EU RISK MANAGEMENT PLAN FOR PECFENT (FENTANYL CITRATE)

RMP version to be assessed as part of this application:

RMP Version number: 8.0

Data lock point for this RMP: 31 March 2021

Date of final sign-off: 17 August 2022

Rationale for submitting an updated RMP:

- To convert the RMP to the new format according to Good Pharmacovigilance Practices Module V Revision 2.
- To update the key messages of the additional risk minimisation measure, 'educational materials', as requested in the Pharmacovigilance Risk Assessment Committee Periodic Safety Update Report assessment report, procedure number EMEA/H/C/PSUSA/00001369/202004.
- To remove the training of field representatives and Dear Doctor letters as additional risk minimisation activities, as training of field representatives is not an additional risk minimisation measure per Good Pharmacovigilance Practices guidance, and Kyowa Kirin has not used Dear Doctor letters as a risk minimisation measure.
- To remove 'paediatric population', 'pregnant and breastfeeding women' and 'patients with renal or hepatic impairment' from missing information, as PecFent is not intended to be used in these populations.
- To remove 'Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs' as an important potential risk, since this safety concern is adequately addressed within the product information and is no longer linked to additional pharmacovigilance activities or risk minimisation measures.
- To remove 'Circulatory depression, including severe bradycardia, hypotension and shock' as an important identified risk, since this safety concern is adequately addressed within the product information and is not linked to additional pharmacovigilance activities or risk minimisation measures.

Summary of significant changes in this RMP:

- Updates to the post-authorisation exposure and the risks sections to align with the new data lock point.
- Changes to the key messages of additional risk minimisation measure ‘educational materials’.
- The training of field representatives and Dear Doctor letters have been removed as additional risk minimisation measures.
- Removal of ‘paediatric population’, ‘pregnant and breastfeeding women’ and ‘patients with renal or hepatic impairment’, previously classified as missing information.
- Removal of ‘Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs’, previously classified as an important potential risk.
- Removal of ‘Circulatory depression, including severe bradycardia, hypotension and shock’, previously classified as an important identified risk.
- In the Pharmacovigilance Plan, Study CP064 has been removed from the list of ongoing studies part of the pharmacovigilance study programme, as the study has been completed.

Details of the currently approved RMP:

Version number: 7.0

Approved with procedure: EMEA/H/C/001164/IB/0029

Date of approval (opinion date): 02 October 2014

QPPV name: Beatriz Mengotti Fernandez de los Rios

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Marketing Authorisation Holder’s QPPV. The electronic signature is available on file.

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List of abbreviations

AE	Adverse event
BTP	Breakthrough pain
BTCP	Breakthrough cancer pain
DDD	Defined daily dose
DEA	Drug Enforcement Administration
EEA	European Economic Area
EU	European Union
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PY	Patient-years
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
RR	Reporting rate
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
SNRI	Serotonin norepinephrine re-uptake inhibitor
SSRI	Selective serotonin re-uptake inhibitor
US	United States

Part I: Product overview

Table 1: Product overview

Active substance (International non-proprietary name or common name)	Fentanyl (as fentanyl citrate)
Pharmacotherapeutic group (Anatomical Therapeutic Chemical Code)	Analgesics; opioids; phenylpiperidine derivatives (N02AB03)
Marketing Authorisation Holder	Kyowa Kirin Holdings B.V. Ltd
Medicinal products to which this Risk Management Plan (RMP) refers	PecFent 100 mcg/spray nasal spray solution PecFent 400 mcg/spray nasal spray solution
Invented name in the European Economic Area (EEA)	PecFent
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Fentanyl is a pure opioid agonist, with a clinical potency of 50 to 100 times that of morphine, which acts primarily through interaction with mu-opioid receptors located in the brain, spinal cord, and smooth muscle. Summary of mode of action: PecFent uses the proprietary PecSys® nasal drug delivery system to modulate the delivery and absorption of fentanyl. The PecSys system allows the product to be sprayed into the front area of the nasal cavity, where it forms a thin gel on contact with the calcium ions present in the nasal mucosa. Fentanyl diffuses from the gel and is absorbed through the nasal mucosa. The system is designed to deliver increased speed of absorption and speed of onset with a controlled maximum plasma concentration to prevent any increase in side effects related to high fentanyl plasma levels. The gel also prevents dripping or runoff and unwanted loss of drug. Important information about its composition: The active ingredient is fentanyl citrate, a white crystalline powder, with the chemical formula of $C_{22}H_{28}N_2O.C_6H_8O_7$ and a molecular weight of 528.5 Daltons.
Hyperlink to the Product Information	Module 1.3.1
Indication in the EEA	PecFent is indicated for the management of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of cancer pain that occurs on a background of otherwise controlled persistent pain. Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 mcg of transdermal

	fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equi-analgesic dose of another opioid for a week or longer.
Dosage in the EEA	Initial dose: The initial dose of PecFent to treat episodes of BTP is always 100 mcg (one spray), even in patients switching from other fentanyl-containing products. Patients must wait at least four hours before treating another episode of BTP with PecFent. Dose titration: PecFent should be titrated to an "effective" dose that provides adequate analgesia and minimises adverse reactions without causing undue (or intolerable) adverse reactions, for two consecutively treated episodes of BTP. The efficacy of a given dose should be assessed over the ensuing 30-minute period. Patients should be carefully monitored until an effective dose is reached. Method of titration: Patients should be prescribed an initial titration supply of one bottle (two spray or eight spray bottles) of PecFent 100 mcg/spray. Patients who need to titrate to a higher dose due to lack of effect can be instructed to use two 100 mcg sprays (one in each nostril) for their next BTP episode. If this dose is not successful, the patient may be prescribed a bottle of PecFent 400 mcg/spray (eight spray bottle) and instructed to change to one 400 mcg spray for their next episode of pain. If this dose is not successful, the patient may be instructed to increase to two 400 mcg sprays (one in each nostril). From treatment initiation, patients should be closely followed, and the dosage titrated until an effective dose is reached and confirmed for two consecutively treated episodes of BTP. Maintenance therapy: Once an effective dose has been established during titration, patients should continue to take this dose up to a maximum of four doses per day. Dose readjustment: Generally, the maintenance dose of PecFent should be increased only where the current dose fails to adequately treat the BTP for several consecutive episodes. A review of the dose of the background opioid therapy may be required if patients consistently present with more than four BTP episodes per 24 hours. If adverse reactions are intolerable or persistent, the dose should be reduced or treatment with PecFent replaced by another analgesic. Discontinuation of therapy: PecFent should be discontinued immediately if the patient no longer experiences BTP episodes. The treatment for persistent background pain should be kept as prescribed. If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor as gradual downward opioid titration therapy is necessary to avoid the possibility of abrupt withdrawal effects.

Pharmaceutical form and strengths	Nasal spray, solution (nasal spray). A clear to practically clear colourless aqueous solution. Each mL of solution contains 1,000 or 4,000 mcg fentanyl (as citrate). One spray (100 mcL) contains 100 or 400 mcg fentanyl (as citrate). Each two-spray bottle contains 0.95 mL (950 mcg fentanyl) ensuring delivery of two sprays of 100 mcg. Each eight-spray bottle contains 1.55 mL (1550mcg or 6200 mcg fentanyl) ensuring delivery of eight sprays of 100 or 400 mcg. PecFent is an intranasal spray solution which uses the PecSys® nasal delivery technology to deliver an aqueous fentanyl citrate solution to the nasal mucosa via a metered-dose nasal spray pump with dose counter. PecFent is available in two strengths providing 100 mcg and 400 mcg of fentanyl (as citrate) per 100 mcL spray.
Is the product subject to additional monitoring in the European Union (EU)?	No.

BTP=breakthrough pain; EEA=European Economic Area; EU=European Union; RMP=Risk Management Plan.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication and target population

Indication: Management of BTP in adults who are already receiving maintenance opioid therapy for chronic cancer pain

Incidence: The reported incidence of BTP varies widely from as low as 16% to as high as 95% of those with persistent pain syndromes (malignant and non-malignant diseases) (Payne, 2007a). In cancer patients, BTP has been reported to occur in 50% to 90% of patients who experience chronic pain (Portenoy et al, 2006).

Prevalence: Episodes of BTP are a common problem for cancer patients with pain. During the course of cancer, the prevalence of BTP is estimated between 19% and 95% (Payne, 2007b; Svendsen et al, 2005; Greco et al, 2011). A large, prospective, multicentre survey of pain specialists in 24 countries found that approximately 65% of 1,095 cancer patients had BTP in addition to continuous background pain. Figures vary across countries with a higher reported frequency of BTP in north-western European countries, the US, Canada, Australia and New Zealand compared with other countries including southern European countries, Russia, China, India and Mexico (Caraceni and Portenoy, 1999).

Demographics of the population in the authorised indication: The demographic profile for patients with BTP mirrors that of cancer in general, and therefore covers all demographic profiles.

Risk factors for the disease: Cancer patients, particularly those with advanced disease.

The main existing treatment options: Strong opioids, especially morphine, are the principal treatments for moderate to severe cancer-related pain. Besides fentanyl, other commonly used compounds include methadone, hydromorphone, oxymorphone, alfentanil, levorphanol, buprenorphine, diamorphine, morphine and oxycodone. The non-parenteral route of administration is advocated where appropriate; however, patients presenting with severe pain requiring urgent relief should routinely be treated with parenteral opioids, usually administered subcutaneously or intravenously (European Society for Medical Oncology (ESMO) Clinical Practice Guidelines, 2018).

According to the National Institute for Health and Care Excellence guidelines (2016), during palliative care treatment for adults, the first-line therapy for BTP in cancer patients who can take oral opioids should be oral immediate-release morphine (in patients on maintenance oral morphine treatment). Fast-acting fentanyl should not be used as first-line rescue medication. If pain remains inadequately controlled despite optimising treatment, specialist advice should be considered (National Institute for Health and Care Excellence guidelines, 2016). Fentanyl transmucosal preparations (buccal soluble film, sublingual tablets, lozenges/buccal tablets) and nasal preparations also exist as alternative treatment options for BTP. However, ESMO guidelines on management of cancer pain in adult patients stated that the pharmacokinetic and pharmacodynamic profiles of oral opioids, such as morphine, do not tend to mirror the temporal characteristics of most BTP in cancer episodes, resulting in delayed or ineffective analgesia and in ongoing adverse effects. ESMO recommends the use of

transmucosal fentanyl formulations for unpredictable and rapid-onset BTP, in addition to limiting the use of oral morphine for the treatment of slow-onset BTP or a pre-emptive administration of oral opioids approximately 30 minutes before a predictable BTP triggered by known events (ESMO guidelines, 2018).

Natural history of the indicated condition in the population, including mortality and morbidity: The morbidity within the target population is variable, depending on the type and stage of the underlying cancer. Mortality in cancer patients is not directly related to BTP, although the incidence of BTP increases with progressive cancer.

Important co-morbidities: Fentanyl is indicated for BTP in cancer patients; therefore, all patients will have localised or disseminated cancer. Although concomitant diseases are variable in this heterogeneous patient population, given that cancer is more common in the older population, other diseases in this cohort such as diabetes, heart disease, pulmonary disease, osteoporosis, arthritis, and hypertension may be present. Older patients may also have pre-existing abnormalities of peripheral nerves, mental status, and cardiac function. Geriatric syndromes such as frailty, urinary incontinence and balance disorders may also exist. Other age-related limitations such as physical disabilities and restricted functional reserve capacity in certain organ systems e.g., renal, may also be present. In addition, patients with BTP will have been extensively pre-treated with other opioids for background pain control, and may have received radiotherapy and chemotherapy, with the resultant adverse effects of treatment.

Part II: Module SII - Non-clinical part of the safety specification

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

Toxicity

Single (acute) or repeat-dose toxicity studies:

Three repeat-dose studies have been conducted in the rat and dog. Clinical signs attributed to the pharmacological effects of fentanyl were noted in both species.

Local findings were reported in the 6-month rat study relating to the intranasal administration of fentanyl (but not the drug-free pectin vehicle). Minimal/slight treatment-related histopathological changes (higher incidence of goblet cell hypertrophy/hyperplasia) were observed in the nasal cavities of female rats that received the high dose (0.48 mg/kg/day) of fentanyl. There were also minimal/slight changes in the lung (higher incidence of alveolar macrophages) in both male and female rats at 0.48 mg/kg/day and male rats in the intermediate dose group dosed at 0.32 mg/kg/day). Some deposition in the lung of the rat is considered to be consequential to the dosing technique (instillation of relatively large dose volumes).

The studies have demonstrated that fentanyl is associated with some local and possibly systemic toxicity when administered via the intranasal route. However, there is a significant safety margin in terms of exposure to fentanyl in toxicology animals (at the no observed adverse effect level) to that in humans across the entire therapeutic dose range. Local tolerability is classified as an important identified risk for PecFent.

In the rat, gastric inflammation/lesions were noted which were considered to be drug-related. There were no other histopathology findings in these animals. It is well documented that opioids including fentanyl can reduce gastrointestinal motility. Furthermore, inflammation of the intestine is known to closely correlate with motility disorder; dysmotility will exacerbate intestinal injury through accumulation of toxic substances or disruption of the intestinal flora (Bossone et al, 2001; Ozaki et al, 2005).

Opioids as a class of drug are well known to be associated with reduced gastrointestinal motility.

Reproductive/developmental toxicity:

Reproductive studies were not conducted with PecFent. Data from the published literature indicate that embryo-foetal developmental toxicity studies conducted in rats and rabbits revealed no compound-induced malformations or developmental variations when administered during the period of organogenesis. In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 mcg/kg/day, subcutaneous) and is consistent with the sedative effects of fentanyl in animal studies. In studies on pre and postnatal development in rats, the survival rate of offspring was significantly reduced at doses causing severe maternal toxicity. Further findings at maternally toxic doses in F1 pups were delayed physical development, sensory functions, reflexes and behaviour. These effects could either be indirect effects due to altered maternal care and/or decreased lactation rate or a direct effect of fentanyl on the pups.

