2 hours before doing so. If you regularly have breakthrough pain episodes that are less than 4 hours apart, contact your doctor as your usual cancer pain treatment may have to be changed.

You can use Instanyl to treat up to four episodes of breakthrough pain per day.

If you experience more than four episodes of breakthrough pain per day, contact your doctor, as your usual cancer pain treatment may have to be changed.

Do not change the dose of Instanyl or your other pain medicines on your own. Change in dose must be done together with your doctor.

Instanyl is for nasal use.

Please read the instruction for use at the end of this leaflet to learn how to use Instanyl.

If you use more Instanyl than you should or if you think someone has accidentally used Instanyl
You should contact your doctor, hospital or emergency room for assessment of the risk and for advice if you have taken more Instanyl than you should.

Symptoms of overdose are:
Sleepiness, drowiness, dizziness, reduced body temperature, slow heart beat, difficulties coordinating arms and legs.
In serious cases taking too much Instanyl may cause coma, sedation, convulsions or severe breathing difficulties (very slow or shallow breathing).
If you feel any of the above symptoms you should seek immediate medical assistance.

Note to carers
If you see the person taking Instanyl suddenly acting slowly, having difficulties breathing or if you have difficulties waking the person up:
- you should immediately call for emergency help.
- while waiting for the emergency help, you must try to keep the person awake by talking to or gently shaking the person every now and then.
- if the person has difficulty breathing, you should prompt the person to breathe in every 5-10 seconds.
- if the person has stopped breathing, you should attempt to resuscitate her/him until emergency help arrives.

If you think someone has accidentally taken Instanyl, please seek immediate medical assistance. Try to keep the person awake until emergency help arrives.

If someone has accidentally taken Instanyl, they may have the same symptoms as described above for overdose.

If you forget to use Instanyl
If the breakthrough pain is still ongoing, you may take Instanyl as prescribed by your doctor. If the breakthrough pain has stopped, do not take Instanyl until the next episode of breakthrough pain occurs.

If you stop using Instanyl
You should discontinue Instanyl when you no longer have any breakthrough pain. You should however continue to take your usual pain relieving medicine to treat your cancer pain. Contact your doctor to confirm the correct dose of your usual medicine if you are not sure.
You may experience withdrawal symptoms similar to the possible side effects of Instanyl when discontinuing Instanyl. If you experience withdrawal symptoms, you should contact your doctor. Your doctor will evaluate if you need medicine to reduce or eliminate the withdrawal symptoms.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The side effects will often stop or reduce in intensity with continued use of the product.

Discontinue the treatment and contact your doctor, hospital or emergency room immediately, if you:
- experience sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating or loss of consciousness.
- experience severe breathing difficulties.
- have a rattling sound when you breathe in.
- have convulsive pain.
- experience extreme dizziness.

These side effects can be very serious.

Other side effects reported after use of Instanyl:

Common (may affect up to 1 in 10 people):
Sleepiness, dizziness even with difficulties keeping balance, headache, irritation of the throat, nausea, vomiting, flushing, feeling very warm, excessive sweating.

Uncommon (may affect up to 1 in 100 people):
Sleeplessness, drowsiness, convulsive muscle contractions, abnormal sensation of the skin even unpleasant, change of taste, motion sickness, low blood pressure, severe breathing problems, nose bleeds, nasal ulcer, runny nose, constipation, inflammation of the mouth, dry mouth, skin pain, itching of the skin, fever.

Not known (frequency cannot be estimated from the available data)**:**
Allergic reaction, fall, diarrhoea, convulsions (fits), loss of consciousness, swelling of arms or legs, seeing or hearing things that are not really there (hallucinations), delirium (symptoms may include a combination of agitation, restlessness, disorientation, confusion, fear, seeing or hearing things that are not really there, sleep disturbance, nightmares), drug dependence (addiction), drug abuse, fatigue, malaise, withdrawal syndrome (may manifest by the occurrence of the following side effects nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating), shortness of breath.

There have also been reports of patients developing a hole in the septum of the nose – the structure, which separates the nostrils.

