PHYSICIAN'S GUIDE FOR PRESCRIBING INSTANYL® SINGLE DOSE NASAL SPRAY

Introduction

This guide is designed to help you understand the proper prescribing of Instanyl®(fentanyl) Single Dose Nasal Spray for patients with breakthrough cancer pain (BTP). Please read this guide carefully before prescribing Instanyl® and keep it for future reference. Critically, select patients based upon labelled information and use the Prescriber's checklist provided. Encourage patients to talk about all medication-related issues.

Instanyl® nasal spray may only be prescribed by physicians who are experienced, knowledgeable, and qualified in the use of opioid therapy in cancer patients. Special care should be taken when patients transition from hospital to home-based care.

The following materials are also available:

- A Patient's Guide for the Safe use of Instanyl® Single Dose Nasal Spray
- A Training video for patients about cancer breakthrough pain and the use of Instanyl® (to be confirmed)
- A Pharmacist's Guide

This Physician's Guide (and the other materials listed above) can be viewed or downloaded from www.medicines.ie or requested from the Takeda Medical Information Department. Tel: 1800 937970, Email: medinfoemea@takeda.com.

Reporting Side Effects
Healthcare Professionals are asked to report any suspected adverse events to HPRA Pharmacovigilance, Website: www.hpra.ie.
Alternatively, suspected adverse events should be reported to Takeda Products Ireland Ltd on 1800 937 970 or AE.GBR-IRL@takeda.com

WHAT IS INSTANYL®?

Instanyl® for the treatment of cancer breakthrough pain

Instanyl® is an intranasal solution of fentanyl, an opioid analgesic. Instanyl® is indicated for the treatment of breakthrough cancer pain (BTP) in adults who are already receiving background opioid therapy for their chronic cancer pain. [1]

Instanyl® is suitable for adult patients with BTP who have been receiving background opioid therapy for at least a week, consisting of:

- At least 60 mg of oral morphine daily, **or**
- At least 25 micrograms of transdermal fentanyl per hour, **or**
- At least 30 mg of oxycodone daily, **or**
- At least 8 mg of oral hydromorphone daily, **or**
- An equianalgesic dose of another opioid daily. [1]

HOW IS INSTANYL® USED?

Correct use of Instanyl®

Important:
The treatment of cancer pain must be initiated by, and remain under the supervision of, a physician who has sufficient knowledge and experience in the management of opioid therapy in cancer patients.

If left untreated, BTP can have serious negative effects on a patient's quality of life.

As a prescribing physician, you must ensure your patient is appropriate for treatment with Instanyl® and that they understand how to use the medication. Specifically:

One puff of Instanyl® per BTP episode, with the possibility of taking one extra puff after at least 10 minutes if the BTP is not relieved.

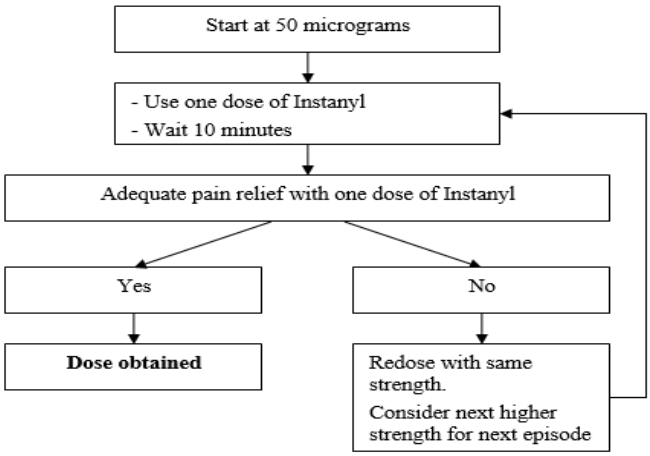
It is important to explain to the patient that there should generally be at least 4 hours between each treatment of a BTP episode, highlighting the risks associated with more frequent use. [1]

- In exceptional cases, if a new episode of pain occurs earlier, patients can use Instanyl® to treat it, but a minimum of at least 2 hours must have passed between treated episodes of BTP.
- Dose adjustment of background opioid therapy should be considered if the patient frequently presents with BTP episodes that are less than four hours apart, or with more than four BTP episodes per 24 hours.

