PRODUCT MONOGRAPH

[N] INSTANYL™

Fentanyl Nasal Spray

50, 100, 200 mcg fentanyl as fentanyl citrate

Opioid Analgesic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Nasal	Nasal spray 1 dose of 100 microliters containing: 50, 100, 200 mcg fentanyl (as fentanyl citrate)	Disodium phosphate dihydrate, Purified water, Sodium dihydrogen phosphate dihydrate

INDICATIONS AND CLINICAL USE

Adults

INSTANYL™ (fentanyl nasal spray) is indicated only for the management of breakthrough pain in cancer patients, 18 years of age and older, who are already receiving, and who are tolerant to, continuous opioid therapy for their persistent baseline cancer pain.

Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine daily or an equianalgesic dose of another opioid daily for a week or longer.

All patients starting treatment with INSTANYL™ must begin with titration from the 50 mcg dose (see **DOSAGE AND ADMINISTRATION**).

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression could occur in patients not taking chronic opiates. For this reason, INSTANYL™ is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room.

INSTANYL™ is intended to be used only by healthcare professionals who are knowledgeable of, and skilled in the use of opioids to treat cancer pain.

Geriatrics (> 65 years of age):
Limited data on pharmacokinetics, efficacy and safety are available for the use of INSTANYL™ in patients above 65 years of age. In clinical trials elderly tend to titrate to a lower effective strength than patients less than 65 years of age. Elderly patients may be more sensitive to the effects of fentanyl than the younger population. In the elderly, elimination of fentanyl may be slower and the terminal elimination half-life may be longer, which may result in accumulation of the active substance and a greater risk of undesirable effects. Therefore, exercise caution when titrating INSTANYL™ in elderly patients.

Pediatrics (<18 years of age):
INSTANYL™ is not indicated for use in children under 18 years of age, as dosage requirements for the safe and effective use of INSTANYL™ have not been established for this patient population.

CONTRAINDICATIONS

Because serious or life-threatening hypoventilation could occur, INSTANYL™ (fentanyl citrate) is contraindicated in:

- Opioid non-tolerant patients (e.g. use in acute or post-operative pain, headache/migraine, dental pain, or use in the emergency room);
- Severe respiratory depression or severe obstructive lung conditions

See boxed Serious Warnings and Precautions for details regarding proper patient selection.

INSTANYL™ is also contraindicated in patients with known intolerance or hypersensitivity to fentanyl or to any ingredient in the formulation or component of the container. Anaphylaxis and hypersensitivity have been reported in association with the use of other fentanyl products. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

The use of INSTANYL™ in patients with damage to the nasal cavity from previous facial radiotherapy and recurrent episodes of epistaxis is also contraindicated.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

PROPER PATIENT SELECTION

INSTANYL™ is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of opioids to treat cancer pain.

INSTANYL™ is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine daily, 25 mcg of transdermal fentanyl per hour, 30 mg oxycodone daily, 8 mg of oral hydromorphone daily, 25 mg oral oxymorphone daily or an equianalgesic dose of another opioid for a week or longer.

INSTANYL™ is contraindicated for use in opioid non-tolerant patients including those using opioids intermittently, on an as needed basis

Fentanyl products which are designed to manage breakthrough pain, including INSTANYL™, should not be used in patients who are receiving partial opioid agonists such as buprenorphine or agents with some opioid effects such as tramadol, as the safety of their concomitant use has not been established

RESPIRATORY DEPRESSION

Fatal respiratory depression can occur in patients treated with INSTANYL™, including following use in opioid non-tolerant patients and improper dosing. The substitution of INSTANYL™ for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression in opioid non-tolerant patients, INSTANYL™ is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room.

Special care must be used when dosing with INSTANYL™. If the breakthrough pain episode is not relieved with one dose, only ONE additional dose may be administered no sooner than 10 minutes after the first dose. Patients should then wait at least 4 hours before taking another dose (see DOSAGE AND ADMINISTRATION).

INSTANYL™ must be kept out of the sight and reach of children.

The concomitant use of INSTANYL™ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression (see DRUG INTERACTIONS).

MEDICATION ERRORS

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl product to INSTANYL™. If patients are using other opioid-containing products for breakthrough pain, they MUST be started on INSTANYL™ at the initial dose of 50 mcg.

Regardless of the opioid dose used for the background cancer pain patients beginning treatment with INSTANYL™ must begin with titration from the 50 mcg dose (see DOSAGE AND ADMINISTRATION).

When dispensing, do not substitute an INSTANYL™ prescription for any other fentanyl product. Substantial differences exist in the pharmacokinetic profile of INSTANYL™ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of INSTANYL™ for any other fentanyl product may result in fatal overdose. INSTANYL™ is NOT a generic version of any other fentanyl product.

Patients and their caregivers must be instructed that INSTANYL™ contains a medicine in an amount which can be fatal to children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All nasal spray units must be kept out of reach and sight of children and opened units properly discarded.

ABUSE POTENTIAL

INSTANYL™ contains fentanyl, an opioid agonist and a Schedule 1 controlled substance, with an abuse liability similar to other opioid analgesics. INSTANYL™ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing INSTANYL™ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Opioid substances which include fentanyl, morphine, oxycodone, hydromorphone, oxymorphone, and methadone have a high potential for abuse and risk of fatal overdose due to respiratory depression.

General

Before patients are titrated with INSTANYL™, it is expected that the patient's background persistent pain is controlled through the use of chronic opioid therapy and that they are experiencing no more than four (4) episodes of breakthrough cancer pain per day.

Cardiovascular

Intravenous fentanyl may produce bradycardia. INSTANYL™ should be administered with caution to patients with bradyarrhythmias.

Concomitant use of Central Nervous System Depressants

The concomitant use of INSTANYL™ with other central nervous system depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages may produce additive depressant effects (e.g. hypoventilation, hypotension, and profound sedation). Patients on concomitant CNS depressants should be monitored for a change in opioid effects that may warrant an adjustment to the dose of INSTANYL™ (see **DRUG INTERACTIONS**).

Concomitant Use of CYP 3A4 Inhibitors

Fentanyl is metabolised mainly via the human cytochrome P450 3A4 isoenzyme system (CYP 3A4). Therefore, caution is advised if fentanyl is given concomitantly with CYP 3A4 inhibitors. The concomitant use of INSTANYL™ with strong CYP 3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, and nelfinavir) or moderate CYP 3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may result in increased fentanyl plasma concentrations possibly causing potentially fatal respiratory depression. Similar effects could be seen after concurrent ingestion of grapefruit juice, which is known to inhibit CYP 3A4.

Patients receiving INSTANYL™ who begin therapy with, or increase the dose of CYP 3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time (see **DRUG INTERACTIONS**).

Concomitant Use of MAO Inhibitors

INSTANYL™ is not recommended for use in patients who have received monoamine oxidase (MAO) inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Dependence/Tolerance and Withdrawal

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

The administration of INSTANYL™ is guided by the response of the patient. Physical dependence is not ordinarily a concern when treating a patient with chronic cancer pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g.,

naloxone, nalmefene or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence does not usually occur, to a clinically significant degree, until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

Potential for Abuse and Diversion

INSTANYL™ contains fentanyl, a μ-opioid agonist and a Schedule I controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse and criminal diversion. Handle INSTANYL™ appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting.

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behaviour is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since INSTANYL™ may be diverted for nonmedical use; careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Drug or Alcohol Dependence
Use of INSTANYL™ in combination with CNS depressants, including alcohol, can result in increased risk to the patient (see **DRUG INTERACTIONS** section).

Ear/Nose/Throat

If recurrent episodes of epistaxis or nasal discomfort is experienced an alternative administration form for treatment of breakthrough cancer pain should be considered. The overall extent of fentanyl exposure in subjects with symptoms of an upper respiratory infection in a common cold (rhinorrhoea, sneezing, and sinus fullness) is comparable to that in healthy subjects. Concomitant use of nasal decongestants should be avoided (see DRUG INTERACTIONS). When initiating treatment with INSTANYL™, alternative administration forms should be considered for concurrent treatment of concomitant diseases that can be treated via nasal administration.

