



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Fentanyl (as citrate)

Proprietary Product Name: PecFent

Sponsor: ERA Consulting (Australia) Pty Ltd¹

March 2013

TGA Health Safety
Regulation

¹ AstraZeneca Pty Ltd is now the sponsor of this product in Australia.

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- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to product submission

Submission details

<i>Type of Submission</i>	Major Variation - New dosage form
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	31 July 2012
<i>Active ingredient:</i>	Fentanyl (as citrate)
<i>Product Name:</i>	PecFent
<i>Sponsor's Name and Address:</i>	ERA Consulting (Australia) Pty Ltd 88 Jephson St, Toowong, QLD 4066 ²
<i>Dose form:</i>	Nasal spray
<i>Strengths:</i>	1.0 mg/mL and 4.0 mg/mL
<i>Container:</i>	Glass bottle fitted with a metered-dose spray pump
<i>Pack sizes:</i>	1 or 4 bottles per carton
<i>Approved Therapeutic use:</i>	The management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain.
<i>Routes of administration:</i>	Intranasal
<i>Dosage:</i>	The initial dose of PecFent nasal spray to treat episodes of breakthrough cancer pain is 100 µg (one spray). Patients who need to titrate to a higher dose due to lack of effect can be instructed to use two sprays (one in each nostril) and if not successful to change to the higher dose 400 µg spray. Patients must wait at least 2 h between doses and are limited to 4 doses per day.
<i>ARTG Numbers:</i>	185934, 185935

Product background

This AusPAR describes the application by ERA Consulting (Australia) Pty Ltd (the sponsor) on behalf of the market authorisation holder Archimedes Pharmaceuticals Ltd to register a new dose form of fentanyl; fentanyl nasal spray (PecFent®) in two dosage strengths of 100 µg and 400 µg. Post-registration sponsorship has been transferred to AstraZeneca Pty Ltd. Fentanyl nasal spray represents a new route of administration for fentanyl citrate. Fentanyl citrate is a narcotic analgesic and it is currently marketed in Australia as lozenges (Actiq; 200, 400, 600, 800, 1200 and 1600 mg strengths), patches

² AstraZeneca Pty Ltd, Alma Road, NSW 2113 is now the sponsor of this product in Australia.

(Durogesic; 12, 25, 50, 75 and 100 µg/hr strengths) and a solution for injection (Sublimaze, Fentanyl; 50 µg/mL strength).

The sponsor proposed the following indication in their application letter:

PecFent is indicated for the “management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain”.

The proposed tradename for the product is “PecFent” but it is also called “NasalFent” in most of the study reports.

Regulatory status

Fentanyl (as the citrate salt) is currently registered in Australia in a number of dosage forms including injections, transdermal delivery systems and oral lozenges.

At the time of this AusPAR, the registered indications for the other Fentanyl products in Australia were as follows:

- Lozenge: *“Breakthrough pain in cancer patients already receiving and tolerant to opioid therapy”.*
- Patch: *“Management of chronic pain”.*
- Injection: *“Short duration analgesia in anaesthesia (premed, induction, maintenance, immediate post op); analgesic supplement to general, regional anaesthesia; combination with neuroleptic for anaesthesia induction (premed), maintenance (adjunct).”*

PecFent was approved via the Centralised Procedure in the European Union (EU) on 31 August 2010. The Rapporteur was Germany (BfArM) and the Co- Rapporteur was France (afssaps). PecFent was submitted under the trade name Lazanda in the USA and approval was granted by the FDA on 30 June 2011.

The product has been launched in the United Kingdom (UK), Ireland, Italy, Poland, Spain, France, and Germany.

The approved indication in the USA, where the product is marketed under the trade name “Lazanda” is:

“Lazanda is an opioid analgesic indicated only for the management of breakthrough pain in cancer patients, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.”

There is one other product approved in Australia for this indication, Actiq®. The indication for this product is:

*“Management of breakthrough cancer pain in patients with malignancies who are already receiving **and are tolerant to opioid therapy for their underlying persistent cancer pain.**”*

The difference in indication is highlighted in bold.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

List of abbreviations used in this AusPAR

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve from time zero to infinity
AUC ₀₋₂₄	area under the plasma concentration time curve from time 0 to 24 h after dosing
AUC _t	area under the plasma concentration time curve from time zero to time of last quantifiable plasma concentration
BMI	body mass index
BP	blood pressure
BTCP	breakthrough cancer pain
CI	confidence interval
CL	confidence limits
C _{max}	maximum plasma concentration
C _{last}	last plasma concentration
CSR	clinical study report
CV(%) or %CV	coefficient of variation expressed as a percentage
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e-diary	electronic diary
EEG	electro encephalogram
FCNS	fentanyl citrate nasal spray
Frel	relative bioavailability
fL	femtolitre
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IRMS	immediate release morphine sulphate
ITT	intention to treat
IU	International Units

λ_z	apparent terminal phase rate constant
LC/MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LOCF	last observation carried forward
LLOQ or LOQ	lower limit of quantification
LS means	least squares means
MAO	monoamine oxidase
maxTOTPAR	maximum total pain relief
mITT	modified intent-to-treat
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
NasalFent	trade name for FCNS, also called PecFent
OTFC	oral transmucosal fentanyl citrate
PCV	packed cell volume
PDIF	p-values for differences in LS means
PK	pharmacokinetic
PI	pain intensity
PID	pain intensity difference
PP	per protocol
PR	pain relief
PSUR	Periodic Safety Update Report
SAE	serious adverse event
SAR	seasonal allergic rhinitis
SD	standard deviation
SE	standard error
SeAE	seasonal allergic rhinitis
SGPT	serum glutamate pyruvate transaminase
SPID	summed pain intensity difference
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
$T_{1/2}$	terminal half life
T_{max}	time to maximum plasma concentration
TOTPAR	total pain relief
TNSS	total nasal symptom score

II. Quality findings

Drug substance (active ingredient)

Fentanyl citrate is a well established drug substance. A European Certificate of Suitability was submitted for drug substance from the manufacturing source and satisfactory controls are applied by the manufacturer of PecFent.

Drug product

PecFent nasal spray consists of a practically clear to clear, colourless, non-sterile aqueous solution of fentanyl (as citrate) 1.0 mg/mL or 4.0 mg/mL plus excipients in a multi-dose container, to which is attached a metered-dose nasal spray pump with a visual and audible spray counter. Each actuation is designed to deliver a spray of 100 µL of solution containing fentanyl citrate equivalent to 100 µg or 400 µg fentanyl base, respectively.

It is presented in a 5.3 mL capacity, Type I glass bottle sealed with a locking screw closure. The bottle has a U-shaped internal chamber to minimise fill volume (the actual fill volume is 1.55 mL).

Prior to use, the pump is primed by actuating four times. Once primed, the pump will deliver eight sprays before it locks. Approximately 0.4 mL of solution remains in the bottle after it locks.

In addition to fentanyl citrate (1.57 or 6.28 mg/mL³), the solution contains a new proprietary gelling agent, , as well as mannitol to adjust the tonicity, hydrochloric acid and/or sodium hydroxide to adjust the pH to 4.0 and the antimicrobial preservatives phenethyl alcohol and propyl hydroxybenzoate.

The gelling agent is a mixture of sucrose and LM pectin). When the spray droplets of drug product are deposited in the nose, the LM pectin interacts with calcium ions in the nasal mucosal fluid to form a gel. Fentanyl diffuses from the pectin gel and is absorbed systemically through the nasal mucosa.

The droplet spray size is critical in order to ensure that the droplets are deposited in the nose and not breathed into the lungs. Droplet size is monitored in each batch by laser diffraction.

A shelf life of 3 years below 25°C has been established for PecFent. Once opened and primed, the product must be used within 14 days or discarded. A bottle must also be discarded if it has been more than 5 days since its last use.

Biopharmaceutics

During product development, the proposed product and two other experimental formulations (100 µg of each) were compared in a bioavailability study (CP037/02) with 200 µg of an oral transmucosal fentanyl citrate lozenge (“Actiq”) obtained in the United Kingdom (UK). An equivalent product is registered in Australia, although it is not known whether the UK and Australian Actiq products are identical. On a dose-normalised basis, the proposed PecFent product was found to have a 2.3 fold higher peak plasma concentration (C_{max}) than Actiq and a 1.3 fold higher area under the plasma concentration time curve (AUC).

³ Sponsor comment: “Equivalent to 1.0 and 4.0 mg/mL of fentanyl base.”

It should be noted that the evaluator's recalculations of the AUC_{obs} (AUC_{∞} based on extrapolation using the last observed concentration) results for this study were in error. The AUC_{obs} ratio for PecFent/Actiq (treatments B/D) has since been re-determined as 144.5% (90% CI 121.4-171.9%). This ratio is slightly higher than the 130% determined by the company but confirms that PecFent gives significantly higher AUC results than Actiq.

A later study (CP042/05), which compared various dose levels of PecFent with 200 µg Actiq, showed a 2.3 fold higher C_{max} and a 1.2 fold higher AUC, independent of dose in the range 100–800 µg.

Both the PecFent and Actiq products showed a high degree of inter-subject variability.

The company provided a detailed justification for not performing an absolute bioavailability study on PecFent. The justification has been referred to the clinical Delegate.

Quality summary and conclusions

A number of matters were raised with the sponsor following the initial evaluation of this submission. All matters have since been satisfactorily resolved except that Good Manufacturing Clearance (GMP) clearance had not yet been provided for the site that performs leachables testing on the finished product, including testing for levels of formaldehyde. Subject to the provision of satisfactory GMP clearance for that site, there are no objections in respect of Chemistry, Manufacturing and Controls to registration of this product.⁴

The submission was referred to the Pharmaceutical Subcommittee of the Advisory Committee on Prescription Medicines (ACPM) prior to the scheduled ACPM meeting.

III. Nonclinical findings

Introduction

Overall quality of the nonclinical dossier

The nonclinical submission included new studies on the pharmacokinetics and repeat-dose toxicity of intranasal fentanyl as well as published data supporting claims regarding the pharmacology, carcinogenicity, genotoxicity and teratology of fentanyl. The overall organisation of the nonclinical dossier was satisfactory, although there were some aspects of the submission that hampered assessment, including the lack of clarity of scanned documents. These issues were addressed in response to a TGA request for information.

Pharmacology

Primary pharmacology, secondary pharmacodynamics and safety pharmacology

For nonclinical data related to these areas, the submission relies on published studies and Summary Basis of Approval (SBA) documents published by the US FDA in connection with the New Drug Application (NDA) approvals for Actiq® and Fentora® (both oral transmucosal fentanyl citrate products approved by FDA). There was nothing in the new studies submitted in relation to pharmacokinetics and repeat dose toxicity using the

⁴ Sponsor comment: "GMP clearance was provided by the sponsor prior to registration."

formulation and route intended for PecFent® to suggest that there would be any differences in the pharmacological actions of the drug from those seen with other forms and routes. No new safety issues were noted.

Pharmacokinetics

Absorption: The absorption profile of intranasal fentanyl was found to be comparable in rats and dogs with time to peak plasma concentration (T_{max}) values of approximately 0.5 h in rats and later in dogs. Exposure (AUC and C_{max}) did not appear to increase with repeat dosing over the 39 weeks in the pivotal repeat dose toxicity study in dogs. The demonstrated exposure in rats and dogs following intranasal administration showed that these species were appropriate choices for toxicological investigations.

Distribution: Fentanyl is highly lipophilic and is distributed in tissues rapidly after administration. The high affinity for fat indicates the possibility of accumulation with repeat dose administration. Fentanyl is known to be plasma protein bound at approximately 80%, predominantly to alpha-1-acid glycoprotein.

Metabolism: Fentanyl is metabolised mainly in the liver of humans and other mammals by cytochrome P450 isozyme CYP3A4 to norfentanyl and other minor metabolites.

Excretion: Fentanyl, once metabolised in the liver, is primarily excreted in the urine.

Conclusion: The pharmacokinetic profiles in rats, dogs and humans (from Phase I data) were sufficiently similar to allow them to serve as appropriate models for the assessment of drug toxicity in humans.

Pharmacokinetic drug interactions

Fentanyl is known to be metabolised by CYP3A4 so the potential for interaction with other drugs metabolised by this enzyme exists for this formulation as with other fentanyl formulations.

Toxicology

Acute toxicity

No new studies on acute toxicity in animals were submitted, the submission again relying on published data. Some acute toxicity with the present formulation and route of administration was seen at the highest doses in the range-finding (WFEN/P33/05) and 26 week (WFEN/P37/05) studies in rats. The cause(s) of this toxicity was (were) not clear. In WFEN/P33/05 and WFEN/P37/05 the deaths occurred rapidly in animals given the highest doses (0.96 mg/kg/day in WFEN/P33/05, 0.64 mg/kg/day in WFEN/P37/05). The rapid deaths all occurred at doses somewhat below those reported to be fatal in the intravenous (IV) studies summarised in the Actiq® NDA. The acute toxicity of fentanyl is well documented in previous investigations.

Repeat-dose toxicity

The major toxicity of fentanyl relates principally to its basic effect on opioid receptors which can lead to fatal respiratory depression. Other behavioural changes are seen with chronic dosing in animals which are also likely to be related to effects at opioid receptors. The opioid-derived toxicological profile of fentanyl has been well documented.

Repeat dose toxicity was assessed in 3 studies in rats (7 day dose-ranging; 3 months + 28 day recovery; 6 months + 28 day recovery) and 2 studies in dogs (10 day MTD; 39 weeks +

28 day recovery). All studies used intranasal administration of the formulation intended for clinical use. Although proposed clinical use can involve 'as needed' (PRN) dosing, dosing in the nonclinical studies was set to a fixed twice daily regimen, which maximised the potential for eliciting any toxic effects. Pivotal studies were Good Laboratory Practice (GLP) compliant and performed with rodent and non rodent species and adequate group sizes. The only inconsistency with European Union (EU) guidelines was the use of only a single route of administration in the toxicity studies but this is acceptable given the extensive animal literature and the current widespread clinical use of fentanyl in other formulations. In the 3 month study in rats (WFEN/P34/05) three animals died, one death occurring in each of Weeks 2, 4 and 5 of treatment. All the deaths occurred in high dose (HD) males (0.52 mg/kg/day) and were associated with pathological findings in the gastrointestinal (GI) tract. Day 1 decedents in the 6 month rat study (WFEN/P37/05) also showed gastric lesions. In the Actiq® NDA the summary of repeat dose toxicity from earlier documents relating to Sublimaze® and Innovar® is redacted and the summary table of these older data in the Fentora® NDA does not contain much detail. One death occurred in a female dog receiving the mid dose in Day 2 of the 39 week study following tremors and convulsions. Dose related convulsions in dogs following IV fentanyl are mentioned in the table summarising repeat-dose toxicity studies in relation to Innovar® although no deaths were recorded. No other toxicological findings of significance were seen in the repeat-dose toxicity studies.

Relative exposure

Exposure ratios (tabulated below) have been calculated based on animal AUC_{x-24h} /human AUC for single doses at the four proposed dose levels (100, 200, 400, 800 µg). The three Good laboratory practice (GLP) studies are included in the table. Exposure measures of AUC were taken from the last day of the chronic studies and male and female values were averaged to enable comparison to the clinical data. Human reference values are from Clinical Study CP042/05 where subjects were given four escalating doses of Fentanyl Citrate Nasal Spray (100, 200, 400, 800 µg) under naltrexone block.