No more than four BTP episodes per day may be treated. [1]

Dosage and titration

- Do not compare Instanyl® Single Dose Nasal Spray dose strengths with those of other fentanyl-containing products. Dose only according to the SmPC.
- To optimise BTP treatment, please make use of the titration flow chart below (also found in the SmPC) with stepwise titration through the appropriate doses until adequate analgesia is achieved.
- Treatment with Instanyl® should be initiated with a dose of 50 micrograms in one nostril, titrating upwards as required through the range of available strengths (50, 100 and 200 micrograms), until the required level of analgesia is achieved.
- If adequate analgesia is not achieved, the same dose may be re-administered after 10 minutes at the earliest.
- Each titration step (dose strength) should be evaluated over several episodes. [1]



Maintenance therapy

- Once the dose has been determined according to the steps described above, the patient should maintained on this strength of Instanyl®
- If the patient has insufficient pain relief, only one additional puff of the same strength can be taken after 10 minutes **at the earliest**. [1]

Dose adjustment

- Generally, the maintenance strength of Instanyl® should be increased if the patient needs more than one dose of Instanyl® per BTP episode for several consecutive BTP episodes.
- Dose adjustment of the background opioid therapy following pain reassessment should be considered if the patient frequently presents:
    - With BTP episodes that are less than four hours apart, or

- With more than four BTP episodes per 24 hours.

➡ If side effects are intolerable or persistent, the strength should be reduced or Instanyl® replaced by another analgesic.

Discontinuation of therapy

➡ Instanyl® should be discontinued if the patient no longer has any BTP episodes. Treatment for persistent background pain should be continued as required.

➡ If discontinuation of all opioid therapy is required, the patient must be closely followed by the physician as gradual downward opioid titration is required to reduce the possibility of withdrawal symptoms.

Overdose and Unintentional exposure

Unintentional exposure to Instanyl® is considered a medical emergency and potentially life-threatening event.

If a child is accidentally exposed to the product, it is considered a medical emergency and may, without professional treatment, cause death.

Make sure that both yourself and colleagues likely to come into contact with patients on fentanyl therapy are aware of the signs of fentanyl overdose/toxicity and the appropriate protocol for its management. Ensure medications such as naloxone are readily accessible and staff are trained in their use.

The most serious signs of opioid overdose/toxicity are:

➡ Deep sedation potentially leading to loss of consciousness.
➡ Hypotension.
➡ Respiratory depression potentially leading to respiratory failure.
➡ Convulsions.
➡ Coma.

Please ensure that your patients and their caregivers are aware of the signs of fentanyl overdose/toxicity and understand the need to seek urgent medical attention.

Patients should be monitored for signs that they are not using Instanyl® as prescribed and be made aware of the serious risks associated with misuse, overdose, and addiction associated[1]

Safety, Storage, and disposal

➡ Instanyl® should only be handled by the patient or their caregivers. Please advise the patient to never allow anyone else to handle or use the product.

➡ Instanyl® single dose nasal spray may only be removed from the child-resistant blister packaging immediately before the patient intends to use it. Until use, the product must be stored in the outer box, upright and below 30°C (do not freeze).

➡ Please draw the attention of patients and their caregivers to the danger if children are exposed to Instanyl®.

➡ Please ensure that patients understand that in order to prevent theft, diversion (misuse for illegal purposes) or other misuse, fentanyl should be stored in a suitably secure place. Fentanyl, the active ingredient in Instanyl® is a target for people who abuse narcotic medicines or other street drugs, and therefore the storage instructions must be closely followed.

➡ Information about proper disposal: Prescribers of Instanyl® nasal spray must also counsel patients on the instructions for opening the child-resistant blister pack.
All unused devices or empty containers should be returned to the pharmacy for correct disposal as per local regulations.

