Part VI: Summary of the risk management plan

Summary of risk management plan for Instanyl (fentanyl citrate)

This is a summary of the risk management plan (RMP) for Instanyl. The RMP details important risks of Instanyl, how these risks can be minimized, and how more information will be obtained about Instanyl's risks and uncertainties (missing information).

Instanyl's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Instanyl should be used.

This summary of the RMP for Instanyl should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Instanyl's RMP.

I. The medicine and what it is used for

Instanyl is authorized for the management of breakthrough pain (BTP) in adults already receiving maintenance opioid therapy for chronic cancer pain. (See SmPC for the full indication). It contains fentanyl citrate as the active substance, and it is given by nasal spray.

Further information about the evaluation of Instanyl's benefits can be found in Instanyl's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000959/human_med_000838.jsp&mid=WC0b01ac058001d124

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Instanyl, together with measures to minimize such risks and the proposed studies for learning more about Instanyl's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Instanyl, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Instanyl is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Instanyl are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Instanyl. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Addiction Misuse Abuse Diversion Off label use Accidental exposure (including potential exposure of other people and children to drug expelled in the patient's proximity during priming.) Overdose (suicide and suicide attempt excluded) Medication errors Respiratory depression Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs
Important potential risks	Brain lesion
Missing information	Long-term use

II.B Summary of important risks

Important identified risk: Addiction	
Evidence for linking the risk to the medicine	Dependence, often confused with addiction, is an expected response in cancer patients necessitating prolonged and continuous opioid therapy for pain management [18].

Important identified risk: Addiction	
	In the case of off label or illicit use, the progression to opioid dependence may have dire consequences, including a yearly mortality rate of approximately 2% [19]. Moreover, sustained remission from opioid dependence is difficult to achieve.
Risk factors and risk groups	The target population is at high risk of opioid dependence as persistent and chronic cancer pain is expected to be managed with long-term strong opioids. Patients with prior substance abuse and underlying concomitant chronic non-cancer pain may be at higher risk for dependence and its associated risks of misuse, abuse, overdose, and off label use. There do not appear to be gender differences among those who exhibit dependence with fentanyl.
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.4 where advice is given in monitoring for dependence • SmPC section 4.8 • PL sections 2, 3, and 4 • Special and restricted prescription status • Development of a single-dose nasal spray • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01 April 2016) **Additional risk minimization measures** Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists.
Additional pharmacovigilance activities	Instanyl Prescriber Survey

Important identified risk: Misuse	
Evidence for linking the risk to the medicine	Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorization (GVP Module VI). Misuse can be characterized as not taking the medication according to prescription, unsanctioned use, altering the route of delivery, among others. Abuse of fentanyl, when it develops, is an issue, which has implications for the patients' quality of life, and which requires treatment for resolution.
Risk factors and risk groups	Patients with prior substance abuse and underlying chronic, non-cancer pain may be at higher risk for dependence and its associated risks of misuse, abuse, overdose, and off label use.

Important identified risk: Misuse	
	When Instanyl is used among those patients who are being treated for BTP, there may be a potential for misuse (overuse) due to inadequate baseline control of cancer pain. Misuse may also occur due to inadequate knowledge in correct use of the medication as prescribed. This is in large part attributable to the nature of the disease and associated polypharmacy used, care given by multiple providers and in some cases, confusion or mental compromise due to disease progression. Among patients who are using the medication for non-cancer indication (off label) those with history of substance abuse, alcohol abuse, family history of either, psychiatric illness or other lifestyle factors that compromise the overall well-being, the risk of intentional drug misuse is considerably higher. The elderly are also more susceptible to pain medication misuse. The elderly comprise 13% of the US population but receive over 30% of all prescribed medications, including analgesics [21].
Risk minimization measures	**Routine risk minimization measures** • SmPC sections 4.1, 4.2 • PL sections 1, 2, 3 • SmPC section 4.3 and PL section 2 prohibiting treatment in opiate-naïve patients and acute pain other than breakthrough pain • SmPC section 6.6 warning of possible misuse of fentanyl and providing special instruction for safe and proper handling and systematic disposal/return of product • PL instructing patients on proper usage as prescribed and to seek physician assistance for dose or treatment adjustments or if dependence is suspected. • Special and restricted prescription status. • Development of a single-dose nasal spray • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01 April 2016) **Additional risk minimization measures** Educational materials for patients, prescribers, and pharmacists including checklists for prescribers and pharmacists.
Additional pharmacovigilance activities	Instanyl Prescriber Survey.