At the 100 µg single dose, exposure ratios achieved in the animal studies at the highest tested doses were acceptable in both rat (4-8) and dog (32) studies but were much lower at the highest clinical dose of 800 µg (rat approximately 1, dog approximately 5). However, up to four doses daily are proposed clinically, which would reduce animal/human relative exposures (over 24 h) by up to 4 fold. Thus, at the maximum recommended human dose (MRHD) of 3200 µg/day, the relative exposures would be approximately 0.25 (rat) and approximately 1 (dog). It is likely that the observed clinical toxicity would have precluded further dose escalation.

Although the estimated exposure ratios values are low, it should also be considered that:

- Many patients will be adequately controlled on doses lower than the MRHD;
- Many of the patients requiring the higher doses will have some developed opioid tolerance, limiting the pharmacological effects of the fentanyl;
- The clinical systemic exposure to fentanyl from PecFent® administration is similar to that from other fentanyl products registered for similar indications (tabulated below).

Table 1. Relative exposure in repeat-dose toxicity studies

Species	Study duration	Dose (mg/kg/day) (day)	AUC _{0-24 h} (ng·h/mL)	Exposure ratio#
Rat (CrI:WI(Han))	3 months (WFEN/P34/05)	0.16 (89)	3.83	^b 1.6 (100 µg) ^b 0.9 (200 µg) ^b 0.5 (400 µg) ^b 0.2 (800 µg)
		0.32 (89)	14.38	^b 5.8 (as above) ^b 3.3 ^b 1.9 ^b 0.8
		0.52 (89)	19.41	^b 7.9 ^b 4.5 ^b 2.6 ^b 1.1
	6 months (WFEN/P37/05)	0.16 (181)	5.80	^c 2.4 ^c 1.3 ^c 0.8 ^c 0.3
		0.32 (181)	8.08	^c 3.3 ^c 1.9 ^c 1.1 ^c 0.5
		0.48 (181)	10.38	^c 4.2 ^c 2.4 ^c 1.4 ^c 0.6
Dog (Beagle)	9 months (WFEN/P36/05)	0.16 (274)	11.08	^d 4.5 ^d 2.5 ^d 1.5 ^d 0.6
		0.48 (274)	34.15	^d 14 ^d 7.8 ^d 4.5 ^d 2.0
		0.96 (274)	78.7	^d 32 ^d 18 ^d 10 ^d 4.6
Human (healthy volunteers; n=12-16) Study CP042/05	Single dose	[100 µg dose] [200 µg dose] [400 µg dose] [800 µg dose]	^a 2.461 ^a 4.360 ^a 7.513 ^a 17.272	-

= animal AUCx-24 h:human plasma AUCsingle dose for each of the 4 clinical doses (100, 200, 400, 800 µg); aAUC from single clinical doses (100, 200, 400, 800 µg); bAUC values from 0.167 - 24 h; cAUC values from 0.5 - 24 h; dAUC values from 6.5 - 24 h.

Table 2. Fentanyl clinical exposure with other fentanyl products

Fentanyl product	C _{max} (ng/mL)	AUC (ng.h/mL)
PecFent® nasal spray [MRHD 3200 µg/day]	0.35 - 2.8 (100 - 800 µg dose) [^]	17 (800 µg dose)
Actiq® lozenge [MRHD 6400 µg /day]	0.4 - 2.5 (200 - 1600 µg dose)	(1023-1275 µg dose)
Durogesic® transdermal patch [MRHD 300 µg/h]	1.9 - 3.8 (100 µg/h)	(100 µg/h)
Onsolis® buccal soluble film [MRHD 4800 µg/day]	(200 - 1200 µg dose)	(200 - 1200 µg dose)

[^] 0.35 ng/mL (100 µg dose); 0.78 ng/mL (200 µg); 1.55 ng/mL (400 µg); 2.84 ng/mL (800 µg) [Study CP042/05]

Confidential information relating to other registered fentanyl products has been hidden.

Genotoxicity

The genotoxicity of fentanyl per se was not investigated for this submission and relied on previous studies, all of which were negative. Submitted studies in the metabolite despropionylfentanyl (Ames test, chromosomal aberrations in human lymphocytes *in vitro*) were also negative.

Carcinogenicity

The carcinogenicity of intranasal fentanyl was not investigated. A previous study⁵ with a different route of administration found no evidence for carcinogenicity. There is no suggestion of carcinogenicity in humans despite extensive clinical use of fentanyl over many years.

Reproductive toxicity

Previous studies⁶ with other routes of administration have found evidence for adverse effects in animal reproductive toxicity studies but no evidence of teratogenicity. The sponsor has proposed Pregnancy Category C which is the appropriate category for this opioid. Fentanyl is known to cross the placental barrier and has been found in fetal blood.

Local tolerance

One study in rats (6 month repeat dose) found some evidence of reversible local effects in the nasal cavities of HD females (minimal/slight goblet cell hypertrophy/hyperplasia; 9/20 animals). Low incidences of this finding were also seen in the pectin control groups in this study (1-4/20 animals), similar to the low dose (LD) and mid dose (MD) treated groups (0-4/20 animals) and this was also reported in the pectin group in the 28 day buprenorphine study (Study 1966/011). This histopathological finding was not considered toxicologically significant as it was not observed in HD male rats treated

⁵ A two year study in rats using SC fentanyl (Durogesic® Product Information).

⁶ Details reported in the Product Information documents of other registered fentanyl-containing products.

similarly for 6 months, was not seen in the other repeat dose intranasal studies (3 month rat, 1 and 9 month dog) and was reversible on cessation of treatment. This cellular response is considered to be a reversible physiological adaptive response following topical exposure to a mild irritant. There were no additional local toxicological findings reported in the 3 month rat and 9 month dog studies.

These animal studies were of sufficient duration to ensure that any local intolerance should have been detectable, under the treatment conditions employed. However, it is acknowledged that such studies may not be fully predictive of clinical local tolerance, and therefore the clinical data should also be assessed on this parameter.

Paediatric use

Fentanyl nasal spray is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary

- The pharmacology and toxicology of fentanyl (a μ -opioid receptor agonist) have been well established in extensive previous nonclinical and clinical studies. Submitted sponsor studies focussed on the pharmacokinetics and repeat dose toxicity of the intranasal formulation of fentanyl only, conducted in rats, dogs and sheep. All pivotal toxicity studies were conducted according to GLP.
- Three developmental single dose pharmacokinetic studies in sheep investigated an appropriate dose to enable quantification with established testing procedures and to evaluate the absorption of fentanyl in solutions of differing composition. There was a trend toward decreased C_{max} and AUC at higher pectin concentrations (20, 40 mg/mL). The systemic absorption profiles of intranasal fentanyl in repeat dose toxicity studies in rats and dogs were comparable, consisting of a sharp early peak post dose followed by an initial rapid decline, then a further steady decline. Maximum plasma concentrations were seen in rats after the first daily dose ($T_{max} = 0.5$ h) while in dogs T_{max} values were 6.5 h (that is, 0.5 h after the final daily dose at $t=6$ h), compared to the human value of approximately 0.3 h (range 0.1-3 h) after a single dose. Systemic exposure did not appear to increase with repeat dosing over the 39 weeks in the pivotal repeat dose toxicity study in dogs.
- No new single-dose toxicity studies were submitted but there was some acute toxicity in both rats and dogs at the highest doses tested in the repeat-dose toxicity studies.
- Repeat-dose toxicity (including local tolerance) studies in rats and dogs using intranasal administration of the clinical formulation were unremarkable. Reversible minimal/slight goblet cell hypertrophy/hyperplasia was reported in HD female rats in a 6 month study but was not observed in male rats or in dogs and was not considered of toxicological concern.
- No new studies on the genotoxicity, carcinogenicity or reproductive toxicity of fentanyl were submitted. The genotoxicity of the metabolite despropionylfentanyl was negative in two new *in vitro* genotoxicity studies.
- In pectin studies, two (non-GLP) investigations evaluated the gelling and clearance properties of pectin *in vivo*. A study in rats noted that pectin solutions formed discrete plaques on the nasopharyngeal mucosa from the nostril to the nasopharynx. A study in sheep analysing mucociliary clearance of radiolabelled pectin solutions found more prolonged clearance with increasing pectin concentrations, suggesting that pectin can enhance nasopharyngeal retention time. A 28 day intranasal study in rats with 20 mg/mL pectin was unremarkable.

Conclusions and recommendation

The pharmacology and toxicology of fentanyl are well established and there is extensive clinical history with the use of this opioid in various formulations. The present nonclinical dossier has focussed on the nonclinical assessment of an intranasal formulation of this medicine. The pivotal studies utilised long term twice daily intranasal dosing in rats and dogs. There were no nonclinical findings which would preclude registration of the product. Fentanyl exposure in the repeat dose studies was modest compared to anticipated clinical exposure at the MRHD, although the results suggest that clinical toxicity in the animals would have limited further dose escalation. It is also noted that human systemic exposure to fentanyl from PecFent administration is not dissimilar to that resulting from clinical doses of other registered fentanyl products used for similar indications. There were no nonclinical signals of concern from the use of pectin as an excipient in the product.

Intranasal local tolerance to both fentanyl and pectin was found to be acceptable in the animal studies, but should still be confirmed from assessment of the clinical studies.

There are no nonclinical objections to the registration of PecFent as proposed. Several recommendations for amendments to the nonclinical sections of the PI were made but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

This was a full submission to register a new dose form of the previously approved active substance fentanyl citrate.

This submission is said to be a combined clinical and literature based submission but does not follow the standard form for a literature based submission for the clinical section. The main use of the literature based submission appears to be the toxicology section (Nonclinical submission). Clinical studies are submitted to support the pharmacokinetics of nasal delivery and the efficacy and safety of the product. No studies are submitted to support the basic pharmacodynamics or pharmacokinetics in special groups, nor were any interaction studies submitted. The *Pharmacology* sections of the sponsor's *Clinical Overview* and *Summary of Clinical Efficacy* are based on the literature but in fact have relied on only a limited number of documents; primarily the USA clinical review of Actiq⁷, the European Public Assessment report of Effentora⁸ and a review article by Dollery from 1999⁹. A literature survey is submitted but this appears to have focussed on efficacy and the 8 papers identified by the sponsor as relevant are not justified or summarised by the sponsor. While some of these publications are referenced in the sponsor's *Clinical Overview* almost all relate to a competitor product; intranasal fentanyl marketed by Nycomed (Denmark) under trade name "Istanyl[®]" and approved in Europe in 2009. These references have not been summarised as part of the efficacy or safety evaluation in this report.

⁷ FDA. (1998). Clinical Review of Actiq

⁸ EPAR. (2008). European Public Assessment Report - Effentora.

⁹ Dollery. (1999). Fentanyl Citrate. *Therapeutic Drugs 2nd Edition*, Vol 1 p40-44.

Clinical rationale

Cancer associated pain is frequently characterised by a highly variable intensity over time, producing for the patient and their clinician the dilemma of whether to use high enough doses of potent analgesics (usually opioids) to control all of the peaks of pain and risk significantly over treating the patient during the troughs, or to err on the side of caution and leave the patient at risk of “breakthrough” pain. In practice the latter course tends to be predominate, leaving a significant proportion of cancer patients (up to 95% of those with pain) suffering from frequent episodes that are characterised by their severe intensity, rapid onset (mean time to peak intensity 3 minutes), relatively brief duration (mean 30 minutes) and profound impact on quality of life and burden of care.¹⁰

Attempts to treat breakthrough cancer pain (BTCP) with additional doses of standard, oral opioids are often highly ineffective due to the mismatch between their onset of action (up to 30 minutes) and the typical time course of BTCP episodes, usually resulting merely in unwanted adverse effects (sedation, nausea, constipation) after the episode has ended.

The approval of the oral transmucosal fentanyl product (Actiq®) for BTCP has improved therapeutic options considerably but the time to onset of effect of 10-15 minutes is still not optimal and their use can be problematic in a significant proportion of patients suffering from complications of their disease such as xerostomia, mucositis, weakness or poor coordination.

Fentanyl is a well established drug with over 20 years of clinical use as both an anaesthetic and an analgesic agent. Fentanyl is available in a variety of pharmaceutical forms including: parenteral, transdermal patches and oral transmucosal (lozenge). One oral transmucosal lozenge is approved in Australia, Actiq® (Orphan Australia), for the BTCP indication. A number of other transmucosal lozenges are approved in the USA and EU (including Effentora®).

Fentanyl nasal spray (FCNS) utilises a new route of administration (intranasal) and pharmaceutical form (nasal spray) for the active ingredient fentanyl citrate; the formulation incorporates PecSys™, a proprietary pectin based drug delivery technology which optimises the profile of fentanyl by modulating absorption, allowing a short time to T_{max} but an attenuated C_{max} .

The development of fentanyl nasal spray was aimed at combining the advantages of the drug fentanyl with the ease of the nasal route of delivery to produce a novel nasal formulation that would be rapidly and efficiently absorbed, thus giving prompt and effective pain relief in a manner which would be simple and convenient and hence highly acceptable to patients.

Guidance

The EU Guidance document: “*Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain*”¹¹ has been adopted in Australia. This is a general guide for all types of nociceptive pain and does not provide specific guidance for breakthrough cancer pain. It is also noted that no specific pain scale is recommended and the no specific endpoints are recommended.

Adverse events were defined according to EU Guidance “*Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports*”. The relationship to investigational product was classified using the causality

¹⁰ Portenoy et al. (1999). Breakthrough Pain: Definition, Prevalence and Characteristics. *Pain* 81: 129-134.

¹¹ CPMP/EWP/612/00. (n.d.). Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain.

assessment system of the World Health Organization (WHO) Monitoring Centre, Uppsala, Sweden.

Scope of the clinical dossier

The sponsor submitted 3 studies under the heading *Controlled Clinical Trials*; however one of these studies CP041/04 was not a comparative study and was stopped without explanation by the sponsor before enrolment of the planned sample size. This was not considered pivotal or comparative and it is presented in the supportive studies section of this report.

The submission contained the following clinical information:

- 4 clinical pharmacology studies, including 4 that provided pharmacokinetic data (CP037/02, CP042/05, CP047/07, and CP048/07) but none that provided pharmacodynamic data
- 2 pivotal efficacy/safety studies; CP043/06 and CP 044/06
- 2 other supportive efficacy/safety studies; CP041/04 and CP045/06
- Other: 1 Periodic Safety Update Reports (PSURs) covering a 6 month period (August 2010 to February 2011), Integrated Summary of Safety and literature references.

Good clinical practice

Studies were conducted in Canada, USA, Argentina, India and Europe (UK, Germany, Italy, Spain, Poland, Czech Republic and France).

Study reports state that studies were conducted in accordance with the local regulatory requirements and the current guidelines:

- The International Conference on Harmonization (ICH) including Good Clinical Practice (GCP);
- The basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312); and
- The principles enunciated in the World Medical Association Declaration of Helsinki (Edinburgh, Scotland, 2000).

All studies required review by appropriate local Human Research Ethics Committees (HRECs) and written informed consent before commencement of the trial.

Pharmacokinetics

Studies providing pharmacokinetic data

A summary of the submitted studies are shown in the table below.

Table 3. Submitted Pharmacokinetic Studies.

PK topic	Subtopic	Study ID	*Primary objectives
PK in healthy adults	General PK - Single dose	CP037/02	Comparison of formulations
		CP042/05	Dose range
	General PK - Multi-dose	CP047/07	Dose escalation
	Bioequivalence† - Single dose	Not applicable	
	Bioequivalence† -Multi-dose	Not applicable	
	Food effect	Not applicable	
PK in special populations	Target population § - Single dose	Not done	
	Target population § - Multi-dose		
	Hepatic impairment	Not done	
	Renal impairment	Not done	
	Neonates/infants/children/adolescents	Not done	
	Elderly	Not done	
	Other special pop'n – Seasonal Rhinitis	CP048/07	PK profile
Genetic/gender-related PK	Males vs. females	Not done	
	Other genetic variables	Not done	
PK interactions	@ {Drug A}	Not done	
	@ {Drug B}		
	@ {Drug C}		
Population PK analyses	Healthy subjects	Not done	
	Target population	Not done	
	Other	Not done	

* Indicates the primary aim of the study.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's overall conclusions on pharmacokinetics

The applicant has provided limited clinical data on the pharmacokinetics of PecFent but has provided the basic information required for a new route of administration for a well documented substance.