The potential risk in humans is unknown. There are no adequate data from the use of fentanyl in pregnant women.

Pregnancy and breastfeeding patients are not considered to be representative of the target population. However, the unknown risk is addressed in the Summary of Product Characteristics (SmPC) under Section 4.6 and the Section 5.3, which describe the preclinical safety findings.

Genotoxicity:

No specific studies on the genotoxicity of fentanyl citrate were considered necessary. The reference products, Effentora and Actiq adequately describe these aspects. In particular the Actiq Summary Basis of Approval includes results from the testing of fentanyl in the Ames, LY5178Y mouse lymphoma and mouse micronucleus tests: all were negative.

These data provide reassurance as to the lack of genotoxic potential for fentanyl.

Carcinogenicity:

Fentanyl is a well-established medicinal product and has been in use for more than 40 years.

Brain lesions/findings were not evident in six-month rat/nine-month dog studies conducted on PecFent. However, high doses of fentanyl and other opioids are reported to cause brain lesions, primarily eosinophilic neuron degeneration in the limbic system and associated areas, following intravenous administration to rats (Kofke et al, 1996a,b). Neuronal degeneration has also been reported in rat spinal cord following intrathecal administration of fentanyl (Abut et al, 2015).

Non-Kyowa Kirin data presented in the Pharmacovigilance Risk Assessment Committee (PRAC) Periodic Safety Update Report (PSUR) assessment report for Procedure EMEA/H/C/PSUSA/00001369/201304 identified that carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) did not reveal any findings indicative of oncogenic potential. Re-evaluation of brain slides from the carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate.

The relevance of these findings to humans is unknown. Cases of fentanyl/opioid-induced neurotoxicity have also been reported in humans (Gallagher, 2007; Okon and George, 2008).

Brain lesions are an important potential risk for PecFent.

Safety pharmacology

General Safety Pharmacology:

No safety pharmacology studies have been undertaken by the MAH in respect of fentanyl use because the MAH is relying on the studies conducted for the reference products, Effentora and Actiq, to fully describe the safety pharmacology of fentanyl citrate. Data cited from the literature was also reviewed.

Gastrointestinal system:

Opioids can induce direct or indirect gastrointestinal effects, in particular nausea and vomiting, and these have been observed in animals and man (Gutstein and Akil, 2002). It is well documented that opioids including fentanyl can reduce gastrointestinal motility. Furthermore, inflammation of the intestine is known to closely correlate with motility disorder; dysmotility will exacerbate intestinal injury through accumulation of toxic substances or disruption of the intestinal flora (Bossone et al, 2001; Ozaki et al, 2005).

As patients receiving PecFent should already be receiving opioids and would therefore already be familiar with these general effects, these effects do not appear to warrant escalation as an important issue.

Cardiovascular system:

A study on the cardiovascular system, in telemetered Beagle dogs, demonstrated the effects of fentanyl on the conduction processes in the heart. High subcutaneous doses (0.05 mg/kg fentanyl citrate) lead to altered conduction within the heart evidenced by an increased incidence of sinus pauses >2.5 seconds in duration, and an increased incidence of escape complexes associated with the period of decreased heart rate and possibly increased escape focus excitability. This increase in focus excitability and therefore heart rate may represent the direct effect of fentanyl at the escape focus site or may reflect an increase in sympathetic tone.

Circulatory depression, including severe bradycardia, hypotension and shock, is an identified risk for PecFent which is addressed sufficiently within the Section 4.4 and 4.8 of the SmPC.

Nervous system:

Single doses of fentanyl 0.3 mg/kg administered subcutaneously produced signs that were indicative of generalised depression of the central nervous system.

Opioids as a class of drug are well known to be associated with central nervous system depression.

Respiratory system:

A plethysmograph study in rats on the respiratory system demonstrated the clear depressant effect on respiration rate and tidal volume caused by fentanyl in rats.

Respiratory depression or insufficiency is an important identified risk for PecFent.

Other toxicity-related information or data:

None.

Part II: Module SIII - Clinical trial exposure

During the Phase II/III studies, a total of 506 subjects were treated with one or more of the four doses of fentanyl nasal spray (100 mcg, 200 mcg, 400 mcg and 800 mcg). Of these subjects, 36.0% were treated with the highest dose of 800 mcg and 62.8% were treated with 400 mcg at least once (Integrated Summary of Safety Phase: II/III: Table 1-2.16). It should be noted that subjects could receive multiple dose levels of fentanyl nasal spray. These clinical trials all studied adult cancer patients who were taking regular, 24-hour medication for underlying cancer pain and who typically had one to four episodes of breakthrough cancer pain (BTCP) per day.

A total of 27,040 days of exposure to PecFent were accumulated in the Phase II/III clinical trials (Table 2), which amounts to a total of 74.0 years of exposure. Of the 74 subject-years of exposure to fentanyl nasal spray, almost two-thirds (64%) of the years were exposure at one of the two highest doses (Table 2). In patients receiving long-term treatment, i.e., >90 days, total exposure to PecFent was 49.5 years (18,078 days).

Table 2: Subject total duration of exposure to PecFent by dose (Phase II/III studies)

	Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
All subjects [a]			
Total	506	27,040	74.0

			Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
100 mcg	460 (90.9)	459 (16.9)	12.5 (16.9)		

			Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
200 mcg	387 (76.5)	5215 (19.3)	14.3 (19.3)		

	Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
400 mcg	318 (62.8)	8529 (31.5)	23.4 (31.5)

			Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
800 mcg	182 (36.0)	8798 (32.5)	24.1 (32.5)		

			Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
All long-term (>90 days) treatment subjects					
Total	153	18,078	49.5		

			Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
100 mcg	140 (91.5)	2857 (15.8)	7.8 (15.8)		

			Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
200 mcg	130 (85.0)	3138 (17.4)	8.6 (17.4)		

				Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
400 mcg	110 (71.9)	5541 (30.7)	15.2 (30.7)			

	Number (%) of subjects	Total days (%) of PecFent exposure	Total years (%) of PecFent exposure
800 mcg	67 (43.8)	6582 (36.4)	18.0

[a] Subjects may have been exposed to more than one dose of PecFent.

Source: Integrated Safety Database: Phase II/III studies: Table 1-2.16.

Of the 506 subjects, 123 were treated for one to seven days, 41 were treated for eight to 14 days, 57 were treated for 15 to 28 days, and 132 were treated for 29 to 89 days; a total of 153 subjects were treated with fentanyl nasal spray for ≥90 days (Table 3).

Table 3: Age of subjects by length of treatment (Phase II/III studies)

	Length of treatment					Total
	1-7 days	**8-14 days**	**15-28 days**	**29-90 days**	**>90 days**	
Total subjects	123	41	57	132	153	523
Age (years)						
Mean	54.7	56.1	52.3	54.1	53.5	54.2
Standard deviation (SD) (standard error)	12.94 (1.17)	11.08 (1.73)	13.60 (1.80)	12.49 (1.09)	11.37 (0.92)	12.28 (0.54)
Median	56.0	57.0	51.0	55.0	53.0	55.0
Minimum, maximum	18, 86	25, 76	23, 84	21, 84	21, 79	18, 86
Age distribution N (%)						
≤60 years	84 (68.3)	28 (68.3)	44 (77.2)	97 (73.5)	115 (75.2)	375 (71.7)
>60 years	39 (31.7)	13 (31.7)	13 (22.8)	35 (26.5)	38 (24.8)	148 (28.3)

SD=standard deviation.

Source: Integrated Safety Database: Phase II/III studies: Tables 2-2.1 and 2-2.10.

The age of subjects enrolled in the Phase II/III clinical studies ranged from 18 to 86 years with a mean of 54.2 years. Twenty-eight percent of subjects were older than 60 years of age (Table 3). Subject gender is presented in Table 4.

Table 4: Gender of subjects by length of treatment (Phase II/III studies)

Gender N (%)	Length of treatment					
	1-7 days	**8-14 days**	**15-28 days**	**29-90 days**	**>90 days**	**Total**
Female	61 (49.6)	20 (48.8)	28 (49.1)	66 (50.0)	63 (41.2)	249 (47.6)
Male	62 (50.4)	21 (51.2)	29 (50.9)	66 (50.0)	90 (58.8)	274 (52.4)

Source: Integrated Safety Database: Phase II/III studies: Tables 2-2.1 and 2-2.10.

The majority (55%) of subjects exposed to PecFent in the Phase II/III clinical trials were Caucasian (Table 5).

Table 5: Race of subjects by length of treatment (Phase II/III studies)

Race N (%)	Length of treatment					
	1-7 days	**8-14 days**	**15-28 days**	**29-90 days**	**>90 days**	**Total**
Caucasian	70 (56.9)	23 (56.1)	26 (45.6)	66 (50.0)	90 (58.8)	288 (55.1)
Black	7 (5.7)	0	4 (7.0)	4 (3.0)	9 (5.9)	24 (4.6)
Chinese/Japanese Asian	1 (0.8)	0	0	0	0	1 (0.2)
Southeast Asian	2 (1.6)	1 (2.4)	0	1 (0.8)	1 (0.7)	5 (1.0)
Other [a]	43 (35.0)	17 (41.5)	27 (47.4)	61 (46.2)	53 (34.6)	205 (39.2)

[a] Includes American Indian, Hispanic and Pacific Islander.

Source: Integrated Safety Database: Phase II/III studies: Tables 2-2.1 and 2-2.10.

PecFent has not been studied in the following special populations: patients who are pregnant or lactating, patients less than 18 years of age or patients with renal or hepatic impairment, although the clearance of fentanyl in patients with hepatic or renal insufficiency is well understood (see Section SIV.2 [Limitations to detect adverse reactions in clinical trial development programmes]).

Due to the intranasal administration of PecFent, the numbers of BTP episodes treated in subjects with a history of allergic or seasonal rhinitis were reviewed. In the Phase II/III clinical trials, a total of 20,093 episodes of BTP have been treated in subjects with a history of allergic or seasonal rhinitis. That is approximately 44% of the total number of treated episodes (20,093/45,599 episodes).

CP045/06/FCNS study

CP045/06/FCNS was an open-label treatment study consisting of the Main Study (16 weeks duration) and the Extension Period (open-ended). Subjects were newly enrolled or were enrolled after successfully completing studies CP043/06/FCNS or CP044/06/FCNS.

A total of 66 subject-years of documented Nasalfent (previous name for PecFent) drug use was obtained during the Main Study phase. The mean (SD) duration of Nasalfent treatment per subject was 60.4 (44.44) days with a maximum duration of 152 days (approximately 5 months).

Subjects who completed and who were ongoing in the CP045/06/FCNS study at closure of the Main Study phase, were offered the option to continue Nasalfent treatment in the Extension Period.

A total of 145 subject-years of exposure to Nasalfent was accumulated in the Extension Period. The mean (SD) duration of Nasalfent treatment per subject was 325 (354) days with a maximum duration of 1,357 days (3 years and 8 months).

No new adverse events (AEs), nor any change in the pattern of AEs were noted in this extension study.

All clinical trial populations exposure

A total of 27,040 days (74.0 years) of exposure to Nasalfent were accumulated in the Phase II/III clinical trials.

A total of 145 subject-years of exposure to Nasalfent were accumulated in the Extension Period**.**

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Severe respiratory depression or severe obstructive lung conditions:

Reason for exclusion: There is a risk of clinically significant respiratory depression associated with the use of fentanyl.

Particularly in patients with chronic obstructive pulmonary diseases, fentanyl may cause more serious adverse reactions. In these patients, opioids may decrease respiratory drive and increase airway resistance.

Is it considered to be missing information? No

Rationale: Respiratory depression is a known complication of opioid therapy, including fentanyl. Use in patients with severe respiratory depression or severe obstructive lung conditions remains a contraindication within the SmPC. In addition, respiratory depression or insufficiency is considered an important identified risk for PecFent.

Opioid naïve patients:

Reason for exclusion: The potential for respiratory depression is greater in those patients who are naïve to opioids. Use of fentanyl in these patients, may cause more serious adverse reactions.

Is it considered to be included as missing information? No

Rationale: It is well recognised that the potential for respiratory depression is greater in those patients who are naïve to opioids and that use of fentanyl within these patients may cause more serious adverse reactions. Use in patients without maintenance opioid therapy remains a contraindication within the SmPC. In addition, off-label use which captures use in opioid naïve patients is considered an important identified risk for PecFent.

Cardiac conditions that may be worsened by opioids:

Reason for exclusion: Intravenous fentanyl may produce bradycardia and so for safety reasons these patients were excluded.

Is it considered to be included as missing information? No

Rationale: Intravenous fentanyl may produce bradycardia. PecFent should therefore be used with caution in patients with pre-existing bradyarrhythmias. This is stated as a specific precaution in Section 4.4 of the SmPC.

Women of childbearing potential unless taking adequate contraceptive precautions:

Reason for exclusion: The potential risk of exposure to fentanyl in pregnancy is not known as no studies have been performed. Non-clinical studies demonstrated developmental effects in offspring. For safety reasons, pregnancy was to be avoided during clinical trials.

Is it considered to be missing information? No

Rationale: PecFent is not intended to be used in pregnant and breastfeeding patients. However, the unknown risk is addressed in the SmPC under Section 4.6 and the Section 5.3, which describe the pre-clinical safety findings.

Nasal passages occluded or congested. History of nasal pathology, including polyps or nasal obstruction. Abnormal nasal physiology or pathology:

Reason for exclusion: Excluded from clinical studies as presence of nasal pathology could prevent adequate intranasal administration and absorption and could impact efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. No changes in the safety profile are predicted in this population when PecFent is used according to the product label.