Head Injuries and Increased Intracranial Pressure

Fentanyl should be used with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure, impaired consciousness or coma. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

Hepatic/Biliary/Pancreatic

Fentanyl should be administered with caution to patients with liver dysfunction. The influence of liver impairment on the pharmacokinetics of INSTANYL™ has not been evaluated. However, when administered intravenously the clearance of fentanyl is decreased in hepatic impairment due to alterations in metabolic clearance and plasma proteins.

Fentanyl may cause spasm of the sphincter of Oddi and INSTANYL™ should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in serum amylase concentration.

Psychomotor Impairment

Opioid analgesics like fentanyl may impair the mental or physical ability required for the performance of potentially hazardous tasks. Patients should be advised not to drive or operate machinery if they are feeling sleepy or dizzy, have blurred or double vision, or have difficulty in concentrating while using INSTANYL™.

Renal

The influence of renal impairment on the pharmacokinetics of INSTANYL™ has not been evaluated. However, when administered intravenously the clearance of fentanyl is decreased in renal disease due to alterations in metabolic clearance and plasma proteins.

Respiratory

Respiratory Depression (Hypoventilation)
Respiratory depression is the chief hazard of opioids, including fentanyl, the active ingredient in INSTANYL™. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

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

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

Use in Patients with Chronic Pulmonary Disease
Fentanyl should be used with caution in patients with chronic pulmonary disease, patients with decreased respiratory reserve and others with potentially compromised respiration. Normal analgesic doses of opioids may further decrease respiratory drive in these patients to the point of respiratory failure.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. INSTANYL™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. INSTANYL™ should not be used in pregnancy unless clearly necessary.

Following long-term treatment, fentanyl may cause withdrawal in the new-born infant. It is advised not to use fentanyl during labour and delivery (including caesarean section) because fentanyl passes through the placenta and may cause respiratory depression in the fetus. If INSTANYL™ is administered; an antidote for the child should be readily available.

Nursing Women: Fentanyl is excreted into human milk; therefore, women should not breast-feed while taking INSTANYL™ because of the possibility of sedation and respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using INSTANYL™.

Pediatrics (< 18 years of age):
INSTANYL™ is not indicated for use in children under 18 years of age, as dosage requirements for the safe and effective use of INSTANYL™ have not been established for this patient population.

Geriatrics (> 65 years of age):
Limited data on pharmacokinetics, efficacy and safety are available for the use of INSTANYL™ in patients aged 65 years and older. In clinical trials elderly tend to titrate to a lower effective strength than patients less than 65 years of age. Elderly patients may be more sensitive to the effects of fentanyl, than the younger population. In the elderly, elimination of fentanyl may be slower and the terminal elimination half-life may be longer, which may result in accumulation of the active substance and a greater risk of undesirable effects. Therefore, exercise caution when titrating INSTANYL™ in elderly patients.

Information for Patients/Caregivers

The physician should advise the patient/caregiver that a Consumer Information leaflet is included in the package of INSTANYL™ dispensed to the patient. The patient/caregiver should read this leaflet very carefully before starting treatment with INSTANYL™. Patients receiving INSTANYL™ or their caregiver should be given the following instructions by the physician:

Patients and their caregivers must be instructed that children, especially small children, exposed to INSTANYL™ **are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep INSTANYL™ out of the sight and reach of children.

1. Patients should be informed that accidental use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.

2. Patients should be advised that INSTANYL™ contains fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone and oxymorphone.

3. Patients should be advised that INSTANYL™ should be taken as directed by the physician and the dose of INSTANYL™ should never be adjusted without the prescribing physician's instruction.

    a. The dose of INSTANYL™ will be adjusted until the physician finds the right dose for the patient that achieves adequate analgesia with tolerable side effects.

    b. INSTANYL™ should be used a maximum of twice for each episode of breakthrough cancer pain. The initial dose is taken at the onset of the breakthrough cancer pain episode, if adequate pain relief is not achieved after a minimum of 10 minutes a second dose can be administered. The patient should be instructed to wait four hours before treating the next episode of breakthrough cancer pain.

c. INSTANYL™ should not be used for more than four episodes of breakthrough cancer pain in one day. If the patient has more than four episodes of breakthrough cancer pain each day, the dose of the opioid pain medicine for the persistent background cancer pain may need to be changed.

d. Once the right dose for the patient has been found, the patient should not change the dose of INSTANYL™ unless directed by their physician.

4. INSTANYL™ comes in single-dose nasal sprays sealed in child-resistant blister packages. Patients should be advised not to open the package until ready to use.

5. Patients should be advised that INSTANYL™ may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).

6. Patients should be advised that INSTANYL™ should not be combined with alcohol or other CNS depressants (e.g. sleep medications, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.

7. Patients should be advised to consult their physician or pharmacist if other medications are being or will be used with INSTANYL™.

8. Patients should be advised that INSTANYL™ contains fentanyl, a drug with high potential for abuse. Patients, family members and caregivers should be advised to protect INSTANYL™ from theft or misuse in the work or home environment.

9. Patients should be instructed to keep INSTANYL™ in a secure place out of the sight and reach of children due to the high risk of fatal respiratory depression.

10. When INSTANYL™ is no longer needed, the unused INSTANYL™ single-dose nasal sprays should be returned to the pharmacy in the child-resistant blister for safe disposal.

11. Patients should be informed that accidental exposure or misuse may lead to death or other serious medical problems.

12. Patients should be advised to report episodes of uncontrolled breakthrough cancer pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

13. Patients should be advised of the most common adverse reactions that may occur while taking INSTANYL™: nausea, vertigo, vomiting, somnolence.

14. Patients should be advised that INSTANYL™ should never be given to anyone other than the individual for whom it was prescribed.

15. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with INSTANYL™. Women who are breast-feeding or pregnant should not use INSTANYL™.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Typical opioid adverse reactions are to be expected with INSTANYL™. Frequently, most opioid-associated adverse reactions will cease or decrease in intensity with continued use of INSTANYL™. The most serious adverse reactions associated with all opioids, including INSTANYL™, are respiratory depression (potentially leading to apnoea or respiratory arrest), circulatory depression, hypotension and shock. **Follow all patients for symptoms of respiratory depression.**

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of INSTANYL™ has been evaluated in 364 adult patients with breakthrough cancer pain exposed to nasal fentanyl. INSTANYL™ was generally well tolerated in clinical trials with a low incidence of adverse drug reactions. The overall safety profile was similar to other fentanyl products.

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

Common Clinical Trial Adverse Events (≥ 5%)

Treatment Emergent Adverse Events with an overall frequency of ≥ 5% that occurred during two pivotal trials (N=166), which include all events whether considered by the clinical investigator to be related to the study drug or not (regardless of causality), are listed in Table 1.

Table 1. Treatment Emergent Adverse Events which occurred during 2 pivotal clinical trials of nasal fentanyl in breakthrough pain in cancer patients at a frequency of ≥ 5% (regardless of causality)

System Organ Class Preferred Term	50 µg (N=152) %	100 µg (N=154) %	200 µg (N=150) %	Total, (N=166) %
Ear and Labyrinth Disorders				
Vertigo	2.0	3.2	3.3	7.2
Gastrointestinal Disorders				
Nausea	2.0	5.8	4.7	12.0
Vomiting	1.3	3.9	4.0	8.4
Constipation	3.3	3.2	3.3	9.0
General disorders and administration site conditions				
Asthenia	1.3	2.6	2.7	6.0

Less Common Clinical Trial Adverse Events (≥ 0.01% to <5%)

Additional adverse events occurring in clinical trials with an incidence of less than 1% include the following:

Cardiovascular: Hypotension
Ear and labyrinth: Motion sickness
Gastrointestinal: Constipation, stomatitis, dry mouth
General: Pyrexia
Nervous system: Sedation, myoclonus, paraesthesia, dysaesthesia, dysgeusia, somnolence, dizziness, headache
Psychiatric: Dependence, insomnia
Respiratory, thoracic and mediastinal: Respiratory depression, epistaxis, nasal ulcer, rhinorrhea, throat irritation
Skin and subcutaneous tissue: Pain of skin, pruritus, hyperhidrosis
Vascular disorders: Hot flushes

Post-Market Adverse Drug Reactions

Not known
Respiratory, thoracic and mediastinal: nasal septum perforation

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

Additive Effects of Other CNS Depressants
The concomitant use of other central nervous system depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages may produce additive depressant effects (e.g. hypoventilation, hypotension and profound sedation).