WHAT ARE THE RISKS ASSOCIATED WITH OFF-LABEL USE (OLU) OF INSTANYL ®?

Importance of preventing off-label use (OLU)

The use of Instanyl® outside the approved indications is considered OLU. **Please note that different fentanyl formulations have different indications.** Make sure that you are familiar with the specific indications for Instanyl® before prescribing. The use of Instanyl® for indications other than those approved increases the risk of misuse, abuse, medication error, overdose, addiction and death.

Off label use would include the following prescriptions:

➡ All indications except breakthrough cancer pain, including any other pain therapy.

➡ Patients who do not already receive background opioid therapy.

➡ More frequent dosing than recommended.

➡ Patients under 18 years of age.

Medication errors are also particularly important to avoid when prescribing Instanyl®
Types of medication errors include:

- Unintentional drug prescribing error.
- Drug administration error.
- Drug dispensing error.
- Incorrect dose administered.
- Use of an incorrect route of administration.

In order to minimize the risk of medication errors, all Instanyl® labels are colour-coded differently for each of the strengths of action

RISKS ASSOCIATED WITH "OPIOID USE DISORDER" (OUD)

How to recognize abuse-related side effects and OUD

The following considerations may help you identify patients who have developed OUD. In patients where OUD is strongly suspected, a consultation with an addiction specialist should be considered.

1. Pay particular attention to patients who have an increased risk of OUD.

The risk of developing OUD is increased in patients with a personal or family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users and in patients with a personal history of other mental health problems (e.g. depression, anxiety and personality disorders).

2. Carefully monitor prescription requests

Patients must be observed for signs of drug-requesting behavior (e.g. desire for early follow-up prescriptions). This includes monitoring concomitant opioids and other psychoactive drugs (such as benzodiazepines).

3. Recognize the symptoms of dependence, addiction, and withdrawal.

Withdrawal symptoms are one of the criteria associated with OUD. The context of withdrawal symptoms must be accurately assessed. A patient suffering from withdrawal symptoms may complain of nausea and vomiting, anxiety, insomnia, heat and cold flushes, excessive sweating, muscle cramps, watery discharge from the eyes and nose, and/or diarrhea. [3]

Some OUD criteria may be difficult to distinguish from behaviors that are frequently observed in cancer patients receiving opioid pain therapy. Some classical opioid withdrawal symptoms are also "normal" side effects that have been reported after the use of Instanyl® (e.g. facial redness, insomnia, sweating). [1] The complexity of treating BTP, together with the risks associated with off-label use, poses unique challenges to OUD diagnosis.

WHAT TO DO IF YOU SUSPECT THAT YOUR PATIENT IS SUFFERING FROM OUD?

A patient suffering from OUD can still receive cancer treatment and have their pain relieved. Several treatment options for patients with OUD can be considered and tailored to individual needs. [4] These options include:

- Treatment with opioid agonists (Opioid Agonist Treatment, OAT), including methadone or buprenorphine, currently the most effective drugs for opioid dependence and addiction. [5]
- Behavioral medicine and psychosocial interventions.

A combination of behavioral and pharmacotherapeutic approaches (so-called drug-assisted therapy) has proven to be the most successful in helping patients overcome OUD. [5] If you do not feel qualified to offer effective behavioral and/or pharmacotherapeutic treatment of the OUD, please refer your patient to an appropriately qualified specialist.

*Report any known OLU, misuse or abuse via **HPRA Pharmacovigilance website: www.hpra.ie.** Alternatively, suspected adverse events should be reported to Takeda Products Ireland Ltd on 1800 937 970 or AE.GBR-IRL@takeda.com*

OTHER IMPORTANT POINTS ABOUT INSTANYL®

Please counsel the patient on the following points from the Instanyl® SmPC:

1. The following adverse reactions have been reported with Instanyl® and/or other fentanyl-containing compounds during clinical studies and post-marketing experience: dyspnoea, drug dependence (addiction), drug abuse, neonatal withdrawal syndrome, loss of consciousness. (See SmPC Section 4.8.)

