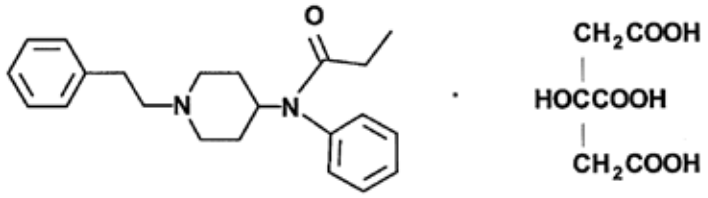
PRODUCT INFORMATION

INSTANYL® NASAL SPRAY

NAME OF THE MEDICINE

Fentanyl citrate

Chemical Structure



Molecular formula: C22H28N2O•C6H8O7

Molecular mass: 528.6

CAS Number

990-73-8

DESCRIPTION

Fentanyl citrate is a white to off-white crystalline powder, sparingly soluble in water, soluble in methanol, with pKa: 8.3.

Instanyl is a nasal spray solution containing fentanyl citrate. It is presented in (a) single dose vials integrated within a plastic nasal spray unit and containing 50, 100 or 200 micrograms of fentanyl (as fentanyl citrate), or (b) multi-dose glass bottles with metering pump and dust cap containing 50, 100 or 200 micrograms of fentanyl (as fentanyl citrate) per dose. The solution also contains sodium phosphate - monobasic dihydrate, sodium phosphate - dibasic dihydrate and water – purified.

PHARMACOLOGY

Pharmacodynamics

Fentanyl is an opioid analgesic interacting primarily with the opioid μ-receptor as a pure agonist with low affinity for the d- 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.

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

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

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

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

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

The clinical experience with Instanyl in patients with background opioid treatment equivalent to ³ 500 mg/day morphine or ³ 200 micrograms/hour transdermal fentanyl is limited.

Pharmacokinetics

Instanyl has been specifically formulated as a preservative-free, isotonic nasal spray solution, providing rapid absorption of fentanyl through the nasal mucosa. 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. If switching to INSTANYL from another fentanyl product for breakthrough pain, independent dose titration with INSTANYL is required as the bioavailability between products differs significantly (see DOSAGE AND ADMINISTRATION).

Absorption

Fentanyl is highly lipophilic. Fentanyl exhibits three compartment distribution kinetics. The absolute bioavailability of INSTANYL is close to 100% (when described as a one-compartment model). 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 Cmax level of 0.35 to 1.2 ng/ml. The corresponding median Tmax are 12-15 minutes. However, higher values for Tmax were observed in a dose-proportionality study in healthy volunteers.

Dose linearity

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

Bioequivalence

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

Distribution

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%. 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. The mean volume of distribution at steady-state (Vss) is 4 L/kg.

Metabolism

Fentanyl is metabolised primarily in the liver via CYP3A4. The major metabolite, norfentanyl is inactive. Fentanyl is metabolised in the liver to norfentanyl by cytochrome CYP3A4 isoform. Norfentanyl is not pharmacologically active in animal studies. It is more than 90% eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.

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.

CLINICAL TRIALS

The efficacy and safety of INSTANYL (50, 100 and 200 micrograms) have been assessed in two randomised, double-blind, cross-over, placebo-controlled pivotal Phase III studies in 279 opioid-tolerant adult cancer patients (age 32-86 years) with breakthrough pain (BTP). BTP is transitory exacerbation of pain that occurs in addition to otherwise stable persistent pain, is typically rapid in onset with mean peak pain at 3 minutes, moderate to severe in intensity and relatively short in duration (30 to 60 minutes). The patients had an average of 1 to 4 episodes per day while taking maintenance opioid therapy. Patients in the second pivotal study had earlier participated in the INSTANYL pharmacokinetic study or in the first pivotal study. The clinical studies demonstrated the efficacy and safety of INSTANYL. No distinct correlation between the maintenance opioid dose and INSTANYL doses have been established, however in the second pivotal study patients with low maintenance opioid dose tended to achieve effective pain relief with a correspondingly lower strength of INSTANYL compared to patients taking higher levels of maintenance opioid dose. This was most distinct for patients ending on INSTANYL 50 micrograms.