Prolonged treatment with fentanyl during pregnancy may cause withdrawal symptoms in the newborn which can be life-threatening (see section 2)

You should tell your doctor if you experience recurrent episodes of nose bleeding or nasal discomfort.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Instanyl

The pain-relieving medicine in Instanyl is very strong and can be life-threatening to children. Instanyl must be kept out of reach and sight of children.
Do not use Instanyl after the expiry date which is stated on the carton and the single-dose container after EXP. The expiry date refers to the last day of that month.
Store below 30 °C. Keep the blister in the outer carton. Keep stored upright.

Instanyl can be harmful to other people, especially children. Do not throw away any medicines via wastewater or household waste. Any unused single-dose containers should be returned systematically and suitably in the child-resistant blister and discarded according to local requirements or returned to the pharmacy. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Instanyl contains
The active substance is fentanyl. The content is:
50 micrograms: 1 dose (100 microlitres) contains fentanyl citrate equivalent to 50 micrograms fentanyl.
100 micrograms: 1 dose (100 microlitres) contains fentanyl citrate equivalent to 100 micrograms fentanyl.
200 micrograms: 1 dose (100 microlitres) contains fentanyl citrate equivalent to 200 micrograms fentanyl.

The other ingredients are sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, and water for injections.

What Instanyl looks like and contents of the pack
Instanyl is a nasal spray, solution in a single-dose spray container. The solution is clear and colourless.

The single-dose container contains 1 dose of Instanyl and and is supplied in a child-resistant blister.
Instanyl comes in different pack sizes of 2, 6, 8 and 10 single-dose containers.
Not all pack sizes may be marketed.

The labelling of the three Instanyl strengths is differentiated by colour:
50 micrograms labelling is orange.
100 micrograms labelling is purple.
200 micrograms labelling is greenish-blue.

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Manufacturer
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This leaflet was last revised in {MM/YYYY}.

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

INSTRUCTIONS FOR USE OF INSTANYL SINGLE-DOSE NASAL SPRAY

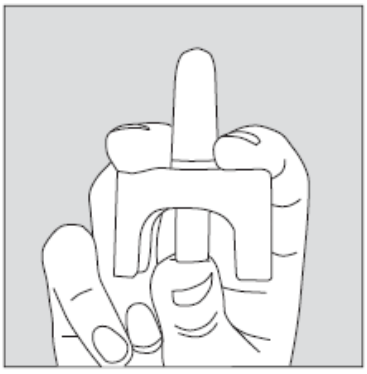
Please read the following instructions carefully to learn how to use Instanyl single-dose nasal spray:

- Each single-dose container is sealed in a child-resistant blister. Do not open the blister before you are ready to use the spray. Each single-dose container contains only one dose of Instanyl. Do not test before use.

- To open cut with scissors along the line (above the scissors symbol) on the blister. Hold the edge of the foil, peel the foil back and take the nasal spray out.

- Blow your nose if it feels blocked or you have a cold.

- Gently hold the single-dose container with your thumb supporting it at the plunger at the bottom and your index and middle finger on either side of the spray tip (see drawing). Do not press the plunger yet.



- Block one nostril by placing your other index finger against the side of your nose and insert the spray tip into the other nostril (approximately 1 cm). It does not matter which nostril you use. If you have to take a second dose after 10 minutes to get sufficient pain relief, this dose should be taken in the other nostril.

- Keep your head upright

- Press the plunger upwards firmly to release the dose with your thumb while inhaling gently through the nose and then remove the spray container from the nose. You may not feel the dose in your nose, but you have received it when the plunger has been pressed up.

Your single-dose container is now empty

Package leaflet: Information for the user

Instanyl 50 micrograms/dose nasal spray, solution
Instanyl 100 micrograms/dose nasal spray, solution
Instanyl 200 micrograms/dose nasal spray, solution
fentanyl

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Instanyl is and what it is used for

Instanyl contains the active substance fentanyl and belongs to a group of strong painkillers called opioids. Opioids act by blocking the pain signals to the brain.
Instanyl acts rapidly and is used for relieving breakthrough pain in adult cancer patients already treated with opioids for their usual pain. Breakthrough pain is an additional sudden pain that occurs despite you having taken your usual opioid pain relieving medicines.