Patients on concomitant CNS depressants must be monitored for a change in opioid effects that may warrant adjustment to the dose of INSTANYL™.

Drug or Alcohol Dependence

Use of INSTANYL™ in combination with CNS depressants, including alcohol, can result in increased risk to the patient.

CYP 3A4 Inhibitors
Fentanyl is metabolised mainly via the human cytochrome P450 3A4 isoenzyme system (CYP 3A4), therefore potential interactions may occur when INSTANYL™ is given concurrently with agents that affect CYP 3A4 activity. The concomitant use of INSTANYL™ with CYP 3A4 **inhibitors** (e.g. indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, verapamil or cimetidine) could cause a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving INSTANYL™ who begin therapy with, or increase the dose of, CYP 3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases of both INSTANYL™ and CYP 3A4 inhibitors should be done conservatively (see **WARNINGS AND PRECAUTIONS**).

CYP 3A4 Inducers
The concomitant use of INSTANYL™ with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of INSTANYL™. Patients receiving INSTANYL™ who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased INSTANYL™ activity and the dose of INSTANYL™ should be adjusted accordingly.

MAO Inhibitors
INSTANYL™ is not recommended for use in patients who have received monoamine oxidase (MAO) inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Serotonergic Drugs
Coadministration of fentanyl with a serotonergic agent, such as a selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life threatening condition.

Use of Other Nasal Products
In a pharmacokinetic interaction study it was found that the maximum plasma concentration of INSTANYL™ 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™. The concomitant use of nasal decongestants should be avoided.

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

Drug-Food Interactions

The ingestion of grapefruit and grapefruit juice, which are CYP 3A4 inhibitors, could result in an increase in fentanyl plasma concentrations.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

General

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their approved labelling with respect to patient selection, dosing, and proper conditions for use (see **WARNINGS AND PRECAUTIONS**).

Dosing Considerations

Adults

INSTANYL™ is indicated for the management of breakthrough cancer pain in adults already receiving and who are tolerant to maintenance opioid therapy for chronic cancer pain. Patients considered opioid tolerant are those who are taking continuous medicine consisting of one of: at least 60 mg of oral morphine daily, at least 25 mcg/hr of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, **or** an equianalgesic dose of another opioid daily for a week or longer.

Recommended Dose and Dosage Adjustment

Dose Titration

INSTANYL™ doses should be individually titrated to the dose that provides adequate analgesia (pain relief) with tolerable side effects. Patients must be carefully monitored during the titration process.

The dose of INSTANYL™ for the treatment of breakthrough cancer pain is not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and **MUST** be determined by 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 (4) episodes of breakthrough cancer pain per day.

Starting Dose: All patients MUST begin treatment using one 50 mcg dose in one nostril.

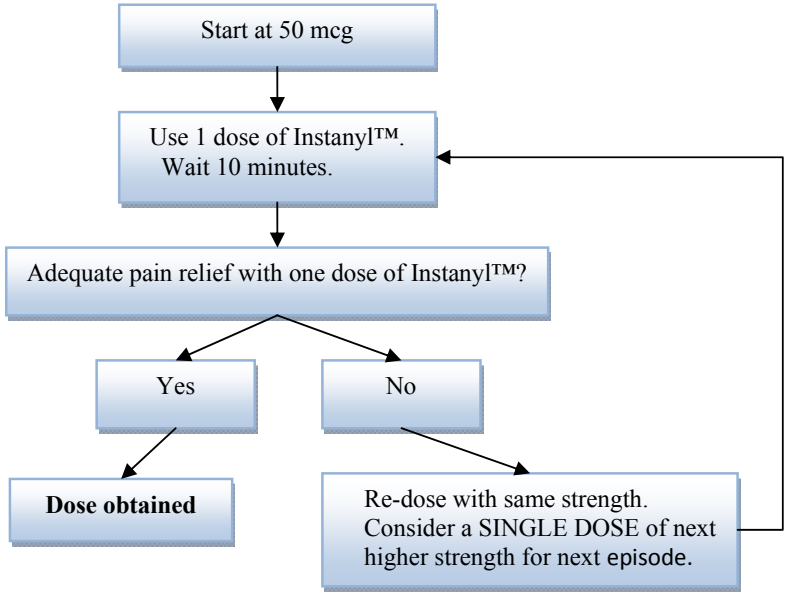
Due to differences in pharmacokinetic properties and individual variability, patients switching from another fentanyl product for breakthrough pain must be started on **no greater than 50 mcg of INSTANYL™.**

When prescribing, do not switch patients from any other fentanyl product to INSTANYL™ as INSTANYL™ is not equivalent on a mcg per mcg basis with any other fentanyl product.

Method of Titration

The initial strength should be one dose of 50 mcg in one nostril, titrating upwards as necessary through the range of available strengths (50, 100 and 200 mcg). If adequate analgesia is not obtained re-dosing of the same strength may be administered at the earliest after 10 minutes, preferably in the other nostril. **DO NOT ADMINISTER MORE THAN TWO DOSES FOR EACH BREAKTHROUGH PAIN EPISODE.** Each titration step (dose strength) should be evaluated in several episodes.

Figure 1. Dose Titration



Maintenance Therapy
Once the appropriate dose for pain management 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 re-dosing with the same strength can be done at the earliest after 10 minutes, this dose should preferably be taken in the other nostril.

Dose Re-Adjustment
Generally, the maintenance strength of INSTANYL™ should be increased when a patient requires more than one dose per breakthrough cancer pain episode for several consecutive episodes. Dose adjustment of the background opioid therapy may be required if the patient consistently presents with more than four breakthrough cancer pain episodes in 24 hours. If adverse reactions are intolerable or persistent, the strength should be reduced or treatment with INSTANYL™ replaced by other analgesics.

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

Patients should wait at least 4 hours before treating another breakthrough cancer pain episode with INSTANYL™ during both titration and maintenance therapy.

Discontinuation of Therapy
INSTANYL™ can be discontinued immediately if the patient no longer experiences breakthrough cancer pain episodes, provided the treatment for the persistent background pain

is kept as prescribed. If discontinuation of all opioid therapy is required, the recent INSTANYL™ dose should be taken into consideration for a gradual downward opioid titration to avoid the possibility of abrupt withdrawal effects.

Administration of INSTANYL™
INSTANYL™ is intended for nasal use and is delivered as a fine mist.

It is recommended that the patient's head is in an upright position when administrating INSTANYL™.

Use in Children
INSTANYL™ is not indicated for use in children under 18 years of age, as dosage requirements for the safe and effective use of INSTANYL™ have not been established for this patient population.

Use in the Elderly
In clinical trials elderly tend to titrate to a lower effective strength than patients less than 65 years of age. Elderly patients may be more sensitive to the effects of fentanyl, compared with the younger population. In the elderly, elimination of fentanyl may be slower and the terminal elimination half-life may be longer, which may result in accumulation of the active substance and a greater risk of undesirable effects. Therefore, exercise caution when titrating INSTANYL™ in elderly patients.

Use in Special Patient Populations
Special care should be taken during the titration process in patients with renal or liver dysfunction.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Clinical Presentation

The manifestations of INSTANYL™ overdosage are an extension of its pharmacological actions with the most serious effect being respiratory depression.

Treatment of Overdosage

Treatment of Overdosage (Accidental Ingestion) in the Opioid Non-Tolerant Person
For treatment of accidental ingestion *in the opioid non-tolerant person*, provide ventilatory support, intravenous access should be obtained, and naloxone or other opioid antagonists should be employed as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration of naloxone or other

opioid antagonists may be necessary. Consult the product monographs of the individual opioid antagonist for details about such use.