Upper respiratory tract infection, chronic rhinitis or had used decongestants within two weeks prior to screening. Taking any medication likely to affect the physiology of the nasal mucosa:

Reason for exclusion: Excluded from clinical studies as presence of upper respiratory infection including chronic rhinitis and/or use of decongestants could prevent adequate intranasal administration and absorption and could impact efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. Clinical trial CP048/07 studied subjects with symptomatic seasonal allergic rhinitis. There were no safety issues pertaining to this group of patients.

Use of concomitant nasally administered decongestants during titration is therefore not recommended as this may lead to patients titrating to a dose that is higher than required. In addition, patients should be made aware that pain control may be less effective following co-administration with a decongestant. If pain control is not as effective, patients should discontinue their decongestant treatment. The use of PecFent requires a dose titration to reach efficacy and adequate guidance on this is found in Section 4.2 of the SmPC.

Information regarding concomitant use with nasally administered vasoconstrictive decongestants is provided in Sections 4.5 and 5.2 of the SmPC.

Sleep apnoea or active brain metastases with increased intracranial pressure:

Reason for exclusion: PecFent can cause respiratory depression. The effect may be enhanced in patients with sleep apnoea or those with raised intracranial pressure who will be more susceptible to the effects of carbon dioxide retention.

Is it considered to be missing information? No

Rationale: Opioids can exacerbate respiratory depression. PecFent is contraindicated in patients with severe respiratory depression.

PecFent should be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of carbon dioxide retention, such as those with evidence of increased intracranial pressure.

Opioids can cause sleep-related breathing disorders including central sleep apnoea and sleep related hypoxemia. Opioid use increases the risk of central sleep apnoea in a dose-dependent fashion. In patients who present with central sleep apnoea, consider decreasing the total opioid dosage.

This precaution can be found in Section 4.4 of the SmPC.

Clinically significant renal or hepatic dysfunction test results:

Reason for exclusion: Excluded for safety reasons as when administered intravenously the clearance of fentanyl has been shown to be altered in significant hepatic and renal impairment due to alterations in clearance and plasma proteins.

Is it considered to be missing information? No

Rationale: PecFent is not intended to be used in patients with renal or hepatic impairment. Information regarding use in this patient population is provided in Sections 4.2 and 4.4 of the SmPC.

Patients under the age of 18 years of age:

Reason for exclusion: The objective of the clinical studies was to assess efficacy and safety in the adult population.

Is it considered to be missing information? No

Rationale: The indication for use of PecFent is for the management of BTP in the adult population. Section 4.2 of the SmPC states that the safety and efficacy of PecFent in children aged below 18 years have not yet been established.

Too frail or unwell:

Reason for exclusion: Excluded from clinical studies as presence would prevent adequate assessment of efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. No changes in the safety profile are predicted in this population when PecFent is used according to the product label.

Psychological distress felt to significantly contribute to pain:

Reason for exclusion: Excluded from clinical studies as presence would prevent adequate assessment of efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. No changes in the safety profile are predicted in this population when PecFent is used according to the product label.

Uncontrolled or escalating pain:

Reason for exclusion: Excluded from clinical studies as presence would prevent adequate assessment of efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. No changes in the safety profile are predicted in this population when PecFent is used according to the product label.

Unstable or rapidly deteriorating condition:

Reason for exclusion: Excluded from clinical studies as presence would prevent adequate assessment of efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. No changes in the safety profile are predicted in this population when PecFent is used according to the product label.

Uncontrolled infection:

Reason for exclusion: Excluded from clinical studies as presence would prevent adequate assessment of efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. No changes in the safety profile are predicted in this population when PecFent is used according to the product label.

Radiotherapy within 30 days prior to study entry:

Reason for exclusion: Excluded from clinical studies as presence would prevent adequate assessment of efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. No changes in the safety profile are predicted in this population when PecFent is used according to the product label.

Planning to undergo chemotherapy, radiotherapy or surgery during the treatment period:

Reason for exclusion: Patients who had recently received radiotherapy or who were planned to receive radiotherapy or chemotherapy that might have affected pain levels were excluded from the double-blind studies. However, these patients were eligible to enrol in the open-label safety study.

Is it considered to be missing information? No

Rationale: Administration of either radiotherapy or chemotherapy concurrently with PecFent did not appear to affect the safety profile observed in the open-label study.

Recent history of alcohol or substance abuse:

Reason for exclusion: Excluded from clinical studies as presence would prevent adequate assessment of efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. The risks of dependence and misuse are described in Section 4.4 of the SmPC. No changes in the safety profile are predicted in this population when PecFent is used according to the product label.

History of or current neurological or psychiatric impairment or cognitive dysfunction:

Reason for exclusion: Excluded from clinical studies as presence would prevent adequate assessment of efficacy endpoints.

Is it considered to be missing information? No

Rationale: The exclusion from clinical trials was not based on safety concerns. No changes in the safety profile are predicted in this population when PecFent is used according to the product label.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical trial development programme was unlikely to detect certain types of adverse reactions such as rare adverse reactions, those caused by prolonged exposure, or local effects.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Categories of patients under-represented in the clinical trial development programmes are summarised in Table 6.

Table 6: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant or breastfeeding women	Not included in the clinical trial development programmes. No pregnancies were reported during the clinical trial development programmes.
Patients aged below 18 years	The safety and efficacy of PecFent in children aged below 18 years have not been studied in clinical trials.
Patients with relevant comorbidities: • Patients with hepatic or renal impairment	Patients with test results indicating clinically significant renal or hepatic dysfunction were excluded from the clinical trials. There is no data in patients receiving fentanyl intranasally.

Type of special population	Exposure
Patients with other relevant co-morbidity: • Patients with allergic (seasonal) rhinitis	Patients with a history of abnormal nasal pathology, including polyps or nasal obstructions, were excluded from the pivotal clinical trials. Study CP048/07, a single-centre, three-way, crossover study was conducted to assess the bioavailability, pharmacokinetics, safety and tolerability of single doses of PecFent when administered to subjects with seasonal allergic rhinitis in symptomatic, symptomatic but treated (oxymetazoline), and asymptomatic states. Following a single-dose administration of PecFent to subjects who suffered from symptomatic seasonal allergic rhinitis, the relative exposure to PecFent was generally unaffected when compared with asymptomatic subjects but was reduced in symptomatic subjects following treatment with oxymetazoline to an extent that may be clinically significant. Accordingly, the efficacy and safety of PecFent should not be affected by untreated allergic rhinitis, but fentanyl absorption is slowed in a patient with rhinitis when administered concomitantly with a decongestant (oxymetazoline), which may result in PecFent being less effective. Use of concomitant nasally administered decongestants during titration is therefore not recommended as this may lead to patients titrating to a dose that is higher than required. In addition, patients should be made aware that pain control may be less effective following co-administration with a decongestant. If pain control is not as effective, patients should discontinue their decongestant treatment.
Patients with a disease severity different from the inclusion criteria in the clinical trial programme	Not relevant as the approved indication is consistent with the clinical trial population.
Subpopulations carrying known and relevant polymorphisms	Not studied specifically with PecFent, but polymorphisms are not known to affect the clearance of fentanyl. As such, the efficacy and safety are not expected to be impacted.

Type of special population	Exposure
Patients of different racial and/or ethnic origin	In the clinical trial programme, the racial distribution was as follows: Caucasian 55.1 %, Black 4.6%, Southeast Asian 1.0%, Chinese/Japanese Asian 0.2%, and other (American Indian, Hispanic and Pacific Islander) 39.2%. Whilst the majority of the patient population was Caucasian, it can be seen that other races were represented. There is no reason to consider that further studies are required in patients of different race or ethnic background.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

PecFent is available in 100 mcg and 400 mcg strengths. The optimal dose of PecFent is determined by upward titration on an individual patient basis. The initial starting dose of PecFent should be 100 mcg, titrating upwards as necessary. Once an appropriate dose is established, the patient is maintained on this dose.

PecFent exposure estimates have been calculated based upon total sales of PecFent sold. A defined daily dose (DDD) of 600 mcg/day has been assumed.

Patient-days=total micrograms sold/DDD.

This exposure estimate represents the maximum amount of product distributed to the market and therefore the maximum possible exposure. However, the spray bottles contain an overage of fentanyl because they require priming prior to use, after which only the stated number of doses (i.e., two or eight sprays) are available for administration to the patient. Based on a patient using the maximum number of sprays in each pack, a more realistic estimate of patient treatment exposure (based on a DDD of 600 mcg) would be approximately half the maximum exposure.

SV.1.2 Exposure

Following the acquisition of Archimedes by the Marketing Authorisation Holder in August 2014, cumulative exposure data is estimated from the cumulative data presented in PSUR 7 (data lock point: 30 April 2017; 52,087 patient-years [PY]) plus data from 01 May 2017 to 31 March 2021 (44,367 PY; Table 7). Assuming a DDD of 600 mcg of PecFent, the cumulative patient exposure can therefore be estimated to be 96,454 PY. Considering the need to prime the spray prior to use

as described above, the estimated patient treatment exposure would be approximately half the maximum exposure and in the order of 48,227 PY.

Table 7: Total number of units distributed worldwide from 01 May 2017 to 31 March 2021

Region	Total mcg sold	Patient-days	PY
EEA	9,512,380,553	15,853,968	43,436
Non-EEA	203,893,200	339,822	931
Total	**9,716,273,753**	**16,193,790**	**44,367**

EEA=European Economic Area; PY=patient-years.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The potential for abuse with fentanyl appears to be of a similar level to other prescription opioids (such as hydrocodone, oxycodone, methadone, morphine and hydromorphone).

In view of the recognised possibility for the abuse, misuse, and diversion of fentanyl-containing products, comprehensive measures were undertaken throughout the clinical trial programme to minimise the opportunity for such.

During the clinical study programme, no meaningful evidence of abuse, misuse or diversion of study materials has emerged. Two patients in Study CP045 were withdrawn due to intentional drug misuse and drug abuse reported as a dependency on narcotics. None of the Investigators reported any specific concerns regarding abuse or diversion during the trials. To minimise abuse by patients and non-patients, Kyowa Kirin continues to implement the educational principles used in the clinical trials, adapted as appropriate to the post-marketing environment.

Educational materials are available to prescribing physicians and dispensing pharmacists to facilitate the screening of patients for risks of abuse of prescription pain medication and following accepted guidelines for the management of high-risk patients. In addition, educational materials are available to patients, family members and carers about the risks of abuse of prescription pain medication and the importance of secure medication storage.

To minimise diversion, the supply chain is tightly controlled in accordance with national regulations for controlled substances; a tamper-evident container-closure system is used.

The SmPC emphasises that treatment should occur under the supervision of an experienced clinician.

Drug misuse, abuse, diversion or dependence is an important identified risk for PecFent.

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

Table 8: Known risks that do not impact the benefit-risk profile

SOC	Risk	Frequency per the SmPC
Infections and infestations	Pneumonia, nasopharyngitis, pharyngitis and rhinitis	Uncommon
Blood and lymphatic system disorders	Neutropenia	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Dehydration, Hyperglycaemia, Decreased appetite, Increased appetite	Uncommon
Psychiatric disorders	Disorientation	Common
	Delirium, Hallucination, Confusional state, Depression, Attention deficit hyperactivity disorder, Anxiety, Euphoric mood, Nervousness	Uncommon
	Insomnia	Unknown
Nervous system disorders	Dysgeusia, Dizziness, Somnolence, Headache,	Common
	Depressed level of consciousness, Loss of consciousness, Convulsion, Ageusia, Memory impairment, Speech disorder, Sedation, Lethargy, Tremor	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Vascular disorders	Cardiovascular insufficiency, Lymphoedema, Hypotension, Hot flush	Uncommon
	Flushing	Unknown
Respiratory, thoracic and mediastinal disorders	Upper airway obstruction, Upper respiratory tract congestion, Pharyngolaryngeal pain, Throat irritation, Cough, Rhinalgia	Uncommon
Gastrointestinal disorders	Vomiting, Nausea, Constipation	Common
	Intestinal perforation, Peritonitis, Oral hypoaesthesia, Oral paraesthesia, Diarrhoea, Retching, Abdominal pain, Dyspepsia, Tongue disorder, Mouth ulceration, Dry mouth	Uncommon
Skin and subcutaneous tissue disorders	Pruritus	Common
	Hyperhidrosis, Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia, Muscle twitching	Uncommon
Renal and urinary disorders	Anuria, Dysuria, Proteinuria, Urinary hesitation	Uncommon
Reproductive system and	Vaginal haemorrhage	Uncommon

SOC	Risk	Frequency per the SmPC
breast disorders		
General disorders and administration site conditions	Non-cardiac chest pain, Asthenia, Malaise, Fatigue, Chills, Face oedema, Oedema peripheral, Gait disturbance, Pyrexia, Thirst	Uncommon
	Withdrawal syndrome, Neonatal withdrawal syndrome	Unknown
Investigations	Platelet count decreased, Weight increased	Uncommon
Injury, poisoning and procedural complications	Fall	Uncommon

SmPC=Summary of Product Characteristics.

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

Important identified risks:

Respiratory depression or insufficiency

In common with other opioid agonists, fentanyl can induce respiratory depression. It is well recognised that the potential for respiratory depression is greater in patients who are naïve to opioids and that use of fentanyl within these patients may cause more serious adverse reactions. Respiratory depression can potentially be life-threatening and may eventually result in respiratory failure with a fatal outcome. This is supported by the clinical trial experience whereby serious adverse events (SAEs) that may be indicative of respiratory depression or insufficiency were reported and included events of Dyspnoea, Respiratory failure, Cardio-respiratory arrest, Pneumonia, Hypoxia and Acute respiratory distress syndrome, all of which were considered severe, and some of which were associated with a fatal outcome.