In the clinical studies in cancer patients, the most frequent strength used were 100 and 200 micrograms. All three strengths of INSTANYL showed statistically significant ($p<0.001$) higher pain intensity difference at 10 minutes (PID10) 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 (SPID0-60) showed that all strengths of INSTANYL had significantly higher mean SPID0-60 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 BTP episode. INSTANYL should not be used pre-emptively. The clinical experience with INSTANYL in patients with background opioid treatment equivalent to ^{3} 500 mg/day morphine or ^{3} 200 micrograms/hour transdermal fentanyl is limited.

Study FT-017-IM was a randomized, double-blind, placebo-controlled, cross-over study in cancer patients with BTP. All patients in FT-017-IM were receiving stable doses of chronic opioid treatment. Chronic opioid treatment is defined as equivalent to 60-500 mg/day oral morphine or to 25-200 µg/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 BTP episodes at least 3 times per week but not more than 4 episodes per day.

Pain intensity was assessed using an 11-point numerical rating scale. The primary efficacy outcome measure was Pain Intensity Difference at 10 minutes after dosing with the first study drug (PID10). Patients received a single dose of 50, 100 or 200 µg INSTANYL or placebo in a randomized order for the treatment of 8 BTP episodes. Each dose and placebo were administered for two BTP 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.

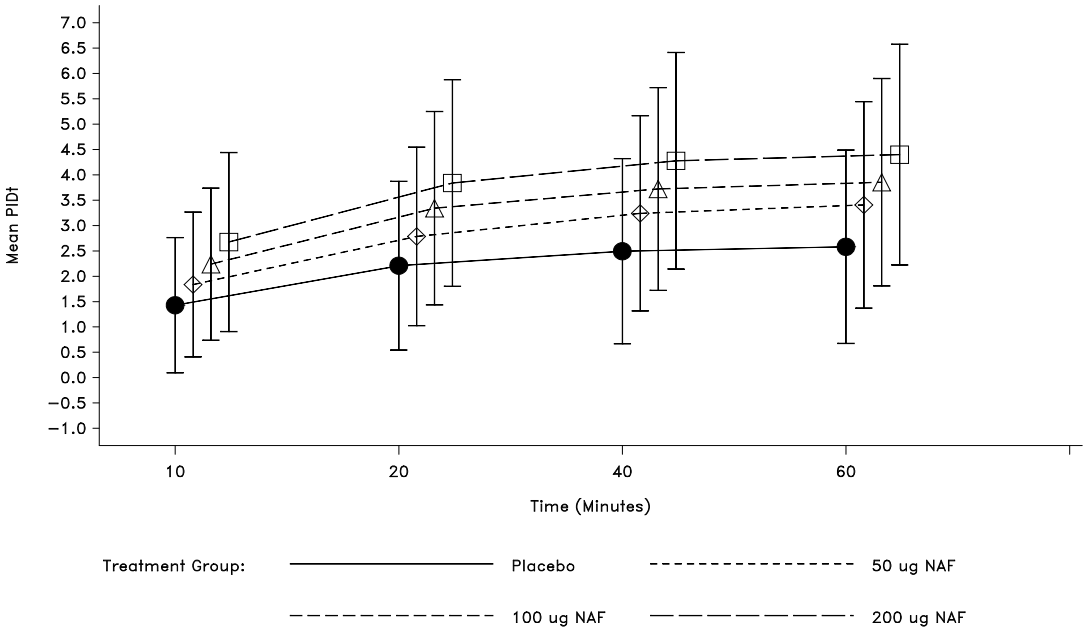
A clinically meaningful improvement in pain control for BTP by 10 minutes post-dose was demonstrated (pain intensity difference at 10 minutes (PID10) and PID10 responder rate). The PID10, primary endpoint, was statistically significantly higher for all doses of INSTANYL (50, 100 and 200 µg) than placebo ($p<0.001$) (Table 1). The proportion of responders at 10 minutes increased with dose. The mean PID can be seen in Figure 1 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 1. Study FT-017-IM Primary Efficacy Endpoint – PID_{10} 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 µg (N=148)	1.82 (1.43)	0.41 (0.17, 0.64)*	29.05 (37.35)
Fentanyl 100 µg (N=148)	2.23 (1.51)	0.81 (0.57, 1.04)*	41.55 (41.40)
Fentanyl 200 µg (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 1. 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 (SPID0-60) and general impression scores (GI), were also statistically significantly higher (p<0.001) for all doses of INSTANYL compared with placebo (Table 2).

