EU RISK MANAGEMENT PLAN (RMP)

for

Instanyl® (fentanyl citrate)

RMP Version number: 20.0

Date: 25-September-2023

EU Risk Management Plan for Instanyl® (fentanyl citrate)

RMP version to be assessed as part of this application:

RMP Version number: 20.0

Data lock point for this RMP: 20-September-2023

Date of final sign-off: 25-September-2023

Rationale for submitting an updated RMP: To reflect updated milestones and status of post-authorisation safety study (PASS) Instanyl-5002 and associated questionnaire.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Not applicable
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Updated as per recent data.
• **Module SII Non-clinical part of the safety specification**	Updated as per latest guidance in accordance with GVP Module V Revision (Rev) 2.
• **Module SIII Clinical trial exposure**	Updated as per latest guidance in accordance with GVP Module V Rev 2.
• **Module SIV Populations not studied in clinical trials**	Not applicable
• **Module SV Post-authorisation experience**	Data and methodology updated for calculating post-authorisation experience.
• **Module SVI Additional EU requirements for the safety specification**	Updated as per the recent information as applicable.
• **Module SVII Identified and potential risks**	Updated the search criteria for some risks and updated the counts of clinical trials and post-marketing events as per recent data for all safety concerns.
• **Module SVIII Summary of the safety concerns**	Not applicable.
Part III Pharmacovigilance plan	• III.1: Removed six-month periodic report detailing progress of development of Instanyl DoseGuard (LEG-028) since it was considered fulfilled and reports are no longer expected. • III.2 and III.3: Removed the Instanyl Prescriber Survey summary (Instanyl-PASS 5002 study) from additional pharmacovigilance (PV) activities since this study was completed.

RMP Module:	Significant Changes:
Part IV Plans for post-authorisation efficacy studies	Not applicable.
Part V Risk minimisation measures	• V.1: Updated the Instanyl DoseGuard launch details for the risks as applicable. • V.2: Updates made to the existing Instanyl educational materials (EMs) as per the updated EMs. Added Objectives and Conclusions from Instanyl Prescribers survey PASS 5002 study under "evaluation and effectiveness of the updated EMs". Added Instanyl DoseGuard EMs as new additional risk minimisation measure. V.3: Risk minimization measures updates made in alignment with Parts V.1 and V.2. Removed LEG 28 from routine PV activities and removed Instanyl Prescribers survey PASS 5002 study from the additional PV activities.
Part VI Summary of the risk management plan	Updates made to risk minimisation measures and additional PV activities in alignment with Part III and Part V.
Part VII Annexes	• Annex 2: Updated the PASS study Instanyl Prescriber Survey (Instanyl-5002) from ongoing as completed. Milestones updated for PASS study Instanyl Prescriber Survey (Instanyl-5002). • Annex 6: Updated as per the revised Instanyl EMs. • Annex 8: Updated Instanyl 5002 Survey Questionnaire added.

Other RMP versions under evaluation:

Not applicable.

Details of the currently approved RMP:

Version number: 19.6

Approved with procedure: EMEA/H/C/000959/II/0052

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QPPV name: Stéphane Brouckaert, MPharm

Please note that e-signature may also be performed by Deputy EU QPPV [redacted] on behalf of the EU and UK QPPV (i.e., 'per procurationem').

QPPV signature: RMP signatures are kept on file.

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List of Abbreviations

Abbreviation	Definition/Description
ADRs	Adverse Drug Reactions
aRMM	Additional Risk Minimisation Measures
ATC code	Anatomical Therapeutic Chemical classification system
BTP	Breakthrough Pain
CASA	National Centre on Addiction and Substance Abuse
CAT	Committee for Advanced Therapies
CDC	Centers for Disease Control and Prevention
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures (human)
COPD	Chronic Obstructive Pulmonary Disease
CNS	Central Nervous System
CYP3A4	Cytochrome P450 3A4
DAWN	Drug Abuse Warning Network
DLP	Data Lock Point
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision
EC	European Commission
eCTD	electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practice
HCP	Health Care Professional
IMD	Improved multi-dose
IMP	Investigational Medicinal Product
INFS	Intranasal fentanyl spray
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MAOI	Monoamine oxidase inhibitor
MED	Morphine Equivalent Dose
MedDRA	Medical Dictionary for Regulatory Activities
NA	Noradrenaline
NCFTA	National Cyber-Forensics and Training Alliance

Abbreviation	Definition/Description
OUD	Opioid use disorder
PASS	Post-authorisation safety study
PID	Pain intensity difference
PIUS	Patient reported Instanyl Use Study
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PPP	Pregnancy Prevention Programmes
PT	Preferred Term
QoL	Quality of Life
QPPV	Qualified Person Responsible for Pharmacovigilance (in the European Union)
RMP	Risk Management Plan
RR	Reporting Rate
RTU	Temporary recommendations for use
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SNRIs	Serotonin Norepinephrine Reuptake Inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors
SUD	Substance Use Disorder
UK	United Kingdom
US	United States

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Fentanyl citrate 646624793
Pharmacotherapeutic group(s) (ATC Code)	N02A B03
Marketing Authorisation Holder	Takeda Pharma A/S
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Instanyl®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Fentanyl is a phenylpiperidine derivative
	Summary of mode of action A potent opioid analgesic chemically related to pethidine with affinity mainly to the μ-receptor present in the brain and spinal cord.
	Important information about its composition The active drug substance in the product is fentanyl citrate.
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.
Indication(s) in the EEA	Current: Fentanyl nasal spray (Instanyl) is indicated for the management of breakthrough pain (BTP) in adults already receiving maintenance opioid therapy for chronic cancer pain.
	Proposed: Not applicable.
Dosage in the EEA	Current: Patients should be individually titrated to a dose that provides adequate analgesia with tolerable adverse drug reactions (ADRs). Patients must be carefully monitored during the titration process. Titration to a higher dose necessitates contact with the health care professional. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered. The dose of Instanyl for treatment of BTP was independent of the daily maintenance dose of opioid in the clinical studies. Maximum daily dose: Treatment of up to 4 BTP episodes, each with no more than 2 doses separated by at least 10 minutes. Patient should wait 4 hours before treating another BTP episode with Instanyl, during both titration and maintenance therapy. On exceptional occasions, where a new episode occurs earlier, patients can use Instanyl to treat it, but they must wait at least

	2 hours before doing so. Dose adjustment of the background opioid therapy following pain reassessment should be considered if the patient frequently presents with BTP episodes that are less than 4 hours apart or with more than 4 BTP episodes per 24 hours. Route of administration Intranasal use.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Multi-dose nasal spray, single-dose nasal spray and improved multi-dose nasal spray (DoseGuard) in dose strengths of 50,100 and 200 µg/dose fentanyl.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Management of breakthrough pain (BTP) in adults already receiving maintenance opioid therapy for chronic cancer pain.	
Incidence:	Not available.
Prevalence:	Though BTP is recognised as an important clinical phenomenon, variations in how it is defined, assessed, and treated have led to disparate figures for BTP prevalence (range 19-95%).
Demographics of the target population in the indication:	As the underlying cancer may be any kind of (solid tumour) cancer and BTP may occur at any stage of the disease, a description of the epidemiology is difficult. Cancer patients in need of BTP treatment are, however, typically characterised by advanced disease with risk of co-morbidity, short life expectancy, and impaired quality of life (QoL).
Risk factors for the disease:	As the underlying cancer may be any kind of cancer and BTP may occur at any stage of the disease, a description of the risk factors is difficult, as this may vary for different cancers.
The main existing treatment options:	As the underlying cancer may be any kind of cancer, concomitant medication use will vary depending on the type of cancer that the patient is being treated for.
Natural history of the indicated condition in the population, including mortality and morbidity:	Patients who are opioid-tolerant and receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 µg of transdermal fentanyl per hour, at least 30 mg oxycodone daily, at least 8 mg of oral hydromorphone daily or an equi-analgesic dose of another opioid for a week or longer. Instanyl is indicated only for patients already receiving maintenance opioid therapy for chronic cancer pain.
Important co-morbidities:	The target population will typically have a high degree of co-morbidities due to their underlying cancer disease. As the underlying cancer may be any kind of cancer and BTP may occur at any stage of the disease, a description of the co-morbidity is difficult as this will vary for different cancers. - Instanyl is indicated in opioid-tolerant patients only. As the target population is already treated with opioids for the background pain, to a large extent they will have developed tolerance to the immediate adverse effects like nausea, vomiting, sedation, euphoria and respiratory depression.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity: Carcinogenicity	The marketing authorisation holder (MAH) has not conducted any carcinogenicity studies to date. Based on Pharmacovigilance Risk Assessment Committee (PRAC) recommendation following assessment of previous Instanyl Periodic Safety Update Report (PSUR) no. 7 (20-April-2012 – 30-April-2013) (refer to CTD Module 5.3.6 for PSUR references) Section 5.3 of the Instanyl Summary of Product Characteristics (SmPC) now states that a carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. This study was conducted by the MAH of another fentanyl product. The relevance of these findings to humans is unknown.
Toxicity: Reproductive/developmental toxicity	Information from non-clinical studies regarding the potential effects of fentanyl on reproduction is publicly available from a number of sources. Studies in animals at extremely high doses where maternal toxicity was observed, have also documented embryotoxicity. This observation has not been replicated in studies with clinically relevant doses. The potential risk for humans is unknown. Treatment of neonatal rat pups with fentanyl for 72 hours caused dependence. As fentanyl has been shown to cross the placenta during pregnancy, it may therefore be expected to cause withdrawal symptoms in the new-born infant.
Safety pharmacology: None	Not applicable
Other toxicity-related information or data:	Nasal tolerability findings assessed in human use.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Table SIII.1: Duration of exposure

Duration of continuous exposure for all BTP cancer patients who participated in protocols FT-003/-011-IN, FT-016-IM, FT017-IM, and FT018-IM

	INFS Dose strength (µg)					
Duration	**50**	**100**	**200**	**400**	**800**	**Total**
<1 week	0	0	0	0	0	0
1 to 2 weeks	0	3	1	0	0	4
>2 to 4 weeks	1	6	3	0	0	10
1 to 2 months	5	7	9	0	2	23
>2 to 3 months	2	8	7	1	0	18
>3 to 6 months	7	23	11	2	2	45
>6 months	7	14	22	0	0	43
Total	22	61	53	3	4	143

Note: Each BTP patient is counted only once although they participated in more than 1 trial (patients in FT003-IN also were in FT011-IN and patients in FT-016-IM and FT-017-IM also were in FT018IM).
Source: Clinical Trial Reports for FT-003/011-IN, FT-016-IM, FT-017-IM, FT-018-IM
BTP = breakthrough pain, INFS = Instanyl.

Table SIII.2: Age group and gender

Number of BTPs by Age Group and Gender: Trial FT-017-IM

	Placebo		**INFS 50 µg/dose**		**INFS 100 µg/dose**		**INFS 200 µg/dose**	
Age Group	Males	Females	Males	Females	Males	Females	Males	Females
≥18 to ≤49 years	13	20	13	20	13	20	13	20
≥50 to ≤64 years	83	58	84	60	84	61	83	62
≥65 to ≤74 years	42	35	43	35	42	34	42	34
≥75 years	13	22	13	22	13	22	13	22

Source: FT-017-IM, Clinical Trial Report, 2009
BTP = breakthrough pain, INFS = Instanyl.

Number of BTPs by Age Group and Gender: Trial FT-018-IM

	Placebo		**INFS 50 µg/dose**		**INFS 100 µg/dose**		**INFS 200 µg/dose**	
Age Group	Males	Females	Males	Females	Males	Females	Males	Females
≥18 to ≤49 years	10	18	20	63	38	66	20	56
≥50 to ≤64 years	61	54	146	143	192	178	181	80
≥65 to ≤74 years	30	26	78	90	96	68	78	24
≥75 years	8	12	14	34	16	32	10	30

Source: FT-018-IM, Clinical Trial Report, 2009
BTP = breakthrough pain, INFS = Instanyl.

Table SIII.3: Dose

Refer to Table SIII.1 for duration of exposure by dose strength.