Benefit-risk impact: This safety concern is well characterised and well managed by routine risk minimisation measures. Following inclusion in the analysis of benefits and risks, the benefit-risk balance remains positive for PecFent.

Local tolerability

Due to the route of administration of PecFent, local tolerability is a potential issue due to the direct action of the drug on the nasal mucosa. However, clinical data have not identified this as a real issue as nasal tolerability of PecFent was high. Nonetheless, serious nasal AEs of Epistaxis and Nasal congestion were reported from clinical trials. The most frequently reported nasal events from post-marketing experience were Epistaxis, Nasal discomfort, Nasal dryness, and Nasal congestion.

Benefit-risk impact: This safety concern is well characterised and well managed by routine risk minimisation measures. Following inclusion in the analysis of benefits and risks, the benefit-risk balance remains positive for PecFent.

Drug misuse, abuse, diversion or dependence

Opioids have a considerable addictive potential and thereby are prone to misuse and abuse. The potential clinical consequences of misuse are serious and can include a risk of respiratory depression and/or physical and psychological dependence. However, when opioids are used under medical supervision as part of analgesia, the risk of abuse or misuse is low. Data from the US Drug Enforcement Administration (DEA) indicate that fentanyl is mainly diverted via pharmacy theft, fraudulent prescriptions, and illicit distribution by patients and registrants (DEA, 2016). Hundreds of diverted items are identified in the US each year.

The phenomenon is also a concern in Europe, although precise figures are not available because systematic searches for fentanyl are not performed (European Monitoring Centre for Drugs and Drug Addiction, 2012). Deaths associated with fentanyl diversion, however, have been reported in the United Kingdom and several EU countries, including Sweden and Italy. To minimise diversion, the supply chain is tightly controlled in accordance with national regulations for controlled substances and a tamper-evident container-closure system is used.

Opioids have a considerable addictive potential and therefore patients can be prone to drug dependence. The potential clinical consequences of drug dependence are serious and can include both physical and psychological dependence. Drug dependence can produce significant and lasting changes in brain chemistry and function. Opioids disinhibit dopamine neurons, producing increased firing rates. Opioids also have direct effects on endogenous opioid and possibly the gamma-aminobutyric acid systems. Once dependant, there is a tendency to relapse after abstinence, possibly due to integration of reward circuitry with motivational, emotional and memory centres connected in the limbic system of the brain (McLellan et al, 2000). However, when opioids are used under medical supervision as part of analgesia, the risk of drug dependence is low.

Benefit-risk impact: This safety concern is well characterised and well managed by routine and additional risk minimisation measures. Following inclusion in the analysis of benefits and risks, the benefit-risk balance remains positive for PecFent.

Off-label use

PecFent is indicated for the management of BTP in adult patients using opioid therapy for chronic cancer pain. It is contra-indicated in the treatment of acute pain other than BTP. The potential clinical consequences of off-label use are serious and can include a risk of respiratory depression and/or physical and psychological dependence. In addition, there is a potential for lack of effect or AE when used outside of an indication for which there is no clinical data.

Benefit-risk impact: This safety concern is well characterised and well managed by routine and additional risk minimisation measures. Following inclusion in the analysis of benefits and risks, the benefit-risk balance remains positive for PecFent.

Medication error

Medication errors refer to unintentional prescribing/administration and or dispensing of PecFent, in addition to incorrect dose and route of administration. The potential consequences associated with medication errors can be serious if associated with an AE and include the risk of respiratory depression or a lack of pain control.

Benefit-risk impact: This safety concern is well characterised and well managed by routine and additional risk minimisation measures. Following inclusion in the analysis of benefits and risks, the benefit-risk balance remains positive for PecFent.

Overdose

In association with opioid treatment, including fentanyl, there is significant tolerability to all effects (efficacy and side effects) except constipation after a few weeks of constant dosing. Therefore, the therapeutic window is wider for opioid-tolerant patients which reduces the risk of severe adverse effects following intentional overdosing. It is well known that all opioid mu-receptor agonists, including fentanyl, produce dose-dependent respiratory depression and as with other potent opioids, fentanyl has been associated with cases of serious and fatal respiratory depression in opioid non-tolerant individuals. To reiterate, the potential clinical consequences associated with overdose are serious if associated with an AE.

Benefit-risk impact: This safety concern is well characterised and well managed by routine and additional risk minimisation measures. Following inclusion in the analysis of benefits and risks, the benefit-risk balance remains positive for PecFent.

Accidental exposure

Accidental exposure refers to the accidental exposure of a person (adult or child) for whom PecFent was not prescribed. The impact on the individual accidently exposed to PecFent is potentially serious. Respiratory depression may occur, particularly in non-opioid tolerant individuals, and has the potential of a fatal outcome.

Benefit-risk impact: This safety concern is well characterised and well managed by routine and additional risk minimisation measures. Following inclusion in the analysis of benefits and risks, the benefit-risk balance remains positive for PecFent.

Important potential risks:

Brain lesion

Non-Kyowa Kirin data presented in the PRAC PSUR assessment report for Procedure EMEA/H/C/PSUSA/00001369/201304 identified that carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) did not induce any findings indicative of oncogenic potential. Evaluation of brain slides from the

carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate.

The carcinogenicity potential of fentanyl for humans is unknown, therefore the impact on individual patients is not known. As a result of the findings from the carcinogenicity study in rats, brain lesion is considered an important potential risk.

The PRAC PSUR assessment report Procedure EMEA/H/C/PSUSA/00001369/201704 noted that the data was difficult to interpret and a correlation of the cases, which are mostly poorly documented, with mineralisation/necrosis retrieved in carcinogenicity studies of animals, seemed hard to identify without medical imagery data such as magnetic resonance imaging scans.

Benefit-risk impact: Given PecFent is used to treat BTP in cancer patients, the presence of pre-existing malignancy makes it difficult to determine if a causal relationship exists between PecFent and brain lesions. The background history of cancer within this population makes it challenging to determine whether brain lesions are primary disease or secondary to the established cancer. Currently, there is insufficient data to allow classification as an important identified risk for PecFent.

Missing information:

Long-term use

A total of 145 PY of exposure to Nasalfent were accumulated in the Study CP045 Extension Period. The mean (SD) duration of Nasalfent treatment per patient was 325 (354) days with a maximum duration of 1,357 days (3 years and 8 months).

Benefit-risk impact: The impact on individual patients is unknown due to there being insufficient data for analysis during long-term use.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Cardiovascular depression, including severe bradycardia, hypotension and shock was previously classified as an important identified risk, but it is proposed to be removed. The safety concern is adequately addressed in the SmPC and is not associated with any additional pharmacovigilance activities or risk minimisation measures. Statements applicable to Cardiovascular depression are provided in Section 4.4 and 4.8 of the SmPC.

Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs was previously classified as an important potential risk, but it is proposed to be removed. This safety concern is considered to be adequately addressed in the SmPC and is no longer associated with any additional pharmacovigilance activities or risk minimisation measures. Statements applicable to Serotonin syndrome are provided in Section 4.4 and Section 4.5 of the SmPC.

Use in the paediatric population, use in pregnant and breastfeeding women, and use in patients with renal or hepatic impairment were previously classified as missing information but it is proposed to remove these safety concerns. This change will ensure adherence to Good Pharmacovigilance Practices Module V Revision 2 guidance, which advises that excluded populations from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indications, i.e., “on-label” use. PecFent is not intended to be used in patients under the age of 18 years, in pregnant and breastfeeding women, or in patients with renal or hepatic impairment, hence use in these populations is not considered as missing information but as off-label use. Off-label use has already been classified as an important identified risk for PecFent. Use in the paediatric population, in pregnant and breastfeeding women and in patients with renal or hepatic impairment will continue to be monitored under the safety concern of off-label use. Statements applicable to use in the paediatric population are provided in Sections 4.2 and 4.4 of the SmPC. Statements applicable to use in pregnant and breastfeeding women are provided in Section 4.6 and the Section 5.3 of the SmPC. Statements applicable to use in patients with renal or hepatic impairment are provided in Section 4.2 and Section 4.4 of the SmPC.

SVII.3 Details of important identified risks, important potential risks, and missing information

Information on the important identified risks is summarised in Table 9 (Respiratory depression or insufficiency), Table 10 (Local tolerability), Table 11 (Drug misuse, abuse, diversion or dependence), Table 12 (Off-label use), Table 13 (Medication error), Table 14 (Overdose) and Table 15 (Accidental exposure).

Table 9: Important identified risk: Respiratory depression or insufficiency

<table>
<tr><th colspan="2">Important identified risk: Respiratory depression or insufficiency</th></tr>
<tr><td>Medical Dictionary for Regulatory Activities (MedDRA) terms</td><td>Standardised MedDRA Queries (SMQs) of Acute central respiratory depression (broad) and Respiratory failure (broad) [a]</td></tr>
<tr><td>Potential mechanisms</td><td>Fentanyl is known to induce respiratory depression by direct activation of opioid receptors, which are abundant in respiratory control centres (including the brainstem) of the central nervous system (Pattinson, 2008). Respiratory depression involves both a reduction in responsiveness of the brain stem respiratory centres to increases in carbon dioxide tension and to electrical stimulation.</td></tr>
<tr><td>Evidence sources and strength of evidence</td><td>Clinical trial development programmes and post-marketing surveillance including post-marketing reports and literature.

In common with other opioid agonists, fentanyl can induce respiratory depression. It is well recognised that the potential for respiratory depression is greater in patients who are not receiving opioids and that use of fentanyl in these patients may cause more serious adverse reactions. Respiratory depression can potentially be life-threatening and may eventually result in respiratory failure with a fatal outcome. Respiratory depression or insufficiency is therefore considered an important identified risk for PecFent.</td></tr>
<tr><td>Characterisation of the risk</td><td><u>Clinical trial experience:</u>
The following respiratory AEs were included in the Integrated Safety Database.
<table>
<tr><th>PT</th><th>N</th><th>Frequency per 100</th><th>95% confidence interval</th></tr>
<tr><td>Dyspnoea</td><td>23</td><td>4.5</td><td>2.9 to 6.7</td></tr>
<tr><td>Apnoea</td><td>1</td><td>0.2</td><td>0 to 1.1</td></tr>
<tr><td>Hypoxia</td><td>2</td><td>0.4</td><td>0.1 to 1.4</td></tr>
<tr><td>Respiratory depression</td><td>1</td><td>0.2</td><td>0 to 1.1</td></tr>
<tr><td>Pneumonia</td><td>10</td><td>1.0</td><td>1.0 to 3.6</td></tr>
<tr><td>Respiratory failure</td><td>2</td><td>0.4</td><td>0 to 1.1</td></tr>
<tr><td>Cardio-respiratory arrest</td><td>6</td><td>1.2</td><td>0.4 to 2.6</td></tr>
<tr><td>Acute respiratory distress syndrome</td><td>1</td><td>0.2</td><td>0 to 1.1</td></tr>
</table>
All of the above AEs were considered unrelated except for one case of severe pneumonia and two case reports of dyspnoea (one mild, one severe).</td></tr>
</table>

Important identified risk: Respiratory depression or insufficiency	
	During clinical trials, SAEs that may be indicative of respiratory depression or insufficiency were reported and included events of Dyspnoea, Respiratory failure, Cardio-respiratory arrest, Pneumonia, Hypoxia and Acute respiratory distress syndrome, some of which were associated with a fatal outcome. None of these AEs were considered to be related to the administration of PecFent. <u>Post-marketing experience:</u> Cumulatively, 83 valid case reports describing 94 events (17 fentanyl nasal spray, 77 unspecified fentanyl formulation) pertaining to respiratory depression or insufficiency have been identified from the post-marketing setting. This equates to a reporting rate (RR) of 3.5 events per 10,000 PY for fentanyl nasal spray and 19.5 events per 10,000 PY for fentanyl nasal spray and unspecified fentanyl formulation combined. The most frequently reported PTs were Dyspnoea, Cardiac arrest, Respiratory depression, Hypoxia, Respiratory arrest, Respiratory failure, Asphyxia and Cyanosis. Of the 94 events, 83 were serious, for which event outcome was resolved (18), resolved with sequelae (1), resolving (7), not resolved (7), fatal (21) and unknown (29). The most frequently reported events associated with a fatal outcome were Asphyxia, Cardiac arrest and Respiratory failure.
Risk factors and risk groups	Patients at increased risk of developing respiratory depression include those who: • Are opioid-naïve • Are elderly • Are debilitated • Have underlying pulmonary pathology • Have impaired respiratory drive of sleep apnoea • Are also receiving concomitant sedatives
Preventability	Patients with pain who receive chronic opioid therapy develop tolerance to respiratory depression and hence the risk of respiratory depression in these patients is reduced. Section 4.4 of the SmPC also warns that the use of concomitant central nervous system depressants may increase the risk of respiratory depression, and that in patients with chronic obstructive pulmonary diseases, fentanyl may cause more serious adverse reactions and opioids may decrease respiratory drive and increase airway resistance.
Impact on the benefit-risk balance of the product	This safety concern is well characterised and managed by routine risk minimisation measures. Following inclusion in the analysis of overall benefits and risks, the benefit-risk balance remains positive for PecFent.
Public health impact	Low, when used as part of palliative care in opioid-tolerant individuals.

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; PY=patient-years; RR=reporting rate; SAE=serious adverse event; SmPC=Summary of Product Characteristics; SMQ=Standardised MedDRA Query.

[a] The MedDRA terms listed were used to search the Kyowa Kirin Global Safety Database for post-marketing events pertaining to the risk.