Treatment of Overdose in Opioid Tolerant Patients

For treatment of overdose *in opioid-tolerant patients*, provide ventilatory support and obtain intravenous access as clinically indicated. The judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

General Considerations for Overdose

Management of severe INSTANYL™ overdose includes: Securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and where swallowed, gastrointestinal decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, assist or control ventilation, and administer oxygen as indicated.

Although muscle rigidity interfering with respiration has not been seen following the use of INSTANYL™, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by the administration of an opioid antagonist, and, as a final alternative, by the administration of a neuromuscular blocking agent.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fentanyl is an opioid analgesic interacting primarily with the opioid μ-receptor, located in the brain, spinal cord and smooth muscle, as a pure agonist with a low affinity for the δ- and κ-opioid receptors. The principal pharmacological effects of fentanyl are on the central nervous system (CNS). The primary therapeutic action, and clinically most useful pharmacological effect, of INSTANYL™ is rapid analgesia.

Pharmacodynamics

The pharmacological effects of opioid agonists include analgesia, anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis and cough suppression. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by tolerability of side effects, the more serious of which may include somnolence and respiratory depression. Secondary actions include increase in the tone and decrease in the contractions

of the gastrointestinal smooth muscle, which results in prolongation of gastrointestinal transit time and may be responsible for the constipation typically seen with opioids.

Analgesia
The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life). The duration of analgesia of INSTANYL™ is 30 to 60 minutes. In opioid-naive individuals, analgesia occurs at blood levels of 1 to 2 ng/mL, while blood levels of 10-20 ng/mL would produce surgical anaesthesia and profound respiratory depression.

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of INSTANYL™ should be individually titrated to achieve the desired effect.

Central Nervous System
The precise mechanism of the analgesic action is unknown although fentanyl is known to be a μ-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid- like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation. Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g. pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

Urinary and Gastrointestinal Systems
Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.

Other opioid induced-effects may include a reduction in gastric, biliary, and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase. While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.

Cardiovascular System
Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and orthostatic hypotension.

Endocrine System
Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans.

They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species (rats, dogs). Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Respiratory System
All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects.

Peak respiratory depressive effect has been observed as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours. Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with intranasal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication.

Pharmacokinetics

Table 2. Summary of INSTANYL™'s Pharmacokinetic Parameters in opioid tolerant cancer patients

Parameter*	INSTANYL™ dose		
	50 mcg	100 mcg	200 mcg
C_{max} (pg/mL)	350.9 (225.88)	595.2 (400.06)	1194.8 (700.13)
$AUC_{0-\infty}$ (pg•h/mL)	925.6 (570.0)	1802.6 (928.0)	2354.5 (1270.7)
$T_{½}$ (h)	3.2 (1.8)	4.2 (3.2)	3.5 (1.3)
T_{max} (min)	15 [6, 90]	12 [6, 90]	15 [6, 25]

*** Mean (SD); Median [range]**

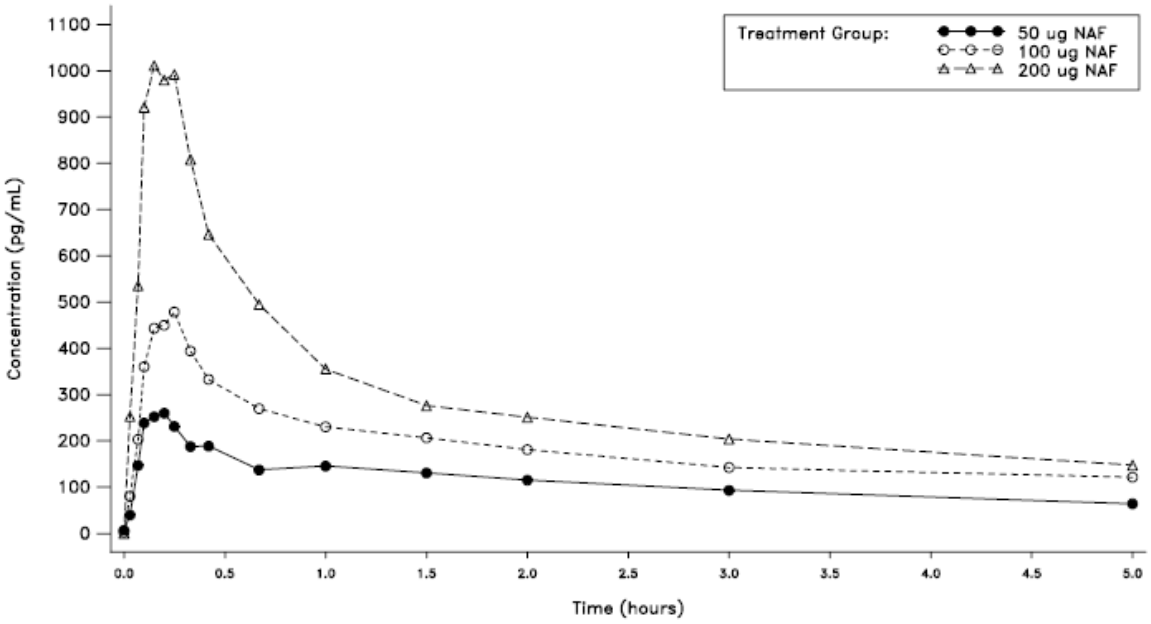
Absorption:
Fentanyl is highly lipophilic. Clinical data show that fentanyl is absorbed very rapidly through the nasal mucosa. Nasal drug absorption is aided by a highly vascular epithelium and relatively large surface area. Upon intranasal administration, fentanyl becomes available to the systemic circulation and after a lag-time of only a few minutes the clinical effects can be observed.

Administration of INSTANYL™ in single doses ranging from 50 to 200 mcg 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 to 15 minutes. Overall, the pharmacokinetic parameters after intranasal administration were similar in healthy patients, however, higher values for T_{max} were observed in a dose-proportionality study in healthy volunteers.

Following nasal application of INSTANYL™ the absolute bioavailability is about 89%. The absorption of INSTANYL™ across the nasal mucosa avoids first-pass hepatic metabolism, yielding a bioavailability substantially higher than oral or oral transmucosal administration.

Average plasma fentanyl levels following single doses of INSTANYL™ in cancer patients are shown in Figure 2.

Figure 2. Average Fentanyl Plasma Concentrations over Time, after 50, 100 and 200 mcg INSTANYL™



INSTANYL™ shows linear kinetics. Dose linearity of INSTANYL™ from 50 mcg to 400 mcg has been demonstrated in healthy subjects.

In a study comparing the bioavailability of the same nominal doses of INSTANYL™ and an oral transmucosal fentanyl citrate (OTFC) in 24 healthy subjects, the fentanyl absorption rate and extent of absorption were substantially greater with INSTANYL™ (76% greater maximum plasma concentration (C_{max}) and approximately 59% greater systemic exposure ($AUC_{0-\infty}$)

The effect of upper respiratory infections on the absorption of INSTANYL™ was assessed in subjects with the common cold. Following one 200 mcg INSTANYL™ dose, the extent of absorption was comparable between subjects with a common cold and matched healthy subjects. Thus, symptoms of the common cold (rhinorrhoea, sneezing and sinus fullness) do not alter the absorption of INSTANYL™.

In another study the effect of nasal vasoconstriction on fentanyl absorption was investigated. Subjects with allergic rhitinis received oxymetazoline nasal spray (nasal vasoconstrictor) 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 vasocontrictor is comparable

to that in healthy subjects. Concomitant use of nasal vasoconstrictor should be avoided (see **DRUG-DRUG INTERACTIONS**).

Distribution:
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 volume of distribution for fentanyl is 4 L/kg. 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™.

Metabolism:
Fentanyl is metabolised primarily in the liver via CYP 3A4. The major metabolite, norfentanyl is inactive.

Excretion:
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. The elimination half-life is approximately 3-4 hours for INSTANYL™ in cancer patients. The terminal elimination half-life was up to 15 hours in healthy subjects.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of INSTANYL™ has not been studied in children aged less than 18 years.

Geriatrics: Elderly patients may have a reduced clearance, a prolonged half-life and higher sensitivity to fentanyl than younger patients, which may result in accumulation of the active substance and a greater risk of undesirable effects.