Table 2. Study FT-017-IM Secondary Efficacy Endpoints - General Impression Score at 60 minutes and SPID0-60 by INSTANYL Dose

ITT population	GI at 60 minutes Mean (SD)	$SPID_{0-60}$ Mean (SD)
Placebo (N=146)	0.96 (0.86)	2.02 (1.50)
Fentanyl 50 µg (N=148)	1.32 (0.96)*	2.64 (1.59)*
Fentanyl 100 µg (N=149)	1.57 (0.85)*	3.10 (1.68)*
Fentanyl 200 µg (N=148)	1.90 (0.97)*	3.53 (1.83)*

GI=general impression; ITT=intent to treat; SD=standard deviation; $SPID_{0-60}$=sum of pain intensity differences from 0 to 60 minutes.
* p<0.001 compared to 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 BTP in cancer patients 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 µg for the treatment of BTP in cancer patients, and to establish the long-term safety of INSTANYL treatment. All patients in the study were receiving stable doses of chronic opioid treatment. Chronic opioid treatment is defined as equivalent to 60-500 mg/day oral morphine or to 25-200 µg/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 BTP episodes at least 3 times per week but not more than 4 episodes per day and many patients enrolled in this study had previously demonstrated tolerance of opiods for BTP.

In the dose titration phase, the INSTANYL dose was increased from 50 to 200 µg 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 BTP (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 BTP (up to 4 per day), with a second dose allowed after 10 minutes if the first dose provided inadequate pain relief. In the safety follow-up phase, patients continued treatment with the dose of INSTANYL selected in the titration phase, with dose adjustment if needed. In the efficacy phase, the primary efficacy endpoint was PID10 reflecting the importance of a fast onset of action and rapid pain relief. The secondary efficacy variables were SPID0-60, 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 BTP in cancer patients, all doses of INSTANYL provided higher mean PID10 scores in comparison with placebo. For all fentanyl doses pooled, PID10 scores were statistically and clinically significantly higher than placebo, with a least squares (LS) mean versus placebo of 1.26 ($p<0.001$). INSTANYL was statistically and clinically superior to placebo for the primary efficacy endpoint of PID10 (Table 3).

Table 3. 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

All of the INSTANYL dose groups had statistically significantly higher mean SPID0-60 and general impression scores compared with placebo ($p<0.001$). Table 4 summarizes the results of the secondary endpoints. For all INFS dose groups combined, mean general impression and mean SPID0-60 were statistically significantly higher than placebo.

Table 4. Study FT-018-IM Secondary Efficacy Endpoints – General Impression Score at 60 minutes and $SPID_{0-60}$

ITT population	GI at 60 minutes Mean (SD)	$SPID_{0-60}$ Mean (SD)
Placebo (N=110)	0.94 (0.97)	1.89 (1.75)
Fentanyl (all doses) (N=111)	1.87 (0.54)	3.63 (1.51)
LS mean [95% CI] fentanyl all doses versus placebo	0.93 [0.77, 1.08]*	1.70 [1.45, 1.94]*

CI=confidence interval; GI=general impression; ITT=intent to treat; SD=standard deviation; $SPID_{0-60}$=sum of pain intensity differences from 0 to 60 minutes.
* $p<0.001$ compared to placebo.

One supportive study, FT-019-IM, was conducted to compare the efficacy of INSTANYL with an active comparator, oral transmucosal fentanyl citrate lozenge (Actiq), in the management of BTP in cancer patients on maintenance opioid therapy. This study was an open-label, randomised, cross-

over, active-controlled trial. All patients in the study were receiving stable doses of chronic opioid treatment. Chronic opioid treatment is defined as equivalent to 60-500 mg/day oral morphine or to 25-200 µg/hour transdermal fentanyl, which in general reduced the intensity of the background pain to a mild level (≤ 4 on an 11-point NRS). Patients were randomly assigned to receive either INSTANYL or Actiq during the first titration and efficacy phase. In the titration phase, the dose was increased (50 to 200 µg for INSTANYL; 200 to 1600 µg for Actiq) depending on efficacy and tolerability for the patient, until 3 of 4 BTP episodes were treated successfully. In the efficacy phase, the optimal dose from the titration phase was tested for treatment of 6 BTP episodes over a period of approximately 2 weeks. The process was then repeated for the other study drug. At the onset of each BTP episode (up to a maximum of 4 per day) patients took a single dose of study drug. A second dose was allowed if the first dose provided inadequate pain relief after 10 minutes with INSTANYL, or after 30 minutes with the active comparator.