Table 10: Important identified risk: Local tolerability

<table>
<tr><th colspan="2">Important identified risk: Local tolerability</th></tr>
<tr><td>MedDRA terms</td><td>PTs of Anosmia, Epistaxis, Hyposmia, Intranasal hypoaesthesia, Intranasal paraesthesia, Nasal cavity mass, Nasal congestion, Nasal cyst, Nasal discomfort, Nasal disorder, Nasal dryness, Nasal mucosa atrophy, Nasal mucosal discolouration, Nasal mucosal disorder, Nasal mucosal hypertrophy, Nasal necrosis, Nasal odour, Nasal oedema, Nasal polyps, Nasal septum deviation, Nasal septum disorder, Nasal septum perforation, Nasal septum ulceration, Nasal turbinate abnormality, Nasal turbinate hypertrophy, Nasal ulcer, Parosmia, Rhinolithiasis, Rhinorrhoea, Sneezing and Upper-airway cough syndrome [a]</td></tr>
<tr><td>Potential mechanisms</td><td>Because of the route of administration of PecFent, there is a direct action of the drug on the nasal mucosa, which may therefore cause local chemical or mechanical irritation.</td></tr>
<tr><td>Evidence sources and strength of evidence</td><td>Clinical trial development programme and post-marketing surveillance, including post-marketing reports and literature.

Because of the route of administration of PecFent, local tolerability is a potential issue due to the direct action of the drug on the nasal mucosa. However, clinical data have not identified this as a meaningful issue as nasal tolerability of PecFent was high. Nonetheless, serious nasal AEs of epistaxis and nasal congestion were reported from clinical trials; post-marketing safety data are in-line with that reported from the clinical trials. It is therefore considered that there is sufficient information to classify local tolerability as an important identified risk for PecFent.</td></tr>
<tr><td>Characterisation of the risk</td><td><u>Clinical trial experience:</u>
Nasal AEs included in the Integrated Safety Database are low in frequency, as follows:
<table>
<tr><th>PT</th><th>N</th><th>Frequency per 100</th><th>95% confidence interval</th></tr>
<tr><td>Epistaxis</td><td>15</td><td>2.9</td><td>1.7 to 4.8</td></tr>
<tr><td>Cough</td><td>14</td><td>2.8</td><td>1.5 to 4.6</td></tr>
<tr><td>Nasal discomfort</td><td>11</td><td>2.1</td><td>1.1 to 3.9</td></tr>
<tr><td>Nasal mucosal disorder</td><td>4</td><td>0.8</td><td>0.2 to 2.0</td></tr>
<tr><td>Pharyngolaryngeal pain</td><td>14</td><td>2.7</td><td>1.5 to 4.6</td></tr>
<tr><td>Postnasal drip</td><td>6</td><td>1.2</td><td>0.4 to 2.6</td></tr>
<tr><td>Rhinorrhoea</td><td>11</td><td>2.1</td><td>1.1 to 3.9</td></tr>
<tr><td>Nasal congestion</td><td>6</td><td>1.2</td><td>0.4 to 2.6</td></tr>
<tr><td>Nasal dryness</td><td>2</td><td>0.4</td><td>0.1 to 1.4</td></tr>
</table></td></tr>
</table>

<table>
<tr><td colspan="2">Important identified risk: Local tolerability</td></tr>
<tr><td></td><td>
<table>
<tr><td>Intranasal hypoaesthesia</td><td>2</td><td>0.4</td><td>0.1 to 1.4</td></tr>
<tr><td>Nasal turbinate hypertrophy</td><td>1</td><td>0.2</td><td>0.1 to 1.1</td></tr>
<tr><td>Sneezing</td><td>2</td><td>0.4</td><td>0.1 to 1.4</td></tr>
</table>

No consistent pattern of findings on objective nasal examinations was found during the studies that would indicate that PecFent is associated with changes in nasal obstruction, inflammation, discharge, or colour of mucosa. In subjective assessments, no consistent pattern of abnormal nasal findings such as stuffy or blocked nose, runny nose, itching or sneezing, crusting or dryness of the nose, burning or discomfort, nasal bleeding, cough, postnasal drip, sore throat, or taste disturbance was reported.

The following serious nasal AEs were reported in the clinical trials: epistaxis and nasal congestion. These were considered by the Investigator to be unrelated to PecFent. Of the nasal AEs reported, most resolved on the same day. Two severe nasal AEs were reported in the clinical trials (epistaxis and cough). All other events were mild or moderate in severity.

<u>Post-marketing experience:</u>
Cumulatively, 49 valid case reports describing 53 events (39 fentanyl nasal spray, 14 unspecified fentanyl formulation) pertaining to local tolerability have been identified from the post-marketing setting. This equates to a RR of 8.1 events per 10,000 PY for fentanyl nasal spray and 11 events per 10,000 PY for fentanyl nasal spray and unspecified fentanyl formulation combined.

The most frequently reported PTs were Epistaxis, Nasal discomfort, Nasal dryness, Nasal congestion and Dry mouth. Of the 53 events, 11 were serious, for which event outcome was resolved (6), resolving (1), not resolved (2) and unknown (2).</td></tr>
<tr><td>Risk factors and risk groups</td><td>No risk groups or risk factors have been identified.</td></tr>
<tr><td>Preventability</td><td>Nasal AEs are listed in Section 4.8 of the SmPC. A warning to consider an alternative mode of administration if the patient experiences recurrent episodes of epistaxis or nasal discomfort is included in Section 4.4 of the SmPC. The results from clinical trials do not warrant any additional warning statements to be included in the SmPC.</td></tr>
<tr><td>Impact on the benefit-risk balance of the product</td><td>This safety concern is well characterised and well managed by routine risk minimisation measures. Following inclusion in the analysis of overall benefits and risks, the benefit-risk balance remains positive for PecFent.</td></tr>
<tr><td>Public health impact</td><td>Low.</td></tr>
</table>

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; PY=patient-years; RR=reporting rate; SmPC=Summary of Product Characteristics.

[a] The MedDRA terms listed were used to search the Kyowa Kirin Global Safety Database for post-marketing events pertaining to the risk.

Table 11: Important identified risk: Drug misuse, abuse, diversion or dependence

Important identified risk: Drug misuse, abuse, diversion or dependence	
MedDRA terms	High Level Terms of Intentional product misuses and Intentional product use issues, SMQ of Drug abuse and dependence (broad) [a]
Potential mechanisms	Opioids, including fentanyl, have a considerable addictive potential and thereby are prone to misuse. Fentanyl stimulates mu-opioid receptors in the nucleus accumbens, leading to activation of the mesolimbic dopamine pathway, which is implicated in its rewarding effects (Herz, 1998). The development of physical dependence results from activation of mu1 receptors, which causes functional changes in Gi/o, adenylate cyclase, protein kinases A and C, beta-adrenoceptor and N-mthyl-D-aspartate receptors in the locus coeruleus (Suzuki and Misawa, 1997).
Evidence sources and strength of evidence	Post-marketing surveillance including post-marketing reports and literature. Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. However, iatrogenic addiction following therapeutic use of opioids is known to occur. In addition, repeated use of PecFent may lead to opioid use disorder. Furthermore, the potential clinical consequences of abuse and intentional misuse are serious and can include overdose, a risk of respiratory depression, death and/or physical and psychological dependence. However, when opioids are used under medical supervision as part of analgesia, the risk of abuse or misuse is considered low. Data from the US DEA indicate that fentanyl is mainly diverted via pharmacy theft, fraudulent prescriptions, and illicit distribution by patients and registrants (DEA, 2016). Hundreds of diverted items are identified in the US each year. The phenomenon is also a concern in Europe, although precise figures are not available because systematic searches for fentanyl are not performed (European Monitoring Centre for Drugs and Drug Addiction, 2012). Deaths associated with fentanyl diversion, however, have been reported in the United Kingdom and several EU countries, including Sweden and Italy. It is therefore considered that there is sufficient information to classify drug misuse, abuse, diversion and dependence as an important identified risk for PecFent.
Characterisation of the risk	Clinical trial experience: No clinically significant AEs associated with abuse or misuse were reported in clinical trials.

Important identified risk: Drug misuse, abuse, diversion or dependence	
	Post-marketing experience: Cumulatively, 58 valid case reports describing 58 events (33 fentanyl nasal spray, 25 unspecified fentanyl formulation) pertaining to drug misuse have been identified from the post-marketing setting. This equates to a RR of 6.8 events per 10,000 PY for fentanyl nasal spray and 12 events per 10,000 PY for fentanyl nasal spray and unspecified fentanyl formulation combined. Reported PTs were Intentional product misuse, Intentional product use issue and Intentional device misuse. Of the 58 case reports, 32 were serious and 13 were associated with a fatal outcome. The most frequently reported events associated with a fatal outcome reported in these case reports were Toxicity to various agents, Pulmonary oedema, Brain oedema, Cystocele and Drug diversion. In addition, 341 valid case reports describing 484 events (181 fentanyl nasal spray, 303 unspecified fentanyl formulation) pertaining to drug abuse, dependence or diversion were identified from the post-marketing setting. This equates to a RR of 37.5 events per 10,000 PY for fentanyl nasal spray and 100.4 events per 10,000 PY for fentanyl nasal spray and unspecified fentanyl formulation combined. Of the 484 events, 94 pertained to drug dependence (PTs of Drug dependence, Substance dependence and Dependence) and 29 to drug diversion (PTs of Drug diversion, Prescription form tampering and Prescription drug used without a prescription); other reported PTs included Overdose, Drug abuse, Toxicity to various agents, Accidental overdose, Substance abuse, Drug tolerance and Intentional overdose. Of the 341 case reports, 291 were serious and 105 were associated with a fatal outcome. The most frequently reported events associated with a fatal outcome reported in these case reports were Toxicity to various agents, Overdose, Drug abuse, Accidental overdose, Drug diversion, Death, Pulmonary oedema, Brain oedema and Depressed level of consciousness.
Risk factors and risk groups	Those at an increased risk of misuse include: • Patients who have a history of substance abuse • Patients and prescribers who use PecFent off-label
Preventability	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 for abuse of fentanyl (SmPC Section 4.2). Section 4.4 of the SmPC warns that tolerance and physical and/or psychological dependence may develop upon repeated administration of

Important identified risk: Drug misuse, abuse, diversion or dependence	
	opioids such as fentanyl. However, iatrogenic addiction following therapeutic use of opioids is known to occur; therefore, patients require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). To minimise diversion, the supply chain is tightly controlled in accordance with national regulations for controlled substances and a tamper-evident container-closure system is used.
Impact on the benefit-risk balance of the product	This safety concern is well characterised and managed by routine and additional risk minimisation measures. Following inclusion in the analysis of overall benefits and risks, the benefit-risk balance remains positive for PecFent.
Public health impact	Low, when prescribed in the context of palliative care, although there is a potential public health impact in terms of illegal activities and drug addiction.

AE=adverse event; DEA=Drug Enforcement Administration; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; PY=patient-years; RR=reporting rate; SmPC=Summary of Product Characteristics; SMQ=Standardised MedDRA Query; US=United States.

[a] The MedDRA terms listed were used to search the Kyowa Kirin Global Safety Database for post-marketing events pertaining to the risk.

Table 12: Important identified risk: Off-label use

Important identified risk: Off-label use	
MedDRA terms	PTs of Off-label use, Product use in unapproved indication, Therapy naïve, Drug effective for unapproved indication, Drug ineffective for unapproved indication, Therapeutic product effective for unapproved indication, Therapeutic product ineffective for unapproved indication, Product administered to patient of inappropriate age and Product use issue [a]
Potential mechanisms	Not applicable.
Evidence sources and strength of evidence	Post-marketing surveillance including post-marketing reports. PecFent is indicated for the management of BTP in adult patients who are already receiving maintenance therapy for chronic cancer pain. It is contraindicated in the treatment of acute pain other than BTP. The potential clinical consequences of off-label use are serious and can include a risk of respiratory depression and/or physical and psychological dependence. In addition, there is a potential for lack of effect or AEs when used outside of an indication for which there is no clinical data. It is therefore considered that there is sufficient information to classify off-label use as an important identified risk for PecFent.

Important identified risk: Off-label use	
Characterisation of the risk	Clinical trial experience: There was no off label use reported in the clinical development programme. Post-marketing experience: Cumulatively, 360 valid case reports (202 fentanyl nasal spray, 158 unspecified fentanyl formulation) pertaining to the off-label use of nasal fentanyl have been identified from the post-marketing setting. This equates to a RR of 41.9 case reports per 10,000 PY for fentanyl nasal spray and 74.6 case reports per 10,000 PY for fentanyl nasal spray and unspecified fentanyl formulation combined. Of the 360 case reports, 48 (13.3%) concerned off-label use in paediatric patients. Of the 48 case reports, 20 were serious, none of which were associated with a fatal outcome. Of note, additional off-label uses in these cases included use for non-cancer-related pain, sedative therapy, mucosal damage, dystonic storm, and in an opioid-naïve patient. Of the remaining 312 case reports, the most frequently reported off-label uses were treatment of patients with non-cancer-related pain or unspecified pain (including headache, fracture, surgery, labour and myalgia) and opioid naïve patients. Other off-label indications included dyspnoea and sedation/anaesthesia. Multiple case reports were off-label due to an incorrect starting dose, route of administration or dose/dosing schedule. Of the 312 case reports, 150 were serious and 26 were associated with a fatal outcome. The most frequently reported events associated with a fatal outcome described in these case reports were Death, Malignant neoplasms progression, Disease progression, Cardiac arrest, General physical health deterioration, Sepsis and Toxicity to various agents. Of the fatal events that were assessed as related to PecFent, all had confounding factors including co-suspect products (such as morphine, cocaine, oxycodone and methadone), disease progression, overdose and comorbidities.
Risk factors and risk groups	Not known.
Preventability	The SmPC provides appropriate guidance and warnings to prevent off-label use. In addition, a number of other factors should minimise off-label use: • There is already a range of approved non-opioid analgesics specifically designed for the management of acute pain, some in formulations that offer rapid pain relief • There is a range of approved opioid products approved

Important identified risk: Off-label use	
	for the management of chronic severe pain • Prescribers are generally aware that opioids may provoke respiratory depression in opioid-naive patients unless titrated carefully, particularly in those patients with underlying head injuries or chronic respiratory disease. Educational materials directed at physicians, pharmacists, patients and carers are also prevention methods used to reduce the risk of off-label use. PecFent is also a prescription-only medicine. Distribution controls exist in local European legislation managing the prescription, dispensing and disposal of opioid analgesics within normal medical practice.
Impact on the benefit-risk balance of the product	This safety concern is well characterised and managed by routine and additional risk minimisation measures. Following inclusion in the analysis of overall benefits and risks, the benefit-risk balance remains positive for PecFent.
Public health impact	Low, when used as part of palliative care in opioid-tolerant individuals.