2. What you need to know before you use Instanyl

Do not use Instanyl
- if you are allergic to fentanyl or any of the other ingredients of this medicine (listed in section 6).
- if you are not regularly using a prescribed opioid medicine (e.g codeine, fentanyl, hydromorphone, morphine, oxycodone, pethidine), every day on a regular schedule, for at least a week, to control your persistent pain. If you have not been using these medicines you must not use Instanyl, because it may increase the risk that breathing could become dangerously slow and/or shallow, or even stop.
- If you are taking a medicine which contains sodium oxybate.
- if you suffer from short-term pain other than breakthrough pain.
- if you have serious difficulties breathing or suffer from a serious obstructive lung disease.
- if you have previously received facial radiotherapy.
- if you suffer from recurrent episodes of nose bleeding.

Warnings and precautions
Talk to your doctor or pharmacist before using Instanyl, especially:
- if you suffer from a long-term obstructive lung disease, your breathing may be impaired by Instanyl.
- if you have problems with your heart especially slow heart rate, low blood pressure or low blood volume.

- if you have problems with your liver or kidneys.
- if you have problems with your brain function, e.g. due to a brain tumour, a head injury or increased intracranial pressure.
- if you have ever developed adrenal insufficiency or lack of sex hormones (androgen deficiency) with opioid use.
- if you or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
- if you are a smoker.
- if you have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.
- if you take sedative medicines such as benzodiazepines or related drugs (please also refer to the section 'Other medicines and Instanyl').
- if you take antidepressants or antipsychotics (please also refer to the section 'Other medicines and Instanyl').
- if you take medicines called partial agonist/antagonists e.g. buprenorphine, nalbuphine and pentazocine (medicines for treatment of pain) as you may experience symptoms of withdrawal syndrome. Please refer to the section 'Other medicines and Instanyl' for more information.
- if you use other nasal spray products, e.g. for common cold or allergy.

Sleep-related breathing disorders
Instanyl can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

If you experience difficulties breathing while being treated with Instanyl, it is very important that you contact your doctor or hospital immediately.

Consult your doctor while using Instanyl, if:
- you experience pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of your medicine as prescribed by your doctor.
- you experience a combination of the following symptoms: nausea, vomiting, anorexia, fatigue, weakness, dizziness and low blood pressure. Together these symptoms may be a sign of a potentially life-threatening condition called adrenal insufficiency, a condition in which the adrenal glands do not produce enough hormones.

If you experience recurrent nose bleeding or nasal discomfort whilst being treated with Instanyl, you must contact your doctor, who will consider alternative treatment for your breakthrough pain.

Repeated use of Instanyl may lead to dependence and abuse which may result in life-threatening overdose. If you think you are becoming dependent on Instanyl, it is important that you contact your doctor.

Children and adolescents
Instanyl should not be used in children and adolescents under 18 years of age.

Other medicines and Instanyl
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Instanyl may affect or be affected by other medicines.
Special care should be taken if you are treated with any of the following medicines:
- Other medicines for pain and some painkillers for nerve pain (such as gabapentin and pregabalin).
- any medicines which might normally make you sleepy (have a sedative effect) such as sleeping pills, sedative medicines such as benzodiazepines or related medicines, medicines to treat

anxiety, antihistamines, or tranquillisers, skeletal muscle relaxants and gabapentinoids (gabapentin and pregabalin). The use of such other medicines at the same time as Instanyl, may cause risk of drowsiness, deep sedation and affect your ability to breathe (respiratory depression), which may lead to coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.
However if your doctor does prescribe Instanyl together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.
Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

- any medicines that might have an effect on the way in which your body breaks down Instanyl, such as:
  - ritonavir, nelfinavir, amprenavir, and fosamprenavir (medicines that help control HIV infection);
  - CYP3A4 inhibitors such as ketoconazole, itraconazole, or fluconazole (used for treatment of fungal infections);
  - troleandomycin, clarithromycin, or erythromycin (medicines for treatment of bacterial infections);
  - aprepitant (used to treat severe nausea);
  - diltiazem and verapamil (medicines for treatment of high blood pressure or heart diseases).
- medicines called Monoamine Oxidase Inhibitors (MAOI) used for severe depression, even if you have been treated with one in the past 2 weeks.
- The risk of side effects increases if you are taking medicines such as certain antidepressants or antipsychotics. Instanyl may interact with these medicines and you may experience mental status changes (e.g. agitation, hallucinations, coma), and other effects such as body temperature above 38 °C, increase in heart rate, unstable blood pressure, and exaggeration of reflexes, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Your doctor will tell you whether Instanyl is suitable for you.
- medicines called partial agonist/antagonists e.g. buprenorphine, nalbuphine and pentazocine (medicines for treatment of pain). You could experience symptoms of withdrawal syndrome (nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating).
- Other medicines taken via the nose, especially oxymetazoline, xylometazoline and similar medicines, which are used for relief of nose congestions.