Based on the available data, tabulation by ethnic origin and special populations such as pregnant and lactating women, renal impairment, hepatic impairment, and cardiac impairment, is not possible. However, the majority of patients included in these trials were Caucasian; pregnancy was an exclusion criterion for all clinical trials.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Pregnant or nursing during the trial period (all clinical trials)	
Reason for exclusion:	Patients were excluded from all the clinical trials as there were no adequate and controlled data regarding the use of fentanyl in pregnant women. Furthermore, the substance is known to be secreted into human milk and may cause sedation and respiratory depression in the breast-fed infant.
Is it considered to be included as missing information?	No
Rationale:	Cumulative review of post-marketing safety data does not suggest that the safety profile for Instanyl is different in this population. Adequate risk communication is included in the product label including special warning regarding the use during pregnancy and lactation.

Patients with hepatic impairment	
Reason for exclusion:	Patients with severe hepatic impairment were excluded from clinical trials since Instanyl is metabolised primarily in the liver (via Cytochrome P450 3A4 [CYP3A4]). Published experience from fentanyl use in patients with liver impairment is scarce. Fentanyl is metabolised to inactive metabolites in the liver, so that patients with hepatic impairment might exhibit delayed metabolism and elimination.
Is it considered to be included as missing information?	No
Rationale:	Cumulative review of post-marketing safety data does not suggest that the safety profile for Instanyl is different in this population. Adequate risk communication is included in the product information including special warning and precautions for use in patients with moderate to severe hepatic or renal impairment are included in the SmPC. The influence of hepatic and renal impairment on the PK of Instanyl have not been evaluated; however, when administered intravenously, the clearance of Instanyl has shown to be altered due to hepatic and renal impairment caused by alterations in metabolic clearance and plasma proteins.

Patients with renal impairment	
Reason for exclusion:	The trials FT-001-IN, FT-016-IM and the PK trials, have evaluated the PK profile of fentanyl following intranasal administration. As the clearance of fentanyl has been shown to be altered in patients with renal impairment, patients with severe renal impairment were excluded from clinical studies. Published experience from patients with renal impairment following exposure to fentanyl is scarce. Less than 10% of fentanyl is excreted unchanged by the kidneys, and unlike morphine, there are no known

Patients with renal impairment	
	active metabolites eliminated by the kidneys.
Is it considered to be included as missing information?	No
Rationale:	Cumulative review of post-marketing safety data does not suggest that the safety profile for Instanyl is different in this population. Adequate risk communication is included in the product information including special warning and precautions for use in patients with moderate to severe hepatic or renal impairment. The influence of hepatic and renal impairment on the PK of Instanyl have not been evaluated; however, when administered intravenously, the clearance of Instanyl has shown to be altered due to hepatic and renal impairment caused by alterations in metabolic clearance and plasma proteins.

Paediatric population	
Reason for exclusion:	In the clinical development program, study inclusion was limited to adult cancer patients only. No data from the clinical trials are available in paediatric groups with this (intranasal) formulation.
Is it considered to be included as missing information?	No
Rationale:	Instanyl is not recommended for use in children below 18 years of age. A special warning regarding the use in paediatric patients is included in the SmPC. Cumulative review of post-marketing safety data does not suggest that the safety profile for Instanyl is different in this population.

SIV.2. LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Local tolerability ADRs

Local tolerability ADRs may be more likely to emerge after prolonged treatment.

In the majority of Instanyl clinical trials, patients were exposed between 3-6 months of treatment. However, more than 40 patients were exposed for >6 months. The duration of treatment should also be considered in the context of the approved indication i.e., the palliative care setting in terminally ill patients.

No ADRs associated with prolonged exposure were identified in the clinical trial program.

The NOSE 400 trial was conducted to evaluate 12 weeks safety and nasal tolerability of dose strengths between 50 µg and 400 µg. A total of 46 patients received 1 or more doses of INFS. Tolerability was assessed by changes (signs or abnormalities) in the nasal mucosa, after 12 weeks of treatment. The results of this trial demonstrated a favourable nasal tolerability profile, as only 3 patients showed mucosal signs or abnormalities worsening from absent or mild to moderate or severe (runny nose [increased secretion] and stuffed nose [swollen]) and only 5 of these 7 signs or abnormalities were considered related to the investigational medicinal product.

Local tolerability (nasal adverse effects with nasal formulations and buccal adverse effects with buccal formulations) is a known risk with all transmucosal formulations of fentanyl. All application reactions

and local effects are included in this risk.

Long-term use

Given the duration of treatment in terminally ill patients, ADRs, other than associated with local tolerability, are not anticipated.

SIV.3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breast-feeding women	
Patients with relevant co-morbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable *Renal impairment*: The trials FT-001-IN, FT-016-IM and the PK trials, evaluated the PK profile of fentanyl following intranasal administration. The clearance of fentanyl has been shown to be reduced in patients with severe renal impairment. Patients with severe renal impairment were excluded from clinical studies. Published experience from patients with renal impairment is limited. *Hepatic impairment*: Patients with severe hepatic impairment were excluded from all the clinical trials, as fentanyl is metabolised primarily in the liver by CYP3A4. Published experience following the use of fentanyl in patients with liver impairment, is limited. Fentanyl is metabolised to inactive metabolites in the liver, so patients with hepatic impairment might have a delayed elimination. *Patients with a disease severity different from the inclusion criteria in the clinical trial population:* All clinical trials were in cancer patients with BTP, with a life expectancy of at least 12 weeks and receiving opioid treatment as background pain medication. Most patients already had advanced cancer at the time of inclusion, but cancers of different severity were included.
Population with relevant different ethnic origin	Not applicable Potential associations between opioid receptor polymorphisms and development of tolerance, drug abuse and efficacy of opioids in pain management, have been suggested and studies published so far show conflicting results depending on trial population. The influence of ethnic origin has not been studied in clinical trials. The PK trials (FT-021-IM, FT-022-IM, FT-023-IM, FT024-IM, FT-025-IM, FT-026-IM, FT-1305-028-SP and FT-1301-035-SP) provided data in Caucasian as well as in Black or in African American subjects. There were no obvious PK differences in these ethnic groups.

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not applicable Genetic variability of clinical relevance has only been established for the CYP2D6 gene polymorphisms and the mu-opioid receptor gene A118G polymorphism. Clinical data are either not available or the data are too limited to reach a definitive conclusion regarding other genetic polymorphisms. Also, for other opioids or other candidate genes, clinical data are either not available or the data are too limited to draw a conclusion. Clinical effects are influenced by variations in other biological systems that modify the effects induced by opioid agonists. Clinical data are lacking for most opioids and little is known about the exact mechanisms by which genetic variability interacts with opioid signalling. The concomitant use of CYP450 3A4 inhibitors/inducers was excluded in all PK trials of fentanyl nasal spray. The influence of genetic polymorphism has not been studied in the clinical trial population.
Other: Elderly	All clinical trials were conducted in adults aged at least 18 years of age (and 70 years in trial FT-016-IM). Data from intravenous (IV) studies with fentanyl suggest that elderly patients may have reduced clearance, that fentanyl has a prolonged half-life and that they may be more sensitive to fentanyl than younger patients.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1. POST-AUTHORISATION EXPOSURE

SV.1.1. Method used to calculate exposure

Fentanyl nasal spray: For fentanyl nasal spray solution, the methodology used to calculate the exposure assumes that one dose of fentanyl nasal spray solution is administered for each BTP episode based on the current Reference Safety Information.

Patient exposure = Number of doses/45 (average period of use [days])/2.5 (average number of BTP episodes per day).

SV.1.2. Exposure

Fentanyl nasal spray: Based on the above methodology, the patient exposure can be estimated to be 23.92 million episodes treatment cumulatively, corresponding to approximately 867,983 patient-years of treatment.

The estimated patient exposure for fentanyl nasal spray in the number of doses in mg is presented in Table SV.1.

Table SV.1: Exposure table for Fentanyl nasal spray

Country/Region	Cumulative Patient-years Since Launch
USA	0
EEA**	829,150
ROW*	38,833
Total	**867,983**

Note: Sales data is based till 30-April-2023. The numbers are rounded.
*ROW: South Korea and UK.
**EEA: Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Slovakia, Slovenia, Spain, and Sweden.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Fentanyl is an opioid agonist with an abuse and misuse liability, similar to that of other opioid analgesics. The Instanyl target population is opioid-tolerant cancer patients, i.e., patients who already have access to narcotic drugs for treatment of their background pain.

Due to the potency of fentanyl, its rapid onset of effect and ease of use, there may be a risk of misuse following treatment with Instanyl. Special attention must be taken when prescribing or dispensing Instanyl in situations where the physician or pharmacist, has the suspicion of a risk of misuse, abuse or diversion.

The single-dose nasal spray may reduce the potential risk of abuse and misuse as a smaller number of dosages can be prescribed to patients in whom abuse is suspected.

The development of the improved multi-dose nasal spray may also reduce the risk of abuse and misuse, since the integrated lock ensures that only a certain number of doses can be administered within a specific time period.

As per PRAC recommendation, drug diversion should be defined as the diversion of licit drugs for illicit purposes. It involves the diversion of drugs from legal and medically necessary uses toward uses that are illegal and typically not medically authorised or necessary.

In the non-interventional study Patient reported Instanyl Use Study (PIUS) (FT-1301-402-RD), 2 patients, including one with cancer diagnosis, reported lending Instanyl to another person (0.7% of all patients and 0.6% of cancer patients).

Potential for off label use

Fentanyl is an opioid agonist and analgesic with a potential for off label use, similar to that of other opioid analgesics. Due to its' rapid onset of effect and the ease of use of a nasal spray, there may be a risk of off label use for other types of pain. The use of Instanyl is contraindicated in opioid-naïve patients. The national frameworks, regulatory and other, governing off label use of medicinal products in the various EU Member States are complex and not yet harmonised. There is a difference between the regulation of medicinal products and their use in medical practice. EU legislation does not regulate the way medicinal products are ultimately used in medical practice. The prescribing of a medicinal product, on-label or off label is a decision taken within the relationship between a patient and his or her treating healthcare professional (HCP). The way Member States organise their healthcare system and the way HCPs conduct their practice is not EU responsibility. The delivery of health services and medical care lies with the Member States (Article 168 (7) Treaty on the Functioning of the European Union-TFEU).

Some policy tools for off label use by EU Member States are:

- Legal frameworks can issue temporary recommendations for use and permission to prescribe off label. This includes the "temporary recommendations for use (RTU) scheme" in France and the Hungarian system where prescribers or their organisations have to ask for permission to prescribe a product off label.
- Reimbursement measures, for example in France and Italy allow for reimbursement of off label use when (on-label/authorized/not strictly identical) alternatives exist.
- Guidance for prescribers such as the General Medical Council Guidance (Good practice in prescribing and managing medicines and devices, 2013) in the UK.
- Professional standards, such as in The Netherlands where off label prescription is only allowed if the relevant professional body has developed protocols or standards with regard to that specific off label use.
- Policy based on the patient, for example regarding informed consent needed in many Member States or the fact that for serious interventions, upon request of the patient, an HCP has to register for what intervention the patient has given consent (The Netherlands). In EU Member States without

specific policy tools on off label use, the dominant view is that off label use is an issue to be dealt with at the level of the prescriber rather than at the regulatory or healthcare system level. Prescribers are trusted to know what is best for the well-being of the patient, with the medical need dominant. There is an overall lack of clarity regarding management of off label use and information and communication is required.

The preventive measures taken by the MAH with regard to potential for off label use are discussed further below.

Potential for paediatric off label use

The educational material and the SmPC, emphasise that Instanyl is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Preventive measures for the final product(s) being marketed

Medication errors can occur by unintentional drug prescribing error, by drug administration error, by drug dispensing error, by incorrect dose administered, or by use of an incorrect route of administration. To minimise the risk of medication errors, all labelling materials are colour coded differently for each of the dose strengths.

Approved educational materials for the current multi-dose nasal spray, include a dose counting scheme, which helps the patient count the number of doses that have been self-administered and thus, when to dispose of the product. A dose counting scheme is also provided on the child-resistant box that is used for product storage.