AE=adverse event; BTP=breakthrough pain; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; PY=patient-years; RR=reporting rate; SmPC=Summary of Product Characteristics.

[a] The MedDRA terms listed were used to search the Kyowa Kirin Global Safety Database for post-marketing events pertaining to the risk.

Table 13: Important identified risk: Medication error

Important identified risk: Medication error	
MedDRA terms	SMQ of Medication errors (broad) excluding PTs of Accidental exposure to product, Accidental exposure to product by child, Occupational exposure to product, Overdose, Prescribed overdose, Product use in unapproved indication and Product use issue [a]
Potential mechanisms	Not applicable.
Evidence sources and strength of evidence	Post-marketing surveillance including post-marketing reports. Medication errors refer to unintentional prescribing/administration and or dispensing of PecFent, in addition to incorrect dose and route of administration. The potential consequences associated with medication errors can be serious if associated with an AE and include the risk of respiratory depression or a lack of pain control. It is therefore considered that there is sufficient information to classify medication error as an important identified risk for PecFent.
Characterisation of the risk	Clinical trial experience:

Important identified risk: Medication error	
	There were no reports of medication error during clinical trials with PecFent. Post-marketing experience: Cumulatively, 210 valid case reports describing 244 events (178 fentanyl nasal spray, 66 unspecified fentanyl formulation) pertaining to medication error have been identified from the post-marketing setting. This equates to a RR of 36.9 events per 10,000 PY for fentanyl nasal spray and 50.6 events per 10,000 PY for fentanyl nasal spray and unspecified fentanyl formulation combined. The most frequently reported medication error PTs were Inappropriate schedule of product administration, Incorrect dose administered, Product administered to patient of inappropriate age, Accidental overdose, Dose titration not performed, Incorrect route of product administration and Drug titration error. In addition, 16 PTs pertained to issues with the device/issues using the device. Of the 210 case reports, 92 were serious, of which 24 were associated with a fatal outcome. The most frequently reported events associated with a fatal outcome described in these case reports were Accidental overdose, Toxicity to various agents, Death, Disease progression and Accidental poisoning. Of the fatal events that were assessed as related to PecFent, all had confounding factors including co-suspect products (such as heroin, methadone, methamphetamine, cocaine, cannabis and morphine), history of drug abuse/addictive behaviour, disease progression, overdose and comorbidities.
Risk factors and risk groups	Non-adults and adults who were prescribed PecFent.
Preventability	The SmPC provides appropriate guidance to prevent the associated risk of medication errors. Educational materials directed at physicians, pharmacists, patients and carers are also prevention methods used to reduce the risk of medication errors. In addition, medication errors are minimised by the clearly differentiated colour coded boxes for each formulation strength.
Impact on the benefit-risk balance of the product	This safety concern is well characterised and managed by routine and additional risk minimisation measures. Following inclusion in the analysis of overall benefits and risks, the benefit-risk balance remains positive for Pecfent.
Public health impact	Low, when prescribed in the context of palliative care.

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; PY=patient-years; RR=reporting rate; SmPC=Summary of Product Characteristics; SMQ=Standardised MedDRA Query.

[a] The MedDRA terms listed were used to search the Kyowa Kirin Global Safety Database for post-marketing events pertaining to the risk.

Table 14: Important identified risk: Overdose

Important identified risk: Overdose	
MedDRA terms	PTs of Overdose, Accidental overdose, Intentional overdose and Prescribed overdose [a]
Potential mechanisms	Not applicable.
Evidence sources and strength of evidence	Post-marketing surveillance including post-marketing reports. It is well known that all opioid mu-receptor agonists, including fentanyl, produce dose-dependent respiratory depression and as with other potent opioids, fentanyl has been associated with cases of serious and fatal respiratory depression in opioid non-tolerant individuals. The potential clinical consequences associated with overdose are serious if associated with an AE. It is therefore considered that there is sufficient information to classify overdose as an important identified risk for PecFent.
Characterisation of the risk	Clinical trial experience: There were no reports of overdose during clinical trials with PecFent. Post-marketing experience: Cumulatively, 146 valid case reports describing 147 events (75 fentanyl nasal spray, 72 unspecified fentanyl formulation) pertaining to overdose have been identified from the post-marketing setting. This equates to a RR of 15.6 events per 10,000 PY for fentanyl nasal spray and 30.5 events per 10,000 PY for fentanyl nasal spray and unspecified fentanyl formulation combined. The reported PTs were Overdose (103 events), Accidental overdose (24 events), Prescribed overdose (15 events), and Intentional overdose (5 events). Of the 146 case reports, 110 were serious and 55 were associated with a fatal outcome. The most frequently reported events associated with a fatal outcome described in these case reports were Overdose, Toxicity to various agents, Drug abuse, Accidental overdose, Drug diversion, Death and Substance abuse.
Risk factors and risk groups	Non-adults and adults who were prescribed PecFent.
Preventability	The SmPC provides appropriate guidance and warnings to prevent the risk of overdose. Educational materials directed at physicians, pharmacists, patients and carers are also prevention methods used to reduce the risk of overdose. In addition, overdose resulting from medication errors is reduced by the colour coding of packaging for each formulation strength.
Impact on the benefit-risk balance of the product	This safety concern is well characterised and managed by routine and additional risk minimisation measures. Following inclusion in the analysis of overall benefits and risks, the benefit-risk balance remains positive for PecFent.
Public health impact	Low when used as part of palliative care in opioid-tolerant individuals.

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; PY=patient-years; RR=reporting rate; SmPC=Summary of Product Characteristics.

[a] The MedDRA terms listed were used to search the Kyowa Kirin Global Safety Database for post-marketing events pertaining to the risk.

Table 15: Important identified risk: Accidental exposure

Important identified risk: Accidental exposure	
MedDRA terms	PTs of Accidental exposure to product, Occupational exposure to product and Accidental exposure to product by child [a]
Potential mechanisms	Not applicable.
Evidence sources and strength of evidence	Post-marketing surveillance including post-marketing reports. Accidental exposure refers to the accidental exposure of a person (adult or child) for whom PecFent was not prescribed. The impact on the individual accidently exposed to PecFent is potentially serious. Respiratory depression may occur, particularly in non-opioid-tolerant individuals, and has the potential of a fatal outcome. It is therefore considered that there is sufficient information to classify accidental exposure as an important identified risk for PecFent.
Characterisation of the risk	Clinical trial experience: There were no reports of accidental exposure during clinical trials with PecFent. Post-marketing experience: Cumulatively, six valid case reports describing six events (five fentanyl nasal spray, one unspecified fentanyl formulation) pertaining to accidental exposure have been identified from the post-marketing setting. This equates to a RR of one event per 10,000 PY for fentanyl nasal spray and 1.2 events per 10,000 PY for fentanyl nasal spray and unspecified fentanyl formulation combined. The reported PTs were Occupational exposure to product, Accidental exposure to product and Accidental exposure to product by child. Additional AEs were reported from three of six case reports and included Dizziness, Feeling abnormal and Motor dysfunction. Of the six case reports, one was serious, though no additional AEs were reported in this case; patient outcome was unknown.
Risk factors and risk groups	Those at an increased risk of accidental exposure include individuals who were not prescribed PecFent, who are able to gain access or be exposed to PecFent.

Important identified risk: Accidental exposure	
Preventability	The SmPC provides appropriate warnings regarding the risk of accidental exposure. Educational materials directed at physicians, pharmacists, patients and carers are also prevention methods used to reduce the risk of accidental exposure. In addition, PecFent is provided in a child-resistant container and is a prescription only medicine. Distribution, usage and accounting controls exist in local European legislation managing the disposal of opioid analgesics within normal medical practice.
Impact on the benefit-risk balance of the product	This safety concern is well characterised and well managed by routine and additional risk minimisation measures. Following inclusion in the analysis of benefits and risks, the benefit-risk balance remains positive for PecFent.
Public health impact	Low, when used in a controlled palliative care setting.

MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; PY=patient-years; RR=reporting rate; SmPC=Summary of Product Characteristics.

[a] The MedDRA terms listed were used to search the Kyowa Kirin Global Safety Database for post-marketing events pertaining to the risk.

Information on the important potential risk is summarised in Table 16 (Brain lesions).

Table 16: Important potential risk: Brain lesions

Important potential risk: Brain lesions	
MedDRA terms	PTs of Psychomotor skills impaired, Central nervous system lesion, Neurodegenerative disorder, Motor dysfunction, Cognitive disorder and Central nervous system necrosis [a]
Potential mechanisms	Unknown.
Evidence sources and strength of evidence	Post-marketing surveillance including post-marketing reports and PRAC PSUR assessment reports for Procedures EMEA/H/C/PSUSA/00001369/201304 and EMEA/H/C/PSUSA/00001369/201704. Non-Kyowa Kirin data presented in the PRAC PSUR assessment report for Procedure EMEA/H/C/PSUSA/00001369/201304 identified that carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) with fentanyl did not induce any findings indicative of oncogenic potential. Evaluation of brain slides from the carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The carcinogenicity potential of fentanyl for humans is unknown, although as a result of the findings from the carcinogenicity study in rats, brain lesions is characterised as an important potential risk for PecFent.
Characterisation of the risk	Clinical trial experience: There were no reports of brain lesion during clinical trials with PecFent. Post-marketing experience: Cumulatively, 10 valid case reports describing 10 events (four fentanyl nasal spray, six unspecified fentanyl formulation) possibly pertaining to brain lesion have been identified from the post-marketing setting. This equates to a RR of 0.8 events per 10,000 PY for fentanyl nasal spray and 2.1 events per 10,000 PY for fentanyl nasal spray and unspecified fentanyl formulation combined. The reported PTs were Cognitive disorder, Motor dysfunction, Psychomotor skills impaired and Central nervous system lesion. Of the 10 events, seven were serious, for which event outcome was resolved (1), not resolved (1) and unknown (5).
Risk factors and risk groups	Unknown.
Preventability	Unknown.

Important potential risk: Brain lesions	
Impact on the benefit-risk balance of the product	Given PecFent is used to treat BTP, the presence of pre-existing malignancy makes it difficult to determine if a causal relationship exists between PecFent and brain lesions. The background history of cancer within this population makes it challenging to determine whether brain lesions are primary disease or secondary to the established cancer. Currently, there is insufficient data to consider classification as an important identified risk.
Public health impact	Unknown.

BTP=breakthrough pain; MedDRA=Medical Dictionary for Regulatory Activities; PRAC=Pharmacovigilance Risk Assessment Committee; PSUR=Periodic Safety Update Report; PT=Preferred Term; PY=patient-years; RR=reporting rate.
[a] The MedDRA terms listed were used to search the Kyowa Kirin Global Safety Database for post-marketing events pertaining to the risk.

SVII.3.2. Presentation of the missing information

Information on the missing information is summarised in Table 17 (Long-term use).

Table 17: Missing information: Long-term use

Missing information	**Long-term use**
Evidence source	A total of 145 PY of exposure to Nasalfent were accumulated in the Study CP045 Extension Period. The mean (SD) duration of Nasalfent treatment per patient was 325 (354) days with a maximum duration of 1,357 days (3 years and 8 months). The impact on individual patients is unknown due to there being insufficient data for analysis during long-term use.
Population in need of further characterisation	Long-term surviving patients with cancer experiencing BTP are at risk of long-term use of PecFent. The clinical development programme was unlikely to detect certain types of adverse reactions such as those caused by prolonged exposure; therefore, the safety profile associated with long-term use is unknown.

BTP=breakthrough pain; SD=standard deviation.

Part II: Module SVIII - Summary of the safety concerns

A summary of the safety concerns for PecFent is presented in Table 18.

Table 18: Summary of safety concerns

Important identified risks	Respiratory depression or insufficiency Local tolerability Drug misuse, abuse, diversion or dependence Off-label use Medication error Overdose Accidental exposure
Important potential risks	Brain lesions
Missing information	Long-term use

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No other routine pharmacovigilance activities are proposed beyond adverse reactions reporting and signal detection for all safety concerns referenced in Table 18.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed for any of the safety concerns referenced in Table 18.

Study CP064 (conducted to examine the utilisation and safety of PecFent when used in medical practice in France) has been completed since the last RMP update. A tabulated summary of completed studies part of the pharmacovigilance study programme is presented in Annex 2.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

PART IV: PLANS FOR POST-authorisation efficacy studies

There are no gaps in knowledge about efficacy in the target population. No post-authorisation efficacy studies are applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine risk minimisation measures

Routine risk minimisation measures for PecFent are summarised in Table 19.

Table 19: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Respiratory depression or insufficiency	Routine risk communication: SmPC Sections 4.4, 4.5, and 4.8. Package Leaflet (PL) Section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Severe respiratory depression or severe obstructive lung conditions are listed as contraindications in SmPC Section 4.3. A recommendation not to use PecFent if suffering from breathing problems is given in PL Section 2. Sections 4.4 and 4.5 of the SmPC also warn that the use of concomitant central nervous system depressants may increase the risk of respiratory depression. Other routine risk minimisation measures beyond the Product Information: Pack presentation: Clearly differentiated packaging for each formulation strength and a metered-dose pump to reduce the risk of a patient taking administering the wrong dose before adequate titration has occurred. Legal status: Prescription-only medicine.
Local tolerability	Routine risk communication: SmPC Section 4.8. PL Section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: A recommendation to switch to an alternative route of administration if recurrent episodes of epistaxis or nasal discomfort occur is given in SmPC Section 4.4. A recommendation to consult a doctor if recurrent nose bleeds occur is given in PL Section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription-only medicine.