The primary efficacy endpoint was the proportion of patients who experienced a faster onset of meaningful pain relief with INSTANYL as compared to Actiq. The time to onset of meaningful pain relief was recorded by stopwatch, and was defined as the time at which the patient experienced meaningful pain relief. The secondary efficacy variables were PID at 10 and 30 minutes, SPID0-15 and SPID0-60, general impression at 60 minutes, ease of administration using a 5 point scale (measured at the end of each efficacy phase), and patient's preference (INSTANYL or Actiq, measured at the end of the second efficacy phase). For the analysis of the primary efficacy endpoint of time to the onset of meaningful pain relief, the median total difference between INSTANYL and Actiq was 4.3 minutes, indicating a faster time to meaningful pain relief using INSTANYL, with 66% of patients achieving faster pain relief on INSTANYL. The overall median time to onset of meaningful pain relief was 10.6 minutes for INSTANYL, and 15.7 minutes for Actiq. Analysis of the time to onset by treatment sequence indicated that time to meaningful pain relief was faster with INSTANYL regardless of which treatment was taken first. INSTANYL was statistically significantly superior to Actiq at all time points measured. The additional analysis of PID at 5, 15, 20 and 60 minutes post-dose, showed a statistically and clinically significant separation between the two groups in favour of INSTANYL as early as 5 minutes post-dosing. Using imputed values for fastest median time to meaningful pain relief, 65.7% of patients reported fastest relief using INSTANYL ($p<0.001$, 95% CI: 57.1, 73.6).

All secondary efficacy endpoints were statistically significantly favourable to INSTANYL, even after multiplicity adjustment. The reduction in pain intensity was significantly higher with INSTANYL as early as 5 minutes post-dose, and continued to be so at the 10, 15, 20 and 30 minute time points. All doses of INSTANYL provided statistically significantly higher mean PID10 scores (ranging from 1.63 to 3.00) in comparison to all doses of Actiq (Table 5). Similar results were observed for PID30.

Table 5. PID_{10} (Study FT-019-IM) – ITT population

	INSTANYL PID_{10}	**Actiq PID_{10}**
n	101	100
Number missing	1	0
Mean	2.39	1.10
SD	1.90	1.12
Median	2.00	0.83
Range	0.0 to 7.8	-0.3 to 6.0

ITT=intent to treat; SD=standard deviation; PID_{10}=pain intensity difference at 10 minutes.

All INSTANYL doses provided statistically significantly higher mean overall sum of the pain intensity differences in the first 15 minutes (SPID0-15 scores ranging from 1.25 to 2.14) compared with all Actiq doses (ranging from 0.40 to 1.09). Similar results were observed for SPID0-60 scores (means ranging from 3.27 to 4.33 for INSTANYL and from 1.83 to 3.51 for Actiq). INSTANYL was considered preferable (77.4% INSTANYL compared to 22.6% Actiq, $p<0.001$) and easier to use by a majority of patients in comparison to Actiq ($p<0.001$).

INDICATIONS

INSTANYL is indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain.

CONTRAINDICATIONS

Patients with known hypersensitivity to fentanyl or to any of the excipients (see DESCRIPTION).

Use in patients not receiving opioid maintenance therapy for cancer–related pain unless under the immediate supervision of healthcare professionals such as in a hospital or in-patient clinic.

Severe respiratory depression or severe obstructive lung conditions;

Previous facial radiotherapy;

Recurrent episodes of epistaxis (see Precautions)

PRECAUTIONS

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

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 commencing INSTANYL must be titrated to an appropriate dose (see DOSAGE AND ADMINISTRATION). Do not convert patients on a microgram per microgram basis from any other fentanyl products to INSTANYL. No other product should be substituted for INSTANYL. Failure to titrate as recommended may result in overdose.

Maintenance opioid therapy

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) BTP episodes per day. Maintenance therapy should be continued while patients are using INSTANYL. Patients receiving maintenance opioid therapy are those who are taking at least 60 mg morphine daily, 25 µg of transdermal fentanyl per hour, or an equianalgesic dose of another opioid for a week or longer.

Opioid-naive patients / Patients not receiving opioid maintenance therapy

. INSTANYL is contraindicated in patients not receiving opioid maintenance therapy for cancer-related pain unless under the immediate supervision of healthcare professionals such as in a hospital or in-patient clinic (see 'Contraindications'). Life-threatening respiratory depression could occur at any dose in opioid naive patients. Deaths have occurred in opioid naive patients treated with other fentanyl products.