The single-dose and the future introduction of the improved multi-dose nasal spray will further minimise the risk of medication errors.

The MAH has introduced on all Instanyl products the safety features required in EU aimed at preventing potential falsified medicines entering the legal supply chain and reaching patients.

For the single-dose nasal spray, it is clear to the patient how many doses are left by the visual inspection of unused nasal sprays remaining in the carton (since there is only one dose per nasal spray).

The single-dose nasal spray can also be prescribed to patients where the prescriber considers there may be an increased risk of problems keeping track of doses or where the prescriber would like to prescribe a smaller number of doses than possible with the current multi-dose spray, due to the potential for abuse/misuse.

An improved multi-dose nasal spray with lock-out mechanism has been developed by the MAH and includes a dose-counter and child-resistant cap. Through its lock-out mechanism, this improved multi-dose nasal spray, prevents patients from administering more than 2 doses in quick succession. This is intended to minimise the number of patients who may develop dependence. The lock-out feature also makes the spray less amenable to abuse and potential diversion.

The new improved multi-dose system nasal spray solution was approved by the European Medicines Agency (EMA) in 2016. Subsequent to the launch in all the approved countries, there will be period of time whereby both the current conventional multi-dose and the new improved multi-dose will be available on the market at the same time. As the new system has additional safety features, there are different instructions for use to the existing conventional Instanyl nasal spray.

To ensure the Product Information for the conventional multi-dose and the improved multi-dose are clearly distinguishable, the descriptor "DoseGuard" has been added to the "Pharmaceutical Form" for the improved multi-dose i.e., *Nasal spray, solution (nasal spray) DoseGuard.*

The packaging for the new nasal spray and the conventional multi-dose is also differentiated, as follows: The conventional multi-dose does not come in an outer packaging, but is instead housed within a child-resistant box. The improved nasal spray will be presented within an upright rectangular outer carton with the descriptor name "DoseGuard" clearly presented on the outer packaging.

To prevent the occurrence of drug abuse, misuse, medication error, overdose and addiction, updated educational material proposed for Instanyl will include specific guidance on off label use and its risks. It will further emphasise the correct use of this product, as follows:

1. Explanation of pain management principles and explanation of BTP. Use of opioids in general. High level background on opioid crisis and risks.
2. Information on risks of abuse, misuse, medication error, addiction and overdose. Identification of at-risk patients and suggested management.
3. Adherence to the label, when prescribing Instanyl since it seems that abuse and dependence may be more frequent when the product is used off label. Potency of fentanyl as an opioid (compared to other opioids) is emphasised. Different fentanyl formations with different indications will be explained so doctors are aware of off label use with nasal fentanyl specifically. Types of off label use especially relevant to nasal fentanyl will be discussed.

Discussion on Potential Implications for Prescription Restriction

Breakthrough pain is prevalent in cancer patients being treated with background opioids. These people are generally managed within the community setting. Instanyl is an effective option for patients to control their pain relief. Being able to manage their pain improves patient's QoL. Nasal fentanyl with its transmucosal absorption means the need for intravenous access or repeated specialist physician visits or hospital visits by the patient may be reduced possibly. GPs and other physicians can prescribe and facilitate this palliative management of patients using nasal fentanyl while they are in the community.

Restriction of prescription of nasal fentanyl could potentially result in the undertreatment of BTP for cancer patients being managed outside of hospitals. Lack of effective, accessible pain relief could stop patients being cared for at home. Palliative care specialists and hospital systems would have to manage the extra burden of pain. Patients might take more pain-relieving pills in total while they try to relieve BTP. This might lead to medication errors. At worst case, if a patient cannot find nasal fentanyl available by prescription, they might try more lethal products available on the illicit market.

Prescription restriction of nasal fentanyl to hospitals may impact off label use reports. However, the delivery of health care is complex and altering access would have many downstream impacts on a patient, physician and social level. There is currently no available epidemiological evidence to understand the implications of prescription access of nasal fentanyl. Regulatory alterations on prescription access within Europe requires recognition of the complex interplay of subsequent impact on patients, healthcare delivery, and public health. Each European country would have different impacts. Reactive actions could generate unforeseen harms. Current thinking suggests that education for the prescribing physicians on misuse, abuse, medication error, overdose and addiction as well as other consequences of off label use of opioids, is a more effective manner to ensure that negative consequences of inadequate access are avoided.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

None.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	Risk-benefit impact
Addiction	Patients treated for chronic cancer pain (the target population) are expected to be managed with long-term strong opioids and thus they are highly exposed to the risk of opioid dependence. Patients with prior substance abuse and underlying chronic non-cancer pain are at higher risk for dependence. Physical dependence, demonstrated by symptoms of withdrawal such as agitation, insomnia, diarrhoea, diaphoresis, and palpitations, may occur even within a few days of opioid dosing, although this varies among patients.
Misuse	Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information (Good Pharmacovigilance Practice [GVP] Module VI). Misuse can be characterised as not taking the medication according to prescription, unsanctioned use, and alteration of the route of delivery. The prevalence of lifetime substance use disorders ranges from 36% to 56% in patients treated with opioids for chronic back pain; 43% of this population has current substance use disorder (SUD) and 5% to 24% have aberrant medication-taking behaviours. About 14% to 16% of pain patients not having SUD, use illicit drugs in combination with prescription drugs for pain, while 34% of patients with SUD combine legal pain medication with illicit drug use. These statistics highlight the difficulty of balancing pain treatment with abuse management. Misuse and mismanagement of opioid analgesics would be expected to expose patients to higher risk of developing tolerance and in the case of inconsistent use, a higher risk of experiencing effects of withdrawal or overdose and associated adverse effects.
Abuse	Instanyl has the potential for abuse, misuse, and diversion similar to that of other opioid painkillers. Overdose with misuse or abuse, could have consequences such as respiratory depression that can result in life-threatening or fatal outcomes. Misuse may occur due to inadequate knowledge in correct use of the medication as prescribed. Adherence to the special warning for use in patients with abuse potential and dependence are included in the SmPC and patient information leaflet (PIL) and reiterated in the educational materials. Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as Instanyl. However, iatrogenic addiction following therapeutic use of opioids

Important Identified Risks	Risk-benefit impact
	is rare in the treatment of cancer related pain.
Diversion	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. There are life-threatening consequences of opioid-naïve overdose, at worst, fatal respiratory depression. In the general population, annual health care costs associated with opioid dependence/abuse are high. Costs to society include lost work productivity due to intoxication or complications of use, health care costs for uninsured users with medical complications, prosecution and incarceration expenses for criminal offenses, and economic and psychological costs to family members and victims of crimes.
Off label use	Opioid analgesics in clinical practice may be used 'off label' i.e., prescribed beyond 90 consecutive days or the prescribed dose may exceed 100 mg of morphine equivalent dose (MED) due to inter-individual variability or prescribed in conditions in which some experts recommend against opioid use e.g., fibromyalgia or long-term use of opioids in chronic non-cancer pain. However, the prevalence is not known. Off label use may constitute a risk, when the Instanyl is prescribed for off label indications, if the patients are not closely supervised. Here the use could potentially escalate to abuse and misuse, or cause respiratory depression. Use for off label indications in special patient groups, mentioned in the SmPC under the contraindications and special warnings sections, would also be a safety concern.
Medication errors	Medication errors can lead to moderate-severe adverse effects ranging from uncontrolled pain due to omission or multiplication of dose leading to overdose and adverse effects resulting from the overdose, e.g., moderate to severe respiratory depression. The impact on patients prescribed Instanyl could be both in terms of efficacy and safety. Incorrect use of Instanyl either via prescribing, dispensing or administration error may result in inadequate BTP management. If medication error has occurred surrounding dosing, then again this could mean the patient receives a non-efficacious dose or indeed one that makes them susceptible to ADRs.
Overdose (suicide and suicide attempt excluded)	Due to overdosing, adverse effects such as respiratory depression may be seen. Overdose may lead to a fatal outcome. The target population of Instanyl is opioid-tolerant cancer patients already receiving opioids as part of their maintenance treatment. Respiratory depression is not a clinical issue in cancer patients with opioid-sensitive pain as long as opioid treatment has been individualised and titrated against the patient's need.
Accidental exposure (including potential exposure of other people and children to drug expelled in the patient's proximity during priming)	Accidental or deliberate application or ingestion by a child or adolescent may cause respiratory depression that could result in death.
Respiratory depression	As with all potent opioids, clinically significant respiratory

Important Identified Risks	Risk-benefit impact
	depression may occur following fentanyl administration, 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 central nervous system depressants may increase the risk of respiratory depression. Respiratory depression can be moderate to severe in nature and requires medical intervention. In severe cases, it can be life-threatening and/or fatal. The incidence of respiratory depression associated with opioid treatment for pain is 0.5% or less of total events. The incidence of post-operative opioid-induced respiratory depression in the United Kingdom (UK) has been estimated to be approximately 1%.
Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs	Fentanyl does not cause serotonin syndrome when used alone, but this syndrome can be seen when fentanyl is used together with serotonergic drugs (drugs to treat depression). The severity of serotonin syndrome is highly variable. Reactions can be mild and transient, presenting as tachycardia (increased heart rate). However, reactions may also result in severe hypertension (high blood pressure) and tachycardia that can abruptly deteriorate into cardiovascular shock. Severe and unpredictable interactions with Monoamine oxidase inhibitors (MAOIs), involving the potentiation of opiate effects or the potentiation of serotonergic effects, have been reported. The Instanyl SmPC recommends discontinuation of treatment with Instanyl if serotonin syndrome is suspected. Also, fentanyl should not be used within 14 days after discontinuation of treatment with MAOIs. In addition, the Instanyl SmPC Special warnings and precautions for use advocate that caution is advised when Instanyl is co-administered with drugs that affect the serotoninergic neurotransmitter systems and that the development of a potentially life-threatening serotonin syndrome may occur even with the recommended dose with the concomitant use of serotonergic drugs such as Selective serotonin reuptake inhibitors (SSRIs) and Serotonin and norepinephrine reuptake inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including MAOIs). If serotonin syndrome is suspected, treatment with Instanyl should be discontinued.

Important Potential Risk	Risk-benefit impact
Brain lesion	Animal studies revealed changes in the brain. In a non-clinical study conducted by Kofke WA, et al, 11 of 20 rats showed evidence of brain damage primarily in limbic system structures and association areas which confirmed that fentanyl produces limbic system brain damage in rats, and that the damage occurs over a broad range of doses. There is no relevant data available in humans that allows these observations to be evaluated in the approved clinical context. Histological evaluation of brain tissue from a carcinogenicity study in rats revealed brain lesions in animals administered high

Important Potential Risk	Risk-benefit impact
	doses of fentanyl citrate. The study was conducted by the MAH of another fentanyl product and the relevance of these findings to humans is unknown. This risk is considered potential because the relevance to humans is unknown. Communication of this risk is included in the package information.

Missing Information	Risk-benefit impact
Long-term use	Long-term use of fentanyl could not be studied in clinical trials. Given the duration of treatment in terminally ill patients, safety events that may be associated with the long-term use of fentanyl are anticipated.

SVII.2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable.