Instanyl with food, drink and alcohol
Do not drink alcohol whilst being treated with Instanyl, as it can increase the risk of experiencing dangerous side effects.

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

Instanyl should not be used during pregnancy unless you have discussed this with your doctor.

Instanyl should not be used during childbirth because fentanyl may cause serious breathing problems in the new-born child.

Fentanyl can get into breast milk and may cause side effects in the breast-fed infant. Do not use Instanyl if you are breast-feeding. You should not start breast-feeding until at least 5 days after the last dose of Instanyl.

Driving and using machines
You should not drive or use machinery whilst being treated with Instanyl. Instanyl can cause dizziness, drowsiness and visual disturbances, which may affect your ability to drive or use machines.

3. How to use Instanyl

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

The dose of Instanyl is independent of your usual cancer pain treatment.

When you first start using Instanyl, your doctor will work with you to find the dose that will relieve your breakthrough pain.
The initial dose is one puff of 50 micrograms in one nostril each time you have an episode of breakthrough pain. During the determination of your right dose, your doctor may instruct you to change to a higher dose.

If your breakthrough pain is not relieved after 10 minutes, you may use only one puff more for this episode.

Generally you should wait 4 hours before treating another episode of breakthrough pain. On exceptional occasions where a new episode occurs earlier, you can use Instanyl to treat it but you must wait at least 2 hours before doing so. If you regularly have breakthrough pain episodes that are less than 4 hours apart, contact your doctor as your usual cancer pain treatment may have to be changed.

You can use Instanyl to treat up to four episodes of breakthrough pain per day.

If you experience more than four episodes of breakthrough pain per day, contact your doctor, as your usual cancer pain treatment may have to be changed.

Do not change the dose of Instanyl or your other pain medicines on your own. Change in dose must be done together with your doctor.

Instanyl incorporates an electronic dose counter, and a lock out period between doses to reduce the risk of overdose, and helps you to use it adequately. The dose counter enables you, and your doctor, to monitor and adapt your use. After two doses are taken within 60 minutes, Instanyl will lock for a period of 2 hours, from the first dose taken, until another dose can be administered.

Instanyl is for nasal use.

Please read the instructions for use on the back of this leaflet to learn how to use the nasal spray.

If you use more Instanyl than you should or if you think someone has accidentally used Instanyl
You should contact your doctor, hospital or emergency room for assessment of the risk and for advice if you have taken more Instanyl than you should.

Symptoms of overdose are:
Sleepiness, drowiness, dizziness, reduced body temperature, slow heart beat, difficulties coordinating arms and legs.
In serious cases taking too much Instanyl may cause coma, sedation, convulsions or severe breathing difficulties (very slow or shallow breathing).
If you feel any of the above symptoms you should seek immediate medical assistance.

Note to carers
If you see the person taking Instanyl suddenly acting slowly, having difficulties breathing or if you have difficulties waking the person up:
- you should immediately call for emergency help.
- while waiting for the emergency help, you must try to keep the person awake by talking to or gently shaking the person every now and then.
- if the person has difficulty breathing, you should prompt the person to breathe in every 5-10 seconds.

- if the person has stopped breathing, you should attempt to resuscitate her/him until emergency help arrives.

If you think someone has accidentally taken Instanyl, please seek immediate medical assistance. Try to keep the person awake until emergency help arrives.
If someone has accidentally taken Instanyl, they may have the same symptoms as described above for overdose.

If you forget to use Instanyl
If the breakthrough pain is still ongoing, you may take Instanyl as prescribed by your doctor. If the breakthrough pain has stopped, do not take Instanyl until the next episode of breakthrough pain occurs.