Important identified risk: Abuse	
Evidence for linking the risk to	Abuse corresponds to persistent or sporadic, intentional excessive use of medicinal products which is accompanied by

Important identified risk: Abuse	
the medicine	harmful physical or psychological effects (GVP Module VI). Abuse of fentanyl is considered to present a moderate risk among opioid-tolerant persons due to associated behaviors deriving social, familial, criminal complications. Abuse in terms of overdose or misuse is moderate to severe due to consequences such as respiratory depression that can occur due to overdose (accidental or otherwise) and result in life-threatening or fatal outcomes. This risk is higher when abuse pertains to the opioid-naïve person who may be taking concomitant CNS depressants.
Risk factors and risk groups	Patients with inadequate baseline control of cancer pain may be at risk for abuse. Patients suffering from chronic pain, concomitant to cancer pain or without, requiring opioid treatment. Other factors that may put some patients at increased risk of opioid abuse/addiction include a personal/family history of substance, prescription medication and alcohol abuse, and major psychosocial issues (e.g. psychological/psychiatric disorders). Furthermore, prescription abuse is increasing among women and this may be correlated with a higher prevalence of depression, anxiety or other psychosocial illness.
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.2 recommending treatment and supervision by a physician experienced in the management of opioid therapy in cancer patients. • SmPC sections 4.2 and 4.4 where advice is given to monitor for potential abuse and dependence. • PL where instruction for patients is provided in the proper usage of Instanyl as prescribed and to seek medical assistance if dependence is suspected. • Special and restricted prescription status. • Development of a single-dose nasal spray • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01 April 2016). **Additional risk minimization measures** Educational materials for prescribers, pharmacists, and patients including checklists for prescribers and pharmacists.
Additional pharmacovigilance activities	Instanyl Prescriber Survey

Important identified risk: Diversion	
Evidence for linking the risk to	Diversion of narcotics is a known risk of narcotic analgesics.

Important identified risk: Diversion	
the medicine	Drug diversion, broadly defined, is when the legal supply chain of prescription analgesic drugs is broken, and drugs are transferred from a licit to an illicit channel of distribution or use [12]. There are life-threatening consequences of opioid-naïve overdose, at worst, fatal respiratory depression.
Risk factors and risk groups	Patients inappropriately using fentanyl-containing medicines, patients with family members who suffer from chronic pain or substance abuse disorders, patients identified to have financial or other incentives to divert their supply, or elderly and compromised patients who unknowingly or forcibly are subjected to diversion of their medications by caregiver or other persons [19].
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.1 • SmPC section 6.6 warning of possible misuse of fentanyl and providing special instruction for safe and proper handling and systematic disposal/return of product • PL instructs patients on proper and safe use of Instanyl to prevent harm in others • Special and restricted prescription status. • Development of a single-dose nasal spray • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01 April 2016). **Additional risk minimization measures** Educational materials for prescribers, pharmacists, and patients including checklists for prescribers and pharmacists.
Additional pharmacovigilance activities	Instanyl Prescriber Survey

Important identified risk: Off label Use	
Evidence for linking the risk to the medicine	Off label use relates to situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization (GVP Module VI). Opioid analgesics in clinical practice may be used 'off label' due to inter-individual variability or prescribed in conditions in which some experts recommend against opioid use e.g. use in patient with non-cancer pain, absence of background opioid treatment, administration of high doses and absence of titration, fibromyalgia or long-term use of opioids in chronic non-cancer

Important identified risk: Off label Use	
	pain. If used outside the indication in opioid-naïve patients there is a risk of respiratory depression as stated in the SmPC.
Risk factors and risk groups	Patients with pain other than the indication of BTP in cancer patients and/or patients not taking background opioid treatment.
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.1 • SmPC section 4.3 and PL section 2 prohibiting use in opioid-naïve patients and acute pain other than breakthrough pain • PL section 1 and 3. • Special and restricted prescription status **Additional risk minimization measures** Educational materials for prescribers, pharmacists, and patients including checklists for prescribers and pharmacists.
Additional pharmacovigilance activities	Instanyl Prescriber Survey