While dose proportionality was seen within the dose range proposed it is noted that there was marked variability in the pharmacokinetics within and between studies. This is noted in passing by the applicant but dismissed as they are strongly recommending that dose titration is carried out on all patients including those switching to fentanyl nasal spray from an oral transmucosal fentanyl citrate product. This recommendation is supported by the literature¹² as it has been found that the clinically effective dose of a fentanyl product for the treatment of breakthrough pain cannot be predicted from the dose of background opioid medication or based on the use of other fentanyl based products used previously and so titration to effect is essential.

The study in subjects with seasonal allergic rhinitis (SeAE) is not pivotal to the evaluation of the product. There are no conclusive data as to dosing and the use of PecFent in patients with nasal congestion, as in seasonal allergic rhinitis.

Pharmacodynamics

Studies providing pharmacodynamic data

The sponsor has not conducted any studies to explore the pharmacodynamics of fentanyl arguing that they are already well documented.

Evaluator's overall conclusions on pharmacodynamics

The minimal amount of data provided on the pharmacodynamics is appropriate for a well documented substance such as fentanyl.

Efficacy

Dosage selection for the pivotal studies

The dosing interval in all the clinical studies was at least 4 h. This interval was adopted as a reflection of both the findings from the initial single dose Phase I studies with fentanyl nasal spray and from the accepted practice with existing approved fentanyl products of limiting use to treating up to four episodes per day. This interval was further supported by the findings of the multiple dose PK study (CP047/07) which demonstrated that while increases in C_{max} levels seen following a second 100 µg dose of fentanyl nasal spray given at one, two and four hr intervals, they are not seen at the four hr interval. It should be noted that the increases seen after the first dose were not sufficiently large to suggest accumulation or over-exposure, thus indicating an acceptable safety margin for the recommended dose interval of two hrs.

The dose range chosen for the clinical studies was based on the dose ranges demonstrated to be clinically effective by the transmucosal route and the bioavailability of fentanyl by the transmucosal route (approximately 50%) and by the intranasal route (approximately 70-75%). Based on these considerations, the proposed dose range for the clinical studies were in the range of 100 µg, 200 µg, 400 µg and 800 µg, delivered using one or two sprays

¹² DeGregori et al. (2010). Individualising Pain Therapy with Opioids: The Rational Approach Based on Pharmacogenetics and Pharmacokinetics. *European Journal Pain Suppl* 4: 245-250.

of two strengths (100 µg per spray and 400 µg per spray). All the clinical trials had an individual dose titration step to establish the appropriate dose for each patient. This is also recommended for the marketed product.

Evaluator's conclusions on clinical efficacy for breakthrough cancer pain

The sponsor has provided two pivotal studies to support the efficacy of the Nasalfent (nasal spray fentanyl citrate) in the treatment of BTCP. The first study compared Nasalfent to placebo and demonstrated superiority to placebo consistently in all the endpoints. The second study compared Nasalfent to an approved fentanyl lozenge and demonstrated comparable efficacy with statistically significant improvement in the onset of action.

The two pivotal studies did not have the same primary efficacy outcome:

- Placebo comparison study (CP043/06); summed pain intensity difference (SPID) from 5 to 30 minutes
- Active comparison study (CP044/06); pain intensity difference (PID) at 15 minutes

However, both studies included a range of secondary outcomes which were similar in the two studies.

Study numbers were small and the company did not use a true Intent-to-treat (ITT) analysis. The use of the modified ITT results in less patients being available for analysis; however the results showed statistical significance in favour of the fentanyl nasal spray. The improvement in onset of action is relevant to the patient population.

Overall, efficacy for the fentanyl nasal spray has been demonstrated.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies, CP043/06 and CP044/06, the following safety data were collected:

- General adverse events (AEs) were assessed by the standard procedures. Patients were closely observed and questioned for any kind of AE during study procedures and throughout the study period with non-leading questions. They were instructed to immediately report any symptoms and signs arising between formal observations or visits to study staff. The following information regarding each AE was collected: date and time of onset and resolution (duration); intensity (mild, moderate or severe); outcome; and whether the AE caused withdrawal from the study.

The study investigator was asked to assess the causal relationship between the AE and the investigational product using the following guidance:

- **Not related:** sufficient information existed to indicate that causality was unrelated to investigational product (for example, event due to extraneous cause such as underlying medical condition, other therapeutic interventions, environmental factors and so on)
- **Remote:** the time from the investigational medicinal product administration to occurrence of AE make a relationship improbable but not impossible. The AE was unlikely to have been produced by the patient's underlying medical conditions, environmental or toxic factors, or other therapeutic interventions

- **Possible:** The AE followed a reasonable temporal sequence from the investigational product administration. It is unlikely to have been produced by the patient's underlying medical conditions, environmental or toxic factors, or other therapeutic interventions
- **Probable:** The AE followed a reasonable temporal sequence from the investigational product administration or was associated with established drug concentration in body tissues; improved on stopping or reducing the investigational product dosage (de-challenge); and could not reasonably be explained by the study patient's underlying medical conditions, environmental or toxic factors, or other therapeutic interventions
- **Definite:** Same criteria as "probable" but the AE reappears on repeated exposure (re-challenge)

An adverse event that was assessed by the study investigator as being possibly, probably or definitely related to the associated study medication was defined as an adverse reaction.

The definition of serious and unexpected adverse reactions was the same as is given in the Australian guidelines (TGA, 2006)¹³.

- AEs of particular interest, including:
 - Objective nasal examination was assessed by the study physician at screening and at end of study. Assessment included obstruction (on 3 point scale), inflammation (on 3 point scale), presence of discharge, side most affected overall and colour of mucosa.
 - Subjective nasal assessment was assessed by the patient one hr after each dose of study drug and at the final study visit on a 3 point scale. Assessment included stuffy/blocked nose, runny nose, itching or sneezing, crusting or dryness of nose, burning or discomfort of nose, bleeding, cough, postnasal drip, sore throat and taste disturbance.
- Laboratory tests, including standard haematology, biochemistry and urinalysis were performed at screening and at end of study.
- Physical Examination and vital signs, including measurements of heart rate, systolic and diastolic blood pressure, and respiration rate were assessed at screening and at end of study.
- Urine pregnancy tests were performed at screening to ensure female patients of childbearing potential were not pregnant.

Pivotal studies that assessed safety as a primary outcome

Studies CP045/06 was a pivotal study that assessed safety as a primary outcome.

Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study CP41/04 provided data on adverse events and patient well being, assessed by observation and questionnaire.

Other studies evaluable for safety only

Clinical pharmacology studies

Note: In Pharmacokinetic studies fentanyl was always administered after naltrexone.

¹³ TGA. (2006). The Australian Clinical Trial Handbook. 25-26.

Study CP037/02: Safety and tolerability were assessed by a local nasal tolerance questionnaire, completed after each nasal dose and by monitoring other adverse events throughout the study.

Study CP042/05: Local tolerability was assessed by a reatogenicity questionnaire throughout and completing an overall assessment of the acceptability of nasal dosing at the end of each nasal treatment. There was also a topical safety assessment by an Ear Nose and Throat (ENT) specialist using a conventional rating scale at the beginning and end of the study, and clinical nasal assessment by the study physician.

Study CP047/07: Safety and tolerability were evaluated by physical examination, vital signs, (pulse, blood pressure, respiratory rate, temperature and oxygen saturation), clinical laboratory tests (haematology, biochemistry and urinalysis), 12 lead electrocardiogram (ECGs) and adverse event questioning. The tolerability of intranasal administration was determined by nasal assessments and reatogenicity questionnaire.

Study CP048/07: Safety and tolerability was assessed by monitoring adverse events throughout the study, plus a standard symptom questionnaire that was completed before dosing and the reatogenicity questionnaire completed prior to an after each fentanyl nasal spray. A topical safety assessment was conducted by an ENT specialist at the beginning and end of the study.

Postmarketing experience

One PSUR was included in the submission covering the period 31 August 2010 to 28 February 2011.

From launch on 4 October 2010 to 31 December 2010, 5885 bottles of the 100 µg strength and 4525 bottles of the 400 µg strength have been sold in the EU (ex-factory). Information on the number of bottles actually prescribed is unknown due to the lag in companies obtaining prescribing information.

Estimated postmarketing exposure to PecFent has been calculated as an average of between 11,528 and 34,915 “patient days” of treatment during the PSUR period based on available sales data and fentanyl citrate defined daily dose.

Six adverse reports have been received by the company in this time. The reports were:

- one serious spontaneous unlisted case of a female patient of unknown age who experienced visual disturbance (black spots) whilst taking PecFent (fentanyl citrate) for an unreported indication. The prescriber stopped the treatment with PecFent and outcome of the event was unknown. The patient was said to be “...very sick...” and terminal, was taking a variety of largely unspecified medications and the case is without much detail. The company physician assessed the causal relationship as possible on the basis of the implied temporal relationship.
- five medically confirmed reports concerning non-serious listed adverse events.

To date, there have been no new safety signals and no reports of accidental exposure, overdose, or misuse/abuse.

Evaluator’s overall conclusions on clinical safety

Safety data has been appropriately collected in all the clinical trials. While the total number of patients studied is not large fentanyl is a well documented substance and no new safety issues have emerged with the nasal spray formulation. It is noted that the nasal spray was administered concomitantly with the patient’s regular opioid medication in all cases and the high background rate of adverse events in this patient population makes assessment of safety of the nasal formulation difficult.

Local nasal tolerability appears satisfactory.

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The benefits of FCNS in the proposed usage are:

- Fentanyl is a well established drug with over 20 years of clinical use.
- A total of 45,599 episodes of BTCP were treated with FCNS at doses ranging from 100 to 800 µg in a total of approximately 500 patients. The average duration of therapy was 73 days, with 153 subjects being treated for between 90 and 159 days.
- The studies used well-established and validated measures of efficacy and demonstrated that FCNS has a fast onset of action, with onset of efficacy evident from as early as 5 minutes after administration (on some endpoints) and reached clinically meaningful levels within 10 minutes. The effect was maintained throughout the typical (up to 60 minutes) duration of a BTCP episode.
- FCNS has been shown to be statistically significantly superior to both placebo and the currently approved treatment, immediate release morphine sulphate (IRMS), in the treatment of BTCP in opioid-tolerant cancer patients.
- The effective dose can be easily titrated in each patient to provide maximum pain relief whilst minimising adverse effects.
- Patient acceptability assessments indicate that patients are generally satisfied or very satisfied with fentanyl nasal spray in treating episodes of BTCP and this is supported by the low use of rescue medication following use of the product (6% of episodes during maintenance treatment). The assessments of overall acceptability, speed of relief and the episode-by-episode reliability of the nasal spray used also significantly favoured fentanyl nasal spray over placebo. Patients also considered fentanyl nasal spray was convenient and easy to use.

First round assessment of risks

The risks of FCNS in the proposed usage are:

- The expected known AEs which are those for a potent opioid.
- The potential for misuse and abuse

First round assessment of benefit-risk balance

The benefit-risk balance of fentanyl nasal spray, given the proposed usage, was considered to be favourable.

First round recommendation regarding authorisation

On the basis of the clinical data submitted it was recommended that PecFent be approved.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns. Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the TGA's Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary list of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Important identified risks:

- Respiratory depression or insufficiency
- Circulatory depression, including severe bradycardia, hypotension, and shock

Important potential risks:

- Local tolerability
- Misuse, abuse or diversion
- Off-label use
- Accidental exposure

OPR reviewer comment

It is stated that *"the most serious adverse reactions are respiratory depression (potentially leading to apnoea or respiratory arrest), circulatory depression, hypotension and shock"* (Australian PI January 2012; version 1.1; p.11 of annotated version), which are appropriately classified as Important identified risks in the RMP. Pending the evaluation of the nonclinical and clinical aspects of the SS, the above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance plan***Proposed pharmacovigilance activities***

Routine pharmacovigilance (PV) activities¹⁴, including monitoring of ongoing clinical trials and post-market surveillance for future periodic safety update reports (PSURs), are proposed for all safety concerns. It is stated that the Pharmacovigilance (PV) plan is consistent with the European Economic Area (EEA) PV requirements (EU RMP Version 4.1, p. 44). The PV plan is proposed to be updated biannually or more frequently as required.

The following additional PV activities are proposed for these Important potential risks: misuse, abuse or diversion, off-label use and accidental exposure:

- conduct of a drug utilisation study (DUS) to investigate prescription patterns and usage in general practice clinics to monitor any misuse, abuse or diversion, off-label use and accidental exposure:
 - Observational cohort studies starting at treatment initiation and followed for an approximately 6 month period or at point of censor, with an expected total number of patients of 400.

¹⁴ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- It is anticipated that data from 400-480 patients can be obtained during 2011. It is also anticipated that a sample size of 300 patients (with 80% power) will be required to detect a minimum of 2 cases of interest if the background rate for the case is zero (EU RMP Version 4.0 Annex 5, p. 134 - PecFent EU Modified PEM Study 3 August 2010 version).
- The proposed study duration is for 24 months. The sponsor's response to a TGA request for information has confirmed that data collection has initiated in December 2010 in the UK and that the German and French protocols are undergoing review by the EU Committee for Medicinal Products for Human Use (CHMP), with studies anticipated to start within 6 months of protocol approvals.
- Survey method: Postal questionnaire to be sent to prescribing physician for each identified patient (in UK: based on data for PecFent prescriptions issued by GPs collected by the National Health Service in England) within 3 months after the first GP prescription of PecFent. Targeted follow-up questionnaires to include adverse events due to overdose or suicide, contraindicated usages, unsanctioned diversion (criminal use) and accidental exposure.
- Proposed sample questionnaire is provided in EU RMP Version 4.1, pp.140-143. The information requested includes details of the treatment, patient's history and relevant events relating to potential risks of interests during and after discontinuation of treatment.
- conduct physician surveys to investigate the effectiveness of physician's training for awareness of the use and safety of PecFent:
 - Quantitative market research survey (using online or computer aided telephone interviews) on 100 representative physicians each in France, Germany, Italy, Spain and the UK based on preset quotas for each region according to the country's geographical population density for each region, and for distribution between primary versus secondary care settings. A copy of the proposed study protocol including the sample questions and the assessment criteria for determining the effectiveness of the physician's training is provided in Annex 5 of the EU-RMP.
 - Data collected from physicians who are aware of and are prescribing PecFent will be analysed as a measurement of RMP effectiveness.
 - Proposed duration: survey to be conducted every 6 months after market launch and then annually for unspecified time.¹⁵
 - The sponsor's response to a TGA request for information has indicated that the protocol for the Physician's Survey is currently undergoing review and the studies are expected to commence in the UK, Germany, Italy and Spain in 2012 and in France in 2013.¹⁶

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The proposed routine and additional PV activities appear appropriate unless there are any additional safety concern(s) raised by the nonclinical and/or clinical evaluator(s) that may require additional PV activities. It is expected that the DUS will inform the extent and frequencies of misuse, abuse or diversion, off-label use and accidental exposure, and may also identify any new adverse drug events (ADRs) that will inform if additional risk minimisation activities will be required. The Physician's Survey will be used to assess the effectiveness of the physician training elements of the RMP. It is also indicated that both

¹⁵ Sponsor comment: "The survey was to be conducted one time only."