If you stop using Instanyl
You should discontinue Instanyl when you no longer have any breakthrough pain. You should however continue to take your usual pain relieving medicine to treat your cancer pain. Contact your doctor to confirm the correct dose of your usual medicine if you are not sure.
You may experience withdrawal symptoms similar to the possible side effects of Instanyl when discontinuing Instanyl. If you experience withdrawal symptoms, you should contact your doctor. Your doctor will evaluate if you need medicine to reduce or eliminate the withdrawal symptoms.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The side effects will often stop or reduce in intensity with continued use of the product.

Discontinue the treatment and contact your doctor, hospital or emergency room immediately, if you:
- experience sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating or loss of consciousness.
- experience severe breathing difficulties.
- have a rattling sound when you breathe in.
- have convulsive pain.
- experience extreme dizziness.

These side effects can be very serious.

Other side effects reported after use of Instanyl:

Common (may affect up to 1 in 10 people):
Sleepiness, dizziness even with difficulties keeping balance, headache, irritation of the throat, nausea, vomiting, flushing, feeling very warm, excessive sweating.

Uncommon (may affect up to 1 in 100 people):
Sleeplessness, drowsiness, convulsive muscle contractions, abnormal sensation of the skin even unpleasant, change of taste, motion sickness, low blood pressure, severe breathing problems, nose bleeds, nasal ulcer, runny nose, constipation, inflammation of the mouth, dry mouth, skin pain, itching of the skin, fever.

Not known (frequency cannot be estimated from the available data)**:**
Allergic reaction, fall, diarrhoea, convulsions (fits), loss of consciousness, swelling of arms or legs, seeing or hearing things that are not really there (hallucinations), delirium (symptoms may include a combination of agitation, restlessness, disorientation, confusion, fear, seeing or hearing things that are not really there, sleep disturbance, nightmares), drug dependence (addiction), drug abuse, fatigue, malaise, withdrawal syndrome (may manifest by the occurrence of the following side effects nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating), shortness of breath.

There have also been reports of patients developing a hole in the septum of the nose – the structure, which separates the nostrils.

Prolonged treatment with fentanyl during pregnancy may cause withdrawal symptoms in the newborn which can be life-threatening (see section 2)

You should tell your doctor if you experience recurrent episodes of nose bleeding or nasal discomfort.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Instanyl

The pain-relieving medicine in Instanyl is very strong and can be life-threatening to children. Instanyl must be kept out of the sight and reach of children. Always close after use by putting the child-resistant cap back on to the nasal spray.
Do not use Instanyl after the expiry date which is stated on the nasal spray after EXP. The expiry date refers to the last day of the month.
Store below 30 °C. Keep the nasal spray stored upright. Do not freeze. If Instanyl nasal spray is frozen the spray pump may crack. If uncertain of how the pump has been stored, you should check the spray pump before use.

Instanyl that has passed the expiry date or is no longer required, may still contain enough medicine to be harmful to other people, especially children.

This instrument is labelled in accordance with the EU Waste Electrical and Electronic Equipment Directive (WEEE). Do not throw away any medicines via wastewater or household waste. Any used or unused nasal spray should be returned to the pharmacy or disposed according to other local requirements. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Instanyl contains
The active substance is fentanyl. The content is:
50 micrograms/dose: 1 ml contains fentanyl citrate equivalent to 500 micrograms fentanyl. 1 puff (100 microlitres) contains 50 micrograms fentanyl.
100 micrograms/dose: 1 ml contains fentanyl citrate equivalent to 1,000 micrograms fentanyl. 1 puff (100 microlitres) contains 100 micrograms fentanyl.
200 micrograms/dose: 1 ml contains fentanyl citrate equivalent to 2,000 micrograms fentanyl. 1 puff (100 microlitres) contains 200 micrograms fentanyl.

The other ingredients are sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, and purified water.

What Instanyl looks like and contents of the pack
Instanyl DoseGuard is a nasal spray, solution. The solution is clear and colourless. It is contained in a nasal spray with a metering pump, an electronic display, a dose counter, an in-built lock-out mechanism and a child-resistant cap.
The nasal spray comes in three different pack sizes: 3.2 ml (equal to 20 doses), 4.3 ml (equal to 30 doses) and 5.3 ml (equal to 40 doses).