SVII.3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

Identified Risk – Addiction (Medical dictionary for Medical Dictionary for Regulatory Activities [MedDRA] SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues) Further, the following PTs were considered for evaluation of the risk of Addiction: Dependence, Drug dependence, Drug tolerance, Drug tolerance decreased, Drug tolerance increased, Drug withdrawal syndrome, Drug withdrawal syndrome neonatal, Medication overuse headache, Narcotic bowel syndrome, Needle track marks, Reversal of opiate activity, Withdrawal syndrome, Drug detoxification, Overdose intentional, Pharmaceutical nomadism, Drug dependence, antepartum, and Drug withdrawal maintenance therapy.	
Potential mechanisms	Activation of endogenous mu-opioid receptors results in the prototypic opioid effects of reward, withdrawal, and analgesia. When opioid molecules bind to mu receptors on brain cells in the locus ceruleus (LC) where noradrenaline (NA) is synthesised, they suppress the neurons' release of NA, resulting in drowsiness, slowed respiration, low blood pressure, and effects of opioid intoxication. With repeated exposure to opioids, however, the LC neurons adjust by increasing their level of activity. Now, when opioids are present, their suppressive impact is offset by this heightened activity, with the result that roughly normal amounts of NA are released, and the patient feels more or less normal. When opioids are not present to suppress the LC brain cells' enhanced activity, however, the neurons release excessive amounts of NA, triggering jitters, anxiety, muscle cramps, and diarrhoea. These symptoms are associated with withdrawal and indicative of the patient's physiologic dependence on opioids.
Evidence source(s) and strength of evidence	Dependence, often confused with addiction, is an expected response in cancer patients necessitating prolonged and continuous opioid therapy for pain management. In the case of off label or illicit use, the progression to opioid

Identified Risk – Addiction (Medical dictionary for Medical Dictionary for Regulatory Activities [MedDRA] SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues) Further, the following PTs were considered for evaluation of the risk of Addiction: Dependence, Drug dependence, Drug tolerance, Drug tolerance decreased, Drug tolerance increased, Drug withdrawal syndrome, Drug withdrawal syndrome neonatal, Medication overuse headache, Narcotic bowel syndrome, Needle track marks, Reversal of opiate activity, Withdrawal syndrome, Drug detoxification, Overdose intentional, Pharmaceutical nomadism, Drug dependence, antepartum, and Drug withdrawal maintenance therapy.	
	dependence may have dire consequences, including a yearly mortality rate of approximately 2%. Moreover, sustained remission from opioid addiction is difficult to achieve.
Characterisation of the risk	Frequency *Clinical trials*: Cumulatively, as of 30-April-2023, no events were received for the risk of addiction in the clinical program. *Post-marketing*: Cumulatively, as of 30-April-2023, 187 events reflecting 156 cases have been received post marketing (Reporting Rate [RR] = 156/867,983 x10,000 =1.79 per 10,000 patients). Seriousness/outcomes *Clinical Trials*: Not applicable. *Post-marketing*: Of the 187 events, 115 were deemed serious (27 were serious due to hospitalisation). Outcome for the events were as follows: fatal (3), not recovered/not resolved (44), not reported (14), recovered (15), recovered/resolved (12), recovering/resolving (18), and unknown (81). Background incidence/prevalence An estimated 4.5% of a nationally representative sample of US adults reported non-medical use of prescription opioids; 12.9% of these people met criteria for DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision) diagnoses of opioid abuse or opioid dependence. 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%. Moreover, sustained remission from opioid dependence is difficult to achieve. Severity and nature of risk Physical dependence, demonstrated by symptoms of withdrawal such as agitation, insomnia, diarrhoea, diaphoresis, and palpitations, may occur even within a few days of opioid dosing, although this varies among patients.
Risk groups or risk factors	The target population is at high risk of opioid addiction 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 addiction to fentanyl.
Preventability	A special warning for the use in patients with abuse potential and addiction is included in the SmPC. It is stated that tolerance and physical and psychological dependence may develop upon repeated administration of opioids.

Identified Risk – Addiction (Medical dictionary for Medical Dictionary for Regulatory Activities [MedDRA] SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues) Further, the following PTs were considered for evaluation of the risk of Addiction: Dependence, Drug dependence, Drug tolerance, Drug tolerance decreased, Drug tolerance increased, Drug withdrawal syndrome, Drug withdrawal syndrome neonatal, Medication overuse headache, Narcotic bowel syndrome, Needle track marks, Reversal of opiate activity, Withdrawal syndrome, Drug detoxification, Overdose intentional, Pharmaceutical nomadism, Drug dependence, antepartum, and Drug withdrawal maintenance therapy.	
	Dependence, often confused with addiction, is an expected response in cancer patients necessitating prolonged and continuous opioid therapy for pain management. While it may not be possible to prevent the onset of physiologic opioid dependence (for most cancer patients with chronic persistent cancer pain treated with basal regimen of strong opioids, some level of physiologic dependence may already be present during evaluation for the management of BTP). Titrating to the lowest effective dose, considering periodic switching between strong opioids, supplementing with non-opioid analgesics may help delay progression or severity of opioid dependence.
Impact on the risk-benefit balance of the product	Dependence, often confused with addiction, is an expected response in cancer patients necessitating prolonged and continuous opioid therapy for pain management. 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%. Moreover, sustained remission from opioid dependence is difficult to achieve. Pharmacovigilance and risk minimisation measures in place are considered sufficient to manage the benefit-risk balance for Instanyl.
Public health impact	Opioid use and addiction are associated with significant medical and psychiatric morbidities, as well as adverse social, familial, vocational, and legal consequences. The risk of criminal activity and legal consequences becomes greater as dependence becomes more severe.

Identified Risk – Misuse MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk of misuse: Disturbance in social behaviour, Drug use disorder, Intentional device misuse, Intentional overdose, Intentional product misuse, Intentional product use issue, Incorrect route of product administration, Overdose, Substance use, Toxicity to various agents, Off label use of device, and Product administered at inappropriate site.	
Potential mechanisms	Intentional misuse related to incorrect dosing or frequency of dosing could be attributable to the inadequate training or compliance by prescriber or patient. Intentional misuse as related to abuse or off label use are reflective of the addictive potential and analgesic properties of narcotics as a class and the socio-behavioural tendencies of those at risk for misuse.
Evidence source(s) and strength of evidence	Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the

Identified Risk – Misuse MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk of misuse: Disturbance in social behaviour, Drug use disorder, Intentional device misuse, Intentional overdose, Intentional product misuse, Intentional product use issue, Incorrect route of product administration, Overdose, Substance use, Toxicity to various agents, Off label use of device, and Product administered at inappropriate site.	
	terms of the marketing authorisation (GVP Module VI). Misuse can be characterised 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' QoL, and which requires treatment for resolution.
Characterisation of the risk	Frequency *Clinical trials*: Cumulatively, till 30-April-2023, no events of misuse were received in the clinical program. *Post-marketing*: Cumulatively, till 30-April-2023, 218 events reflecting 187 cases have been received post-marketing (RR = 187/867,983x10,000 =2.15 per 10,000 patients). Seriousness/outcomes *Post-marketing*: Of the 218 events, 62 were deemed serious (21 were serious due to hospitalisation). Outcome for the events were as follows: fatal (3), not recovered/not resolved (19), not reported (15), recovered/resolved (27), recovering/resolving (7), and unknown (147). Background incidence/prevalence Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information (GVP Module VI). Misuse can be characterised as not taking the medication according to prescription, unsanctioned use, altering the route of delivery, among others. The prevalence of lifetime substance use disorders ranges from 36% to 56% in patients treated with opioids for chronic back pain; 43% of this population has current SUD and 5% to 24% have aberrant medication-taking behaviours. About 14% to 16% of pain patients not having SUD, use illicit drugs in combination with prescription drugs for pain, while 34% of patients with SUD combine legal pain medication with illicit drug use. These statistics highlight the difficult situation of balancing pain treatment with abuse management.
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. 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

Identified Risk – Misuse MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk of misuse: Disturbance in social behaviour, Drug use disorder, Intentional device misuse, Intentional overdose, Intentional product misuse, Intentional product use issue, Incorrect route of product administration, Overdose, Substance use, Toxicity to various agents, Off label use of device, and Product administered at inappropriate site.	
	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 is 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.
Preventability	A special warning for the use in patients with abuse potential and dependence is included in the SmPC. It is stated that tolerance and physical and psychological dependence may develop upon repeated administration of opioids. Intentional misuse can be deterred with vigilant management of dosing and supply by caregiver and/or prescribing physician, frequent reassessment of baseline and BTP experience, adjustments to the regimen as warranted, reinforcing safe and appropriate use of fentanyl for BTP, routine evaluation of psychosocial factors, and monitoring development of tolerance.
Impact on the risk-benefit balance of the product	Misuse and mismanagement of opioid analgesics would be expected to expose patients to higher risk of developing tolerance and in the case of inconsistent use, a higher risk of experiencing effects of withdrawal or overdose and associated adverse effects. Pharmacovigilance activities and risk minimisation measures in place for the risk of misuse of Instanyl are considered sufficient to manage the benefit-risk balance for Instanyl.
Public health impact	Misuse and mismanagement of opioid analgesics would be expected to expose patients to higher risk of developing tolerance and in the case of inconsistent use, a higher risk of experiencing effects of withdrawal or overdose and associated adverse effects.

Identified Risk – Abuse MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk of abuse: Drug abuse, Drug abuser, Drug level increased, Substance abuse, and Substance use disorder.	
Potential mechanisms	The risk of abuse is reflective of the addictive potential and analgesic properties of narcotics as a class and the socio-behavioural tendencies of those at risk for abuse. Activation of mu receptors in the central nervous system results in responses such as analgesia and euphoria.
Evidence source(s) and strength of evidence	Abuse corresponds to persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects (GVP Module VI). Abuse of fentanyl is considered to present a moderate risk among

Identified Risk – Abuse MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk of abuse: Drug abuse, Drug abuser, Drug level increased, Substance abuse, and Substance use disorder.	
	opioid-tolerant persons due to associated behaviours 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 central nervous system (CNS) depressants.
Characterisation of the risk	Frequency *Clinical trials*: Cumulatively, till 30-April-2023, no events of abuse were received in the clinical program. *Post-marketing*: Cumulatively, till 30-April-2023, 108 events reflecting 102 cases have been received post-marketing (RR = 102/867,983x10,000 =1.17 per 10,000 patients). Seriousness/outcomes *Clinical trials*: Not applicable. *Post-marketing*: Of the 108 events, 35 were deemed serious (8 were serious due to hospitalisation). Outcome for the events were as follows: fatal (4), not recovered/not resolved (19), not reported (16), recovered/resolved (9), recovering/resolving (7), and unknown (53). Background incidence/prevalence The past 2 decades have witnessed an expansion of analgesic use, especially opioid use for patients who have chronic non-cancer pain. The National Centre on Addiction and Substance Abuse (CASA) found that from 1992 to 2002 the number of prescriptions for controlled drugs increased 154.3% compared to 56.6% for non-controlled drugs during a time when the US population only rose 13%. It is estimated that 7 million people abuse/misuse prescription drugs every month and 5.3 million people abuse/misuse pain relievers (ACPM, n.d.). If not managed closely by the treating physician, patients can inadvertently slide into a pattern of misuse and abuse, due to lack of education on effects of narcotics, inadequate background control of chronic cancer pain or escalation in nature, frequency and intensity of BTP. In the general population in the US, the true prevalence of narcotic abuse is unknown, but appears to be increasing. The US Drug Abuse Warning Network (DAWN) reported a 7-fold increase in oxycodone-related emergency department visits from 1996 to 2002. One study estimated that among 10.89 million individuals projected to have used prescription opioids non-medically, a minimum of 430.61 million doses were used non-medically per year, which represents 1/25th of all prescription opioids dispensed. In the chronic pain population, opioids are the most abused drugs. The prevalence of lifetime substance use disorders ranges from 36% to 56% in patients treated with opioids for chronic back pain; 43% of this population has current SUD and 5% to 24% have

Identified Risk – Abuse MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk of abuse: Drug abuse, Drug abuser, Drug level increased, Substance abuse, and Substance use disorder.	
	aberrant medication-taking behaviours. About 14% to 16% of pain patients not having SUD use illicit drugs in combination with prescription drugs for pain, while 34% of patients with SUD combine legal pain medication with illicit drug use (ACPM, n.d.). Indeed, the research demonstrates correlative evidence between increased availability/ease of use of narcotic analgesics and abuse. As such, there tends to be an under-prescribing or at least, an overtly cautious prescriber mentality that translates to possibly under-serving a valid need for pain control among patients who need it, such as those suffering from cancer pain.
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.
Preventability	Screening for medical and family history should always be undertaken at the start of treatment. Equally important is screening for pain level using clinical guidelines and validated pain scoring to establish goals in pain relief. The results of comprehensive intake, status of cancer progress and ongoing or anticipated treatment, in combination with risk stratification for addiction liability, make it easier for physicians to determine individualised treatment strategies to appropriately manage pain. Additionally, keeping patients accountable in communicating pain level, dosing regimen, self-use/safe use is necessary in avoiding abuse, misuse and diversion. The Instanyl SmPC Special warnings and precautions for use states that tolerance and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. However, iatrogenic addiction following therapeutic use of opioids is known to occur in the treatment of cancer related pain. Furthermore, the SmPC posology and method of administration explains that 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.
Impact on the risk-benefit balance of the product	Abuse may be initially unrecognisable as an abuser may still maintain normal function and activities of daily living. If abuse persists, it may impact a person's ability to work, family life, decision making and lead to associated socio-behavioural tendencies or other substance abuse. If not managed closely by the treating physician, patients can inadvertently slide into a pattern of misuse and abuse, due to lack of education on effects of narcotics, inadequate background

Identified Risk – Abuse MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk of abuse: Drug abuse, Drug abuser, Drug level increased, Substance abuse, and Substance use disorder.	
	control of chronic cancer pain or escalation in nature, frequency and intensity of BTP. Screening for medical and family history should always be undertaken at the start of treatment. Equally important is screening for pain level using clinical guidelines and validated pain scoring to establish goals in pain relief. The results of comprehensive intake, status of cancer progress and ongoing or anticipated treatment, in combination with risk stratification for addiction liability, make it easier for physicians to determine individualised treatment strategies to appropriately manage pain. Additionally, keeping patients accountable in communicating pain level, dosing regimen, self-use/safe use is necessary in avoiding abuse, misuse and diversion. Pharmacovigilance activities and risk minimisation measures in place are considered sufficient to ensure a positive benefit-risk balance for Instanyl.
Public health impact:	The public health impact is considered to be moderate. In the general US population, annual health care costs associated with opioid dependence/abuse have been found to exceed one billion dollars. Costs to society include lost work productivity due to intoxication or complications of use, health care costs for uninsured users with medical complications, prosecution and incarceration expenses for criminal offenses, and economic and psychological costs to family members and victims of crimes.