¹⁶ Sponsor comment: "All of these studies were initiated in 2012."

the DUS and Physicians surveys “*would be extended to Australia if any safety issues were detected in the EU that merit additional study in Australia*” (Australian-specific annex, p. 36).

Risk minimisation activities

Planned actions

Routine¹⁷ and additional risk minimisation activities are planned to address the Important identified and Potential risks (EU RMP Version 4.0, pp.47-51, 55-64). Routine risk minimisation activities include monitoring of ongoing clinical trials and post-market surveillance and the provision of relevant safety information and instruction for use in the PI and consumer medicine information (CMI).

The following additional risk minimisation activities are proposed:

- Training of field representatives to alert healthcare professionals on the identified and potential risks (synopsis of content of training provided in EU RMP Version 4.0, pp. 188-192).
- Provision of additional educational materials and correspondences on risks of medication abuse, misuse or diversion, off-label use and accidental exposure, including targeted education programs to prescribing physicians and other healthcare providers and education materials/correspondences to healthcare providers and pharmacists (summary of proposed principles to be covered in education and programs provided in Annex 8 and proposed sample letters /prescribing information are provided as attachments to the Australian specific annex EU RMP Version 4.0, pp. 184-186). These education materials/correspondences include Dear Healthcare professional and Pharmacist letters, letters to professional society, medication guides to prescribers and pharmacists.
- Provision of additional educational materials to consumers on risks of medication abuse, misuse or diversion, including brochures targeted for patients’ education (sample proposed brochure is provided as an attachment to the Australian-specific annex of EU RMP Version 4.0).

OPR reviewer comment

The proposed Dear Healthcare Professional, Pharmacist, Professional Society letters v1.0 6 June 2011, Prescriber and patient brochures v1.0 6 June 2011 are considered satisfactory. DUS, Physician surveys and routine pharmacovigilance are appropriate to inform the effectiveness of the proposed additional risk minimisation activities. The implementation of DUS and Physician Survey may be required in Australia if there are safety concerns detected in the global market that need to be monitored and/or mitigated more closely in Australia.

Some discrepancies in information provided in the EU Summary of Product Characteristics (SmPC) and Australian PI have been noted. These have been satisfactory clarified in the sponsor’s response to a TGA request for information:

- The statement “*patients should be advised not to blow their nose immediately after PecFent administration*” was used as an instruction for use in the Phase III clinical trials and was included in the EU SmPC. This statement has been included in the updated Australian PI and is acceptable.

¹⁷ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

- The statement “other nasally administered treatments should be avoided within 15 minutes of dosing with PecFent” is included in the EU SmPC (EU RMP Version 4.0, p.77) and in the initial Australian CMI. This statement is not included in the Australia PI because the company does not have data to support this statement and is removed from the updated Australian CMI (Version 1.1; 5 January 2012). However, a class warning on concomitant use with nasal constrictive decongestant is included in the *Interactions with other medicinal products and other forms of interaction* section of the Australian PI. This is considered acceptable.

In regard to the proposed routine risk minimisation activities, the draft Australian PI is considered satisfactory except for the comments noted below (please note that any actual changes to the draft PI will not be expected until further advised by the Delegate):

- It is noted that the indications in the PI has been updated (January 2012) to remove the restriction for use in adult patients:

“PecFent is indicated for the management of breakthrough cancer pain in patients with malignancies who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain”

The indication sought in this submission was initially restricted to adult patients (draft Australian PI, June 2011), which is also maintained in the updated Australian specific Annex to the RMP (January 2012 version; submitted with the response to a TGA request for information):

“PecFent is indicated for the management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain”

The initial restriction for use in the adult population is also supported by the statement of the original dossier submitted, that “Given that fentanyl is a potent opioid, Archimedes considers that it is vital to gain post-marketing experience in adults with PecFent before expanding to a potentially more vulnerable paediatric population.....”

The restricted use to the adult patient population is in line with the indications approved by the EMA and FDA:

“PecFent is indicated for the management of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain” (EU SmPC, updated 10/01/2012)

“Lazanda is an opioid agonist indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain” (US product label, revised 12/2011)

The EU-RMP submitted is also in line with the restricted use in adult patients, as discussed in Sections 1.3.1 and 1.9.5 of the EU-RMP:

“The use of PecFent in patients under 18 years of age has not been studied in clinical trials. Therefore, PecFent is not recommended for use in this age group.....”

There is a risk of off-label use of PecFent in older children because of the convenience of the dosage form, even though the product is not approved for paediatric use, in contrast to some other fentanyl-containing products, which are approved. The presentations of PecFent that have been developed have not been shown to be suitable for younger children (those weighing <65 kg) in terms of strength and dosing volume.”

Therefore, it would appear that the EU-RMP provided in support of this submission has been explicitly developed to support the use of PecFent in adult patients as defined as those who are 18 years old and older. Therefore, the EU-RMP did not

adequately address the potential risks associated with the use of PecFent in paediatric patients (under 18 years old) in the Australian market.

- Specific precaution on the PecFent excipient propylhydroxybenzoate (E216), which “may cause allergic reactions (possibly delayed) and, exceptionally, bronchospasm (if the product is not correctly administered)” is included in the EU SmPC (EU RMP Version 4.0, p.77). This precaution is not included in the Australian PI, although it is acknowledged that the PI contained a statement to contraindicate the use in individuals who are hypersensitive to any components of PecFent. The inclusion of the precautionary statement in the PI on the possible delayed allergic reactions if administered incorrectly may also be considered to be useful information to minimise the potential risks in susceptible individuals, who may not otherwise be specifically identified as being at risk for developing a hypersensitive reaction to the excipient propylhydroxybenzoate.

In regard to the proposed routine risk minimisation activities, the draft consumer medicine information (CMI) is considered satisfactory. The CMI is to be supplied with each PecFent carton (as advised in the sponsor’s response to a TGA request for information).

Summary of recommendations

As the final nonclinical and clinical evaluation reports were not available at the time of finalising this report, the final RMP may need to be updated to take into account any additional safety concern(s) identified in the final nonclinical and/or clinical evaluation report(s). The OPR offers the recommendations as stated below pending the final nonclinical and clinical evaluation reports.

In the event that this application was successful, the OPR recommended the implementation of the EU Risk Management Plan Version 4.0 and the Australian Annex (dated January 2012) and any subsequent updated versions be implemented as a condition of registration.

Two comments were provided in regards to information that was not clearly presented in the proposed Australian PI (see above).

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate’s overview and recommendations:

Quality

- Fentanyl citrate is a well-established drug substance. Fentanyl (as the citrate salt) is currently registered in Australia in a number of dosage forms including injections, transdermal delivery systems and oral lozenges. The present submission seeks registration of a new dosage form: a nasal spray containing fentanyl (as citrate) 1.0 mg/mL and 4.0 mg/mL, to be registered under the trade name ‘PecFent’.
- The initial dose of PecFent nasal spray to treat episodes of breakthrough cancer pain is 100 µg (one spray). Patients who need to titrate to a higher dose due to lack of effect can be instructed to use two sprays (one in each nostril) and if not successful to change to the higher dose 400 µg sprays. Patients must wait at least 4 h between doses and are limited to 4 doses per day.
- In addition to fentanyl citrate (1.57 or 6.28 mg/mL), the solution contains a new proprietary gelling agent, as well as mannitol to adjust the tonicity, hydrochloric acid

and/or sodium hydroxide to adjust the pH to 4.0, and the antimicrobial preservatives phenethyl alcohol and propyl hydroxybenzoate.

- The droplet spray size is critical in order to ensure that the droplets are deposited in the nose and not breathed into the lungs. Droplet size is monitored in each batch by laser diffraction.
- A shelf life of 3 years below 25°C has been established for PecFent. Once opened and primed, the product must be used within 14 days or discarded. A bottle must also be discarded if it has been more than 5 days since its last use.
- During product development, the proposed product and two other experimental formulations (100 µg of each) were compared in a bioavailability study (CP037/02) with 200 µg of an oral transmucosal fentanyl citrate lozenge (“Actiq”) obtained in the UK. An equivalent product is registered in Australia, although it is not known whether the UK and Australian Actiq products are identical. On a dose-normalised basis, the proposed PecFent product was found to have a 2.3 fold higher C_{max} than Actiq and a 1.3 fold higher AUC.
- It should be noted that the evaluator’s recalculations of the AUC_{obs} (AUC_{∞} based on extrapolation using the last observed concentration) results for this study were in error. The AUC_{obs} ratio for PecFent/Actiq (treatments B/D) has since been re-determined as 144.5% (90% CI 121.4-171.9%). This ratio is slightly higher than the 130% determined by the company but confirms that PecFent gives significantly higher AUC results than Actiq.
- A later study (CP042/05), which compared various dose levels of PecFent with 200 µg Actiq, showed a 2.3 fold higher C_{max} and a 1.2 fold higher AUC, independent of dose in the range 100–800 µg.
- Both the PecFent and Actiq products showed a high degree of inter-subject variability.
- The company provided a detailed justification for not performing an absolute bioavailability study on PecFent (see *Sponsor response* below). The justification has been referred to the Clinical Delegate. The company also provided some additional thoughts, by e-mail, regarding the issue on 23 February 2012.

Sponsor response

‘Archimedes agrees with the evaluator that the risk of high C_{max} values in an absolute bioavailability study versus PecFent could potentially be reduced by adjusting the fentanyl dose and infusion time as well as by using naltrexone. However, this argument was part of a collective set of reasons for why a study of absolute bioavailability was not conducted and although small, any risk must be taken into account in relation to the value of the information that would be obtained. The company still considers the conduct of an absolute bioavailability study to be unnecessary for the following reasons.

1. IV Fentanyl has a high and wide-ranging AUC coefficient of variation (CV) compared to other IV drugs and consequentially use of this absolute reference drug has limited clinical value. Specifically the evidence-base suggests a CV for IV fentanyl, with a range between 27.3% to 56.0% as detailed in the studies shown in Table 5.

Table 5. IV Fentanyl single dose AUC and Coefficients of Variation

Study	Dose (IV)	N	AUC _t (SD), ng · min/mL	Coefficient of Variation
Darwish 2007	400 µg	29	1.43 (0.39)	27.3%
Christrup 2008	75 µg	5	AUC _{inf} (SD), ng · min/mL 46.6 (26.1)	56.0%
	100 µg	7	82.7 (23.3)	28.2%
Vasisht 2010	200 µg	12	AUC _{inf} (SD), hour/ng/mL 4.62 (1.51)	32.7%

- The average duration of a typical episode of Breakthrough Pain (BTPc) in patients with cancer is 30-120 minutes.¹⁸ Estimates from the first pharmacokinetic study with PecFent (Study CP037/02), suggested that only between 10-20% of total measurable PecFent was available for treatment during this period. Consequently the clinical relevance of determining absolute bioavailability over a 24 hr period for BTPc, which has a mean duration of 30-120 minutes, seems to have limited value. Additional analysis of pharmacokinetic data from clinical study CP042/05¹⁹ confirmed the view that only a small proportion of the total measurable drug (14%-22%) is available during the key period of BTPc (derived from AUC₀₋₁/AUC_t).
- At the time that these studies were being performed, Actiq was the first and only fast acting fentanyl product licensed for BTPc and determined absolute bioavailability values were unsurprisingly wide, ranging from 0.36 to 0.71.²⁰ It was therefore considered that Actiq would be a more clinically relevant pharmacokinetic reference than IV fentanyl.

‘These data together with those above for IV fentanyl, further support the point that an absolute bioavailability study using PecFent would be of questionable pharmacological and clinical value. However, since the absolute bioavailability of Actiq was determined to be approximately 50% from a 15 µg/kg dose²⁰, and the relative bioavailability of PecFent is 11-23% higher than OTFC (Actiq) from CP042/05 then the approximate bioavailability of PecFent would be 60-70% with a range of 45-90%.

‘PecFent was developed in order to address the unmet medical need to provide a rapid treatment for BTPc, where earlier onset and increased consistency of effect, compared to existing oral transmucosal products approved for BTPc, could be achieved. To date, PecFent (tradename Lazanda in the US) has been registered for BTPc in two major regions: EU approval was granted in August 2010, with product launch in October 2010; and US approval was granted in June 2011, with product launch in October 2011.

‘In conclusion Archimedes consider that the selection of a relative reference for pharmacokinetic comparisons with PecFent, rather than an absolute reference as being the most relevant and do not believe that conducting a new absolute

¹⁸ Mercandante S, Zagonel V, Breda E *et al.* Breakthrough Pain in Oncology: A Longitudinal Study. *J Pain Symptom Manage.* 2010; 40:183-190.

¹⁹ Fisher A, Watling M, Smith A *et al.* Pharmacokinetics and relative bioavailability of fentanyl pectin nasal spray 100 – 800 µg in healthy volunteers. *Int J Clin Pharmacol Ther.* 2010;48:860-867

²⁰ Streisland JB, Varvet JR, Stanski DR *et al.* Absorption and Bioavailability of Oral Transmucosal Fentanyl Citrate. *Anesthesiology* 1991;75:223-229.

pharmacokinetic study comparison will add further clinical value to the use of PecFent in BTPc.

Another three responses to TGA requests for information are summarised below:

- i. The batch of Actiq lozenges used in the submitted bioavailability study was sourced from the UK market, and no additional quality testing was performed prior to use in the study. The study showed that PecFent has substantially higher bioavailability than Actiq. A study relative to Australian-sourced Actiq is not considered necessary as the products are not claimed to be bioequivalent and the safety and efficacy of PecFent have been determined in clinical studies.
- ii. The nasal spray formulations used in the submitted bioavailability study were very small scale batches (250 mL).
- iii. Satisfactory details of acceptance criteria for sample re-assays have been provided.

In addition to providing the above responses, the sponsor also addressed a question that was raised in the evaluation report but not included in the list of questions. Details of the mobile phase used in the assay for PPA in the drug substance have now been provided.

Clinical Delegate's Comment: Given the proposed company's statement in the draft production information for PecFent regarding switching between fentanyl containing products, especially trans-mucosal routes, the justification is acceptable.

- The sponsor has responded to the Microbiology report which stated that preservative efficiency testing (PET) was unacceptable. Based on further clarification provided by the company, the PET is now deemed acceptable.
- The poison schedule of the drug product has now been corrected from S4 to S8 in the Provisional Australian Register of Therapeutic Goods (ARTG) Records.
- The sponsor requested that the excipient, hydrochloric acid, be removed from the formulation details in the Provisional ARTG Records (PAR) because it is only used for pH adjustment if and when required. The PARs have not been amended because it is routine practice to include pH-adjusting excipients in the formulation details even if they may not always be used in a particular batch.
- In summary, the evaluator noted that a number of matters were raised with the applicant following the initial evaluation of this submission. All matters have since been satisfactorily resolved except that GMP clearance had not yet been provided for the site that performs leachables testing on the finished product, including testing for levels of formaldehyde. Subject to the provision of satisfactory GMP clearance for that site²¹, there are no objections in respect of Chemistry, Manufacturing and Controls to registration of this product. That is, a satisfactory GMP clearance letter from one site in the USA should be submitted prior to registration approval.²² The submission was referred to the Pharmaceutical Subcommittee of the ACPM prior to the scheduled ACPM meeting.

²¹ Sponsor comment: GMP clearance was provided for this site prior to the approval of this application"

²² Sponsor comment: GMP clearance was provided for this site prior to the approval of this application."