Not all pack sizes may be marketed.

The labelling of the three Instanyl strengths is differentiated by colour:
50 micrograms/dose labelling is orange.
100 micrograms/dose labelling is purple.
200 micrograms/dose labelling is greenish-blue.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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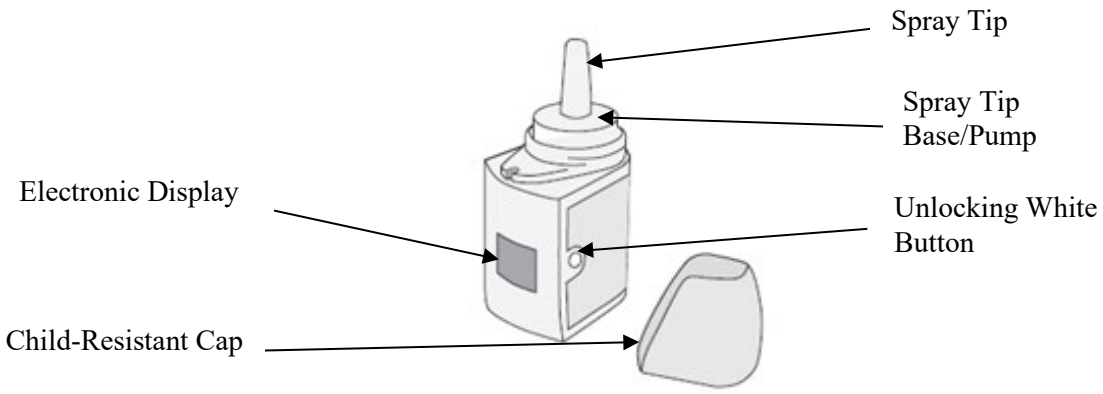
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

INSTRUCTIONS FOR USE OF INSTANYL

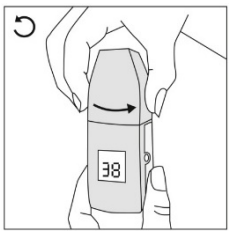
Please read the following instructions carefully to learn how to use the Instanyl nasal spray.

Important information before use:
- Do not modify the device.
- Keep liquids from entering the device.

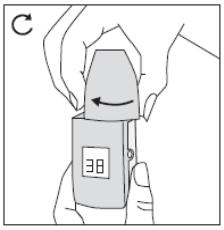
The Instanyl nasal spray has:
- A built-in lock-out feature which controls how often the nasal spray can be used
- A child-resistant cap, which must be put on the nasal spray, when the nasal spray is not used
- An electronic display which:
  - shows how many times to pump (prime) your product before using
  - shows the number of doses left
  - shows whether the nasal spray is locked or ready for use



How to remove and re-attach the child-resistant cap



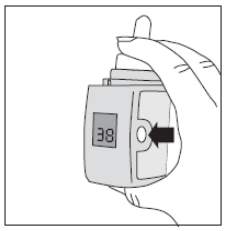
Remove the child-resistant cap by pressing on both sides of the cap and then turn it counter clockwise and lift it off.



To re-attach the child-resistant cap, place it on the nasal spray tip and turn the cap clockwise. The child-resistant cap will click when re-attached.

Always put the child-resistant cap back on to the nasal spray after use.

Preparing the Instanyl nasal spray



Before using the nasal spray for the first time, it must be primed until the display shows the number of doses.
Instructions for priming the device are listed below ("Priming steps").
Note: To pump, place 2 fingers on top of either side of the spray tip base and place thumb under the device, then squeeze.

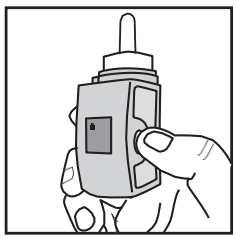
Warning: During this priming process some medicine will be expelled. Therefore:

- **Priming must be performed in a well ventilated area.**
- **Do not point the nasal spray in the direction of yourself or other people.**
- **Do not point the nasal spray in the direction of surfaces and objects that could come into contact with other people, particularly children.**
- **Do not inhale the medicine expelled during priming.**

Priming steps:

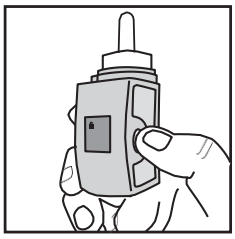
1. Press and release the white button on the side of the nasal spray. The display will now turn on and show 'P5'.