Identified Risk – Off label use MedDRA HLGT: Off label uses and intentional product misuses/use issues and MedDRA TMQ of Off-label use (Narrow)	
Potential mechanisms:	Not applicable.
Evidence source(s) and strength of evidence	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 authorisation (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 pain. If used outside the indication in opioid-naïve patients there is a risk of respiratory depression as stated in the SmPC.
Characterisation of the risk:	Frequency *Clinical trials*: Cumulatively, till 30-April-2023, no events of off label were received in the clinical program. *Post-marketing*: Cumulatively, till 30-April-2023, 831 events reflecting 534 cases have been received post-marketing (RR = 534/867,983x10,000 =6.15 per 10,000 patients).

Identified Risk – Off label use MedDRA HLGT: Off label uses and intentional product misuses/use issues and MedDRA TMQ of Off-label use (Narrow)	
	Seriousness/outcomes Of the 831 events, 212 were deemed serious (54 were deemed serious due to hospitalisation). Outcome for the events were as follows: fatal (9), not recovered/not resolved (97), not reported (57), recovered/resolved (62), recovering/resolving (27), and unknown (579). Background incidence/prevalence Opioid analgesics in clinical practice may be used 'off label' i.e., prescribed beyond 90 consecutive days or the prescribed dose may exceed 100 mg of MED due to inter-individual variability or prescribed in conditions in which some experts recommend against opioid use e.g., fibromyalgia or long-term use of opioids in chronic non-cancer pain. However, the prevalence is not known.
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.
Preventability	The Instanyl SmPC states the labelled indications and doses. The use of Instanyl should be followed per SmPC. Steps have been taken in order to remind the staff directly in touch with prescribers in all the local affiliates in EU/EEA of the importance of stressing to the physicians not to prescribe Instanyl to non-cancer patients, and opioid-naïve cancer patients. Educational material further emphasises the importance of adherence to the labelled indication.
Impact on the risk-benefit balance of the product	Off label use may constitute a risk, when Instanyl is prescribed for off label indications, if the patients are not closely supervised. Here the use could potentially escalate to abuse and misuse or cause respiratory depression. Use for off label indications in special patient groups, mentioned in the SmPC under the contraindications and special warnings sections, would also be a safety concern. Pharmacovigilance activities and risk minimisation measures including educational materials are considered sufficient to ensure a positive benefit-risk balance for Instanyl.
Public health impact:	Not known.

Identified Risk – Diversion MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk diversion: Drug diversion, Prescription drug used without a prescription, and Prescription form tampering.	
Potential mechanisms	Potential mechanisms include voluntary provision, theft from patients or hospital supply, fraudulent prescriptions, doctor shopping, and recycled use of disposed product, as suggested by such reports involving transdermal patch. The desirable responses of analgesia and euphoria attained from narcotic use and addictive properties of this class of medications are motivating factors. Furthermore, new fast acting and more convenient formulations are more prone to the risk of diversion, due to ease of access and

Identified Risk – Diversion MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk diversion: Drug diversion, Prescription drug used without a prescription, and Prescription form tampering.	
	administration.
Evidence source(s) and strength of evidence	Diversion of narcotics is a known risk of narcotic analgesics. 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. There are life-threatening consequences of opioid-naïve overdose, at worst, fatal respiratory depression.
Characterisation of the risk:	Frequency *Clinical trials*: Cumulatively, till 30-April-2023, no events of diversion were received in the clinical program. *Post-marketing*: Cumulatively, till 30-April-2023, 10 events reflecting 8 cases have been received post-marketing (RR = 8/867,983x10,000 =0.09 per 10,000 patients). Seriousness/outcomes *Post-marketing*: Of the 10 events, 5 were deemed serious (none were serious due to hospitalisation). Outcome for the serious events were as follows: not recovered/not resolved (3), and unknown (2). Background incidence/prevalence Not known.
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.
Preventability	Findings suggest a need to strengthen vulnerable points in the process, associated with prescribing, patient behaviours, and disposal of medical waste. With regard to diversion and misuse by medical staff, vigilance in healthcare settings is important. In addition, close monitoring of prescriptions by health authorities is indicated in areas where over-prescribing or 'doctor shopping' is a concern. A need for clear prescribing guidelines was one important conclusion of a working group responding to the published Bavarian outbreak. The Instanyl Educational material states that in order to prevent theft and misuse of Instanyl nasal spray, it should be kept in a safe place. In addition, patients are advised that unused product must be returned systematically to the pharmacy.
Impact on the risk-benefit balance of the product	For the patient who is legitimately prescribed fentanyl for BTP management, the voluntary or forced diversion of their prescription could result in inadequately controlled BTP, up titration of background medication, tolerance, initiation of additional analgesics and risk of associated side effects. Pharmacovigilance activities and risk minimisation measures including Instanyl educational materials are considered sufficient

Identified Risk – Diversion MedDRA SMQ: Drug abuse, dependence, and withdrawal and HLGT: Off label uses and intentional product misuses/use issues. Further, the following PTs were considered for the evaluation of the risk diversion: Drug diversion, Prescription drug used without a prescription, and Prescription form tampering.	
	to ensure a positive benefit-risk balance for Instanyl.
Public health impact	In the general population, annual health care costs associated with opioid dependence/abuse are high. Costs to society include lost work productivity due to intoxication or complications of use, health care costs for uninsured users with medical complications, prosecution and incarceration expenses for criminal offenses, and economic and psychological costs to family members and victims of crimes.

Identified Risk – Accidental exposure (including potential exposure of other people and children to drug expelled in the patient's proximity during priming) MedDRA PT: Accidental exposure to product, Accidental exposure to product by child	
Potential mechanisms	Not applicable.
Evidence source(s) and strength of evidence	Accidental exposure of fentanyl can result in death due to respiratory depression, particularly in opiate-naïve people and in particular children.
Characterisation of the risk	Frequency *Clinical trials*: Cumulatively, till 30-April-2023, no events of accidental exposure were received in the clinical program. *Post-marketing*: Cumulatively, 5 events reflecting 5 cases have been received post-marketing (RR: = 5/867,983x10,000 =0.058 per 10,000 patients). Seriousness/outcomes *Post-marketing*: Of the 5 events, 2 were deemed serious (none were serious due to hospitalisation). Outcome for the events were as follows: not reported (1), unknown (2), and recovered/resolved (2). Background incidence/prevalence According to the Centers for Disease Control and Prevention (CDC), in 2007, there were 27,658 unintentional drug overdose deaths reported in the United States. In 2007, the number of deaths involving opioid analgesics (approximately 12,000 deaths) was 1.93 times the number involving cocaine and 5.38 times the number involving heroin. Recently, the Food and Drug Administration (FDA) evaluated a series of 26 cases of paediatric accidental exposures to fentanyl patches reported over the past 15 years. Of these 26 cases, 10 resulted in death and 12 in hospitalisation. Sixteen of the 26 cases occurred in children 2 years old or younger (CDC, 2010).
Risk factors and risk groups	Children and opioid-naïve patients.
Preventability	With the introduction of the single-dose nasal spray, the risk of accidental overdose may be reduced as 2 consecutive doses will require the active opening of 2 separate blister packages. Development of the improved multi-dose nasal spray with lock-out mechanism, dose-counter and child-resistant cap will prevent and

Identified Risk – Accidental exposure (including potential exposure of other people and children to drug expelled in the patient's proximity during priming) MedDRA PT: Accidental exposure to product, Accidental exposure to product by child	
	minimise the risk of accidental overdose, abuse, misuse and diversion, and unintended use by children. In the single-dose nasal spray, the residual volume has been decreased to 25 µL. Tests have shown that it is only possible to extract approximately 10 µL with a syringe from the glass vial of the nasal spray after removal of the actuator and stopper. Removal of the stopper requires usage of a tool. Given the highest concentration of 200 µg, an amount of 10 µL is consistent with a dose of 20 µg. In children, a dose of 25 µg fentanyl I.V. is considered to be safe as starting dose for opioid-naïve children from 2-5 years of age (Sublimaze UK SmPC). Therefore, the amount of residual volume is not considered to put children at risk of accidental exposure and/or overdose from a used single-dose bottle. Thus, it is not considered necessary to have a return-system for the used single-dose nasal sprays. The unused single-dose and multi-dose nasal sprays must, however, still be systematically returned for disposal according to national regulation in order to limit the risks of overdose and accidental exposure. The SmPC for the nasal spray states the following in section 6.6, Special precautions for disposal and other handling. Multi-dose: Because of the possible misuse of fentanyl and the possible amount of the solution left, the used and unused nasal spray solutions must be returned systematically and suitably in the child-resistant outer box according to local requirements or returned to the pharmacy. Single-dose: Because of the possible misuse of fentanyl unused nasal spray containers must be returned systematically and suitably in the child-resistant blister according to local requirements or returned to the pharmacy.
Impact on the risk-benefit balance of the product	Accidental or deliberate application or ingestion by a child or adolescent may cause respiratory depression that could result in death. Pharmacovigilance activities and risk minimisation measures including educational materials are considered sufficient to ensure a positive benefit-risk balance for Instanyl.
Public health impact	The impact is on an individual level and although the risk can be severe in nature the numbers of accidental exposure are relatively low and therefore the potential public impact is considered low.

Identified Risk – Overdose (suicide and suicide attempt excluded) MedDRA PT: Accidental Overdose	
Potential mechanisms	Potential mechanism for the risk of overdose is not applicable as this risk is not an adverse effect caused upon usage of fentanyl.
Evidence source(s) and strength of evidence	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 authorised product information (GVP Module VI). In 2007, 27,658 unintentional drug overdose deaths occurred in the United

Identified Risk – Overdose (suicide and suicide attempt excluded) MedDRA PT: Accidental Overdose	
	States (CDC, 2010).
Characterisation of the risk	Frequency *Clinical trials*: Cumulatively, till 30-April-2023, no events of accidental overdose were received in the clinical program. *Post-marketing*: Cumulatively, till 30-April-2023, 9 events reflecting 9 cases have been received post-marketing (RR: = 9/867,983x10,000 =0.10 per 10,000 patients). Seriousness/outcomes Of the 9 events, 4 were deemed serious (2 were serious due to hospitalisation). Outcome for the events were as follows: fatal (2), recovered/resolved (2), and unknown (5). Background incidence/prevalence 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.
Preventability:	Accidental overdose for fentanyl intranasal spray can be prevented by using single-dose containers. In addition, a dose counting scheme is provided with the multi-dose formulation. Also, development of the new multi-dose nasal spray with lock-out mechanism, dose-counter and child-resistant cap will prevent more than 2 doses in quick succession.
Impact on the risk-benefit balance of the product	Due to overdosing adverse effects such as respiratory depression may be seen. Overdosing may even lead to fatal outcome. Pharmacovigilance activities and risk minimisation measures including educational materials are considered sufficient to ensure a positive benefit-risk balance for Instanyl.
Public health impact	Since the prevalence of accidental overdose of Instanyl cannot be estimated, the impact on public health is not known.