Nonclinical

The toxicological evaluator (TE) summarised that:

- The pharmacology and toxicology of fentanyl (a μ -opioid receptor agonist) have been well established in extensive previous nonclinical and clinical studies. Submitted sponsor studies focussed on the pharmacokinetics and repeat dose toxicity of the intranasal formulation of fentanyl only, conducted in rats, dogs and sheep. All pivotal toxicity studies were conducted according to GLP.
- Three developmental single dose pharmacokinetic studies in sheep investigated an appropriate dose to enable quantification with established testing procedures and to evaluate the absorption of fentanyl in solutions of differing composition. There was a trend toward decreased C_{max} and AUC at higher pectin concentrations (20, 40 mg/mL). The systemic absorption profiles of intranasal fentanyl in repeat dose toxicity studies in rats and dogs were comparable, consisting of a sharp early peak post-dose followed by an initial rapid decline, then a further steady decline. Maximum plasma concentrations were seen in rats after the first daily dose (T_{max} = 0.5 h) while in dogs T_{max} values were 6.5 h (that is, 0.5 h after the final daily dose at t=6 h), compared to the human value of approximately 0.3 h (range 0.1-3 h) after a single dose. Systemic exposure did not appear to increase with repeat dosing over the 39 weeks in the pivotal repeat dose toxicity study in dogs.
- No new single-dose toxicity studies were submitted but there was some acute toxicity in both rats and dogs at the highest doses tested in the repeat-dose toxicity studies.
- Repeat-dose toxicity (including local tolerance) studies in rats and dogs using intranasal administration of the clinical formulation were unremarkable. Reversible minimal/slight goblet cell hypertrophy/hyperplasia was reported in HD female rats in a 6 month study but was not observed in male rats or in dogs and was not considered of toxicological concern.
- No new studies on the genotoxicity, carcinogenicity or reproductive toxicity of fentanyl were submitted. The genotoxicity of the metabolite despropionylfentanyl was negative in two new *in vitro* genotoxicity studies.
- In pectin studies, two (non-GLP) investigations evaluated the gelling and clearance properties of pectin *in vivo*. A study in rats noted that pectin solutions formed discrete plaques on the nasopharyngeal mucosa from the nostril to the nasopharynx. A study in sheep analysing mucociliary clearance of radiolabelled pectin solutions found more prolonged clearance with increasing pectin concentrations, suggesting that pectin can enhance nasopharyngeal retention time. A 28-day intranasal study in rats with 20 mg/mL pectin was unremarkable.
- Intranasal local tolerance to both fentanyl and pectin was found to be acceptable in the animal studies but should still be confirmed from assessment of the clinical studies.
- There are no nonclinical objections to the registration of (PecFent®) as proposed. Several recommendations for amendments to the nonclinical sections of the PI were made but these are beyond the scope of this AusPAR.

Clinical

The clinical evaluator (CE) has identified the following data:

- 4 clinical pharmacology studies, including 4 that provided pharmacokinetic data (CP037/02, CP042/05, CP047/07, and CP048/07 and none that provided pharmacodynamic data

- 2 pivotal efficacy/ safety studies: CP043/06 and CP044/06
- 2 other supportive efficacy/ safety studies: CP041/04 and CP045/06
- Other: 1 PSURs covering a 6 month period (August 2010 to February 2011), Integrated Summary of Safety and literature references.

Pharmacokinetic studies

The CE stated that the information summary provided in the clinical evaluation report (CER) has been derived from conventional pharmacokinetic studies unless otherwise stated.

CP042/05

In this study, fentanyl was shown to be rapidly absorbed following single dose intranasal administration of fentanyl nasal spray with median T_{max} ranging from 15 to 20 minutes (compared to T_{max} for Actiq® of approximately 90 minutes).

The variability of the pharmacokinetics for fentanyl was considerable following treatment with both fentanyl nasal spray and oral transmucosal fentanyl citrate (OTFC) lozenge.

CP 037/02

Phase I Study conducted in healthy volunteers to compare three prototype 100 µg fentanyl nasal spray formulations under naltrexone blockade, with the oral transmucosal fentanyl citrate (OFTC) lozenge (Actiq 200 µg) as comparator. The prototype nasal formulations were fentanyl-chitosan, fentanyl-pectin and fentanyl-chitosan-poloxamer 188. All fentanyl treatments appeared to be well tolerated both systematically and locally. Fentanyl appeared to be absorbed more rapidly and gave greater C_{max} values when administered nasally compared to the OFTC lozenge; the relative bioavailability of fentanyl nasal spray (pectin formulation) was 132.4% (geometric mean) compared to the OFTC lozenge indicating bioavailability to be greater than the oral transmucosal route. From this study, the sponsor chose the fentanyl-pectin nasal formulation for use in the subsequent Phase I studies as a clinically significant plasma concentration was quickly reached (median T_{max} =20 minutes), suggesting that a rapid onset of pain relief may be possible with the pectin formulation. The mean observed C_{max} for this formulation was the lowest of the three nasal formulations (albeit still likely to be an effective concentration). This formulation was assessed as being most likely to match the time course of the typical breakthrough pain episode, delivering fentanyl quickly while producing fewer side effects associated with large, early spikes in plasma concentration.

The key characteristics of this formulation are:

- Its low viscosity enabling delivery from a conventional nasal spray pump
- Its ability to form a soft, mildly adherent gel on contact with the nasal mucosa that modulates the delivery of fentanyl to the systemic circulation to better match the time course of the typical breakthrough pain episode
- Its avoidance of the dripping and running that are a problem with conventional non-gelling, non-modulating nasally administered products.

This formulation is stated to have been used throughout the remaining Phase I, II and III studies.

CP037/02 and CP042/05

The above two studies also compared the relative bioavailability of fentanyl nasal spray (at 100 µg, 200 µg, 400 µg and 800 µg) with the reference product OFTC lozenge (Actiq® 200 µg). The relative bioavailability was calculated to be approximately 120 – 130%. This

difference in bioavailability from the oral transmucosal route is likely to be due principally to the avoidance with the intranasal route of swallowing much of the administered dose from the lozenge.

CP042/05

This study was also used to demonstrate dose proportionality of single doses for C_{max} range 100 µg to 800 µg fentanyl delivered in the fentanyl-pectin nasal formulation. The departure from dose proportionality seen following the administration of eight immediately consecutive doses to the same nostril indicates a lower than expected availability of fentanyl from such repeated dosing. This is stated as likely due to the limited capacity of the nasal cavity to hold liquid formulations but may also reflect an overwhelming of the gel forming properties which would lead to the run-off (an impaired absorption) of un-gelled fentanyl.

CE's Comment: The company stated that this is a positive result as it indicates an additional safety feature of the formulation but it is disappointing that the study was designed in this way and did not allow for alternate nose dosing which is more in keeping with standard recommendations for nasal delivery and might have provided a different result which removes this potential safety feature.

Note: The applicant did not submit new data on distribution, metabolism and excretion of fentanyl nasal spray given, the previous review and report on those topics for fentanyl in general.

CP047/07

The primary objective of this study was to evaluate the PK of NasalFent following eight immediate consecutive administrations of 100 µg (8 x 100 µL) and after various time periods between two 100 µg (2x100 µL) doses. The safety objective was to determine and compare the local and systemic safety and tolerability profiles of single and multiple doses of NasalFent (albeit in the presence of naltrexone). This was a 5 period cross over study conducted in healthy volunteers. The following five treatments were administered in the order listed below (dose escalation), with a washout of at least 3 days between each treatment.

- Treatment A: single dose of 100 ug NasalFent (100 uL) into the right nostril
- Treatment B: two doses of 100 ug NasalFent (2 x 100 uL) 4 h apart into the right nostril
- Treatment C: two doses of 100 ug NasalFent (2 x 100 uL) 2 h apart into the right nostril
- Treatment D: two doses of 100 ug NasalFent (2 x 100 uL) 1 hr apart into the right nostril
- Treatment E: eight doses of 100 ug NasalFent (8 x 100 uL) consecutively into the right nostril.

There was concomitant naltrexone use. Each treatment period was performed under a naltrexone block. Subjects received 100 mg naltrexone 12 h pre-dose, 1 hr pre-dose and 12 h post-dose. The dose could be increased to 150 mg naltrexone if necessary.

The PK data indicated moderate and statistically significant increases in C_{max} values following second doses, given at one and two hr intervals but not at the four hr interval.

The safety data reported adverse events related to opioid such as headache, vomiting, dizziness and nausea. The incidence of those adverse events did increase with fentanyl dose used in conjunction with naltrexone.

On *pharmacokinetics*, the CE commented overall that:

- The applicant has provided limited clinical data on the pharmacokinetics of PecFent but has provided the basic information required for a new route of administration for a well documented substance.
- While dose proportionality was seen within the dose range proposed it is noted that there was marked variability in the pharmacokinetics within and between studies. This is noted in passing by the applicant but dismissed as they are strongly recommending that dose titration is carried out on all patients including those switching to fentanyl nasal spray from an oral transmucosal fentanyl citrate product. The recommendation is supported by the literature²³ as it has been found that the clinically effective dose of a fentanyl product for the treatment of breakthrough pain cannot be predicted from the dose of background opioid medication or based on the use of other fentanyl-related products used previously and so titration to effect is essential.

The clinical evaluator noted concerns about the study in subjects with seasonal allergic rhinitis (SeAE) and currently there are no PK data to determine the dosing regimen of PecFent in patients with nasal congestion, as in seasonal allergic rhinitis.

Pharmacodynamic data

The CE stated that the applicant has not conducted any studies to explore the pharmacodynamics of fentanyl arguing that they are already well documented.

Efficacy/safety studies

Pivotal

CP043/06

A Multicentre, Placebo-controlled, Double-blind, Two-phase Crossover Study of Nasalfent (Fentanyl Citrate Nasal Spray- FCNS) in the Treatment of Breakthrough Cancer Pain (BTCP) in Subjects Taking Regular Opioid Therapy.

Male or female patients, aged 18 and older, who had a histologically documented diagnosis of a malignant solid tumour or a haematological malignancy causing cancer-related pain were enrolled in the study. Patients had to be taking regular; 24 hr medication (960 mg oral morphine or equivalent opioid) for underlying persistent cancer pain and typically having 1 to 4 episodes of BTCP per day to be eligible for participation.

Patients with uncontrolled or rapidly or escalating pain or whose condition was unstable or rapidly deteriorating were not to be enrolled. Additionally, patients with a medical position (that is, respiratory, cardiac, hepatic or renal, neurological or psychiatric) that would have made them unsuitable for the study were excluded. Patients with a history of alcohol or substance abuse or who had radiotherapy or other interventions that could have affected their pain within 30 days were also excluded.

A total of 139 patients were enrolled to enter Phase I (Open, Dose-Titration) of the study and 83 patients were randomised to the double blind treatment sequence (Phase II) of the study.

The study consisted of 4 parts:

1. Screening phase (up to 10 days)

²³ DeGregori *et al.* (2010). Individualising Pain Therapy with Opioids: The Rational Approach Based on Pharmacogenetics and Pharmacokinetics. *European Journal Pain Suppl*, 4: 245-250

2. Open, Dose Titration Phase (up to a maximum of 14 days) - Phase I. During this phase, the dose of Nasalfent was titrated for each patient until 2 consecutive episodes of target BTCP were successfully treated with the same dose without unacceptable adverse events (AEs). Study staff assisted patients in determining their individual effective doses using daily telephone contact. In this phase, patients received an initial dose of 100µg of Nasalfent, which could then be titrated up to 200 µg, 400 µg or 800 µg, until an effective dose for each patient was identified.
3. Double Blind Treatment Phase (a minimum of 2 days and a maximum of 21 days) - Phase II. Patients who successfully completed the open, dose titration phase then entered the double-blind phase. Each patient was supplied with a treatment pack containing 10 'blinded' bottles (each in child-resistant container), which contained in a random order either active Nasalfent, to be administered at the 'effective' dose found during Phase I (total of 7 bottles) or placebo (total of 3 bottles). The bottles were numbered 1 to 10 and each bottle was used to treat 1 episode of BTCP. For each treated episode, patients recorded a baseline pain intensity (PI) score, then after dosing with blinded study drug, recorded PI and pain relief (PR) at various time points out to 60 minutes, using an electronic diary (e-diary). Assessment also included specific questions about nasal tolerability.
4. End of Treatment Phase (occurred between 1 and 14 days after last dose). Patients returned to the clinic for final efficacy and safety assessments. Patients who discontinued early or did not enter the double-blind treatment phase but had taken at least 1 dose of study drug also returned for a final assessment.

Study treatments:

- Two concentrations of fentanyl citrate (Nasalfent) were available; 1.57 mg/mL and 6.28 mg/mL fentanyl citrate (equivalent to 1.0 and 4.0 mg/mL of fentanyl base) with each 0.1 mL spray providing a dose of 100 µg and 400 µg fentanyl respectively. Details of the formulation were not provided other than to state that it was the pectin formulation designed to modify fentanyl delivery.
- Nasalfent was packaged in a multidose Pfeiffer® spray device with the capacity for administration of eight 0.1 mL sprays. The device featured a self-advancing counter mechanism and emitted a loud click upon each actuation. Once 8 sprays had been administered, the mechanism locked out to prevent patients attempting to administer further doses from a spent bottle.
- Four dose levels were examined in the study: 100 µg, 400 µg, and 800 µg. Up to 4 episodes per day could have been treated with the study drug.
- For the Phase I (open, dose titration phase) study, drug was supplied as 1 bottle of 100 µg and 1 bottle of 400 µg per spray. For the Phase II (double blind, treatment phase) bottles marked 1 through 10 were supplied, each containing either Nasalfent at the strength used for the effective dose (total 7 bottles) or placebo (total 3 bottles), in a randomly designated order.
- For Phase II, there were therefore 2 possible drug packs:
 - Low strength: containing bottles with Nasalfent at 100 µg per spray for patients needing doses of 100 µg or 200 µg.
 - High strength: containing bottles with Nasalfent at 400 µg per spray for patients needing doses at 400 µg or 800 µg.
- The dosing interval in all clinical studies was at least 4 hrs.
- Compliance was assessed by reconciling doses recorded on the returned medication and the patient's record usage.

The *main efficacy variables* were:

- Summed pain intensity difference (SPID) at 10, 15, 45 and 60 minutes. The primary efficacy outcome was the patient's averaged SPID from 5 to 30 minutes post dose.
- PI scores at 5, 10, 15, 30, 45 and 60 minutes.
- Pain Intensity Difference (PID) from baseline at 5, 10, 15, 30, 45, and 60 minutes post dose.
- Pain relief (PR) score at 5, 10, 15, 30, 45 and 60 minutes post dose.
- Total pain relief (TOTPAR) score at 10, 15, 30, 45 and 60 minutes post dose.
- Patient acceptability scores at 30 and 60 minutes post dose.

Pain intensity was recorded in an e-diary using a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain'. The Last Observation Carried Forward (LOCF) method was used to input missing scores for evaluable episodes due to omission or use of rescue medication, prior to calculating the average value for each patient/treatment group. The higher the SPID score the better.

Pain relief scores were recorded in an e-diary using a 5 point rating scale where 0=none and 4= complete pain relief.

Patient acceptability scores were assessed using a 4 point scale: 1= not satisfactory, 2=not satisfied or dissatisfied, 3 = satisfied and 4= very satisfied. Patient average acceptability score was derived as the averaged acceptability scores across all episodes by treatment group.

Other efficacy variables included.