2. Hold the nasal spray upright and pump the nasal spray once in the air. The display now shows 'P4' and a lock symbol appears.



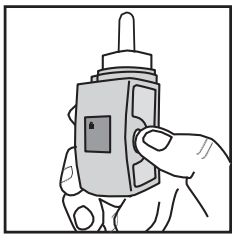
3. When the lock symbol starts flashing, press and release the white side button again; the lock symbol will disappear in the display.

4. Hold the nasal spray upright and pump the nasal spray in the air again. The display will now show 'P3' and the lock symbol.

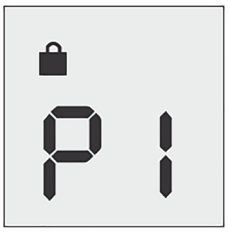


5. When the lock symbol starts flashing, press and release the white side button again; the lock symbol will disappear in the display.

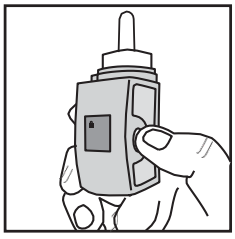
6. Hold the nasal spray upright and pump the nasal spray in the air again. The display will now show ‘P2’ and the lock symbol.



7. When the lock symbol starts flashing, press and release the white side button again; the lock symbol will disappear in the display.



8. Hold the nasal spray upright and pump the nasal spray in the air again. The display will now show ‘P1’ and the lock symbol.

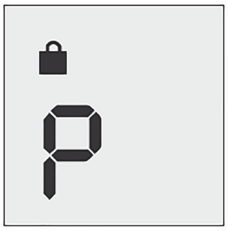


9. When the lock symbol starts flashing, press and release the white side button again; the lock symbol will disappear in the display.

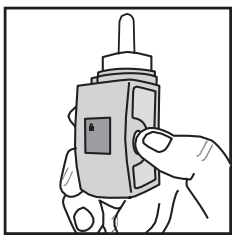
10. Hold the nasal spray upright and pump the nasal spray in the air again. The display will now change to show the number of doses in the nasal spray (i.e. 20, 30 or 40 doses) and flashing lock symbol.

The nasal spray is now ready for use.
Note: Depending on your prescription, the starting number can be 20, 30 or 40.

Re-priming the Instanyl nasal spray (after 7 days or more)



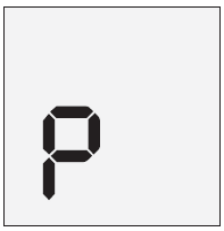
If you have not used Instanyl for 7 days or more, the nasal spray must be primed again by pumping once before the next dose is taken. This will be indicated by a 'P' in the display.



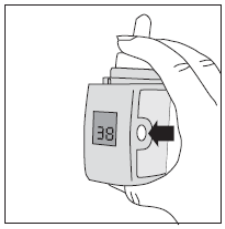
Re-priming steps:

1. Remove the cap.

2. Press and release the white side button; the lock symbol will disappear in the display.



3. The display will show a 'P' without the lock symbol, indicating that the device can be primed.



4. Hold the nasal spray upright and pump the nasal spray once in the air.

Warning: During this priming process some medicine will be expelled. Therefore:

- **Priming must be performed in a well ventilated area.**
- **Do not point the nasal spray in the direction of yourself or other people.**
- **Do not point the nasal spray in the direction of surfaces and objects that could come into contact with other people, particularly children.**

5. Once primed, the display shows the number of doses left and the nasal spray is ready for use again.

How to use Instanyl nasal spray

The nasal spray can only be used when the lock symbol is not visible in the display.

1. Blow your nose if it feels blocked or you have a cold.
2. Wash your hands.
3. Sit or stand in upright position.
4. Hold the nasal spray upright.
5. Press and release the white button on the side of the nasal spray (the flashing lock symbol disappears).
6. Bend your head slightly forward.