Gender: After adjustment for body weight, there were no gender related differences in pharmacokinetics of INSTANYL™.

Hepatic Insufficiency: The influence of liver impairment on the pharmacokinetics of INSTANYL™ has not been determined. However, the clearance of intravenously administered fentanyl is decreased in hepatic disease due to alterations in metabolic clearance and plasma proteins.

Renal Insufficiency: The influence of renal impairment on the pharmacokinetics of INSTANYL™ has not been determined. However, the clearance of intravenously administered fentanyl is decreased in renal disease due to alterations in metabolic clearance and plasma proteins.

STORAGE AND STABILITY

Store at room temperature (15 to 30 °C), in the child-resistant blister.

SPECIAL HANDLING INSTRUCTIONS

Patients and their caregivers must be instructed that INSTANYL™ (fentanyl) contains medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. Patients and their caregivers must be instructed to keep INSTANYL™ out of the sight and reach of children.

In the case of a damaged nasal spray unit, caused from dropping the unit following removal from the blister packaging, the INSTANYL™ nasal spray unit should be discarded.

Disposal of INSTANYL™
Patients and members of their household must be instructed to dispose of any unused nasal spray units remaining from a prescription as soon as they are no longer needed. The unused nasal spray units should be returned, in their child-resistant blisters, to the pharmacy.

DOSAGE FORMS, COMPOSITION AND PACKAGING

INSTANYL™ is supplied as a fine mist nasal spray solution within a single-dose nasal spray unit, consisting of a vial (clear type I glass) and coated rubber stopper integrated within a plastic nasal spray unit, and are available in three colour-coded strength presentations:

1 dose of 100 microliters containing 50 mcg of fentanyl - Orange
1 dose of 100 microliters containing 100 mcg of fentanyl - Purple
1 dose of 100 microliters containing 200 mcg of fentanyl - Greenish-Blue

Each single-dose nasal spray unit is individually packed in a child-resistant blister. The blisters are also colour-coded, as above, by strength and are available in pack sizes of 2, 6, 8 and 10 nasal sprays.

Not all pack sizes may be marketed.

INSTANYL™ contains the following non-medicinal ingredients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, and purified water.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Fentanyl citrate

Chemical name: a) Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)

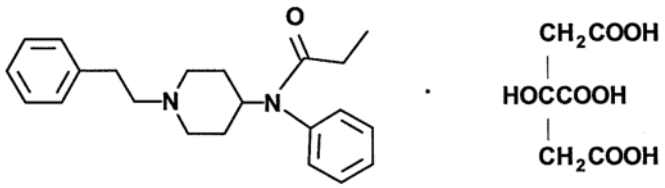
b) N-(1-Phenethyl-4-piperidyl)propionanilide citrate (1:1)

Molecular formula and molecular mass:

Molecular formula: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$

Molecular mass: 528.6

Structural formula:



Physicochemical properties:

Physical Description: white to off-white crystalline powder

Solubility: Sparingly soluble or soluble in water. Soluble in methanol.

pKa: 8.3

CLINICAL TRIALS

Study Demographics and Trial Design

Table 3. Summary of Patient Demographics for Pivotal (FT-017-IM and FT-018-IM) Clinical Trials in the Management of Breakthrough Cancer Pain

Study #	Trial Design and Duration	Route of Administration and Dosage	Study Subjects	Mean Age (Range)	Gender (%)
FT-017-IM	Randomized, double-blind, placebo-controlled, cross-over 8 BTCP episodes (~ 3 weeks)	Intranasal spray Fixed dose (50, 100 or 200 mcg) of INSTANYL™ and placebo	159 randomised 152 in ITT 138 completed	61.6 (35-79)	M: 52.6 F: 47.4
FT-018-IM Kress et al. 2009	Open-label dose-titration Up to 6 weeks Randomized, double-blind, placebo-controlled, cross-over 8 BTCP episodes (up to 3 weeks) Uncontrolled safety follow-up	Intranasal spray Titrated effective dose (50, 100 or 200 mcg) of INSTANYL™ and placebo	113 randomised 110 completed efficacy phase	60.6 (35-79)	M: 50 F: 50

BTCP = Breakthrough Cancer Pain

Pivotal Studies

The efficacy and safety of INSTANYL™ in opioid-tolerant cancer patients with breakthrough cancer pain was investigated in two pivotal studies. These studies demonstrated the efficacy and safety of INSTANYL™. No distinct correlation between the maintenance opioid dose and INSTANYL™ dose have been established.

Study FT-017-IM was a randomized, double-blind, placebo-controlled, cross-over study. All patients in FT-017-IM were receiving stable doses of chronic opioid treatment equivalent to 60-500 mg/day oral morphine or to 25-200 mcg/hour transdermal fentanyl, which in general reduced the intensity of the background pain to a mild level (≤ 4 on an 11-point NRS). Patients included in this study were also experiencing breakthrough cancer pain episodes at least 3 times per week but not more than 4 episodes per day.

All patients initially received a test dose of 200 mcg INSTANYL™ in order to assess tolerability. Patients who tolerated the test dose then received a single dose of 50, 100 or 200 mcg INSTANYL™ or placebo in a randomized order for the treatment of 8 breakthrough cancer pain episodes. Each dose and placebo were administered for two breakthrough cancer pain episodes, for a total of 8 self-treated episodes over approximately 3 weeks (maximum of

one episode per day), if insufficient pain relief was experienced a second dose of the same strength was taken after 10 minutes.

The pain intensity difference at 10 minutes (PID_{10}) after the first treatment spray was the primary efficacy endpoint. The secondary efficacy variables were the sum of the pain intensity differences over the time interval of 0-60 minutes ($SPID_{0-60}$), the general impression score, and the relationship between the dose of background pain opioid treatment and the titrated dose of INSTANYL™.

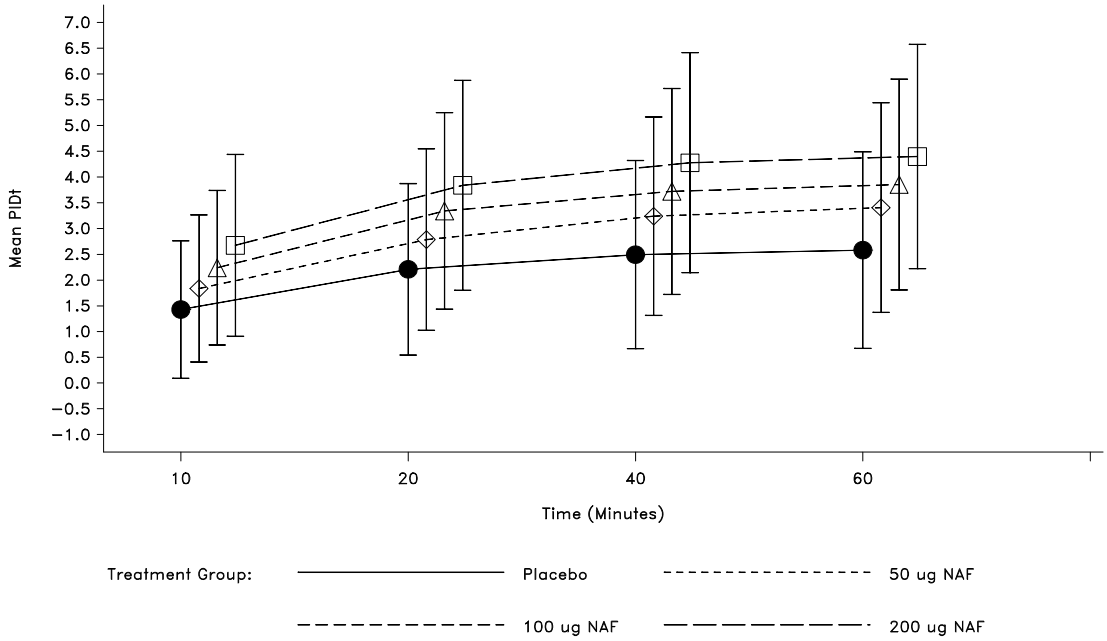
A clinically meaningful improvement in pain control for breakthrough cancer pain by 10 minutes post-dose was demonstrated (PID_{10} and PID_{10} responder rate). The PID_{10}, primary endpoint, was statistically significantly higher for all doses of INSTANYL™ (50, 100 and 200 mcg) than placebo ($p<0.001$) (Table 4). The proportion of responders at 10 minutes increased with dose. In both the pivotal clinical trials clinically meaningful pain relief was achieved by 10 minutes post-dose, as demonstrated by the primary endpoint, PID_{10}. The mean pain intensity difference (PID) can be seen in Figure 3 below, the persistence of pain relief beyond the first 10 minutes was sustained for 60 minutes, with PID_{max} occurring at between 30 to 60 minutes post-dose.