Identified Risk – Medication errors Standard MedDRA Query (SMQ): Medication errors (Broad)	
Potential mechanisms	Potential mechanism for the risk of medication errors is not applicable as this risk is not an adverse effect caused upon usage of fentanyl.
Evidence source(s) and strength of evidence	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 222facilities 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.

Identified Risk – Medication errors Standard MedDRA Query (SMQ): Medication errors (Broad)	
Characterisation of the risk	Frequency *Clinical trials:* Cumulatively, till 30-April-2023, no events of medication error were received in the clinical program. *Post-marketing:* Cumulatively, till 30-April-2023, 308 events reflecting 250 cases have been received post-marketing (RR: = 250/867,983x10,000 =2.88 per 10,000 patients). Seriousness/outcomes Of the 308 events, 67 were deemed serious (14 were serious due to hospitalisation). Outcome for the events were as follows: fatal (9), not recovered/not resolved (27), recovered/resolved (25), recovering/resolving (2), not reported (13), and unknown (232).
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.
Preventability:	The current SmPC includes information on the correct use and dosage of the drug to be taken/prescribed. In addition, the updated Instanyl education material reiterates to patients that they should only use Instanyl if they have received the proper information regarding the use of the spray and the safety precautions from the prescriber and/or the pharmacist. The patient educational material also includes visual instructions on the correct use of Instanyl. This is also reiterated in the prescriber material, highlighting prescriber responsibility to ensure that the patient understands how to use Instanyl correctly, according to the SmPC and PIL. A Pharmacist's checklist has also been provided, and the pharmacist educational material instructs that before dispensing, they must ensure that all staff qualified to supply opioids are familiar with the Instanyl SmPC. The introduction of the single-dose and the improved multi-dose nasal spray will further minimise the risk of medication errors. The packaging for the new nasal spray and the conventional multi-dose is also differentiated, as follows: The conventional multi-dose does not come in an outer packaging but is instead housed within a child-resistant box. The improved nasal spray will be presented within an upright rectangular outer carton with the descriptor name "DoseGuard" clearly presented on the outer packaging.
Impact on the risk-benefit balance of the product	The impact on patients prescribed Instanyl could be both in terms of efficacy and safety. Incorrect use of Instanyl either via prescribing, dispensing or administration error may result in inadequate BTP management. If medication error has occurred surrounding dosing, then again this could mean the patient receives a non-efficacious dose or indeed one that makes them susceptible to ADRs. Pharmacovigilance activities and risk minimisation measures including improved pharmaceutical dosage forms and educational materials are considered sufficient to ensure a positive benefit-risk

Identified Risk – Medication errors Standard MedDRA Query (SMQ): Medication errors (Broad)	
	balance for Instanyl.
Public health impact	Since the prevalence of medication error for Instanyl cannot be estimated, the impact on public health is not known.

Identified Risk – Respiratory depression SMQ: Acute central respiratory depression (Broad)	
Potential mechanisms:	Activation of endogenous mu-opioid receptors results in the prototypic opioid effects of reward, withdrawal, and analgesia. When opioid molecules bind to mu receptors on brain cells in the LC where NA is made, they suppress the release of NA, resulting in drowsiness, slowed respiration, low blood pressure effects of opioid intoxication. Respiratory depression associated with concomitant medication (e.g., CYP3A4 inhibitors) is caused by increased fentanyl plasma concentrations, due to the competitive effect of these products potentially causing serious ADRs including fatal respiratory depression.
Evidence source(s) and strength of evidence	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.
Characterisation of the risk:	Frequency *Clinical trials*: Cumulatively, till 30-April-2023, 10 events (10 cases) of respiratory depression were received in the clinical program. *Post-marketing*: Cumulatively, till 30-April-2023, 37 events reflecting 32 cases have been received post-marketing (RR= 32/867,983x10,000 =0.36 per 10,000 patients). Seriousness/outcomes *Clinical trials*: Of the 10 events, 8 were deemed serious (3 were serious due to hospitalisation). Outcome for the events were as follows: fatal (4), not recovered/not resolved (1), recovered/resolved with sequelae (1), and recovered/resolved (4). *Post-marketing:* Of the 37 events, 25 were deemed serious (11 were serious due to hospitalisation). Outcome for the events were as follows: fatal (5), not recovered/not resolved (4), recovered/resolved (16), not reported (2), and unknown (10). Background incidence/prevalence Incidence of respiratory depression associated with opioid treatment for pain is 0.5% or less of total events. The incidence of post-operative opioid-induced respiratory depression in the UK has been estimated to be approximately 1% [18] .

Identified Risk – Respiratory depression SMQ: Acute central respiratory depression (Broad)	
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 anaesthetics, 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.
Preventability:	The Instanyl SmPC contains a contraindication of severe respiratory depression or severe obstructive lung conditions and includes text in the warning and precautions, interactions and pregnancy sections: Respiratory depression – • Clinically significant respiratory depression may occur with fentanyl, and hence patients must be observed for these effects. • The use of concomitant CNS depressants (including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines and alcohol) may increase the risk of respiratory depression. • Fentanyl is metabolised mainly via the human CYP3A4, therefore potential interactions may occur when Instanyl is given concurrently with medicinal products that affect CYP3A4 activity. i.e., 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. • Fentanyl should not be used by pregnant women as it crosses placenta and nursing women as it is excreted in human milk or women during labour and delivery.
Impact on the risk-benefit balance of the product	The patient requires medical intervention and hospitalisation if suffering from respiratory depression. In severe cases it can be life-threatening and fatal. Pharmacovigilance activities and risk minimisation measures

Identified Risk – Respiratory depression SMQ: Acute central respiratory depression (Broad)	
	including educational materials are considered sufficient to ensure a positive benefit-risk balance for Instanyl.
Public health impact	The impact is on an individual level and although the risk can be severe in nature the numbers of cases of respiratory depression are relatively low and therefore the potential public impact is considered to be low.

Identified Risk – Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs MedDRA PTs: Clonus, Hyperreflexia, Muscle rigidity, Diarrhoea, Pupil dilation procedure, Akathisia, Agitation, Delirium, Hyperthermia, Serotonin syndrome SMQ: Neuroleptic Malignant Syndrome (Broad)	
Potential mechanisms:	The serotonin syndrome is a complex of symptoms that are thought to be largely attributable to changes in sensitivity in the serotonin receptor systems in the brainstem and the spinal cord due to drugs. Severe cases are almost always caused by a combination of 2 or more 'serotonergic' drugs, of which at least one is a SSRI or a MAOI. The combination of SSRIs and fentanyl has been shown to cause this syndrome. Fentanyl is an agonist to the 5HT1A receptor, increasing serotonin flux. It has also been shown that fentanyl decreases serotonin reuptake. Synthetic opioids such as fentanyl, can cause increased norepinephrine release from sympathetic nerve endings and inhibit neuronal uptake of norepinephrine in animal models.
Evidence source(s) and strength of evidence	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. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotonergic effects, have been reported.
Characterisation of the risk	Frequency Clinical trials: Cumulatively, till 30-April-2023, 7 events of serotonin syndrome were received in clinical program. Post-marketing: Cumulatively, till 30-April-2023, 73 events reflecting 59 cases have been received post-marketing (RR = 59/867,983x10,000 =0.67 per 10,000 patients). Seriousness/outcomes Clinical trials: Of the 7 events, 2 were deemed serious (1 was serious due to hospitalisation). Outcome for the events were as follows: fatal (2), and not recovered/not resolved (5). Post-marketing: Of the 73 events, 41 were deemed serious (15 were serious due to hospitalisation). Outcome for the events were as follows: fatal (1), not recovered/not resolved (14), recovered/resolved (38), recovered/resolved with sequelae (1), recovering/resolving (3), not reported (1), and unknown (15). Background incidence/prevalence

Identified Risk – Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs MedDRA PTs: Clonus, Hyperreflexia, Muscle rigidity, Diarrhoea, Pupil dilation procedure, Akathisia, Agitation, Delirium, Hyperthermia, Serotonin syndrome SMQ: Neuroleptic Malignant Syndrome (Broad)	
	Boyer & Shannon, (2005) cited a report showing that in 2002 there were 7,349 cases of serotonin syndrome, resulting in 93 deaths. It is estimated that 14% to 16% of those who overdose with SSRIs display symptoms of serotonin syndrome.
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 SNRI. 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.
Preventability	Thomson et al. (1986) suggested that the incidence of hyperdynamic responses that may occur in patients given high-dose fentanyl may be decreased with p-adrenergic blocking drugs and benzodiazepines. As per the Instanyl SmPC, if serotonin syndrome is suspected, treatment with Instanyl should be discontinued. Also, fentanyl should not be used within 14 days after discontinuation of treatment with MAOIs. In addition, the Instanyl SmPC Special warnings and precautions for use advocate that caution is advised when Instanyl is co-administered with drugs that affect the serotoninergic neurotransmitter systems and that the development of a potentially life-threatening serotonin syndrome may occur even with the recommended dose with the concomitant use of serotonergic drugs such as SSRIs and SNRIs, and with drugs which impair metabolism of serotonin (including MAOIs). If serotonin syndrome is suspected, treatment with Instanyl should be discontinued.
Impact on the risk-benefit balance of the product	Serotonin syndrome has a negative impact on the patient's QoL as it is a medical emergency situation and may turn fatal. Pharmacovigilance activities and risk minimisation measures including educational materials are considered sufficient to ensure a positive benefit-risk balance for Instanyl.
Public health impact	The true incidence of serotonin syndrome may be under-represented in figures for a number of reasons. Manifestations may be wrongly attributed to another cause, mild cases may be dismissed, or clinicians may not suspect the condition. Thus, it is difficult to enumerate the impact on public health.

Potential Risk – Brain lesion MedDRA System Organ Class: Nervous system disorders MedDRA High level terms: Central Nervous System Imaging Procedures, Neurologic Diagnostic Procedures, Skull and brain therapeutic Procedures	
Potential mechanisms:	The potential mechanism of action has not been evidenced definitively. There is only one non-clinical data source that supports the risk of brain lesion however the precise mechanism is not known.
Evidence source(s) and strength of evidence	Background incidence/prevalence of brain lesion caused by opioids in target population is unknown.
Characterisation of the risk	Frequency *Clinical trials:* Cumulatively, till 30-April-2023, 12 events in 11 cases of brain lesion were received in clinical program. *Post-marketing:* Cumulatively, till 30-April-2023, 150 events reflecting 120 cases have been received post-marketing (RR = 120/867,983x10,000 =1.38 per 10,000 patients). Seriousness/outcomes As per wording adopted in the Instanyl SmPC, evaluation of brain slides from a carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The study was conducted by the MAH of another fentanyl product and the relevance of these findings to humans is unknown. *Clinical trials:* Of the 12 events, 7 were deemed serious (4 were serious due to hospitalisation). Outcome for the events were as follows: fatal (2), not recovered/not resolved (4), recovered/resolved (4), and recovered/resolved with sequelae (2). *Post-marketing:* Of the 150 events, 60 were deemed serious (24 were serious due to hospitalisation). Outcome for the events were as follows: fatal (7), not recovered/not resolved (22), recovered/resolved (72), recovering/resolving (3), not reported (7), recovered/ resolved with sequelae (1), and unknown (38).
Risk factors and risk groups:	Factors which may lead to increased risk of brain lesion have not been characterised.
Preventability	Not known.
Impact on the risk-benefit balance of the product	Specific brain lesions in humans with use of Instanyl have not yet been causally attributed to drug, hence impact on individual patient with existing co-morbidities and intercurrent medications could not be ascertained. Pharmacovigilance activities and risk minimisation measures including educational materials are considered sufficient to ensure a positive benefit-risk balance for Instanyl.
Public health impact	Since the frequency in human is unknown, the impact on public health cannot be estimated.