Safety concern	Routine risk minimisation activities
Drug misuse, abuse, diversion or dependence	Routine risk communication: SmPC Sections 4.4 and 4.8. PL Section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 warns about the risk factors and consequences of abuse and misuse and recommends monitoring for signs and symptoms of drug-seeking behaviour. Considerations to be taken upon manifestation of signs and symptoms are also provided. The consequences of abuse and misuse are included in PL Section 2, as are the risk factors for abuse and also the recommendation to consult a doctor if concerned about developing dependency. Details on how to dispose of PecFent are given in SmPC Section 6.6 and PL Section 5. Other routine risk minimisation measures beyond the Product Information: Packaging: • PecFent is available in two dose strengths, 100 mcg and 400 mcg. Each dosage strength bottle is identified by a colour code. These colours (yellow for 100 mcg and violet for 400 mcg) have been chosen as they provide sufficient visual differentiation, even in colour-blind patients. • The metered-dose pump has been modified to deliver eight sprays, equivalent to only one day's supply at the maximum dosing frequency at a dose of one spray of 100 mcg or 400 mcg. • A red bar appears in a window on the device when the device is not ready to use (e.g., not primed) and moves to green when the device is ready to use (the bars are also different sizes to accommodate colour-blind individuals). • The spray pump incorporates a numerical clearly visible and audible dose counter. • The dose counter serves as a tamper-evident seal on the primary pack, and confirms to the patient when each spray has been delivered. • There is an audible click after each actuation to indicate a spray has been delivered. • The counting pump is attached to the bottle by a locking screw-thread mechanism. • The U-save bottle design has an internal U-shape base to minimise filling overage and hence minimise residual liquid in the bottle at the end of use (around 200 mcL). Legal status: Prescription-only medicine. The supply chain is tightly controlled in accordance with national regulations for controlled substances.

Safety concern	Routine risk minimisation activities
Off-label use	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: The indication of use, posology and method of administration, and contraindications are included in SmPC Sections 4.1, 4.2 and 4.3, respectively, and PL Sections 1, 3 and 2, respectively. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription-only medicine.
Medication error	Routine risk communication: SmPC Section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: The posology and method of administration is included in SmPC Section 4.2 and PL Section 3, contraindications in SmPC Section 4.3 and PL Section 2, symptoms, management and treatment of overdose in SmPC Section 4.9, and precautions for storage in SmPC Section 6.4 and PL Section 5. Other routine risk minimisation measures beyond the Product Information: Packaging: • PecFent is available in two dose strengths, 100 mcg and 400 mcg. Each dosage strength bottle is identified by a colour code. These colours (yellow for 100 mcg and violet for 400 mcg) have been chosen as they provide sufficient visual differentiation, even in colour-blind patients. • The metered-dose pump has been modified to deliver eight sprays, equivalent to only one day's supply at the maximum dosing frequency at a dose of one spray of 100 mcg or 400 mcg. • A red bar appears in a window on the device when the device is not ready to use (e.g., not primed) and moves to green when the device is ready to use (the bars are also different sizes to accommodate colour-blind individuals). • The spray pump incorporates a numerical clearly visible and audible dose counter. • The dose counter serves as a tamper-evident seal on the primary pack, and confirms to the patient when each spray has been delivered. • There is an audible click after each actuation to indicate a spray has been delivered. • The counting pump is attached to the bottle by a locking screw thread mechanism. • The U-save bottle design has an internal U-shape base to minimise filling overage and hence minimise residual liquid in the bottle at the end of use (around 200 mcL). • Each nasal spray bottle is provided in child-resistant special packaging

Safety concern	Routine risk minimisation activities
	Legal status: Prescription-only medicine.
Overdose	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: Details on dosing is included in SmPC Section 4.2 and PL Section 3. PL Section 3 also details the symptoms and consequences of overdose and instructs when to call an ambulance. Details of the symptoms, management and treatment of overdose are included in SmPC Section 4.9. Other routine risk minimisation measures beyond the Product Information: Packaging: • PecFent is available in two dose strengths, 100 mcg and 400 mcg. Each dosage strength bottle is identified by a colour code. These colours (yellow for 100 mcg and violet for 400 mcg) have been chosen as they provide sufficient visual differentiation, even in colour-blind patients. • The metered-dose pump has been modified to deliver eight sprays, equivalent to only one day's supply at the maximum dosing frequency at a dose of one spray of 100 mcg or 400 mcg. Legal status: Prescription-only medicine.
Accidental exposure	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 and PL Section 2 warn that PecFent can be fatal to a child. Sections 4.2 and 6.4 of the SmPC and PL Sections 2 and 5 include information on storing PecFent in a child-resistant container. SmPC Section 6.6 and PL Section 5 also instruct how to safely dispose of PecFent. Symptoms of overdose and the treatment of overdose in the opioid-naïve person are included in SmPC Section 4.9. Other routine risk minimisation measures beyond the Product Information: Packaging: • PecFent is available in two dose strengths, 100 mcg and 400 mcg. Each dosage strength bottle is identified by a colour code. These colours (yellow for 100 mcg and violet for 400 mcg) have been chosen as they provide sufficient visual differentiation, even in colour-blind patients. • The metered-dose pump has been modified to deliver eight sprays, equivalent to only one day's supply at the maximum dosing frequency at a dose of one spray of 100 mcg or 400 mcg. • A red bar appears in a window on the device when the device is not ready to use (e.g., not primed) and moves to green when the device is ready to use (the bars are also different sizes to accommodate colour-blind individuals).

Safety concern	Routine risk minimisation activities
	• The spray pump incorporates a numerical clearly visible and audible dose counter. • The dose counter serves as a tamper-evident seal on the primary pack, and confirms to the patient when each spray has been delivered. • There is an audible click after each actuation to indicate a spray has been delivered. • The counting pump is attached to the bottle by a locking screw thread mechanism. • The U-save bottle design has an internal U-shape base to minimise filling overage and hence minimise residual liquid in the bottle at the end of use (around 200 mcL). • Each nasal spray bottle is provided in child-resistant special packaging. Legal status: Prescription-only medicine. The supply chain is tightly controlled in accordance with national regulations for controlled substances.
Important potential risks	
Brain lesions	Routine risk communication: SmPC Section 5.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription-only medicine.
Missing information	
Long-term use	Routine risk communication: SmPC Section 4.6 and PL Section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription-only medicine.

PL=Package Leaflet; SmPC=Summary of Product Characteristics.

V.2 Additional risk minimisation measures

Educational materials – Physician Guide, Pharmacist Guide and Patient/Carer Guide

Objectives

To minimise the risks of misuse, abuse, diversion or dependence; off-label use; medication errors; overdose and accidental exposure by providing education to physicians, pharmacists and patients/carers.

Rationale for the additional risk minimisation activity:

Educational materials are available to prescribing physicians and dispensing pharmacists to:

- facilitate the screening of patients for risks of abuse of prescription pain medication
- ensure the following of accepted guidelines for the management of high-risk patients
- highlight the importance of appropriate patient selection.

Educational materials are available to prescribing physicians, pharmacists, patients and their carers to:

- highlight the importance of appropriate use of PecFent
- highlight the importance of following instructions carefully
- minimise the risks of misuse, abuse, diversion or dependence, off-label use, medication errors, overdose, and accidental exposure which have potentially serious clinical consequences.

Educational materials are required to ensure prescribers and patients are as knowledgeable as possible regarding the safe and effective use of PecFent.

Target audience and planned distribution path:

Physicians, pharmacists, and patients/carers exposed to PecFent.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be evaluated using routine pharmacovigilance activities, i.e., adverse reaction reporting and signal detection activities. Such activities are performed on an ongoing basis to identify any specific safety signals that would require immediate/further action. The criteria for judging the success of the educational materials will be demonstrated by a high level of understanding of the correct utilisation of PecFent in addition to a low proportion of cases received against patient exposure. The results of the effectiveness evaluation will be presented within the relevant section of the PSUR.

Note: The training of field representatives has been removed as an additional risk minimisation measure within this version of the RMP and are therefore not included within Section V.2 Additional risk minimisation measures. Field representatives are trained in the risk minimisation measures as part of standard practice and are made aware of the non-promotional nature of educational materials which are the additional risk minimisation measures. In addition, Dear Doctor letters are removed as an additional risk minimisation measure within this version of the RMP as Kyowa Kirin has not used this additional risk minimisation measure. If, in the future, any need arises for this additional risk minimisation measure because of a new or changed risk, Kyowa Kirin would communicate appropriately with the regulatory agencies to implement such a measure.

V.3 Summary of risk minimisation measures

Risk minimisation measures for the safety concerns are summarised in Table 20.

Table 20: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Respiratory depression or insufficiency	Routine risk minimisation measures: SmPC Sections 4.4, 4.5, and 4.8. PL Section 4. SmPC Section 4.3 lists a contraindication. PL Section 2 recommends not to use PecFent if suffering from breathing problems. SmPC Section 4.4 and 4.5 warns of the concomitant use of central nervous system depressants. Pack presentation. Legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Local tolerability	Routine risk minimisation measures: SmPC Section 4.8. PL Section 4. SmPC Section 4.4 provides a recommendation in the case of recurrent episodes of epistaxis or nasal discomfort. PL Section 2 recommends consulting a doctor in the case of recurrent nose bleeds. Legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Drug misuse, abuse, diversion or dependence	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8. PL Section 4. SmPC Section 4.4 warns about the risk factors and consequences of abuse and misuse and recommends monitoring for signs and symptoms of drug-seeking behaviour. Considerations to be taken upon manifestation of signs and symptoms are also provided. PL Section 2 provides the consequences of abuse and misuse, risk factors for abuse, and the recommendation to consult a doctor if concerned about developing dependency. SmPC Section 6.6 and PL Section 5 provides details on how to dispose of PecFent. Pack presentation. Legal status. Additional risk minimisation measures: Physician guide. Pharmacist guide. Patient/Carer guide.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Off-label use	Routine risk minimisation measures: The indication of use, posology and method of administration, and contraindications are included in SmPC Sections 4.1, 4.2 and 4.3, respectively, and PL Sections 1, 3 and 2, respectively. Legal status. Additional risk minimisation measures: Physician guide. Pharmacist guide. Patient/Carer guide.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Medication error	Routine risk minimisation measures: SmPC Section 4.8. SmPC Section 4.2 and PL Section 3 provide the posology and method of administration. SmPC Section 4.3 and PL Section 2 provide details of contraindications.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC Section 4.9 details the symptoms, management and treatment of overdose. SmPC Section 6.4 and PL Section 5 detail precautions for storage. Pack presentation. Lega status. Additional risk minimisation measures: Physician guide. Pharmacist guide. Patient/Carer guide.	
Overdose	Routine risk minimisation measures: SmPC Section 4.2 and PL Section 3 provide dosing details. SmPC Section 4.9 details the symptoms, management and treatment of overdose. Pack presentation. Legal status. Additional risk minimisation measures: Physician guide. Pharmacist guide. Patient/Carer guide.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Accidental exposure	Routine risk minimisation measures: SmPC Section 4.4 and PL Section 2 warn that PecFent can be fatal to a child. Sections 4.2 and 6.4 of the SmPC and PL Sections 2 and 5 include information on storing PecFent in a child-resistant container. SmPC Section 6.6 and PL Section 5 instruct how to safely dispose of PecFent. SmPC Section 4.9 details the symptoms of overdose and the treatment of overdose in the opioid-naïve person. Pack presentation. Legal status. Additional risk minimisation measures: Physician guide. Pharmacist guide. Patient/Carer guide.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
Brain lesions	Routine risk minimisation measures: SmPC Section 5.3. Legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing information		
Long-term use	Routine risk minimisation measures: SmPC Section 4.6. Legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

PL=Package Leaflet; SmPC=Summary of Product Characteristics.

PART VI: SUMMARY OF the Risk Management Plan

Summary of Risk Management Plan for PecFent (fentanyl citrate)

This is a summary of the Risk Management Plan for PecFent. The Risk Management Plan details important risks of PecFent, and how these risks can be minimised, and how more information will be obtained about PecFent's risks and uncertainties (missing information).

PecFent's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how PecFent should be used.

This summary of the Risk Management Plan for PecFent should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of PecFent's Risk Management Plan.

I. The medicine and what it is used for

PecFent is authorised for the management of breakthrough pain (BTP) in adult patients using opioid therapy for chronic cancer pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain (see SmPC for the full indication). It contains fentanyl (as citrate) as the active substance and is taken via intranasal administration.

Further information about the evaluation of PecFent's benefits can be found in PecFent's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/pecfent.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important identified risks of PecFent, together with measures to minimise such 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 PL 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.

- Formulation of the medicine.
- 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 PecFent, 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 Periodic Safety Update Report 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 PecFent is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of PecFent 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 PecFent. 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	Respiratory depression or insufficiency Local tolerability Drug misuse, abuse, diversion or dependence Off-label use Medication error

List of important risks and missing information	
	Overdose Accidental exposure
Important potential risks	Brain lesions

List of important risks and missing information	
Missing information	Long-term use

II.B Summary of important risks

Important identified risk: Respiratory depression or insufficiency	
Evidence for linking the risk to the medicine	In common with other opioid agonists, fentanyl can induce respiratory depression. It is well recognised that the potential for respiratory depression is greater in patients who are not receiving opioids and that use of fentanyl in these patients may cause more serious adverse reactions. Respiratory depression can potentially be life-threatening and may eventually result in respiratory failure with a fatal outcome. Respiratory depression or insufficiency is therefore considered an important identified risk for PecFent.
Risk factors and risk groups	Patients at increased risk of developing respiratory depression include those who: • Are opioid-naïve • Are elderly • Are debilitated

	• Have underlying pulmonary pathology • Have impaired respiratory drive of sleep apnoea • Are also receiving concomitant sedatives
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4, 4.5, and 4.8. PL Section 4. SmPC Section 4.3 lists a contraindication. PL Section 2 recommends not to use PecFent if suffering from breathing problems. SmPC Section 4.4 and 4.5 warns of the concomitant use of central nervous system depressants. Pack presentation. Legal status. Additional risk minimisation measures: None.