Table 4. Study FT-017-IM Primary Efficacy Endpoint – PID10 by INSTANYL™ Dose

ITT population	PID_{10} Mean (SD)	PID_{10} versus placebo LS mean (CI)	PID_{10} responder rate (%) Mean (SD)
Placebo (N=145)	1.41 (1.33)		22.07 (33.27)
Fentanyl 50 mcg (N=148)	1.82 (1.43)	0.41 (0.17, 0.64)*	29.05 (37.35)
Fentanyl 100 mcg (N=148)	2.23 (1.51)	0.81 (0.57, 1.04)*	41.55 (41.40)
Fentanyl 200 mcg (N=147)	2.65 (1.77)	1.24 (1.01, 1.48)*	49.66 (43.99)

CI=confidence interval; ITT=intent to treat; LS=least squares; SD=standard deviation; PID_{10}=pain intensity difference at 10 minutes.
* $p<0.001$ compared to placebo.

Figure 3. Mean PID over Time by INSTANYL™ Dose (Study FT-017-IM)



ITT population. Note that symbols for each dose level are offset to enable visual comparison.
ITT=intent to treat; NAF=nasal fentanyl (INSTANYL™); PID=pain intensity difference.

Both of the secondary endpoints, sum of the pain intensity difference at the first 60 minutes post-dose ($SPID_{0-60}$) and general impression scores, were supportive of the primary efficacy endpoint and were statistically significantly higher ($p<0.001$) for all doses of INSTANYL™ compared with placebo.

The effect for all efficacy parameters increased with dose, and all doses of INSTANYL™ were well tolerated and clinically effective regardless of the background level of opioid use.

A second pivotal study, FT-018-IM, for breakthrough pain in cancer patient consisted of three phases: an open-label dose-titration phase, a double-blind, randomized, placebo-controlled, cross-over efficacy assessment phase, and an uncontrolled safety follow-up phase. The primary objectives of the study were to confirm the efficacy of INSTANYL™ titrated to doses 50, 100 or 200 mcg for the treatment of breakthrough pain in cancer patients. All patients in the study were receiving stable doses of chronic opioid treatment equivalent to 60-500 mg/day oral morphine or to 25-200 mcg/hour transdermal fentanyl, which in general reduced the intensity of the background pain to a mild level (≤ 4 on an 11-point NRS). Patients included in this study were also experiencing breakthrough cancer pain episodes at least 3 times per week but not more than 4 episodes per day.

In the dose titration phase, the INSTANYL™ dose was increased from 50 to 200 mcg depending on efficacy and tolerability, until 3 of 4 episodes were treated successfully. In the

efficacy phase, the optimal dose from the titration phase was tested against placebo for the treatment of 8 episodes of breakthrough cancer pain (6 with INSTANYL™, 2 with placebo) over a period of approximately 3 weeks. Patients received a single dose at the onset of each episode of breakthrough cancer pain (up to 4 per day), with a second dose allowed after 10 minutes if the first dose provided inadequate pain relief.

In the efficacy phase, the primary efficacy endpoint was PID_{10} reflecting the importance of a fast onset of action and rapid pain relief. The secondary efficacy variables were $SPID_{0-60}$, general impression score, and the relationship between the dose of background pain opioid treatment and the titrated INSTANYL™ dose.

INSTANYL™ (all doses pooled) was found to be superior to placebo in treating breakthrough pain in cancer patients, all doses of INSTANYL™ provided higher mean PID_{10} scores in comparison with placebo. For all fentanyl doses pooled, PID_{10} scores were statistically significantly higher than placebo, with a least squares (LS) mean versus placebo of 1.26 ($p<0.001$). INSTANYL™ was statistically superior to placebo for the primary efficacy endpoint of PID_{10} (Table 5).

Table 5. Study FT-018-IM Primary Efficacy Endpoint – PID10

ITT population	PID_{10} Mean (SD)	PID_{10} responder rate (%) Mean (SD)
Placebo (N=110)	1.28 (1.45)	20.91 (34.12)
Fentanyl (all doses) (N=111)	2.56 (1.38)	51.08 (38.11)
LS mean [95% CI] fentanyl all doses versus placebo	1.26 (1.03, 1.48)*	ND

CI=confidence interval; ITT=intent to treat; LS=least squares; ND=not done; SD=standard deviation; PID_{10}=pain intensity difference at 10 minutes.
* $p<0.001$ compared to placebo

Secondary efficacy endpoints were generally supportive of the primary outcome. All of the INSTANYL™ dose groups (combined), when compared with placebo, had statistically significantly higher mean $SPID_{0-60}$ (1.87 vs. 0.94, respectively; $p<0.001$) and general impression scores (3.63 vs. 1.89, respectively; $p<0.001$).

DETAILED PHARMACOLOGY

Primary Pharmacodynamics

It is well-established that fentanyl is a potent, short-acting, synthetic, pure μ-opioid receptor agonist with the main pharmacologic activity being analgesia. The analgesic potency of fentanyl is approximately 100-fold greater than that of morphine. Fentanyl produces effective analgesia without significant respiratory depression at plasma concentrations ranging from 0.6-2 ng/mL. At higher plasma concentrations (>2 ng/mL), significant respiratory depression may occur. Significant non respiratory side effects associated with fentanyl include muscle rigidity, bradycardia, hypotension, nausea and vomiting, pruritus, and urinary retention. As with other narcotic analgesics, subjects may become tolerant to the effects of fentanyl after repeated administration.

Dependence
Recently, the effects of fentanyl withdrawal on brain reward function and somatic withdrawal symptoms were evaluated in male Wistar rats. The rats were trained on a modified discrete-trial intracranial self-stimulation procedure and implanted with 14-day minipumps containing saline or fentanyl citrate (1.2 mg/kg/day). Abrupt cessation of fentanyl administration resulted in a time-dependent elevation in brain reward thresholds and somatic withdrawal signs suggesting a severe deficit in brain reward function. Naloxone resulted in a dose-dependent elevation in brain reward thresholds and somatic withdrawal signs in fentanyl-treated rats; however, it did not alter the response latencies.

Pharmacokinetics
The pharmacokinetic profile of fentanyl is well established and consistent. Immediately following administration by any route, fentanyl is rapidly taken up by the brain, heart, and lung. Within 30 min, there is redistribution to other organs such as fat, muscle, and glandular tissues, followed by subsequent elimination mainly via urine.

TOXICOLOGY

Single and Repeat Dose Toxicity
Acute toxicity of fentanyl has been extensively studied in a range of non-clinical species by a range of different routes. At high doses marked clinical signs are observed, such as loss of muscle control, respiratory depression, cyanosis and mortality, with death generally considered to be due to respiratory depression. These effects are consistent with observed serious and fatal respiratory depression in cases of fentanyl and other μ-opioid receptor agonist overdose. Fentanyl has been shown to be safe and effective in clinical use for a number of years and is currently marketed in a number of different formulations. A single dose acute toxicity study in the rat showed a range of 14-29 mg/kg for the oral LD_{50}, the LD_{50} in mice is 11.2mg/kg following i.v. administration and 62 mg/kg following s.c. administration.

Repeat-dose toxicology studies have been performed for other fentanyl products administered by other routes. In a 4-week intravenous (i.v.) toxicity study in rats, no adverse effects were noted at 0.025 mg/kg/day. The exposure at the dose of 0.025 mg/kg/day i.v. and the dose of 0.010 mg/kg i.v. have been looked at in two studies where no adverse effects were seen.