SVII.3.2. Presentation of the missing information

Missing information: Long-term use	
Evidence source:	In the majority of Instanyl clinical trials, patients were exposed

Missing information: Long-term use	
	between 3-6 months. However more than 40 patients were exposed for >6 months. The duration of treatment should also be seen in the context of the patient indication i.e., palliative care setting with terminally ill patients. No ADRs associated with prolonged exposure were detected in the clinical trial program. Given the duration of treatment in terminally ill patients, adverse drug reactions, other than associated with local tolerability, are not anticipated.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
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 risk	• Brain lesion
Missing information	• Long-term use

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

Specific adverse reaction follow-up questionnaires

None.

Other forms of routine pharmacovigilance activities for: Addiction, Abuse, Misuse, Off label use, Accidental exposure, Overdose, Medication errors

An annual information update providing status of the implementation of the product information and educational material (for the marketed single-dose, multi-dose Instanyl and multi-dose Instanyl DoseGuard) with a summary of the safety data received in relation to the important identified risks, as described within the Instanyl RMP is prepared and submitted with a DLP of 30 April every year (REC 027).

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

None.

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. ROUTINE RISK MINIMISATION MEASURES

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified risk: **Addiction**	**Routine risk communication:** • SmPC section 4.4 'Special warnings and precautions' • SmPC section 4.8 'Undesirable effects' • PL section 2 'What you need to know before using Instanyl' • PL section 3 'How to use Instanyl' • PL section 4 'Possible side effects' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Monitoring for dependence and possible iatrogenic addiction following therapeutic use of opioids when treating cancer related pain is included in SmPC section 4.4. • How to detect signs and symptoms of dependence and instruction to seek medical assistance if recognised in PL sections 2 and 3. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner).
Important Identified risk: **Misuse**	**Routine risk communication:** • SmPC section 4.1'Therapeutic indications' • SmPC section 4.2 'Posology and administration' • SmPC section 4.3 'Contraindications' • SmPC section 6.6 'Special precautions for disposal and other handling' • PL section 1 'What is Instanyl used for' • PL section 2 'What you need to know before using Instanyl' • PL section 3 'How to use Instanyl' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Prohibiting use in opioid-naïve patients and acute pain other than BTP in SmPC section 4.3 and PL section 2. • Instruction for systematic and appropriate return of unused product or appropriate disposal of nasal spray per local requirements to prevent possible misuse of fentanyl is included in SmPC section 6.6. • PL instructs patients on proper usage as prescribed and to seek

Safety concern	Routine risk minimisation activities
	physician assistance for dose or treatment adjustments and if dependence is suspected. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner).
Important Identified risk: **Abuse**	**Routine risk communication:** • SmPC section 4.2 'Posology and administration' • SmPC section 4.4 'Special warnings and precautions' • PL section 2 'What you need to know before using Instanyl' • PL section 3 'How to use Instanyl' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommending treatment and supervision by a physician experienced in the management of opioid therapy in cancer patients in SmPC section 4.2. • Monitoring for potential abuse and dependence in SmPC section 4.2 and 4.4. • PL section 2 and 3 includes instructions for proper usage as prescribed and to seek medical assistance if dependence is suspected. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner).
Important Identified risk: **Diversion**	**Routine risk communication:** • SmPC section 4.1'Therapeutic indications' • SmPC section 6.6 'Special precautions for disposal and other handling' • PL instructs patients on the proper usage of Instanyl and to not pass it on to others to prevent harm. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC section 6.6 'Special precautions for disposal and other handling' describes potential for misuse of fentanyl and provides instructions for systematic and appropriate return of unused product or appropriate disposal of nasal spray per local requirements.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner).
Important Identified risk: **Off label use**	**Routine risk communication:** • SmPC section 4.1'Therapeutic indications' • SmPC section 4.3 'Contraindications' • PL section 1 'What is Instanyl used for' • PL section 2 'What you need to know before using Instanyl' • PL section 3 'How to use Instanyl' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Prohibiting use in opioid-naïve patients and acute pain other than BTP in SmPC section 4.3 and PL section 2. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status.
Important Identified risk: **Accidental exposure (including potential exposure of other people and children to drug expelled in the patient's proximity during priming.)**	**Routine risk communication:** • SmPC (conventional and improved multi-dose) section 4.2, 'Posology and method of administration' • SmPC section 6.6 'Special precautions for disposal' • PL section 2 'What you need to know before using Instanyl' • PL section 3 'How to use Instanyl' • PL section 5 'How to store Instanyl' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Precautions in product handling and administration specifying proper and safe priming technique to prevent exposure to other people, particularly children in SmPC section 4.2 and PL section 5. • Special precautions for safe 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 SmPC section 6.6 and PL section 5. • Prohibiting use in children in PL section 2. • Recognising symptoms and instructions for caring for the accidentally exposed person and to seek immediate medical attention in PL section 3. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on

Safety concern	Routine risk minimisation activities
	29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner).
Important Identified risk: **Overdose (suicide and suicide attempt excluded)**	**Routine risk communication:** • SmPC, section 4.2 'Posology and method of administration' • SmPC section 4.9 'Overdose' • SmPC (conventional multi-dose, improved multi-dose) section 6.6 'Special precautions for disposal and other handling' • PL section 3 'How to use Instanyl' • PL section 5 'How to store Instanyl' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Monitoring for potential overdose of fentanyl in SmPC section 4.2. • Monitoring for specific signs and symptoms and treating overdose in SmPC section 4.9 and PL. • Special precautions for safe storage and disposal requiring systematic and suitable return of used and unused nasal spray solution (single-dose, conventional multi-dose); disposal per local requirements or pharmacy (improved multi-dose) to prevent misuse of fentanyl in SmPC section 6.6 and PL section 5. • PL section 3 provides reminders for tracking the number of doses of Instanyl: o Using the tick-boxes in the booklet placed on top of the child-resistant outer box (conventional multi-dose). o Using electronic display showing the number of doses left, shows whether the nasal spray is locked or ready to use (improved multi-dose). • PL instructs patients on proper usage as prescribed and to seek physician assistance for dose or treatment adjustments to prevent overdose. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner).
Important Identified risk: **Medication errors**	**Routine risk communication:** • SmPC section 4.1 'Therapeutic indications' • SmPC section 4.2 'Posology and administration' • SmPC section 6.5 'Nature and contents of container' • PL section 1 'What is Instanyl used for' • PL section 2 'What you need to know before using Instanyl' • PL section 3 'How to use Instanyl' • PL section 6 'Contents of the pack and other information'

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Precautions in product handling, administration and dose titration specifying carefully monitored during the titration process in SmPC section 4.2 and PL section 3. • Information provided on difference between SmPCs for the conventional multi-dose, improved multi-dose and single-dose formulations in SmPC section 6.5. • PL instructs patients on proper usage as prescribed and to seek physician assistance for dose or treatment adjustments. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner).
Important Identified risk: **Respiratory depression**	**Routine risk communication:** • SmPC section 4.3 'Contraindications' • SmPC section 4.4 'Special warnings and precautions' • SmPC section 4.5 'Interaction with other medicinal products and other forms of interaction' • SmPC section 4.8 'Undesirable effects' • SmPC section 5.1 'Pharmacodynamic properties' • PL section 2 'What you need to know before using Instanyl' • PL section 4 'Possible side effects' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Prohibiting use in severe respiratory depression or obstructive lung conditions and use in opioid-naïve patients in SmPC section 4.3 and PL section 2. • Special monitoring of respiratory depression and warning with concomitant use of CNS depressants that may increase the risk of respiratory depression in SmPC section 4.4 and 4.8. • Prohibiting use with other CNS depressants and alcohol that may produce additive depressant effects in SmPC section 4.5 and PL section 2. • Instructions to discontinue treatment and seek immediate medical attention if difficulties in breathing occur with Instanyl treatment is included in PL section 2. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status.
Important Identified risk: **Serotonin syndrome induced by**	**Routine risk communication:** • SmPC section 4.4 'Special warnings and precautions' • SmPC section 4.5 'Interaction with other medicinal products and other forms of interaction'

Safety concern	Routine risk minimisation activities
interaction between fentanyl and serotoninergic drugs	• PL section 2 'What you need to know before using Instanyl' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Special warning for the development of potentially life-threatening serotonin syndrome when Instanyl is co-administered with drugs that affect the serotoninergic neurotransmitter systems is included in SmPC section 4.4 and PL section 2. • Recommending stopping Instanyl treatment if serotonin syndrome is observed in SmPC section 4.4. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status.
Important Potential risk: **Brain lesion**	**Routine risk communication:** • SmPC section 5.3 'Preclinical safety data' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status.
Missing information: **Long-term use**	**Routine risk communication:** • SmPC section 4.4 'Special warnings and precautions' • PL section 2 'What you need to know before using Instanyl' **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Special warning on the development of tolerance and physical and/or psychological dependence upon repeated administration of opioids such as fentanyl is included in SmPC section 4.4 and PL section 2. **Other routine risk minimisation measures beyond the Product Information:** • Special and restricted prescription status.

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Updated Educational Materials for Patients, Physicians (Prescribers), and Pharmacists

Objectives:

Ensure proper patient selection and to highlight the important identified risks of addiction, misuse, abuse, misuse for illegal purpose, accidental exposure, medication error, accidental overdose, and off label use with Instanyl, and the measures to mitigate against them.

Rationale for the additional risk minimisation activity:

Fentanyl, belonging to a group of painkillers called opioids, has a danger of abuse, misuse and diversion similar to other opioid painkillers. There is an increased need for awareness of the potency of fentanyl (compared to other opioids). Patients treated for chronic cancer pain (the target population) are expected to be managed with long-term strong opioids and thus they are highly exposed to the risk of opioid dependence. Patients with prior substance abuse and underlying chronic non-cancer pain are at higher risk for dependence. Due to rapid onset of effect and ease of use of a nasal spray, there may be a risk that Instanyl would be prescribed to treat patients without cancer pain or who are not taking background opioids. This is known as off label use. There are several types of off label use that have

been identified by the MAH in post-marketing reports. These include Off label indication, No background opioid, Off label dosing, Off label age (<18 years), Unknown reason/indication, Breakthrough pain (non-cancerous). When case narratives were coded as unknown reason/indication, the MAH initiated a targeted questionnaire response to all informers to enable more accurate understanding of real reasons for off label use when not identified by the narrative. Accidental exposure of fentanyl can result in death due to respiratory depression, particularly in opiate-naïve people and in children. Due to the nature of the product, there is a risk of overdose especially in cases of unintended child exposure, medication error, abuse and accidental exposure. As well as hard copy education material, there was website access for each intended user group. Information for prescribers and pharmacists was separated from patient materials. Instructional video in the local language on using Instanyl facilitated message delivery of proper use of the product.

Target audience and planned distribution path:

Targeted audience for prescribers included oncology and onco-radiotherapists, anesthesiology, pain management, palliative care physicians, internal medicine doctors and GPs. Pharmacists were identified in each European country according to market knowledge. The patients who are expected to use Instanyl were identified, and the patient focused material were distributed in each Member State as per a local implementation plan agreed with National Competent Authority. Hard copy material and easily downloadable information from local website locations were agreed with National Competent Authorities in local languages. Professional information and patient information were kept separated on local websites.

In addition to the updated EMs for the existing Instanyl single dose and multidose, new EMs for the Instanyl DoseGuard also serve as additional risk minimisation measures. In the Instanyl DoseGuard EMs all the key messages that are present in the updated Instanyl EMs are included in addition to the instructions to the usage of DoseGuard device.

Evaluation of effectiveness of the (additional) risk minimisation interventions and criteria for success:

Additional Pharmacovigilance Activities (Instanyl Prescriber Survey - PASS 5002)

Objectives: The overall objective of this study was to measure the changes in understanding and self-reported behaviour of Instanyl prescribers regarding Instanyl off-label use and the key information contained in the updated EM.