Respiratory depression

As with all potent opioids clinical significant respiratory depression may occur with fentanyl, and patients must be observed for these effects. Patients with pain who receive chronic opioid therapy develop tolerance to respiratory depression and hence the risk of respiratory depression in these patients is reduced. The use of concomitant central nervous system depressants may increase the risk of respiratory depression (see INTERACTIONS WITH OTHER MEDICINES).

Chronic pulmonary disease

In patients with chronic obstructive pulmonary diseases, fentanyl may have more severe adverse reactions. In these patients, opioids may decrease respiratory drive and increase airway resistance.

Hepatic and renal impairment

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

Increased intracranial pressure

Fentanyl should be used with caution in patients with evidence of increased intracranial pressure, impaired consciousness or coma. INSTANYL should be used with caution in patients with cerebral tumour or head injury.

Cardiac disease

Fentanyl may produce bradycardia. Fentanyl should therefore be administered with caution to patients with bradyarrhythmias. INSTANYL should be used with caution in patients with hypotension and/or hypovolaemia.

Nasal conditions

If the patient experiences recurrent episodes of epistaxis or nasal discomfort while taking INSTANYL, an alternative administration form for treatment of BTP 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 INTERACTIONS WITH OTHER MEDICINES.

Abuse potential and dependence

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

Withdrawal symptoms

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

Treatment with other nasally administered medicinal products

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

Local tolerance

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

Effects on Fertility

In humans, the prolonged use of opioid analgesics may result in sexual dysfunction, infertility or impairment of fertility in both sexes, and menstrual disturbance in women. Impairment of fertility has been observed in female rats given subcutaneous fentanyl 160 µg/kg/ day no-effect dose not

established) or intravenous fentanyl 400 µg/kg/ day (no-effect dose L00 1tg/kg/day). No effect was observed on the fertility of male rats at 400 µg/kg/ day intravenous fentanyl.

Use in Pregnancy (Category C)

There are no adequate data from the use of fentanyl in pregnant women. Fentanyl crosses the placenta in humans (fetal blood concentrations about 40% of maternal blood concentrations]. 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. No epidemiological studies of congenital abnormalities in infants born to women treated with fentanyl during pregnancy have been reported. chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioural changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

In pregnant rats, fentanyl is embryocidal as evidenced by increased resorptions at doses of 30 µg/kg/ day intravenously or 160 µg/kg/day or greater subcutaneously. Intravenous administration to rats at 30 µg/kg/day during organogenesis was associated with prolonged delivery time and increased postnatal mortality of offspring. There was no effect on embryofetal development when rats received fentanyl at subcutaneous doses up to 500 µg/kg/day throughout gestation, and no evidence of teratogenicity in rabbits administered fentanyl at intravenous doses up to 400 µg/kg/day during organogenesis. The significance of these findings for potential human risk is unknown. The potential risk for humans is unknown. INSTANYL should not be used in pregnancy unless clearly necessary. Following long-term treatment, fentanyl may cause withdrawal in the new-born infant. It is advised not to use fentanyl during labour and delivery (including caesarean section) because fentanyl passes through the placenta and may cause respiratory depression in the foetus. If INSTANYL is administered, an antidote for the child should be readily available.

Use in Lactation

Fentanyl is excreted into human milk and may cause sedation and respiratory depression in the breast-fed infant. Fentanyl should only be used by breast-feeding women if the benefits outweigh the potential risks for both mother and child. Administration of fentanyl to female rats from early gestation to weaning was associated with reduced early postnatal survival. This could be a direct effect on the pups or secondary to maternal toxicity.

Paediatric Use

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

Use in the Elderly

Limited data on pharmacokinetics, efficacy and safety are available for the use of INSTANYL in patients above 65 years of age. Elderly patients may have a reduced clearance, a prolonged half-life and higher sensitivity to fentanyl than younger patients. Caution should therefore be taken in treatment of elderly, cachectic or debilitated patients. In clinical trials elderly patients tend to titrate to a lower effective strength than patients less than 65 years of age. Particular caution should be exercised when titrating INSTANYL in elderly patients.

Genotoxicity

Fentanyl showed no evidence of genotoxic potential in assays for gene mutations (Ames reverse mutation test, mouse lymphoma thymidine kinase assay), chromosomal damage (Chinese hamster ovary cells, mouse micronucleus test) and other genotoxic effects (unscheduled DNA synthesis in rat hepatocytes, mammalian cell transformation assay). The metabolite despropionylfentanyl was negative in assays for reverse mutation in bacteria and chromosomal damage in human lymphocytes. The genotoxic potential of fentanyl is considered to be low.