Genotoxicity
The genotoxic potential of fentanyl and remifentanil, a fentanyl opiate analogue, has been extensively assessed. Fentanyl has been shown to be non-genotoxic in the Ames bacterial mutation, in vitro cytogenetics, in vitro mouse lymphoma mutagenesis assays, as well as an in vivo micronucleus cytogenetic assay and in a UDS assay. The results with the structurally related compound remifentanil are consistent with fentanyl and lend support for the lack of genotoxicity with this class of drug.

Carcinogenicity
Carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) did not induce any findings indicative of oncogenic potential.

Reproductive and Developmental Toxicity
In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 mcg/kg/day, s.c.) and is consistent with the sedative effects of fentanyl in animal studies. 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
The local tolerance of INSTANYL™ has been evaluated in two studies in the Göttingen mini-pigs. These studies showed no adverse clinical signs indicative of systemic toxicity or local toxicity at the site of administration, and demonstrated that INSTANYL™ administration was well tolerated.

REFERENCES

1. Ashburn MA, Streisand J, Zhang J, Love G, Rowin M, Niu S, et al. The iontophoresis of fentanyl citrate in humans. Anesthesiology 1995;82(5):1146-53
2. Christrup LL, Foster D, Popper LD, Troen T, Upton R. Pharmacokinetics, efficacy and tolerability of fentanyl following intranasal versus intravenous administration in adults undergoing third-molar exraction: a randomized, double-blind, double-dummy, two-way, crossover study. Clin Ther 2008;30(3):469-481
3. Hagen NA, Fisher K, Victorino C, Farrar JT. A titration strategy is needed to manage breakthrough cancer pain effectively: observations from data pooled from three clinical trials. J Palliat Med 2007;10(1):47-55
4. Kassa S, Moksnes K, Nolte T, Lefebvre-Kuntz D, Popper L, Kress HG. Pharmacokinetics of intranasal fentanyl spray in patients with cancer and breakthrough pain. J Opioid Mang 2010;6(1):17-26
5. Kress HG, Oronska A, Kaczmarek Z, Kaasa S, Colberg T, Nolte T. Efficacy and Tolerability of Intranasal Fentanyl Spray 50 to 200 mcg for breakthrough pain in patients with cancer: a phase II, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. Clin Thera 2009;31(6):1177-1191
6. McClain D, Hug C. Intravenous Fentanyl Kinetics. Clin Pharmcol Ther. 1980; 28(1):106-114
7. Moksnes K, Fredheim OV, Klepstad P, Kassa S, Angelsen A, Nilsen T, Dale O. Early pharmacokinetics of nasal fentanyl: is there a significant arterio-venous difference? Eur J Clin Pharmacol 2008;64(5):497-502
8. O'Neil G, Paech M, Wood F. Preliminary clinical use of a patient-controlled intranasal analgesia (PCINA) device. Anaesth Intensive Care 1997;25(4):408-12
9. Peng PW, Sandler AN. A review of the use of fentanyl analgesia in the management of acute pain in adults. Anesthesiology 1999;90(2):576-599
10. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 1999;81:129-134
11. Villiger JW, Ray LJ, Taylor KM. Characteristics of [3H] fentanyl binding to the opiate receptor. Neuropharmacology 1983; 22:447-452
12. Zeppetella G. Nebulized and intranasal fentanyl in the management of cancer-related breakthrough pain. Palliat Med 2000;14(1):57-8
13. Zeppetella G. An assessment of the safety, efficacy, and acceptability of intranasal fentanyl citrate in the management of cancer-related breakthrough pain: a pilot study. J Pain Symptom Manage 2000;20:253-8

PART III: CONSUMER INFORMATION

^{N}INSTANYL™

Fentanyl Nasal Spray

This leaflet is part III of a three-part "Product Monograph" published when INSTANYL™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INSTANYL™. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this before you start using INSTANYL™, and every time you get a new prescription. Remember, this information does not take the place of your doctor's instructions

- Keep INSTANYL™ in a safe place away from children and pets, and to prevent theft, misuse or abuse. Accidental use by a child or pet is a medical emergency and may result in death. If a child or pet accidentally uses INSTANYL™ get emergency help right away.
- Do not use INSTANYL™ if the blister pack is broken.
- Do not use INSTANYL™ in front of children.
- Make sure you read the **PROPER USE OF THIS MEDICATION** and **WARNINGS AND PRECAUTIONS** sections. Follow the instructions and always use INSTANYL™ the right way. INSTANYL™ can cause serious breathing problems and death, especially if it is used the wrong way.
- Tell your doctor if you (or a family member) have ever abused or been dependent on alcohol, prescription medicines or street drugs.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT INSTANYL™

INSTANYL™ is a nasal spray that contains fentanyl. **Fentanyl is a very strong opioid narcotic pain medicine that can cause serious and life-threatening breathing problems because of an overdose or if the dose you are using is too high for you. Get emergency medical help immediately if you:**

- Have trouble breathing, or have slow or shallow breathing
- Have a slow heartbeat
- Have severe sleepiness
- Have cold, clammy skin
- Feel faint, dizzy, confused, or cannot think, walk or talk normally
- Have a seizure
- Have hallucinations

ABOUT THIS MEDICATION

IMPORTANT

INSTANYL™ can cause serious breathing problems that can progress to death. Read this information carefully before you take INSTANYL™ and every time you get a new prescription.

What the medication is used for:

Adults

INSTANYL™ is a strong prescription pain medicine that is used to relieve the sudden flares of pain that can occur unexpectedly, while you are taking regular doses of opioid pain killers for your constant cancer pain.

Those sudden flares of pain are described as "breakthrough pain" because they happen or break through your regularly taken opioid pain killers for your constant cancer pain, and usually last for a short while

INSTANYL™ is intended for patients already treated with opioids for their usual pain.

What it does:

INSTANYL™ contains fentanyl which belongs to a group of strong painkillers called opioids. Opioids act by blocking the pain signals to the brain. INSTANYL™ acts very fast, giving you pain relief starting as early as 10 minutes after administration

When it should not be used:

- **Do not use INSTANYL™ unless you are using another opioid pain medication regularly for your cancer pain and your body is used to this medicine (opioid tolerant).**
- Do not use INSTANYL™ if you have severe problems with your breathing or your lungs.
- Do not use INSTANYL™ if you know you are allergic to fentanyl or any of the other ingredients of INSTANYL™ (See "**What the medicinal ingredient is**" and "**What the non-medicinal ingredients are**")
- Do not use INSTANYL™ if you are currently taking monoamine-oxidase (MAO) inhibitors (used for severe depression) or have done so in the past 2 weeks.
- Do not use if you suffer from recurrent nose bleeding
- If you have damage to the nasal cavity from previous facial radiotherapy

Pediatrics:

INSTANYL™ is not indicated, and should not be used, in children under 18 years of age as safety and efficacy have not been established.

What the medicinal ingredient is:

Fentanyl

What the nonmedicinal ingredients are:

Disodium phosphate dihydrate, purified water, and sodium dihydrogen phosphate dihydrate.

What dosage forms it comes in:
INSTANYL™ is a nasal spray; each nasal spray unit contains one dose. It is supplied in a child-resistant blister package, colour coded by strength. INSTANYL™ comes in three strengths (per spray):
50 mcg: labelling is orange
100 mcg: labelling is purple
200 mcg: labelling is greenish-blue

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious adverse reactions, including death can occur if you take INSTANYL™ without being opioid-tolerant, i.e. if you have not regularly used other opioid medicine for your cancer pain before you start taking INSTANYL™ for your sudden flares of pain. INSTANYL™ is not indicated for you if you use opioids only intermittently, on an as needed basis.

You or a family member should call your doctor or get emergency medical help immediately if you have trouble breathing, drowsiness with slow breathing, slow shallow breathing (little chest movement with breathing) or feel faint, dizzy, confused or have other unusual symptoms. These can be symptoms of an overdose with INSTANYL™. Your dose of INSTANYL™ may be too high for you. These symptoms may lead to serious problems or death if not treated immediately. If you have any of the above symptoms, do not take another dose of INSTANYL™.