PL=Package Leaflet; SmPC=Summary of Product Characteristics.

Important identified risk: Local tolerability	
Evidence for linking the risk to the medicine	Because of the route of administration of PecFent, local tolerability is a potential issue due to the direct action of the drug on the nasal mucosa. However, clinical data have not identified this as a real issue as nasal tolerability of PecFent was high. Nonetheless, serious nasal AEs of epistaxis and nasal congestion were reported from clinical trials; post-marketing safety data are in-line with that reported from the clinical trials. It is therefore considered that there is sufficient information to classify local tolerability as an important identified risk for PecFent.
Risk factors and risk groups	No risk groups or risk factors have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8. PL Section 4. SmPC Section 4.4 provides a recommendation in the case of recurrent episodes of epistaxis or nasal discomfort. PL Section 2 recommends consulting a doctor in the case of recurrent nose bleeds. Legal status. Additional risk minimisation measures: None.

PL=Package Leaflet; SmPC=Summary of Product Characteristics.

Important identified risk: Drug misuse, abuse, diversion or dependence	
Evidence for linking the risk to the medicine	Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. However, iatrogenic addiction following therapeutic use of opioids is known to occur. In addition, repeated use of PecFent may lead to opioid use disorder. Furthermore, the potential clinical consequences of abuse and intentional misuse are serious and can include overdose, a risk of respiratory depression, death and/or physical and psychological dependence. However, when opioids are used under medical supervision as part of analgesia, the risk of abuse or misuse is considered low. Data from the United States Drug Enforcement Administration indicate that fentanyl is mainly diverted via pharmacy theft, fraudulent prescriptions, and illicit distribution by patients and registrants. Hundreds of diverted items are identified in the United States each year. The phenomenon is also a concern in Europe, although precise figures are not available because systematic searches for fentanyl are not performed. Deaths associated with fentanyl diversion, however, have been reported in the United Kingdom and several European Union countries, including Sweden and Italy. It is therefore considered that there is sufficient information to classify Drug misuse, abuse, diversion and dependence as an important identified risk for PecFent.
Risk factors and risk groups	Those at an increased risk of misuse include: • Patients who have a history of substance (drug) abuse • Patients and prescribers who use PecFent off-label
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8. PL Section 4. SmPC Section 4.4 warns about the risk factors and consequences of abuse and misuse and recommends monitoring for signs and symptoms of drug-seeking behaviour. Considerations to be taken upon manifestation of signs and symptoms are also provided. PL Section 2 provides the consequences of abuse and misuse, risk factors for abuse, and the recommendation to consult a doctor if concerned about developing dependency. SmPC Section 6.6 and PL Section 5 provides details on how to dispose of PecFent. Pack presentation. Legal status. <u>Additional risk minimisation measures:</u> Physician guide. Pharmacist guide. Patient/Carer guide.

PL=Package Leaflet; SmPC=Summary of Product Characteristics.

Important identified risk: Off-label use	
Evidence for linking the risk to the medicine	PecFent is indicated for the management of BTP in adult patients who are already receiving maintenance therapy for chronic cancer pain. It is contraindicated in the treatment of acute pain other than BTP. The potential clinical consequences of off-label use are serious and can include a risk of respiratory depression and/or physical and psychological dependence. In addition, there is a potential for lack of effect or AEs when used outside of an indication for which there is no clinical data. It is therefore considered that there is sufficient information to classify off-label use as an important identified risk for PecFent.
Risk factors and risk groups	Not known.
Risk minimisation measures	Routine risk minimisation measures: The indication of use, posology and method of administration, and contraindications are included in SmPC Sections 4.1, 4.2 and 4.3, respectively, and PL Sections 1, 3 and 2, respectively. Legal status. Additional risk minimisation measures: Physician guide. Pharmacist guide. Patient/Carer guide.

AE=adverse event; BTP=breakthrough pain; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

Important identified risk: Medication error	
Evidence for linking the risk to the medicine	Medication errors refer to unintentional prescribing/administration and or dispensing of PecFent, in addition to incorrect dose and route of administration. The potential consequences associated with medication errors can be serious if associated with an AE, and include the risk of respiratory depression or a lack of pain control. It is therefore considered that there is sufficient information to classify medication error as an important identified risk for PecFent.
Risk factors and risk groups	Non-adults and adults who were prescribed PecFent.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8. SmPC Section 4.2 and PL Section 3 provide the posology and method of administration. SmPC Section 4.3 and PL Section 2 provide details of contraindications. SmPC Section 4.9 details the symptoms, management and treatment of overdose. SmPC Section 6.4 and PL Section 5 detail precautions for storage.

Important identified risk: Medication error	
	Pack presentation. Lega status. <u>Additional risk minimisation measures:</u> Physician guide. Pharmacist guide. Patient/Carer guide.

AE=adverse event; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

Important identified risk: Overdose		
Evidence for linking the risk to the medicine	It is well known that all opioid mu-receptor agonists, including fentanyl, produce dose-dependent respiratory depression and as with other potent opioids, fentanyl has been associated with cases of serious and fatal respiratory depression in opioid non-tolerant individuals. The potential clinical consequences associated with overdose are serious if associated with an AE. It is therefore considered that there is sufficient information to classify overdose as an important identified risk for PecFent.	
Risk factors and risk groups		Non-adults and adults who we

Important identified risk: Overdose		
		prescribed PecFent.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and PL Section 3 provide dosing details. SmPC Section 4.9 details the symptoms, management and treatment of overdose. Pack presentation. Legal status. Additional risk minimisation measures: Physician guide. Pharmacist guide. Patient/Carer guide.	

AE=adverse event; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

Important identified risk: Accidental exposure	
Evidence for linking the risk to the medicine	Accidental exposure refers to the accidental exposure of a person (adult or child) for whom PecFent was not prescribed. The impact on the individual accidently exposed to PecFent is potentially serious. Respiratory depression may occur, particularly in non-opioid-tolerant individuals, and has the potential of a fatal outcome. It is therefore considered that there is sufficient information to classify accidental exposure as an important identified risk for PecFent.

Important identified risk: Accidental exposure	
Risk factors and risk groups	Those at an increased risk of accidental exposure include individuals who were not prescribed PecFent, who are able to gain access or be exposed to PecFent.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and PL Section 2 warn that PecFent can be fatal to a child. Sections 4.2 and 6.4 of the SmPC and PL Sections 2 and 5 include information on storing PecFent in a child-resistant container. SmPC Section 6.6 and PL Section 5 instruct how to safely dispose of PecFent. SmPC Section 4.9 details the symptoms of overdose and the treatment of overdose in the opioid-naïve person. Pack presentation. Legal status. Additional risk minimisation measures: Physician guide. Pharmacist guide. Patient/Carer guide.

PL=Package Leaflet; SmPC=Summary of Product Characteristics.

Important potential risk: Brain lesions	
Evidence for linking the risk to the medicine	Non-Kyowa Kirin data presented in the Pharmacovigilance Risk Assessment Committee Periodic Safety Update Report assessment report for Procedure EMEA/H/C/PSUSA/00001369/201304 identified that carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) with fentanyl did not induce any findings indicative of oncogenic potential. Evaluation of brain slides from the carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The carcinogenicity potential of fentanyl for humans is unknown, although as a result of the findings from the carcinogenicity study in rats, brain lesions is characterised as an important potential risk for PecFent.
Risk factors and risk groups	Unknown.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3. Legal status. Additional risk minimisation measures: None.

SmPC=Summary of Product Characteristics.

Missing information: Long-term use	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6. Legal status. Additional risk minimisation measures: None.

SmPC=Summary of Product Characteristics.

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 PecFent.

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

There are no studies required for PecFent.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Available in electronic format only.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

No additional pharmacovigilance activities are proposed or ongoing. Completed studies that are part of the pharmacovigilance study programme are summarised below.

Table 1: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of final study report submission Link to report
Study to measure the effectiveness of PecFent Risk Management Plan in ensuring physician training on the safe and appropriate use of the product (Study CP066-11)	• Assess level of understanding of physicians who have prescribed PecFent of the potential risks of the product • Assess knowledge and use of the training materials • Collect and assess physician's observations of misuse, abuse, diversion, overdose, and accidental exposure.	• Effectiveness of educational programme. • Potential risks (misuse, abuse, diversion, overdose, and accidental exposure).	30 April 2013 Link to final study report
UK study protocol: A modified prescription event monitoring study on fentanyl nasal spray (PecFent) for the management of breakthrough cancer pain (M-PEM study).	• To examine the utilisation and safety of PecFent when used in general medical practice in the UK	• Effectiveness of educational programme. • Drug utilisation characteristics (demographics, indications, co-morbidities, pain origin)	11 July 2013 Link to final study report
A drug utilisation study (DUS) on fentanyl nasal spray (PecFent®) for the management of breakthrough pain in cancer patients (Study CP064)	• To examine the utilisation and safety of fentanyl in nasal spray (PecFent®) when used in general medical practice in France	• Effectiveness of the educational programme. • Drug utilisation characteristics (demographics, indications, co-morbidities, pain origin)	01 October 2014 Link to final study report

DUS=drug utilisation study; UK=United Kingdom.

Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 – Protocols for proposed and on-going studies in Risk Management Plan Part IV

Not applicable.

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

Prior to the launch or use of PecFent in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the Educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The MAH shall ensure that, all physicians, pharmacists and patients expected to prescribe/dispense/use PecFent 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

- PecFent 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, patient's 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 PecFent 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 PecFent.

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 for periodic review by prescribers
    - Encouragement for reporting 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 PecFent must critically select the patients and counsel them on:

- Instructions for use of PecFent.
- 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 PecFent. Please complete all of the following before prescribing PecFent:

- Ensure that all elements of the approved indication are fulfilled.
- Provide instructions for using PecFent to patient and/or carer.
- Ensure the patient reads the package leaflet inside the PecFent box.

- Supply the patient with the PecFent patient brochure provided covering the below:
    - Cancer and Pain.
    - PecFent. What is it? How do I use it?
    - PecFent. Risk of misuse.
- Explain the risks of using more than the recommended amount of PecFent.
- Explain the use of the dose monitoring cards.
- Advise the patients 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.
- Remind the patient and/or caregiver that they should ask their doctor if they have any questions or concerns about how to use PecFent 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 recognized.
- Pharmacist must be familiar with the educational materials before is given to the patient.
- PecFent is not interchangeable with other fentanyl products.

The pharmacist dispensing PecFent must counsel patients on:

- Instructions for use of PecFent.
- The pharmacist must inform the patients that in order to prevent theft and misuse of PecFent they have to keep it in a safe place to avoid misuse and diversion.
- The pharmacist must make use of the checklist for pharmacists.

Dispensing checklist

Required actions before supplying PecFent. Please complete the following before PecFent is supplied:

- Ensure that all elements of the approved indication are fulfilled.
- Provide instructions for using PecFent to the patient and/or carer.
- Ensure the patient reads the package leaflet inside PecFent carton box.
- Supply the patient with the PecFent patient brochure provided covering the below:
    - Cancer and Pain.
    - PecFent. What is it? How do I use it?
    - PecFent. Risks of misuse.
- Explain the risks of using more than the recommended amount of PecFent.
- 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

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, as appropriate.

Annex 7 – Other supporting data (including referenced material)

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Annex 8 – Summary of changes to the Risk Management Plan over time

Version	Approval date	Change
1.0	04 February 2009	Important identified risks: Respiratory depression Circulatory depression Important potential risks: Local tolerability Drug misuse, abuse or diversion Accidental exposure Off label use Missing information: None
2.0	24 April 2009	As above
3.0	08 March 2010	As above
4.0	10 September 2010	As above
5.0	31 August 2012	As above

Version	Approval date	Change
6.0	30 April 2013	Important identified risks: Respiratory depression Circulatory depression Local tolerability Drug misuse, abuse or diversion Accidental exposure Off label use Important potential risks: None Missing information: Use in children
7.0	02 July 2014	Important identified risks: Respiratory depression or insufficiency Circulatory depression, including severe bradycardia, hypotension, and shock Local tolerability Drug misuse, abuse, diversion or dependence Off-label use Medication error Overdose Accidental exposure Potential risks Brain lesions Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs Missing information Pregnant and breastfeeding women Paediatric population Long term use Patients with renal or hepatic impairment

Version	Approval date	Change
8.0	To be submitted	Conversion to Good Pharmacovigilance Practices Module V Rev. 2 <u>Safety concerns</u> - Removal of 'Circulatory depression, including severe bradycardia, hypotension and shock' from important identified risks - Removal of 'Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs' from important potential risks - Removal of 'paediatric population', 'pregnant and breastfeeding women' and 'patients with renal or hepatic impairment' from missing information <u>Pharmacovigilance Plan</u> - Study CP064 was removed as the study has been completed and the obligation has been fulfilled <u>Risk minimisation measures</u> - The key messages for the educational materials were updated as recommended by the Pharmacovigilance Risk Assessment Committee (EMEA/H/C/PSUSA/00001369/202004) - The training of field representatives has been removed as an additional risk minimisation measure. - Dear Doctor letters have been removed as an additional risk minimisation measure.