Carcinogenicity

Non-clinical data reveal no special hazard for humans based on conventional studies of carcinogenicity. In a two year study in rats, there was no evidence of carcinogenicity following daily subcutaneous administration of fentanyl at the maximum tolerated dose.

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 should be advised not to drive or operate machinery if they experience somnolence, dizziness, visual disturbances or other adverse reaction which can impair their ability to drive and operate machinery.

INTERACTIONS WITH OTHER MEDICINES

INSTANYL is not recommended for use in patients who have received monoamine oxidase inhibitors (MAO) within 14 days because severe and unpredictable potentiation by MAO 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. Co-administration 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 Cmax (Tmax) was doubled. This may reduce the efficacy of INSTANYL. It is recommended that concomitant use of nasal decongestants is avoided.

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

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

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

ADVERSE EFFECTS

Typical opioid adverse reactions are to be expected with INSTANYL. Frequently, most of these will cease or decrease in intensity with continued use of the medicinal product. The most serious adverse reactions are respiratory depression (potentially leading to apnoea or respiratory arrest), circulatory depression, hypotension and shock and all patients should be closely monitored for these. The clinical trials of INSTANYL were designed to evaluate safety and efficacy in treating breakthrough pain. All patients were also taking concomitant opioids, such as sustained-release

morphine or transdermal fentanyl, for their persistent pain. Thus, it is not possible to definitively separate the effects of INSTANYL alone.

Adverse that occurred during the pivotal clinical trials for INSTANYL for breakthrough pain in cancer patients are listed in Table 6.

Table 6. Adverse Events which occurred during FT-017-IM and FT-018-IM at a frequency of ³ 1%

System Organ Class	INSTANYL (N= 166)
Blood and lymphatic system disorders	
Anaemia	3.6%
Ear and labyrinth disorders	
Vertigo	7.2%
Gastrointestinal disorders	
Nausea	12.0%
Constipation	9.0%
Vomiting	8.4%
Diarrhoea	2.4%
Abdominal pain	1.8%
Abdominal pain upper	1.2%
Dry mouth	1.2%
Faecal incontinence	1.2%
Stomatitis	1.2%
General disorders and administration site conditions	
Asthenia	6.0%
Oedema peripheral	3.6%
Catheter related complication	2.4%
Pyrexia	1.8%
Disease progression	1.2%
Crepitations	1.2%
Infections and infestations	
Nasopharyngitis	2.4%
Urinary tract infection	1.8%
Pneumonia	1.2%
Infection	1.2%
Respiratory tract infection	1.2%
Upper respiratory tract infection	1.2%
Bronchitis	1.2%
Metabolism and nutrition disorders	
Anorexia	3.0%
Cachexia	1.8%
Decreased appetite	1.8%
Musculoskeletal and connective tissue disorders	
Osteoarthritis	1.8%

System Organ Class	INSTANYL (N= 166)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Malignant neoplasm progression	46.4%
Metastases to liver	1.2%
Nervous system disorders	
Headache	3.0%
Somnolence	2.4%
Dizziness	1.8%
Sciatica	1.8%
Psychiatric disorders	
Anxiety	3.6%
Insomnia	2.4%
Depressed mood	2.4%
Depression	1.8%
Renal and urinary disorders	
Dysuria	3.0%
Urinary incontinence	1.2%
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	1.8%
Hiccups	1.8%
Skin and subcutaneous tissue disorders	
Decubitus ulcer	4.2%
Pruritus	2.4%
Hyperhidrosis	1.8%
Dry skin	1.2%
Rash	1.2%
Vascular disorders	
Hypertension	3.0%
Flushing	1.2%
Hot flush	1.2%
Venous stasis	1.2%

Additional adverse events occurring in clinical trials with an incidence of (³ 0.01% to < 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

Psychiatric: Dependence, insomnia

Respiratory, thoracic and mediastinal: Respiratory depression, epistaxis, nasal ulcer, rhinorrhea

Skin and subcutaneous tissue: Pain of skin, pruritus

Post-marketing Experience

Psychiatric: Hallucination

Respiratory, thoracic and mediastinal: Nasal septum perforation.

Because these reactions are reported voluntarily from a population of uncertain size and are not always confirmed with a health care professional, it is not possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

DOSAGE AND ADMINISTRATION

Treatment should be initiated by and remain under the supervision of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential of abuse of fentanyl.

Patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions. Patients must be carefully monitored during the titration process. Titration to a higher dose necessitates contact with the health care professional. The dose of INSTANYL for treatment of breakthrough pain was independent of the daily maintenance dose of opioid in the clinical studies (see PHARMACOLOGY).

Maximum daily dose: Treatment of up to four breakthrough pain episodes, each with no more than two doses separated by at least 10 minutes. Patient should wait at least 4 hours before treating another breakthrough pain episode with INSTANYL during both titration and maintenance therapy. Rescue medication can be used if adequate analgesia is not achieved after use of INSTANYL.

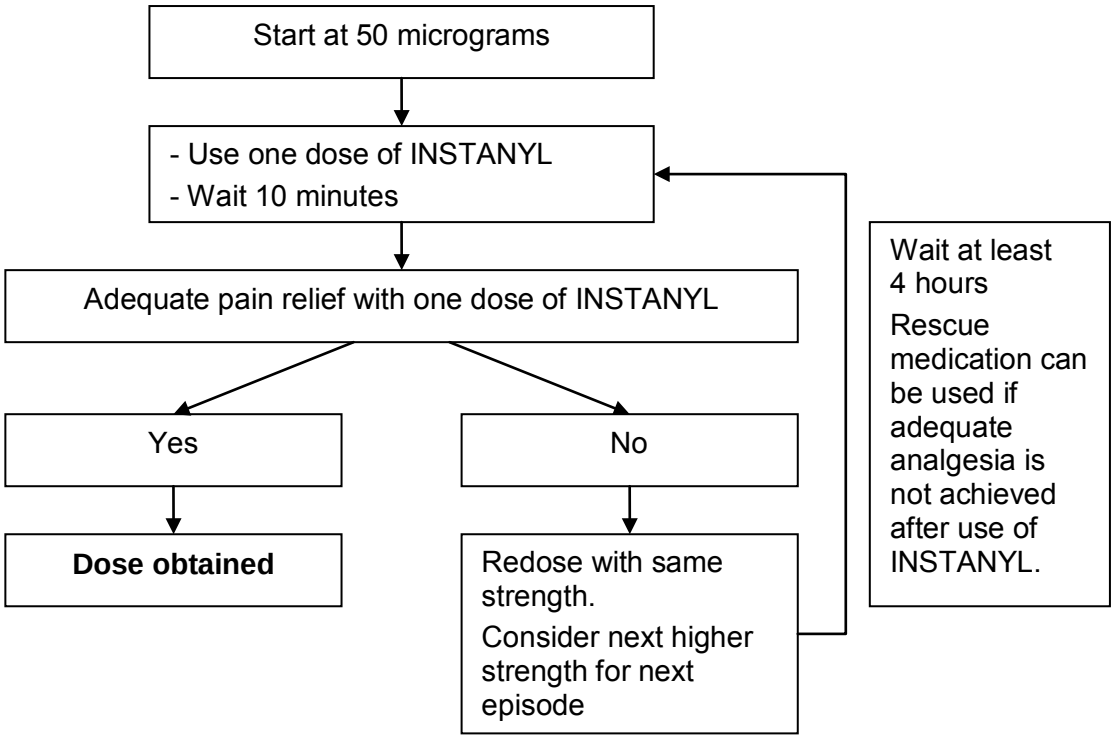
Patients should be instructed not to use more than one fentanyl product concurrently for the treatment of BTP, and to dispose of any fentanyl product prescribed for BTP when switching to INSTANYL.

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



Titration in patients switching between immediate-release fentanyl containing products

Fatal respiratory depression has occurred in patients treated with immediate-release transmucosal fentanyl, 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. When prescribing, do not convert patients on a microgram per microgram basis from any other fentanyl products to INSTANYL. Substantial differences may exist in the pharmacokinetic profile of immediate-release fentanyl products, which result in clinically important differences in the rate and extent of absorption of fentanyl. Therefore, when switching between fentanyl containing products indicated for treatment of breakthrough pain, including intranasal formulations, it is essential that patients are again titrated with the new product, and not switched on a dose-for-dose (µg-for-µg) basis.

Maintenance therapy

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

Dose adjustment

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

Discontinuation of therapy

INSTANYL should be discontinued immediately if the patient no longer experiences BTP episodes. The treatment for the persistent background pain should be kept as prescribed.