Important identified risk: Accidental exposure (including potential exposure of other people and children to drug expelled in the patient's proximity during priming)	
Evidence for linking the risk to the medicine	Accidental exposure of fentanyl can result in death due to respiratory depression, particularly in opiate-naïve people and children.
Risk factors and risk groups	Children and opioid-naïve patients
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.2 (conventional and improved multi- dose) and PL section 5 provides special precautions in product handling and administration specifying proper and safe priming technique to prevent exposure to other people, particularly children. • SmPC section 6.6 and PL section 5 includes special precautions for safe and proper storage (in child-resistant blister, outer box, or replacing child-resistant cap, keeping out of reach of children) and disposal requiring systematic and suitable return (storage in child-resistant blister or outer box) of used and unused nasal spray solution or disposal per local requirements or pharmacy (improved multi-dose) to prevent accidental exposure particularly to children. • PL section 2 prohibits use in children.

Important identified risk: Accidental exposure (including potential exposure of other people and children to drug expelled in the patient's proximity during priming)	
	• PL section 3 includes instructions for monitoring, seeking immediate medical attention, and caring for the accidentally exposed person. • Special and restricted prescription status. • Development of a single-dose nasal spray • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01 April 2016). **Additional risk minimization measures** Educational materials for prescribers, pharmacists, and patients including checklists for prescribers and pharmacists.
Additional pharmacovigilance activities	Instanyl Prescriber Survey

Important identified risk: Overdose (suicide and suicide attempt excluded)	
Evidence for linking the risk to the medicine	Overdose refers to administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information (GVP Module VI). In 2007, 27,658 unintentional drug overdose deaths occurred in the United States (CDC, 2010).
Risk factors and risk groups	Caretakers or patients who have lack of knowledge on how to administer a dose of intranasal spray or who have forgetfulness about if a dose was administered already or not may increase the risk of accidental overdose due to repeated administration of a product.
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.2 where advice is provided for monitoring for potential overdose of fentanyl • SmPC section 4.9 and PL where advice is provided in monitoring for specific signs and symptoms and treating overdose • SmPC section 6.6 and PL provides special precautions for safe storage and systematic disposal/return of product to prevent the possible misuse of fentanyl • PL section 3 PL provides reminders for tracking the number of doses of Instanyl • PL instructs patients on proper usage as prescribed and to seek physician assistance for dose or treatment adjustments

Important identified risk: Overdose (suicide and suicide attempt excluded)	
	• Special and restricted prescription status. • Development of a single-dose nasal spray • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01 April 2016). **Additional risk minimization measures** Educational materials for patients, prescribers, and pharmacists including checklists for prescribers and pharmacists.
Additional pharmacovigilance activities	Instanyl Prescriber Survey

Important identified risk: Medication errors	
Evidence for linking the risk to the medicine	Medication error refers to an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (GVP Module VI). Dy et al., (2007) observed 644 harmful error reports in opioid medication errors from 222 facilities and found that 60% were errors in route of administration and 21% were prescribing errors. About one-fourth (23%) caused underdosing and 52% caused overdosing of an opioid medication. Morphine and hydromorphone had the highest improper dose errors (40% and 41%) than other opioids [24].
Risk factors and risk groups	Opioid-naïve patients and children are at a high risk of developing adverse effects due to possible overdose as a result of a medication error. Respiratory depression may occur, and the event may become fatal.
Risk minimization measures	**Routine risk minimization measures:** • SmPC section 4.1 • SmPC section 4.2 and PL where advice is provided for product handling, administration and dose titration specifying carefully monitored during the titration process • SmPC section 6.5 and PL where information is provided on difference between SmPCs for the conventional multi-dose, improved multi-dose and single-dose formulations • PL instructs patients on proper usage as prescribed and to seek physician assistance for dose or treatment adjustments. • Special and restricted prescription status. • Development of a single-dose nasal spray. • Development of an improved multi-dose nasal spray with

	dose counting, lock-out and child-resistant cap (approved on 01 April 2016). **Additional risk minimization measures:** Educational materials for patients, prescribers, and pharmacists including checklists for prescribers and pharmacists.
Additional pharmacovigilance activities	Instanyl Prescriber Survey