1. *Patient level endpoints:*

- Number and percentage of patients in each treatment group with a mean reduction in SPID of ≥ 2 , ≥ 3 , and ≥ 4 at 10, 15, 30, 45 and 60 minutes post dose.
- Number and percentage of patients in each treatment group with a $\geq 33\%$, $\geq 50\%$ and $\geq 66\%$ reduction in PI score from baseline at 5, 10, 15, 30, 45 and 60 minutes.
- Number and percentage of patients in each treatment group with %max TOTPAR of $\geq 33\%$, $\geq 50\%$, and $\geq 66\%$ at 10, 15, 30, 45 and 60 minutes.
- Number and percentage of patients in each treatment group with a mean patient acceptability score of ≥ 2 and ≥ 3 at 30 and 60 minutes post dose.
- Rescue medication usage.

2. *Episode level endpoints*

- Episode averaged SPID from time 0 to 30 minutes post dose
- Number and percentage of total treated episodes in each treatment group with a reduction in PI score of ≥ 1 and ≥ 2 at 5, 10, 15, 30, 45 and 60 minutes.
- Number and percentage of total treated episodes in each treatment group with a reduction in SPID score of ≥ 2 , ≥ 3 and ≥ 4 at 10, 15, 30, 45 and 60 minutes.
- Number and percentage of total treated episodes in each treatment group with a $\geq 33\%$, $\geq 50\%$, and $\geq 66\%$ reduction from baseline in PI score 5, 10, 15, 30, 45 and 60 minutes post dose.
- Episode time for a $\geq 33\%$, $\geq 50\%$, and $\geq 66\%$ reduction in PI score within 30 and 60 minutes post dose.

- Number and percentage of episodes where a patient experienced no increase in PI at any time point compared to baseline.
- Number and percentage of episodes achieving PR scores of ≥ 1 and ≥ 2 at 5, 10, 15, 30, 45 and 60 minutes post dose
- Episode time to achieve a PR score of ≥ 1 and ≥ 2 in episodes with and without rescue medication.
- Number and percentage of episodes in each treatment group with a %max TOTPAR of $\geq 33\%$, $\geq 50\%$, and $\geq 66\%$ at 10, 15, 30, 45 and 60 minutes post dose.
- Episode time to achieve total pain relief.
- Number and percentage of total treated episodes in each treatment group with episode acceptability scores of ≥ 2 and ≥ 3 at 30 and 60 minutes.
- Episode rescue medication usage.

The primary statistical analysis of efficacy was performed on what the applicant called the modified intent-to-treat (mITT) population. Supportive analyses for efficacy were performed on the mITT and per protocol (PP) population. $n=73$ for the mITT population defined as all patients in the randomised population that had treated at least 1 mITT evaluable episode with Nasalfent and 1 with placebo, where mITT evaluable episode was defined as the patient who had treated episode with study drug, had a baseline and at least 1 post baseline PI measurement and it was the only episode associated with a single bottle number. The PP population ($n=58$) was defined as all patients who were part of the mITT population and in whom at least 2 episodes identified as evaluable PP episodes had been treated, 1 with each of the 2 treatments (Nasalfent or placebo). All episodes identified as evaluable PP episodes were treated using part of an ascending sequence of bottle numbers. To demonstrate a difference in mean of 2.25 with a SD of 4.35 between Nasalfent and placebo with a power of 90% at a significance level of 0.05, a sample size of 80 patients was required for a crossover study. Assuming 33% of patients would not complete Phase I (open, dose titration phase) and an additional 33% would not complete taking the full 10 doses of study drug, 180 patients (about 4 – 5 patients per site) were needed to be enrolled into the Phase I (open dose titration) to ensure 80 patients completed the Phase II (double blind treatment phase).

All statistical tests were associated with significance criteria of $\alpha = 0.05$ (2 sided). Confidence intervals (CIs), where detailed, had 95% coverage probability, were 2 sided and were based on normal approximation.

The *CE's efficacy* conclusions are:

- The primary efficacy endpoint of this study was the SPID 30 minutes post dose. BTCP episodes treated with Nasalfent showed a mean SPID that was significantly higher than that for episodes treated with placebo (6.57 versus 4.45, respectively, $p < 0.0001$). This indicates that the overall degree of pain reduction at 30 minutes was significantly higher following Nasalfent treatment than following placebo treatment.
- The mean PI score was significantly lower following Nasalfent treatment than following placebo treatment at each observed time point from 5 to 60 minutes post dose.
- All secondary efficacy end points supported the superiority of Nasalfent to placebo.
- The use of rescue medication was significantly lower in Nasalfent treated episodes compared with placebo treated episodes up to 60 minutes after treatment.
- Patients reported significantly greater acceptability and satisfaction scores for Nasalfent spray as compared to placebo spray.

CP044/06

A Multicentre, Double-Blind, Double-Dummy, Two Phase, Crossover Study of Nasalfent (Fentanyl Citrate Nasal Spray) compared to immediate Release Morphine Sulphate (IRMS) tablets in the treatment of Breakthrough Cancer Pain (BTCP) in Subjects Taking Regular Opioid Therapy. The inclusion criteria were:

- Male or female patients, aged 18 or older, with a histological documented diagnosis of malignant solid tumour or a haematological malignancy causing cancer related pain
- Taking 60 mg of oral morphine or equivalent opioid for at least 1 week as regular, 24 hr medication for their underlying persistent cancer pain
- Typically had 1 to 4 episodes of BTCP per day
- Had an Eastern Cooperative Oncology Group (ECOG) score of ≤ 2 and a life expectancy at entry consistent with requirements of study.

Exclusion criteria were otherwise similar to those for Study CP043/06.

A total of 135 patients were enrolled and 110 patients entered the Phase II open dose titration phase. A total of 84 patients completed the Phase II and entered the Phase III treatment phase. A total of 79 patients completed the study.

The study consisted of 4 phases as follows:

1. Screening Phase (up to 10 days).
2. Open Dose Titration Phase (up to a maximum of 14 days): the dose of Nasalfent was titrated for each patient until 2 consecutive episodes for target BTCP were successfully treated with the same dose without unacceptable adverse events (AEs). Study staff assisted patients in determining their individual effective doses using daily telephone contact. Patients received an initial dose of 100 μg of Nasalfent, which could be titrated up to 200 μg , 400 μg or 800 μg until an effective dose for each patient was identified.
3. Double-blind, double-dummy Treatment Phase (3 to 21 days): Patients treated 10 episodes of BTCP with treatments from blinded samples of both nasal spray and tablets.
4. End of Treatment Phase: (between 1 and 14 days after last dose): final assessments were performed in the clinic after 10 episodes of BTCP were completed.

For the study treatments:

- Nasalfent was provided in 2 strengths: 1.57 mg/mL and 6.28 mg/mL fentanyl citrate²⁴
- The dose titration phase in this study was the same as for Study CP043/06.
- Once the effective dose was determined in the Phase II dose titration phase, the "effective" dose for each patient was supplied in the Phase III double-blind phase. Possible effective doses were 100 μg , 200 μg , 400 μg and 800 μg . Both the 100 μg and 200 μg doses were administered using a 100 μg /spray "low dose" bottle. The 400 μg and 800 μg were administered using a 400 μg /spray "high dose" bottle. Since the Nasalfent packs come in 2 different strengths (low and high), separate randomisation code lists were generated for each of these 2 dose level drug packs using blocks of 2 sequences (AB or BA).

²⁴ Sponsor comment: "Equivalent to 1.0 and 4.0 mg/mL of fentanyl base."

- The immediate release morphine sulfate (IRMS) comparator was Sevredol (Napp Pharmaceuticals, UK). It comes in 3 strengths: 10 mg, 20 mg and 50 mg of morphine sulphate.
- The dose of IRMS was determined according to the established principal of one-sixth of the daily morphine dose equivalent of background opioid medication or the patient's previously "effective" dose of IRMS for BTCP if known prior to study entry.
- To preserve the blinding of the study, the tablets were over-encapsulated using a brown size 1 hard gelatine capsule. Placebo capsules were manufactured to match.
- The IRMS was dispensed in blister packs containing the appropriate number of encapsulated tablets. Each IRMS blister pack contained 6 capsules allocated to each dose (a total of 60 capsules) consisting of the following:
 - 3 of the 50 mg, 2 of the 20 mg and 1 of the 10 mg strengths so that all doses up to 200 mg could be selected from the capsules supplied
 - or matching placebo capsules
- The blister pack was designed such that the strength of each unmarked capsule in the pack was clearly identified by means of text and colours; capsules were identified as "50 mg", "20 mg", and "10 mg" with both active and matched placebo blister packs being identical in appearance. In addition, each blister pack had a panel in which study staff marked which combination of the 6 capsules were to be taken by an individual patient for each episode treated (and against which the actual dose taken could be checked).
- In the Phase II (open dose titration phase), each patient was supplied with 1 bottle of 100 µg per spray and 1 bottle of 400 µg per spray. After each dose, the patient was instructed to record the dosing details on the diary. During Phase III (double – blind, double dummy phase), each patient was supplied with 2 separate drug packs: 1 for Nasalfent containing 10 blinded bottles and 1 for IRMS containing blinded blisters of encapsulated tablets.
- The 10 bottles from the Nasalfent pack and the corresponding blisters from the IRMS pack were used together in the order in which they were numbered (Dose 01 to Dose 10) for each of the 10 episodes of BTCP being treated. For each dose, this provided treatment with either Nasalfent combined with placebo capsules or IRMS capsules combined with placebo nasal spray. Each patient was randomly allocated to one of 2 treatment sequences (where N = Nasalfent and S = IRMS):
 - A: S N S N N S S N S N
 - B: N S N S S N N S N S

The 2 sequences were balanced with no more than 2 consecutive periods of the same treatment.

The *key efficacy variables* were:

- Summed pain intensity difference (SPID) at 10, 15, 30, 45 and 60 minutes post dose. The *primary efficacy outcome* was pain intensity difference 15 minutes after dosing (PID_{15mins}), defined as the recorded difference between PI at that time point and baseline. The PI was measured on a rating scale of 0 to 10 where 0 = no pain and 10 = worst possible pain.
- Pain intensity (PI) at 5, 10, 30, 45 and 60 minutes post dose
- Pain Intensity Difference (PID) at baseline, 5, 10, 30, 45 and 60 minutes post dose
- Pain relief (PR) at 5, 10, 15, 30, 45 and 60 minutes post dose

- Total pain relief (TOTPAR) at 10, 15, 30, 45 and 60 minutes post dose
- Patient acceptability scores at 30 and 60 minutes post dose including overall satisfaction, ease of use, and convenience.

The scales used to measure pain intensity, pain relief and patient acceptability were the same as for Study 043/06.

Other efficacy variables included:

1. *Patient Level Endpoints*

- Number and percentage of all patients in each treatment group with a mean reduction in PI score of ≥ 1 and ≥ 2 at 5, 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all patients in each treatment group with a mean SPID score of ≥ 2 , ≥ 3 and ≥ 4 at 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all patients in each treatment group with $\geq 33\%$, $\geq 50\%$ and $\geq 66\%$ reduction in PI score from baseline at 5, 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all patients in each treatment group with a %max TOTPAR score of $\geq 33\%$, $\geq 50\%$ and $\geq 66\%$ at 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all patients in each treatment group with a mean patient acceptability score of ≥ 2 and ≥ 3 at 30 and 60 minutes post dose
- Rescue medication usage and time to rescue medication

2. *Episode Level Endpoints*

- Episode PID at 5, 10, 15, 30, 45 and 60 minutes post dose in each treatment group
- Number and percentage of all treated episodes in each treatment group with a reduction in PI score of ≥ 1 and ≥ 2 at 5, 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all treated episodes in each treatment group with a mean SPID score of ≥ 2 , ≥ 3 and ≥ 4 at 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all treated episodes in each treatment group with $\geq 33\%$, $\geq 50\%$ and $\geq 66\%$ reduction in PI score from baseline at 5, 10, 15, 30, 45 and 60 minutes post dose
- Episode time to $\geq 33\%$, $\geq 50\%$ and $\geq 66\%$ reduction in PI score within 30 and 60 minutes post dose
- Number and percentage of episodes where a patient experiences no increase in PI at any time point compared to baseline
- Number and percentage of episodes achieving a PR score of ≥ 1 and ≥ 2 at 5, 10, 15, 30, 45 and 60 minutes post dose
- Episode time to achieve ≥ 1 and ≥ 2 PR score within 30 and 60 minutes post dose
- Number and percentage of episodes in each treatment group with a %max TOTPAR score of $\geq 33\%$, $\geq 50\%$ and $\geq 66\%$ at 10, 15, 30, 45 and 60 minutes post dose
- Episode time to achieve total PR
- Number and percentage of total treated episodes in each treatment group with a episode acceptability score of ≥ 2 and ≥ 3 at 30 and 60 minutes post dose
- Episode rescue medication range and time to rescue medication

The primary statistical analyses of efficacy were performed on the mITT population. All secondary efficacy analyses were performed on the mITT and PP populations. The safety

analyses were performed on the safety population. n= 79 for the mITT population defined as all patients in the randomised population that had treated at least 1 mITT- evaluable episode with Nasalfent and 1 IRMS. A mITT evaluable episode is defined as an episode treated with either Nasalfent spray and placebo capsule or IRMS capsule and placebo spray; and a patient had a baseline and at least 1 post baseline PI measurement; and it was the only episode associated with a single bottle number and a single blister pack row. Both the bottle number used for the episode and the blister pack row must have non-missing records in the dataset for an episode to be considered mITT evaluable. n= 72 for the PP population defined as all patients who were part of the mITT population and in whom at least 2 episodes identified as evaluable PP episodes had been treated, 1 with each of the two treatments (Nasalfent or IRMS), and all episodes identified as evaluable PP episodes were treated using part of an ascending sequence of bottle and blister numbers whose numbers matched. It was estimated that the ratio of the effect size to SE would be about 3.15 for a sample size of 75 patients. Assuming 33% of patients would not complete the Phase II dose titration stage and an additional 33% would discontinue prior to taking all 10 doses of the study drug, 180 patients (about 3-4 per site) were needed to enter the Phase III to ensure 80 patients completed Phase III (double-blind phase).

The *primary end point* was analysed using analysis of covariance (ANCOVA). The PID15mins score was the dependent variable and the model contained terms for treatment groups (Nasalfent and IRMS) and study centre. The centre was created by pooling the sites. The generalised least squares estimates for the 2 treatment groups were obtained with a random effect for patients. The generalised least squares of the estimates of the overall mean and the type 2 tests of fixed effects for treatment and pooled study centre were determined. Covariates for age category (≤ 60 years, >60 years), sequence, treatment pooled centre, and use of rescue medication were also examined.

Summary statistics for the continuous end points (SPID at 10, 15, 45 and 60 mins; TOTPAR at 10, 15, 30, 45 and 60 mins; PI at 5, 10, 15, 30, 45 and 60 mins; PID at 5, 10, 15, 30, 45 and 60 mins; and PR at 5, 10, 15, 30, 45 and 60 mins) included sample size (n), mean, standard deviation (SD), standard error (SE) and minimum and maximum values by Nasalfent and IRMS. SPID at 10, 15, 45 and 60 mins and TOTPAR at 10, 15, 30, 45 and 60 mins were analysed using a similar ANCOVA model as for the primary end point analysis described above. Differences in PID at 5, 10, 15, 30, 45 and 60 mins and PR at 5, 10, 15, 30, 45 and 60 mins between treatments (Nasalfent and IRMS) at each time point and patient averaged acceptability scores were analysed using a Wilcoxin signed rank test. For many endpoints, analyses of patient and episode means were also conducted.

All hypothesis testing was conducted using two-sided tests with alpha set at the 0.05 level of significance. Data were summarised by Nasalfent dose level (all doses, 100 μ g, 200 μ g, 400 μ g and 800 μ g) and IRMS. Descriptive statistics (mean, median, SD, SE, minimum and maximum, frequencies, percentages) were used to describe baseline characteristics for treatment doses (Nasalfent 100 μ g, 200 μ g, 400 μ g and 800 μ g), treatments (Nasalfent and IRMS) and all patients. Summary statistics for categorical patient-level end points included number and percentage for each response category. Categorical episode end points were summarised, by treatment doses and for all patients, by treatments.