7. Close one nostril by placing your finger against the side of your nose and insert the spray tip into the other nostril.
8. Press the pump down completely with two fingers one time while breathing through the nose.
   Note: You will hear a ‘click’ sound when the pump is pressed down completely and the nasal spray has delivered the dose.
9. The display counts down one number and the lock symbol is displayed shortly.
10. If **after 10 minutes** you need a second dose of Instanyl to relieve your pain, repeat step 1 to 8 **in the other nostril**.
11. Clean the nasal spray tip after each use with a clean tissue, and then discard the tissue afterwards.
12. Re-attach the child-resistant cap by placing it on the nasal spray tip and turning the cap clockwise.

Remember to press and release the white button on the side before pumping the nasal spray.

Remember to always put the child-resistant cap back on to the nasal spray and close it after use.

Remember to keep the nasal spray in an upright position at all times.

The nasal spray allows for up to two doses per breakthrough pain episodes.

After the second dose, which may be taken 10 minutes after the first dose the nasal spray will be locked. The lock symbol appears in the display together with a countdown-clock symbol, which shows the remaining time left of the locking period before you can use the nasal spray again (each black mark equals 10 minutes).

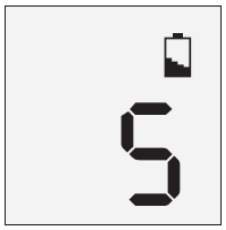
When the time has passed the lock symbol starts flashing. The nasal spray is now ready for use, when the next breakthrough pain episode occurs.
You should wait for 4 hours before treating the next episode of breakthrough pain.

You can use Instanyl to treat up to 4 episodes of breakthrough pain per day. If you experience more than 4 episodes of breakthrough pain per day, you should contact your doctor as your usual cancer pain treatment may have to be changed.

When the nasal spray is empty the display will show ‘0’ and the lock symbol will appear.

Disposal

Do not throw away Instanyl nasal spray via wastewater or household waste. Any used or unused nasal spray should be returned to the pharmacy or disposed according to other local requirements. Ask your pharmacist for further guidance regarding disposal.



Low Battery

If the display shows a battery symbol, this means that the battery life is about to run out. The number of doses on the display will change to ‘5’. This is the approximate number of doses that can be delivered from the nasal spray, before the battery is too low and the display turns off.

If the battery symbol appears in the display, it is recommended that you contact your doctor or pharmacist to get a new nasal spray.

Explanation of the symbols in the electronic display

The nasal spray must be pumped 5 times (primed), before it can be used (see section 'Preparing the Instanyl nasal spray'). The display counts downward after each pump (P5, P4, P3, P2 and P1). The nasal spray is ready, when the display shows the number of doses (i.e. 20, 30 or 40 doses).

When priming, please refer to the above safety warning instructions (See section above "Priming steps").

The nasal spray has not been used for 7 days or more and must be primed again by pumping once in the air in a well-ventilated area before use (see below).

The 'P' symbol will disappear from the display when the nasal spray is primed again.

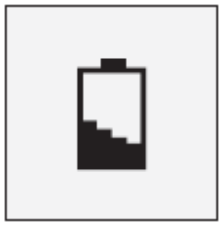
When re-priming, please refer to the above safety warning instructions (See section above "Re-priming steps").

LOCK symbol
The nasal spray is locked and cannot be used.
When the locking period is over, the lock symbol will start flashing. The lock symbol will disappear from the display when the white button on the side of the nasal spray is pressed; the nasal spray can now be used again when an episode of breakthrough pain occurs.

COUNTDOWN-CLOCK symbol
Shows how much time is left of the locking period.
The countdown-clock is counting downwards. Each black mark equals 10 minutes; the maximum locking period is 2 hours. It is recommended that you wait for 4 hours before treating the next episode of breakthrough pain.

The COUNTDOWN-CLOCK symbol is displayed together with the LOCK-symbol.

The number of doses left in the nasal spray is shown. After each dose, the number is counting downwards on the display. Depending on the nasal spray, the starting number can be 20, 30 or 40.



BATTERY symbol
The battery life is about to run out. The number of doses in the display changes to 5. This is the approximate number of doses that can be delivered from the nasal spray, before the battery is too low and the display turns off. The battery cannot be replaced and you will need to contact your doctor or pharmacist to get a new nasal spray.

If you experience that the nasal spray does not work as described in the "Instructions for use" please contact your doctor or pharmacist.