You must begin treatment of INSTANYL™ at the lowest does of 50 mcg.

If your breakthrough cancer pain is not relieved after 10 minutes, you may use only ONE more puff of INSTANYL™ in that episode of breakthrough cancer pain. You must wait at least 4 hours before treating a new episode of breakthrough cancer pain with INSTANYL™.

INSTANYL™ contains a medicine that can be fatal to children, to any other adult for whom it is not prescribed, and to those who are not regularly taking opioid medicine for their cancer pain.

Tell your doctor about all the medicines you take and consult with your doctor before taking any new medications while taking INSTANYL™. Some other medications that you may be using can affect the level of INSTANYL™ in your body and this may potentially cause respiratory problems and death.

Before you use INSTANYL™ talk to your doctor or pharmacist about all of your medical and mental health problems, especially if you have:

- Trouble breathing or lung problems such as asthma, wheezing or being short of breath
- A head injury or brain problems
- Liver or kidney problems
- Seizures (convulsions or fits)
- Slow heart rate or other heart problems
- Low blood pressure
- Mental health problems such as major depression or hallucinations (seeing or hearing things that are not real)
- Past or present drinking problem or alcoholism for you or a family member
- Past or present drug abuse or addiction problems for you or a family member
- You experience recurrent nose bleeding or nasal discomfort.
- You have previously received facial radiotherapy

Tell your doctor if you are:
Pregnant or planning to become pregnant. INSTANYL™ may cause harm to your unborn baby.

Breast feeding. Fentanyl can pass into the breast milk and may cause side effects to the breast-fed child. You should not use INSTANYL™ while breast feeding.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, other nasal spray products, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with INSTANYL™. Sometimes the doses of certain medicines and INSTANYL™ may need to be changed if used together.

- Do not start taking any medicine while using INSTANYL™ until you have talked with your doctor. Your doctor will tell you if it is safe to take other medicines while you are using INSTANYL™.
- Be very careful about taking other medicines that make you sleepy, such as other pain medicines or some depression medicines (antidepressants that make you sleepy), sleeping pills, anxiety medicines, tranquilizer medicines, or some allergy medicines (antihistamines that make you sleepy).
- Do not drive or operate machinery or do other dangerous activities until you know how INSTANYL™ affects you as it can make you sleepy.
- Do not drink alcohol while using INSTANYL™ as it can increase your chance of having dangerous side effects

Know the medicines you take. Keep a list of your medicines to show your doctor and pharmacist.

INTERACTIONS WITH THIS MEDICATION

Interactions can occur between INSTANYL™ and other drugs that use a system called CYP 3A4 in the body. Tell your doctor about all the medicines you are taking as your INSTANYL™ prescribed dose will have to be increased or decreased accordingly.

PROPER USE OF THIS MEDICATION

IMPORTANT:

- Always use INSTANYL™ exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure about the treatment or if you have additional questions.
- INSTANYL™ is for nasal use
- When you first start using INSTANYL™, your doctor will work with you to find the dose that will relieve your breakthrough cancer pain.
- Do not change the dose of INSTANYL™ or your other pain medicines on your own. Change in dosage must be done together with your doctor.
- If your breakthrough cancer pain is not relieved after 10 minutes, you may use only one more puff for this episode. **DO NOT USE MORE THAN TWO PUFFS FOR EACH BREAKTHROUGH PAIN EPISODE**
- You should wait four hours before treating the next episode of breakthrough cancer pain.
- Do not use INSTANYL™ for more than four episodes of breakthrough cancer pain per day.

Starting Dose

The initial dose is one puff of 50 mcg in one nostril. If your breakthrough cancer pain is not relieved after 10 minutes, you may use only one more puff for this episode.

Subsequent Doses

To find the right dose for you, your doctor will instruct you on how to safely increase your dose, which provides you with adequate pain relief and if there are side effects that they are acceptable to you.

If the pain is not relieved adequately after the first dose, a second dose of INSTANYL™ may be taken after 10 minutes for that episode of breakthrough cancer pain. You should wait at least 4 hours before treating the next episode of breakthrough cancer pain.

Your doctor will provide you with a prescription to treat up to four breakthrough cancer pain episodes per day by using the indentified dose.

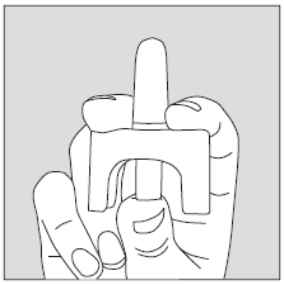
Your doctor will monitor your reaction to the increases in INSTANYL™ dose as well as any side effects that you may experience.

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

How to Use your INSTANYL™ Nasal Spray

Each nasal spray is sealed in a child-resistant blister. Do not open the blister before you are ready to use the spray. If an INSTANYL™ nasal spray unit is dropped following removal from the blister packaging and the unit is damaged, the unit should not be used. The damaged unit should be disposed of. Each nasal spray contains only one dose of INSTANYL™. **Do not test before use.**

- To open cut with scissors along the perforated line 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 nasal spray with your thumb supporting it at the plunger at the bottom and your index and middle finger on either side of the spray tip.



- 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 1cm). 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 preferably 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 nasal spray from the nose.
- You may not feel the dose in your nose, but you have received it when the plunger has been pressed.
- Your nasal spray is now empty.

Overdose:

If you accidentally take more than your prescribed dose of INSTANYL™, seek emergency medical help by calling 911 or going to a hospital emergency department immediately.

Overdose with an opioid medicine such as INSTANYL™ can cause serious problems, the most serious being trouble breathing, extreme drowsiness with slowed breathing, and slow shallow breathing. Other signs of INSTANYL™ overdose may include tiredness, extreme sleepiness or sedation; inability to think, talk or walk normally; and feeling faint, dizzy or confused, seizure and hallucination.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, INSTANYL™ can cause side effects, although not everybody gets them.The most common side effects of INSTANYL™ are nausea, vertigo, vomiting,

drowsiness, dizziness, headache, sweating, throat irritation and hot flash.

INSTANYL™ can cause your blood pressure to drop. This can make you feel dizzy if you get up too fast from sitting or lying down.

INSTANYL™ can cause physical dependence if taken regularly. Do not stop taking INSTANYL™ or any other opioid without talking to your doctor. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.

There is a chance of abuse or addiction with INSTANYL™. The chance is higher if you are or have previously been addicted to or abused other medications, street drugs, or alcohol, or if you have a history of mental health problems. Your doctor can advice you on these risks.

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

Talk with your doctor about any side effects that bother you or do not go away. These are not all the side effects of INSTANYL™. For more information, ask your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

You or a family member should call your doctor or get emergency medical help immediately if you have any of the symptoms below:

- Trouble breathing
- Extreme drowsiness with slowed breathing
- Slow, shallow breathing (little chest movement with breathing)
- Feel faint, dizzy or confused
- Inability to think, talk or walk normally
- Seizure and hallucination

These can be symptoms of an overdose of INSTANYL™. Your dose of INSTANYL™ may be too high for you. **These symptoms may lead to serious problems or death if not treated immediately. Do not take another dose of INSTANYL™.**

This is not a complete list of side effects. For any unexpected effects while taking INSTANYL™, contact your doctor or pharmacist.

HOW TO STORE IT

Keep INSTANYL™ in a safe place away from the sight and reach of children. **The amount of fentanyl contained in INSTANYL™ can be fatal to a child. INSTANYL™ should be used immediately after opening the child-resistant package.**

Store INSTANYL™ at room temperature (15 to 30°C).
Do not use INSTANYL™ after the expiry date which is stated on the nasal spray as EXP.

How to dispose of any unused INSTANYL™
INSTANYL™ can be harmful to other people, especially children. Unused INSTANYL™ should not be disposed of via wastewater or household waste. Any unused nasal sprays should be returned in the child-resistant blister to the pharmacy. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Adverse events may be reported directly to Takeda Medical Information & Pharmacovigilance at: 1-866-295-4636.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.takedacanada.com or by contacting the sponsor, Takeda Canada Inc., at:
1-866-295-4636.

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