Mean, SD, SE, median and range of time was provided for time to event end points. In addition, as the Nasalfent and IRMS episode time to events could have been correlated within patient, time to event end points were analysed using a Cox model for multiple correlated events.

The *CE's efficacy conclusions* are:

- The primary efficacy end point was the PID at 15 minutes post dose. With Nasalfent treatment, the mean PID score was significantly higher than with IRMS treatment

(3.02 versus 2.69, $p=0.0396$) indicating a higher degree of pain reduction with Nasalfent at 15 minutes

- The superiority of Nasalfent over IRMS appeared as early as 5 minutes after dosing in the episode based analyses, with statistically significant differences in the percentage of episodes showing a beneficial change in PI and PR scores following Nasalfent treatment than following IRMS ($p=0.0326$ and $p=0.009$ respectively)
- At the 10 minutes post dose, the episode based analyses showed statistically significant differences in a range of end points:
 - PID ($p=0.0432$)
 - Percentage of episodes with ≥ 1 point improvement in PR ($p=0.011$)
 - Percentage of episodes with ≥ 2 point improvement in PI ($p=0.0181$)
 - Percentage of episodes with $\geq 33\%$ improvement in PI ($p=0.0357$)

Supportive studies

CP/041/04

A Phase II, open label, non comparative, multicentre study to determine the efficacy, acceptability to patients and safety and tolerability of the pectin formulation of nasal fentanyl solution for the relief of breakthrough pain in cancer patients.

Sufficiently well in-patients aged >18 years [mean age (59 ± 9 years), range (43 -75 years)] were enrolled. Patients were given a nasal fentanyl solution for up to a maximum of 7 episodes of breakthrough cancer pain (BTCP). The study was conducted in two parts. Part 1 involved a dose escalation sequence to identify the efficacious dose. Part 2 used the efficacious dose from Part 1 for 4 episodes of BTCP (see Table 5 below).

Table 5. Dosage regimen for Part 2

Episode of BTP	Strength Used	1st Dose	2nd Dose	3rd Dose	Max Cumulative Dose
First BTP	0.25 mg/mL	25 μ g	25 μ g	50 μ g	100 μ g
Second BTP	1.0 mg/mL	100 μ g	100 μ g	200 μ g	400 μ g
Third BTP	4.0 mg/mL	400 μ g	400 μ g	-	800 μ g
Fourth-seventh	Used the effective dose attained in Part I (1 st - 3 rd BTP)				

Of the 29 patients enrolled, 23 entered Part 1, 18 completed it and 3 had no pain relief at the highest dose of 800 μ g. Fifteen of the 18 patients entered Part 2 and 3 failed to complete all 4 episodes of BTCP needed for assessment. Those 3 patients were nonetheless included in efficacy assessment (55 episodes of BTCP in 15 patients included in efficacy assessment). All 23 patients entered in Part 1 were eligible for safety assessment. Pain relief and intensity were assessed by the patient using 9 and 5 point scales respectively.

The *primary efficacy parameters* for effective relief of breakthrough cancer pain include:

- Reduction in the pain score
- Time to meaningful pain relief
- Onset of pain relief
- Duration of pain relief

Pain intensity and pain relief were recorded at regular intervals for up to 4 h after dosing.

The *secondary measures* were nasal and other symptom scores (eg levels of sedation, giddiness, nausea) collected as reported for 4 h after dosing in Part 2 and an overall satisfaction rating.

On the *efficacy outcome* for the 'Run- In Dose Response' (Part 1) phase, the CE stated that all doses of nasal fentanyl were effective in at least one patient. The following table represents the frequency of the successful dose in the patients in the data set.

Dose	Frequency	% of Total	Cumulative %
25 µg	3	20.00%	20.00%
50 µg	3	20.00%	40.00%
100 µg	1	6.67%	46.67%
200 µg	2	13.33%	60.00%
400 µg	4	26.67%	86.67%
800 µg	2	13.33%	100.00%

On the efficacy outcome for Part 2 phase, the CE stated that all 15 patients experienced meaningful pain at their individual selected doses.

On average patients experienced changes in PID and PR within 5 minutes of dosing. Maximal mean (\pm SD) patient PID (1.6 ± 0.5) and PR (2.2 ± 0.9) scores were reached at 60 minutes and 45 minutes post dose respectively (median 60 and 30 min post dose). PIDs remained significantly different from baseline between the time of maximal effect (60 minutes) and the end of the assessment period (240 minutes) despite a reduction in the number of patients assessed. PR scores remained significantly different from baseline between the mean time of maximal effect (45 mins) and 90 mins.

The median (25, 75% quartiles) time to onset of pain relief and time to onset of meaningful time relief was 9.3 mins (8.3, 16.3) and 32.0 mins (26.0, 41.8) based on per patient analysis and 10.0 (6.0, 17.0) and 46.0 (22.0, 218.0) based on per episode analysis. The mean (\pm SD) duration of meaningful pain relief was 86.0 ± 59.6 mins.

Ten (10) out of 13 patients (77%) who responded to the overall satisfaction question rated the drug-product as "good" or "better".

Safety aspects as per CE

The CE stated that there was 'naltrexone block' in the PK studies in healthy volunteers. The Delegate therefore considers the limited safety data from those PK studies to be confounded and of insignificant relevance when assessing the safety of Nasalfent in the management of BTCP. The safety data from short term studies CP043/06, CP044/06, CP041/04 and long term study CP045/06 will be considered in this overview.

(Study CP045/06 was an open label study. The objectives were to provide continued access to Nasalfent for patients who had gained clinical benefit from its use during their participation in the efficacy trial program and to provide additional data on the long term safety of Nasalfent in the treatment of patients with BTCP. In addition to the patients on continued use of nasalfent, new patients were also recruited to enter the 4 phases of study previously described for the efficacy studies except that the double-blind treatment phase

was replaced by an open label phase. The safety data extended from January 2007 to March 2010).

A total of 42,227 BTCP episodes were treated (23,936 episodes for newly treated patients; 12,538 episodes from Study CP043/06 and 5,753 episodes from Study CP044/06). For the short term studies, 389 (75.4%) subjects reported one or more adverse events. Adverse events were experienced by higher proportion of subjects receiving 400 µg (43.6%) and 800 µg (62.1%) than subjects receiving 100 µg (31.0%) or 200 µg (28.0%). This is likely a reflection of the higher numbers of episodes treated with the higher doses.

Most adverse events were mild or moderate in intensity: 142 (27.5%) subjects had severe adverse events at some point during the studies. Adverse events reported by >2.5 % off all subjects in descending order of incidence from the short term studies data are shown in the table below.

Table 7. Adverse events reported by >2.5 % off all subjects in descending order of incidence.

Preferred Term	N (%)				
	100 µg (N=484)	200 µg (N=389)	400 µg (N=319)	800 µg (N=182)	Total (N=516)
Subjects with >1 AE	150 (31.0)	109 (28.0)	139 (43.6)	113 (62.1)	389 (75.4)
Vomiting	20 (4.1)	20 (5.1)	21 (6.6)	14 (7.7)	71 (13.8)
Nausea	23 (4.8)	15 (3.9)	12 (3.8)	14 (7.7)	63 (12.2)
Disease progression	16 (3.3)	8 (2.1)	16 (5.0)	26 (14.3)	62 (12.0)
Constipation	23 (4.8)	6 (1.5)	14 (4.4)	8 (4.4)	50 (9.7)
Dizziness	16 (3.3)	14 (3.6)	8 (2.5)	9 (4.9)	42 (8.1)
Somnolence	10 (2.1)	8 (2.1)	14 (4.4)	7 (3.8)	36 (7.0)
Pyrexia	7 (1.4)	6 (1.5)	9 (2.8)	7 (3.8)	28 (5.4)
Pain	5 (1.0)	4 (1.0)	8 (2.5)	8 (4.4)	24 (4.7)
Dyspnoea	9 (1.9)	4 (1.0)	5 (1.6)	5 (2.7)	23 (4.5)
Diarrhoea	7 (1.4)	4 (1.0)	6 (1.9)	6 (3.3)	22 (4.3)
Headache	9 (1.9)	7 (1.8)	2 (0.6)	2 (1.1)	20 (3.9)
Anaemia	1 (0.2)	8 (2.1)	4 (1.3)	6 (3.3)	19 (3.7)
Fatigue	3 (0.6)	3 (0.8)	9 (2.8)	5 (2.7)	19 (3.7)
Oedema peripheral	1 (0.2)	5 (1.3)	7 (2.2)	6 (3.3)	19 (3.7)
Dehydration	1 (0.2)	7 (1.8)	4 (1.3)	7 (3.8)	18 (3.5)
Anxiety	4 (0.8)	3 (0.8)	7 (2.2)	3 (1.6)	17 (3.3)
Insomnia	2 (0.4)	6 (1.5)	6 (1.9)	3 (1.6)	17 (3.3)
Asthenia	4 (0.8)	3 (0.8)	7 (2.2)	2 (1.1)	16 (3.1)
Epistaxis	6 (1.2)	3 (0.8)	3 (0.9)	5 (2.7)	15 (2.9)
Cough	4 (0.8)	0 (0.0)	7 (2.2)	3 (1.6)	14 (2.7)
Pharyngolaryngeal	4 (0.8)	5 (1.3)	3 (0.9)	3 (1.6)	14 (2.7)

In the long term study (CP045/06) a total of 131 (85.6%) of the 153 long term patients had at least one adverse event. At the 100, 200 and 400 µg dose levels, the majority of patients did not report adverse events. Severity of AEs was mild or moderate for the majority of patients reporting AEs and most patients did not have an AE considered by the investigator to be treatment related. The following table shows the AE reported by >2.5%

of the long term subjects in total descending order of incidence and demonstrates similar AE profile as in the short term treated patients (see table above).

Table 8. AEs reported by >2.5% of the long term subjects in total descending order of incidence.

Preferred Term	N (%)				
	100 µg (N=144)	200 µg (N=130)	400 µg (N=110)	800 µg (N=67)	Total (N=153)
Subjects with ≥ 1 AE	38 (26.4)	30(23.1)	47 (42.7)	52 (77.6)	131 (85.6)
Disease progression	8 (5.6)	2 (1.5)	5 (4.5)	11 (16.4)	24 (15.7)
Vomiting	5 (3.5)	2 (1.5)	7 (6.4)	10 (14.9)	23 (15.0)
Nausea	2 (1.4)	4 (3.1)	5 (4.5)	8 (11.9)	19 (12.4)
Constipation	7 (4.9)	1 (0.8)	6 (5.5)	2 (3.0)	15 (9.8)
Dizziness	4 (2.8)	6 (4.6)	1 (0.9)	4 (6.0)	13 (8.5)
Diarrhoea	3 (2.1)	1 (0.8)	3 (2.7)	4 (6.0)	11 (7.2)
Somnolence	3 (2.1)	2 (1.5)	5 (4.5)	3 (4.5)	11 (7.2)
Pain	2 (1.4)	2 (1.5)	2 (1.8)	5 (7.5)	10 (6.5)
Pharyngolaryngeal pain	3 (2.1)	4 (3.1)	1 (0.9)	2 (3.0)	9 (5.9)
Pyrexia	3 (2.1)	0 (0.0)	4 (3.6)	2 (3.0)	9 (5.9)
Rhinorrhoea	2 (1.4)	2 (1.5)	0 (0.0)	4 (6.0)	8 (5.2)
Oedema peripheral	0 (0.0)	0 (0.0)	3 (2.7)	4 (6.0)	7 (4.6)
Cancer pain	1 (0.7)	0 (0.0)	3 (2.7)	3 (4.5)	6 (3.9)
Dysgeusia	3 (2.1)	1 (0.8)	1 (0.9)	1 (1.5)	6 (3.9)
Headache	3 (2.1)	1 (0.8)	0 (0.0)	2 (3.0)	6 (3.9)
Insomnia	1 (0.7)	1 (0.8)	3 (2.7)	1 (1.5)	6 (3.9)
Nasal discomfort	2 (1.4)	2 (1.5)	2 (1.8)	1 (1.5)	6 (3.9)
Anaemia	0 (0.0)	2 (1.5)	2 (1.8)	1 (1.5)	5 (3.3)
Asthenia	0 (0.0)	2 (1.5)	2 (1.8)	1 (1.5)	5 (3.3)
Dehydration	0 (0.0)	2 (1.5)	2 (1.8)	2 (3.0)	5 (3.3)
Epistaxis	2 (1.4)	2 (1.5)	1 (0.9)	2 (3.0)	5 (3.3)
Fatigue	2 (1.4)	0 (0.0)	3 (2.7)	1 (1.5)	5 (3.3)
Gastritis	2 (1.4)	1 (0.8)	2 (1.8)	0 (0.0)	5 (3.3)
Nasopharyngitis	2 (1.4)	1 (0.8)	0 (0.0)	2 (3.0)	5 (3.3)
Pruritus	1 (0.7)	1 (0.8)	1 (0.9)	2 (3.0)	5 (3.3)
Urinary tract infection	1 (0.7)	0 (0.0)	2 (1.8)	2 (3.0)	5 (3.3)
Abdominal pain	1 (0.7)	0 (0.0)	3 (2.7)	0 (0.0)	4 (2.6)
Anxiety	0 (0.0)	1 (0.8)	2 (1.8)	1 (1.5)	4 (2.6)
Arthralgia	0 (0.0)	0 (0.0)	3 (2.7)	1 (1.5)	4 (2.6)
Bronchitis	0 (0.0)	1 (0.8)	2 (1.8)	1 (1.5)	4 (2.6)
Confusional state	0 (0.0)	0 (0.0)	2 (1.8)	2 (3.0)	4 (2.6)
Cough	1 (0.7)	0 (0.0)	3 (2.7)	0 (0.0)	4 (2.6)
Infection	1 (0.7)	0 (0.0)	2 (1.8)	2 (3.0)	4 (2.6)
Non-cardiac chest pain	1 (0.7)	1 (0.8)	2 (1.8)	0 (0.0)	4 (2.6)
Upper respiratory tract infection	1 (0.7)	0 (0.0)	2 (1.8)	1 (1.5)	4 (2.6)

Adverse events with incidence >1% for the total safety population (that is, short and long term studies) by system organ/ preferred term in descending order are shown below.

Table 9. Adverse events with incidence >1% for the total safety population by System Organ Class/Preferred Term. Table continued across two pages.