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

Special populations

Paediatric Use

The safety and efficacy of INSTANYL in children aged below 18 years have not been established.

Use in the Elderly

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

In clinical trials elderly patients tend to titrate to a lower effective dose 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 PRECAUTIONS).

Renal impairment

INSTANYL should be administered with caution to patients with moderate to severe renal impairment (see PRECAUTIONS).

Method of Administration

INSTANYL is intended for nasal use. It is recommended that the patient sit or stand in upright position when administrating INSTANYL.

INSTANYL single-dose nasal spray:

The nasal spray should only be removed from the child-resistant blister immediately prior to use. Each spray container contains only one dose. Do not test before use.

INSTANYL multi-dose nasal spray:

The nasal spray should only be removed from the child-resistant box and the protective cap removed immediately prior to use. Before using INSTANYL multi-dose nasal spray 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. During priming, aim the spray away from yourself, other people or animals.

If the product has not been used during a period of more than seven days, the nasal spray must be actuated once to waste before the next dose is taken. Cleaning of the nasal spray tip is required after each use. The protective cap should then be replaced and the nasal spray returned to the child-resistant box.

OVERDOSAGE

The symptoms of fentanyl overdose are expected to be an extension of its pharmacological actions with the most serious significant effects being deep sedation, coma and severe respiratory depression. Other symptoms may be miosis, hypothermia, ataxia, decreased muscle tonus, lethargy, bradycardia, hypotonia, and convulsions. For management of respiratory depression immediate countermeasures should be started including physical or verbal stimulation of the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The half-life of the antagonist may be short, therefore repeated administration or continuous infusion may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines. If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube and

oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should be maintained. If severe or persistent hypotension occurs, hypovolemia should be considered and the condition should be managed with appropiate parenteral fluid therapy.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

INSTANYL nasal spray is available as either single-dose or multi-dose packs with 50, 100 or 200 micrograms per actuation of fentanyl (as fentanyl citrate).

The single-dose nasal spray consists of a glass vial integrated in a plastic spray container, packed in a child-resistant blister in pack sizes of 2, 6, 8 and 10's. Not all pack sizes may be marketed.

The multi-dose nasal spray consists of a glass bottle with metering pump and dust cap packed in a child-resistant outer box and contains 10 doses per bottle. Not currently marketed.

Storage Conditions

Single-dose nasal spray:

INSTANYL 50, 100 and 200 microgram: Store below 25ºC.

Multi-dose nasal spray:

INSTANYL 50, 100 and 200 microgram: Store below 25ºC. Do not freeze. INSTANYL multi-dose nasal spray should be stored in an upright position and consumed within 2 months of opening.

Special precautions for disposal

INSTANYL can be harmful to other people, especially children. Because of the possible misuse of fentanyl and the possible amount of solution left, INSTANYL should be disposed of in the following way:

INSTANYL single-dose nasal spray:

Unused nasal spray solutions: Any unused nasal sprays should be returned in the child-resistant blister to the pharmacy.

Used nasal spray solutions: The used nasal spray bottles should be disposed of carefully.

INSTANYL multi-dose nasal spray:

Patients and caregivers must be instructed to properly dispose of all partially used and used bottles. The patient should be instructed how to do this correctly.

- If there are any unwanted doses remaining in the bottle, instruct the patient to expel these by aiming the nasal spray away from themselves (and any other people or animals) until there are no more doses obtainable from the bottle.
- The patient and caregiver must be instructed to continue to store the Instanyl nasal spray bottle in the specially provided child-resistant container out of the reach of children until proper disposal, as described above, is possible.

Any used and unused multi-dose nasal sprays must be returned in the child-resistant outer box to the pharmacy. The patient and caregiver must be instructed to continue to store the INSTANYL nasal sprays in the child-resistant container (box for multi-dose spray and blister for single-dose spray) out of the reach of children until proper disposal, as described above, is possible.

As soon as INSTANYL is no longer needed, patients and members of their household must be advised to systematically dispose of any nasal sprays remaining from a prescription as soon as possible by returning them in their child-resistant container to the pharmacy.

Attachment 1: Product information for AusPAR Instanyl Takeda Pharmaceuticals Australia Pty Ltd PM-2012-00804-3-1, Final 11 November 2013. This Product Information was approved at the time this AusPAR was published.

NAME AND ADDRESS OF THE SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
2-4 Lyonpark Rd
Macquarie Park
NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 8

DATE OF FIRST INCLUSION IN THE ARTG

17 June 2013