2. Hyperalgesia: As with other opioids, in case of insufficient pain control in response to an increased dose of fentanyl, the possibility of opioid-induced hyperalgesia should be considered. Fentanyl dose reduction or discontinuation of fentanyl treatment or treatment review may be indicated. (See SmPC Section 4.2 and 4.4.)

3. Concomitant use of medicinal products containing sodium oxybate and fentanyl is contraindicated. (See SmPC Sections 4.3 and 4.5.)

4. The concomitant use of other central nervous system depressants (including opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, tranquilisers, (benzodiazepines) sedating antihistamines, and alcohol) or skeletal muscle relaxants may produce additive depressant effects: hypoventilation, hypotension, profound sedation, coma, or death may occur. Therefore, the use of any of these medicinal products concomitantly with Instanyl® requires specialist supervision. (See SmPC Section 4.5.)

5. Pregnancy: There are no adequate data from the use of fentanyl in pregnant women. Studies in animals have shown reproductive toxicity (see SmPC Section 5.3). The potential risk for humans is unknown. Instanyl® should not be used in pregnancy unless clearly necessary and if the benefits outweigh the risks. (See SmPC Section 4.6.)

CHECKLIST FOR PRESCRIBING INSTANYL®

- ☐ Ensure that all the criteria of the approved indication are fulfilled. Instanyl® should only be prescribed for breakthrough pain (BTP) in adults who are already receiving opioid maintenance therapy for background cancer pain
- ☐ Give the patient and/or caregiver instructions on how to use the nasal spray
- ☐ Advise the patient/caregiver of the single-use nature of the nasal spray (each nasal spray contains only one dose and the plunger should only be pressed once the spray tip is inserted into the nose; it should not be tested before use)
- ☐ Make sure the patient/caregiver reads the Patient Information Leaflet inside the Instanyl® single-dose package
- ☐ Supply the patient/caregiver with the Instanyl® patient guide
- ☐ Instruct the patient/caregiver on how to open the child-resistant blister as described in the Patient Guide
- ☐ Explain the risks of using more than the recommended amount of Instanyl®
- ☐ Advise the patient/caregiver of signs of fentanyl overdose and the need for immediate medical assistance
- ☐ Explain secure storage and the need to keep Instanyl® out of the reach and sight of children
- ☐ Explain the correct process for disposal of the Instanyl®
- ☐ Encourage the patient/caregiver to discuss their background and breakthrough cancer pain and their use of opioids with you.

References:
1. Instanyl® Nasal Spray — Summary of Product Characteristics (SmPC). https://www.ema.europa.eu/en/documents/product-information/instanyl-epar-product-information_en.pdf.
2. Caraceni A, Shkodra M. Cancer pain assessment and classification. *Cancers*. 2019;11:510. doi:10.3390/cancers11040510. 3. Fallon M, Giusti R, Aielli F, et al. On behalf of the ESMO Guidelines Committee. Management of cancer pain in adult patients: ESMO clinical practice guidelines. *Ann Oncol*. 2018;29(Suppl 4):iv166–iv191.
4. Centers for Disease Control and Prevention. Web site. Module 5. Assessing and addressing opioid use disorder (OUD). https://www.cdc.gov/drugoverdose/training/oud/accessible/index.html. Accessed on 31 March 2020.
5. National Institute on Drug Abuse (NIDA). The science of drug use and addiction: the basics. Last updated July 2018. https://www.drugabuse.gov/publications/media-guide/science-drug-use-addiction-basics. Accessed on 31 March 2020.
6. Klimas J, Gorfinkel L, Fairbairn N, et al. Strategies to identify patient risks of prescription opioid addiction when initiating opioids for pain: a systematic review. *JAMA Netw Open*. 2019 May 3;2(5):e193365. doi:10.1001/jamanetworkopen.2019.3365.
7. Clinical guidelines for withdrawal management and treatment of drug dependence in closed settings. Geneva: World Health Organization (WHO); 2009. 4, Withdrawal management. https://www.ncbi.nlm.nih.gov/books/NBK310652/. Accessed