Important identified risk: Respiratory depression	
Evidence for linking the risk to the medicine	As with all potent opioids clinically significant respiratory depression may occur with fentanyl, and patients must be observed for these effects. Patients with pain who receive chronic opioid therapy may develop tolerance to respiratory depression and hence the risk of respiratory depression in these patients may be reduced. The concomitant use of CNS depressants may increase the risk of respiratory depression. Respiratory depression can be moderate to severe in nature and require medical intervention. In severe cases, it can be life-threatening and fatal.
Risk factors and risk groups	Patients not taking maintenance opioid therapy, opioid-naïve patients. Patients taking 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 ADRs including fatal respiratory depression. The concomitant use of other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines and alcohol may produce additive depressant effects. Unborn children are at risk if the pregnant mother is receiving treatment with fentanyl and breast-feeding infants are also at risk if the mother is receiving treatment with fentanyl. Patients who misuse/abuse fentanyl are at higher risk of overdose and therefore respiratory depression. The manifestations of fentanyl overdose are an extension of its pharmacological actions, the most serious effect being respiratory depression.
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.3 and PL section 2 prohibiting use in opioid-naïve patients, severe respiratory depression, or severe

Important identified risk: Respiratory depression	
	obstructive lung conditions. • SmPC section 4.4 and 4.8 includes special monitoring for respiratory depression and warning with concomitant use of CNS depressants that may increase the risk of respiratory depression. • SmPC section 4.5 and PL section 2 prohibiting use with other central nervous system depressants that may produce additive depressant effects. • SmPC section 5.1 • PL instructs patients to discontinue treatment and seek immediate medical attention if difficulties in breathing occur with Instanyl • Special and restricted prescription status. **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Important identified risk: Serotonin syndrome induces by interaction between fentanyl and serotoninergic drugs	
Evidence for linking the risk to the medicine	The severity of serotonin syndrome is highly variable. However, reactions may also result in severe hypertension and tachycardia that abruptly deteriorates into cardiovascular shock. Fatalities have occurred [29]. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotonergic effects, have been reported.
Risk factors and risk groups	There is a risk of serotonin syndrome when drugs that inhibit the reuptake of serotonin are combined. Classes of drugs inhibiting serotonin reuptake activity include MAOIs, SSRIs and SNRIs. Other risk factors include: • Cytochrome P450 drug interactions or specific patient phenotypes making them more susceptible to serotonin syndrome Medical conditions that decrease the available monoamine oxidase such as hypertension, atherosclerosis, hyperlipidemia [31].
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.4, 4.5 and PL section 2 provides special warning for the development of potentially life-threatening

Important identified risk: Serotonin syndrome induces by interaction between fentanyl and serotoninergic drugs	
	serotonin syndrome when Instanyl is co-administered with drugs that affect the serotoninergic neurotransmitter systems • SmPC section 4.4 recommending stopping Instanyl treatment if serotonin syndrome is suspected • Special and restricted prescription status. **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Important potential risk: Brain lesion	
Evidence for linking the risk to the medicine	Background incidence/prevalence of brain lesion caused by opioids in target population is unknown.
Risk factors and risk groups	Factors which may lead to increased risk of brain lesion have not been characterized.
Risk minimization measures	**Routine risk minimization measures:** • SmPC section 5.3 • Special and restricted prescription status. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Missing information: Long-term use	
Risk minimization measures	**Routine risk minimization measures:** • SmPC section 4.4 and PL provides special warning on the development of tolerance and physical and/or psychological dependence upon repeated administration of opioids such as fentanyl • Special and restricted prescription status. **Additional risk minimization measures:** None

Missing information: Long-term use	
Additional pharmacovigilance activities	None

II.C. Post-authorization development plan

II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Instanyl.

II.C.2. Other studies in post-authorization development plan

There are no studies required for Instanyl.