Specifically, the study objectives were:

- To assess prescribers' awareness of the updated EM
- To assess the changes in prescribers' knowledge and understanding of the key information contained in the updated EM, including risks of off-label use, misuse, abuse, diversion, medication error, addiction, overdose, and death
- To assess the changes in prescribers' self-reported behaviour in prescribing in accordance with approved indication
- To assess the reasons for off-label prescription
- To assess whether prescribers are fully aware about the profile of patients at risk of misuse and addiction

Conclusion: The Instanyl Prescriber survey (Instanyl-5002) provided insight about the awareness, knowledge, and self-reported behaviour of physicians regarding the updated EM for Instanyl.

The updated EM were designed to increase physicians’ awareness of Instanyl's indication and to reduce off-label use and other risks including addiction, misuse, abuse, diversion, overdose, and medication errors. However, the results from the study indicated that the updated EM were neither effective in increasing the percentage of physicians successful in the criteria of knowledge, nor increasing compliance in self-reported behaviour regarding Instanyl. Nevertheless, some results observed in the post-EM survey may be indicators of effectiveness of the updated EM. Moreover, 9 out of 10 physicians in the post-EM survey reported compliant behaviour, prescribing Instanyl to patients with cancer that were all on ongoing maintenance opioid therapy. In the current study, an additional 8.1% of

physicians (about 80%) in the post-EM survey correctly responded that Instanyl should only be prescribed to patients already receiving opioid therapy. Concerning improvements for reducing the risk of abuse, 6.2% fewer physicians reported prescribing Instanyl off-label for fast relief of pain to non-cancer patients with background pain and 10% fewer physicians reported having prescribed Instanyl for the management of musculoskeletal disorders pain, such as for back pain, fibromyalgia, arthritis, after the distribution of the updated EM.

The benefit-risk profile of Instanyl multi-dose nasal spray remains positive.

Takeda is currently launching DoseGuard, an improved Instanyl nasal spray with several additional features supporting patient safety and removing the current Instanyl multi-dose nasal spray from the market. Instanyl multi-dose nasal spray will be completely removed from the European market within a period of 9-12 months from the first launch of DoseGuard (no later than until July-2024). Educational materials for Instanyl DoseGuard have been reviewed with the aim of providing adequate instructions for the efficient use of DoseGuard. In addition, Takeda has proposed to conduct a drug utilisation study (DUS) in the 5 countries where the DoseGuard product will be launched (i.e., Czech Republic, France, Netherlands, Norway, and Poland) to assess how the product is prescribed and used in the real-world clinical setting and help assess the effectiveness of the DoseGuard EM.

Routine Pharmacovigilance Activities

Effectiveness of the risk minimisation interventions will be monitored via ongoing routine pharmacovigilance activities. Risk minimisation measures will be considered successful if there is no unusual increase in reporting rates of the identified risks. Also, the following will be summarised in periodic reports as requested by PRAC:

- Annual report providing summary of safety data of all important risks received in 12-month period (REC 027).

V.3. SUMMARY OF RISK MINIMISATION MEASURES

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: **Addiction**	**Routine risk minimisation 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 (approved on 29-June-2011). • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures:** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients,	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** REC 027 **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.	
Important identified risk: **Misuse**	**Routine risk minimisation 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 (approved on 29-June-2011). • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measure:** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** REC 027 **Additional pharmacovigilance activities:** None.
Important identified risk: **Abuse**	**Routine risk minimisation 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** REC 027 **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Instanyl as prescribed and to seek medical assistance if dependence is suspected. • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures:** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.	
Important identified risk: **Diversion**	**Routine risk minimisation 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 (approved on 29-June-2011). • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures:** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists,	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** REC 027 **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	including checklists for prescribers and pharmacists for Instanyl DoseGuard.	
Important identified risk: **Off label use**	**Routine risk minimisation 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 minimisation measures:** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** REC 027 **Additional pharmacovigilance activities:** None.
Important identified risk: **Accidental exposure (including potential exposure of other people and children to drug expelled in the patient's proximity during priming)**	**Routine risk minimisation 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. • PL section 3 includes instructions for monitoring, seeking immediate medical attention, and caring for the accidentally exposed person. • Special and restricted prescription	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** REC 027 **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures:** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.	
Important identified risk: **Overdose (suicide and suicide attempt excluded)**	**Routine risk minimisation 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. • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** REC 027 **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.	
Important identified risk: **Medication errors**	**Routine risk minimisation 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 (approved on 29-June-2011). • Development of an improved multi-dose nasal spray with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures:** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** REC 027 **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: **Respiratory depression**	**Routine risk minimisation measures:** • SmPC section 4.3 and PL section 2 prohibiting use in opioid-naïve patients, severe respiratory depression, or severe 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 minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important identified risk: **Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs**	**Routine risk minimisation measures:** • SmPC section 4.4. 4.5 and PL section 2 provides special warning for the development of potentially life-threatening 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 minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risk: **Brain lesion**	**Routine risk minimisation measures:** • SmPC section 5.4. • Special and restricted prescription status.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None.	**Additional pharmacovigilance activities:** None.
Missing information: **Long-term use**	**Routine risk minimisation 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 minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

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 minimised, 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 of 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 authorised 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 MINIMISE OR FURTHER CHARACTERISE THE RISKS

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

Measures to minimise 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 authorised 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 minimise 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 risk	• 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. 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%. 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 minimisation measures	**Routine risk minimisation 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 (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on

Important identified risk: Addiction	
	01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.
Additional pharmacovigilance activities	None.

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 authorisation (GVP Module VI). Misuse can be characterised 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' QoL, 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. 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 is also more susceptible to pain medication misuse. The elderly comprises 13% of the US population but receive over 30% of all prescribed medications, including analgesics.
Risk minimisation measures	**Routine risk minimisation 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

Important identified risk: Misuse	
	or if dependence is suspected. • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.
Additional pharmacovigilance activities	None.

Important identified risk: Abuse	
Evidence for linking the risk to the medicine	Abuse corresponds to persistent or sporadic, intentional excessive use of medicinal products which is accompanied by 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 behaviours 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 minimisation measures	**Routine risk minimisation 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 sections 2 and 3 where instruction for patients is provided in the proper usage of Instanyl as prescribed and to seek medical assistance if dependence is suspected.

Important identified risk: Abuse	
	• Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.
Additional pharmacovigilance activities	None.

Important identified risk: Diversion	
Evidence for linking the risk to the medicine	Diversion of narcotics is a known risk of narcotic analgesics. 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. 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.
Risk minimisation measures	**Routine risk minimisation 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 approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists

Important identified risk: Diversion	
	for Instanyl DoseGuard.
Additional pharmacovigilance activities	None.

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 authorisation (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 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 minimisation measures	**Routine risk minimisation 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 minimisation measures** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.
Additional pharmacovigilance activities	None.

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 minimisation measures	**Routine risk minimisation 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,

Important identified risk: Accidental exposure (including potential exposure of other people and children to drug expelled in the patient's proximity during priming)	
	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. • 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 (approved on 29-June-2011) • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.
Additional pharmacovigilance activities	None.

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 authorised 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 minimisation measures	**Routine risk minimisation 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 section 5 provides special

Important identified risk: Overdose (suicide and suicide attempt excluded)	
	precautions for safe storage and systematic disposal/return of product to prevent the possible misuse of fentanyl. • PL section 3 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. • Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.
Additional pharmacovigilance activities	None.

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.
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 minimisation measures	**Routine risk minimisation 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.

Important identified risk: Medication errors	
	• Special and restricted prescription status. • Development of a single-dose nasal spray (approved on 29-June-2011). • Improved multi-dose nasal spray (DoseGuard) with dose counting, lock-out and child-resistant cap (approved on 01-April-2016 and planned for launch in a phased manner). **Additional risk minimisation measures:** Updated educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl. Educational materials for patients, physician prescribers, and pharmacists, including checklists for prescribers and pharmacists for Instanyl DoseGuard.
Additional pharmacovigilance activities	None.

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 anaesthetics, 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 minimisation measures	**Routine risk minimisation measures**

Important identified risk: Respiratory depression	
	• SmPC section 4.3 and PL section 2 prohibiting use in opioid-naïve patients, severe respiratory depression, or severe 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 minimisation 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. 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, hyperlipidaemia.
Risk minimisation measures	**Routine risk minimisation measures** • SmPC section 4.4, 4.5 and PL section 2 provides special warning for the development of potentially life-threatening 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.

Important identified risk: Serotonin syndrome induces by interaction between fentanyl and serotoninergic drugs	
	Additional risk minimisation 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 characterised.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 5.3. • Special and restricted prescription status. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Missing information: Long-term use	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.4 and PL section 2 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 minimisation measures:** None.
Additional pharmacovigilance activities	None.

II.C. Post-authorisation development plan

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

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

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

There are no studies required for Instanyl.

PART VII: ANNEXES

Table of contents

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Approved key messages of the additional risk minimisation measures (EMs related to Instanyl and Instanyl DoseGuard)

Prescriber definition as per on label guidance may include oncologists and onco-radiotherapists, anaesthesiologists, pain management specialists, haematologists, palliative care physicians, internal medicine specialists/ internists and GPs and should be agreed with each national competent authority.

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

Educational material for the patients will contain the following:

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

Patient/carer guide

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

How to use Instanyl

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

Educational material for the physicians will contain the following:

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

Guide for Physicians

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

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

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

Prescribing checklist

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

- Ensure that all elements of the approved indication are fulfilled.
- Provide instructions for using the nasal spray to patient and/or carer.
- For single-dose nasal spray only: Advise the patient on the single use nature of the nasal spray (each nasal spray contains only one dose and the plunger should only be pressed once the spray tip is inserted into the nose, it should not be tested before use).
- Ensure the patient reads the package leaflet inside the Instanyl box.
- Supply the patient with the Instanyl patient brochure provided covering the below:
    - Cancer and Pain.
    - Instanyl. What is it? How do I use it?
    - Instanyl. Risks of misuse.

- Advise patient on how to open the child-resistant blister (for single-use Instanyl), the child-resistant box (for multi-dose Instanyl) or the child resistant cap (for multi-dose Instanyl DoseGuard) as described in the patient brochure 'Instanyl. What is it? How do I use it?'
- Explain the risks of using more than the recommended amount of Instanyl.
- Explain the use of the dose monitoring cards.
- Advise the patient on the signs of fentanyl overdose and the need for immediate medical assistance.
- Explain secure storage and the need to keep out of the reach and sight of children.
- Explain correct disposal of Instanyl single-dose or multi-dose nasal spray or multi-dose nasal spray DoseGuard.
- Remind the patient and/or caregiver that they should ask their doctor if they have any questions or concerns about how to use Instanyl or about the associated risks of misuse and abuse.

Educational material for the pharmacists will contain the following:

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

Guide for Pharmacists

- Treatment to be initiated/supervised by a physician experienced in the management of opioid therapy in cancer patients, in particularly regarding transition from hospital to home.
- Explanation of off label uses (i.e.: indication, age…) and the serious risks of misuse, abuse, medication error, overdose, death and addiction.
- Need for communication to patients/carers:
    - Treatment management and risks of abuse and dependence
    - Need of periodic review by prescribers
    - Encouragement for reporting of any issue with the management of the treatment
- Monitoring of patients at risk of abuse and misuse during the treatment to identify the key features of opioid use disorder (OUD): distinguishing features of opioid related side effects and opioid use disorder.
- Importance of reporting off-label use, misuse, abuse, addiction and overdose
- Physician should be contacted if OUD recognised
- Pharmacist must be familiar with the EM before is given to the patient
- Instanyl nasal spray not interchangeable with other Fentanyl products

The pharmacists dispensing Instanyl nasal spray must counsel the patients on:

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

containers should be returned systematically according to the local regulation.

- For the single-dose nasal spray all unused devices should be returned systematically according to the local regulation.
- The pharmacist must make use of the checklist for pharmacist.

Dispensing checklist

Required actions before supplying Instanyl. Please complete the following before Instanyl single-dose, multi-dose nasal spray or multi-dose nasal spray DoseGuard is supplied:

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

Digital access to educational material

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