System Organ Class Preferred Term	100 µg N=484	200µg N=389	400µg N=319	800µg N=182	Total N=516
Number(%) of Subjects with at Least One AE	125 (25.8)	93 (23.9)	111 (34.8)	90 (49.5)	340 (65.9)
Blood and Lymphatic System Disorders					
Anaemia	1 (0.2)	8 (2.1)	4 (1.3)	6 (3.3)	19 (3.7)
Neutropenia	1 (0.2)	2 (0.5)	0 (0.0)	4 (2.2)	7 (1.4)
Cardiac Disorders					
Cardio-respiratory Arrest	0 (0.0)	2 (0.5)	4 (1.3)	0 (0.0)	6 (1.2)
Gastrointestinal Disorders					
Vomiting	0(4.1)	20 (5.1)	21 (6.6)	14 (7.7)	71 (13.8)
Nausea	23 (4.8)	15 (3.9)	12 (3.8)	14 (7.7)	63 (12.2)
Constipation	23 (4.8)	6 (1.5)	14 (4.4)	8 (4.4)	50 (9.7)
Diarrhoea	7 (1.4)	4 (1.0)	6 (1.9)	6 (3.3)	22 (4.3)
Abdominal Pain	3 (0.6)	1 (0.3)	6 (1.9)	1 (0.5)	11 (2.1)
Gastritis	3 (0.6)	2 (0.5)	3 (0.9)	2 (1.1)	10(1.9)
General Disorders and Administration Site Conditions					
Disease Progression	16 (3.3)	8 (2.1)	16 (5.0)	26 (14.3)	62 (12.0)
Pyrexia	7 (1.4)	6 (1.5)	9 (2.8)	7 (3.8)	28 (5.4)
Pain	5 (1.0)	4 (1.0)	8 (2.5)	8 (4.4)	24 (4.7)
Fatigue	3 (0.6)	3 (0.8)	9 (2.8)	5 (2.7)	19 (3.7)
Oedema Peripheral	1 (0.2)	5 (1.3)	7 (2.2)	6 (3.3)	19 (3.7)
Asthenia	4 (0.8)	3 (0.8)	7 (2.2)	2 (1.1)	16 (3.1)
Non-cardiac Chest Pain	1 (0.2)	1 (0.3)	3 (0.9)	1 (0.5)	6 (1.2)

System Organ Class Preferred Term	100 µg N=484	200µg N=389	400µg N=319	800µg N=182	Total N=516
Immune System Disorders					
Hypersensitivity	1(0.2)	1(0.3)	2(0.6)	3(1.6)	7(1.4)
Infections and Infestations					
Urinary Tract Infection	4 (0.8)	1 (0.3)	4 (1.3)	4 (2.2)	13 (2.5)
Pneumonia	3 (0.6)	4 (1.0)	3 (0.9)	1 (0.5)	10(1.9)
Nasopharyngitis	4 (0.8)	2 (0.5)	0 (0.0)	3 (1.6)	9 (1.7)
Infection	4 (0.8)	0 (0.0)	2 (0.6)	3 (1.6)	8 (1.6)
Rhinitis	2 (0.4)	3 (0.8)	0 (0.0)	1 (0.5)	6 (1.2)
Investigations					
Weight Decreased	2 (0.4)	0 (0.0)	2 (0.6)	2 (1.1)	6 (1.2)
Metabolism and Nutrition Disorders					
Dehydration	1 (0.2)	7 (1.8)	4 (1.3)	7 (3.8)	18 (3.5)
Decreased Appetite	1 (0.2)	3 (0.8)	5 (1.6)	2 (1.1)	11 (2.1)
Hyperglycaemia	3 (0.6)	2 (0.5)	2 (0.6)	1 (0.5)	8 (1.6)
Musculoskeletal and Connective Tissue Disorders					
Back Pain	1 (0.2)	0 (0.0)	5 (1.6)	1 (0.5)	7 (1.4)
Pain In Extremity	0 (0.0)	1 (0.3)	4 (1.3)	2 (1.1)	7 (1.4)
Neoplasms Benign. Malignant and Unspecified (incl Cysts and Polyps)					
Cancer Pain	3 (0.6)	2 (0.5)	5 (1.6)	4 (2.2)	13 (2.5)
Nervous System Disorders					
Dizziness	16 (3.3)	14 (3.6)	8 (2.5)	9 (4.9)	42 (8.1)
Sonmotence	10 (2.1)	8 (2.1)	14 (4.4)	7 (3.8)	36 (7.0)

System Organ Class Preferred Term	100 µg N=484	200µg N=389	400µg N=319	800µg N=182	Total N=516
Headache	9 (1.9)	7 (1.8)	2 (0.6)	2 (1.1)	20 (3.9)
Dysgeusia	5 (1.0)	1 (0.3)	2 (0.6)	1 (0.5)	9 (1.7)
Psychiatric Disorders					
Anxiety	4 (0.8)	3 (0.8)	7 (2.2)	3 (1.6)	17 (3.3)
Insomnia	2 (0.4)	6 (1.5)	6 (1.9)	3 (1.6)	17 (3.3)
Depression	3 (0.6)	2 (0.5)	0 (0.0)	5 (2.7)	10(1.9)
Confusional State	1 (0.2)	0 (0.0)	5 (1.6)	3 (1.6)	9 (1.7)
Disorientation	2 (0.4)	2 (0.5)	4 (1.3)	0 (0.0)	7 (1.4)
Respiratory, Thoracic and Mediastinal Disorders					
Dyspnoea	9 (1.9)	4 (1.0)	5 (1.6)	5 (2.7)	23 (4.5)
Epistaxis	6 (1.2)	3 (0.8)	3 (0.9)	5 (2.7)	15 (2.9)
Cough	4 (0.8)	0 (0.0)	7 (2.2)	3 (1.6)	14 (2.7)
Pharyngolaryngeal Pain	4 (0.8)	5 (1.3)	3 (0.9)	3 (1.6)	14 (2.7)
Nasal Discomfort	6 (1.2)	2 (0.5)	4 (1.3)	1 (0.5)	11 (2.1)
Rhinorrhoea	5 (1.0)	2 (0.5)	1 (0.3)	5 (2.7)	11 (2.1)
Nasal Congestion	3 (0.6)	3 (0.8)	0 (0.0)	0 (0.0)	6 (1.2)
Postnasal Drip	2 (0.4)	1 (0.3)	2 (0.6)	1 (0.5)	6 (1.2)
Skin and Subcutaneous Tissue Disorders					
Pruritus	3 (0.6)	2 (0.5)	3 (2.2)	4 (2.2)	12 (2.3)
Hyperhidrosis	3 (0.6)	1 (0.3)	3 (0.9)	2 (1.1)	9 (1.7)
Decubitus Ulcer	1 (0.2)	1 (0.3)	2 (0.6)	2 (1.1)	6 (1.2)
Vascular Disorders					
Hypertension	5 (1.0)	0 (0.0)	2 (0.6)	1 (0.5)	8 (1.6)
Deep Vein Thrombosis	1 (0.2)	2 (0.5)	1 (0.3)	2 (1.1)	6 (1.2)

Regarding treatment related adverse events (adverse drug reactions), the CE stated that during the short term studies, 28.9% of subjects experienced events that were assessed by the investigator as possibly, probably or definitely treatment related. The most common events included dizziness 6.2 %, vomiting 4.8%, somnolence 4.8%, nausea 4.5% and constipation 2.9%.

Regarding deaths, the CE stated that:

A total of 88 (16.8%) patient deaths were reported during the Phase II/III studies. These deaths included two patients (from Study CP041/04) who were receiving 50 µg FCNS, one subject in (Study CP043/06) with a fatal adverse event associated with placebo, one patient (in Study CP044/06) with a fatal adverse event associated with IRMS and one patient who died due to a non-treatment emergent adverse event (urinary tract infection) following withdrawal from Study CP045/06.

Sixty-five (12.4%) patients died while on-study, 18 (3.4%) patients died following withdrawal and six (1.1%) patients died after they completed their respective studies. An additional six patients died following participation in Study CP041/04 without any adverse event relating to the drug. The last dose of FCNS taken by these patients was 25 µg, 50 µg, 200 µg and 400 µg in one patient each, and 800 µg in two patients. These deaths occurred between three and 25 days following the last dose of study medication.

Two patients had AEs that resulted in death and were assessed by the investigator as possibly treatment related. One patient developed anuria, cardiovascular insufficiency and hypotension during the dose titration phase and one dose maintained patient developed constipation, intestinal perforation and peritonitis.

A total of 15 (9.8%) long-term patients died, 9 of who died due to disease progression. None of the deaths were considered by the investigator to be due to treatment-related adverse events.

As for serious adverse events (SAE), the CE stated that:

A total of 134 (26.0%) patients experienced SAEs during the pivotal studies. The most frequent SAE was disease progression (36 patients 7%). Seven (1.4%) patients had treatment related SAEs.

A total of 22 (4.3%) patients experienced SAEs during the dose titration phase of the studies. Fifteen (2.9%) had non-fatal SAEs. The SAEs included disease progression in 4 (0.8%) patients, pneumonia in 3 (0.6%) patients and anaemia and dyspnoea in 2 (0.4%) patients each. All other SAEs were reported for a single patient.

A total of 99 (28.6%) patients experienced SAEs during dose maintained treatment phase of the studies. Forty-five (13.0%) patients had non-fatal SAEs. The most common SAE overall was disease progression (7.8%); all other SAEs were reported by fewer than 2% of all dose maintained subjects. Most SAEs were considered to be severe in intensity.

Three (0.9%) patients had SAEs during the dose maintained treatment. These were assessed by the study investigator as possibly or probably treatment related. One patient had SAEs that resulted in death (noted above) that were possibly treatment related. Two patients had non-fatal SAEs (dyspnoea in a 200 µg treated patient); cyanosis, loss of consciousness and upper airway obstruction in a 400 µg treated patient, that were possibly or probably treatment related.

A total of 36 (23.5%) long-term subjects had SAEs; 26 (17.0%) long-term subjects had non-fatal SAEs. Three subjects (two in 400 µg and one in 800 µg) had treatment-related non-fatal SAEs, each considered by the investigator to be possibly related to fentanyl nasal spray. The most common SAEs were disease progression (9 patients) and pain (3 patients).

On *the overall conclusions* on clinical safety, the CE stated that:

- Safety data has been appropriately collected in all the clinical trials. While the total number of patients studied is not large, fentanyl is a well documented substance and no new safety issues have emerged with the nasal spray formulation. It is noted that the nasal spray was administered concomitantly with the patient's regular opioid medication in all cases and the high background rate of adverse events in this patient population makes assessment of safety of the nasal formulation difficult.
- Local nasal tolerability appears satisfactory.

Post marketing experience

The CE stated that:

One PSUR was included in the submission, covering the period 31 August 2010 to 28 February 2011.

PecFent was approved in the European Union via the centralised procedure on 31 August 2010. The product was launched in the United Kingdom on 4 October 2010 and it is currently marketed in three countries; UK, Ireland (launched 18 October 2010) and Germany (launched 22 November 2010).

From launch on 4 October 2010 to 31 December 2010, 5885 bottles of the 100 µg strength and 4525 bottles of the 400 µg strength have been sold in the EU (ex-factory). Information on the number of bottles actually prescribed is unknown due to the lag in companies obtaining prescribing information.

Estimated post-marketing exposure to PecFent has been calculated as an average of between 11,528 and 34,915 "patient days" of treatment during the PSUR period based on available sales data and fentanyl citrate defined daily dose.

Six adverse reports have been received by the company in this time. The reports were:

- one serious spontaneous unlisted case of a female patient of an unknown age who experienced visual disturbance (black spots) whilst taking PecFent (fentanyl citrate) for an unreported indication. The prescriber stopped the treatment with PecFent and outcome of the event was unknown. The patient was said to be "...very sick..." and terminal, was taking a variety of largely unspecified medications and the case is without much detail. The company physician assessed the causal relationship as possible on the basis of the implied temporal relationship, and
- five confirmed reports concerning non-serious listed adverse events.

To date, there have been no new safety signals and no reports of accidental exposure, overdose or misuse/abuse.

Another PSUR was submitted by the sponsor after the data lock out point for formal evaluation by the TGA. The PSUR period covered was 1 March 2011 to 31 August 2011. The sponsor's executive summary states that:

Estimated post marketing exposure to PecFent has been calculated as an average of between 95,932 and 293,912 "patient days" of treatment during the PSUR period based on available sales data and fentanyl citrate defined daily dose.

During the period under review, a total of 14 PecFent case reports were received. Two Health Care Provider (HCP) validated case reports concerning serious listed adverse events and three HCP-validated case reports concerning non-serious unlisted adverse events case reports were received. Additionally, eight HCP-validated cases reports concerning non-serious listed adverse events and one consumer reported case report concerning non-serious listed adverse event were received.

Cumulatively, since marketing authorisation of PecFent, a total of 21 cases have been received up until 31 August 2011. This includes two non-serious case reports which were not included in the previous PSUR but were received during the reporting period of the last PSUR.

During the period covered by this report and between data lock point and submission, none of the following actions relating to safety were taken: marketing authorisation withdrawal or suspension, failure to obtain a marketing authorisation renewal, restrictions on distribution, clinical trial suspension, dosage modification, changes in target population or indications, formulation changes or urgent safety restrictions.

The important identified and known safety risks of PecFent are (1) Respiratory Depression of insufficiency and (2) Circulatory depression, including severe bradycardia, hypotension and shock. These are subject to extensive discussion in the PecFent RMP and are established safety risks for fentanyl.

In conclusion, based on cases received, there were no new safety concerns in relation to these identified and potential risks.

Further details on the efficacy and safety of PecFent for the proposed indication are detailed in the Clinical Appendices to this AusPAR.

Regarding the proposed Product Information (pPI), the CE provided the following comments:

The clinical aspects of the draft Product Information are not entirely satisfactory and should be revised, having regard to the comment below:

- The indication should be amended to be identical to the product already approved in Australia with the same indication. This would also make it the same as in the US. The indication should be: "Management of breakthrough cancer pain in patients with malignancies who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain".

A further two comments were made but these are beyond the scope of this AusPAR.

On *benefit/risk assessment*, the CE stated as follows:

- Fentanyl is a well established drug with over 20 years of clinical use.
- A total of 45,599 episodes of BTCP were treated with FCNS at doses ranging from 100 to 800 µg in a total of approximately 500 patients. The average duration of therapy was 73 days, with 153 subjects being treated for between 90 and 159 days.
- The studies used well-established and validated measures of efficacy and demonstrated that FCNS has a fast onset of action, with onset of efficacy evident from as early as 5 minutes after administration (on some endpoints), and reached clinically meaningful levels within 10 minutes. The effect was maintained throughout the typical (up to 60 minutes) duration of a BTCP episode.
- FCNS has been shown to be statistically significantly superior to both placebo and the currently approved treatment, IRMS, in the treatment of BTCP in opioid-tolerant cancer patients.
- The effective dose can be easily titrated in each patient to provide maximum pain relief whilst minimising adverse effects.
- Patient acceptability assessments indicate that patients are generally satisfied or very satisfied with fentanyl nasal spray in treating episodes of BTCP and this is supported by the low use of rescue medication following use of the product (6% of episodes during maintenance treatment). The assessments of overall acceptability, speed of relief and the episode-by-episode reliability of the nasal spray used also significantly

favoured fentanyl nasal spray over placebo. Patients also considered fentanyl nasal spray was convenient and easy to use.

Assessment of risks as per the CE:

- The expected known AEs which are those for a potent opioid.
- The potential for misuse and abuse

Assessment of benefit-risk balance, the CE stated that:

The benefit-risk balance of fentanyl nasal spray, given the proposed usage, is favourable.

Recommendation regarding authorisation, the CE stated that:

On the basis of the clinical data submitted it is recommended that PecFent be approved.

Risk management plan

In the *Summary of recommendations*, the RMP evaluator stated that:

As the final nonclinical and clinical evaluation reports were not available at the time of finalising this report, the final RMP may need to be updated to take into account any additional safety concern(s) identified in the final nonclinical and/or clinical evaluation report(s). The OPR offers the recommendations as stated below pending the final nonclinical and clinical evaluation reports.

In the event that this application is successful, the OPR recommended the implementation of the EU Risk Management Plan Version 4.0 and the Australian Annex (dated January 2012) and any subsequent updated versions be implemented as a condition of registration.

Product Information

Two comments were provided in regards to the information that was not clearly presented in the proposed Australian PI (See *Pharmacovigilance Findings, Risk Minimisation Activities* section above). As the OPR did not directly evaluate any of the submitted nonclinical and clinical data, no conclusion could be offered on the relevance of these comments in context of this submission. If this submission is approved, it was recommended that the Delegate gives consideration to the comments in context of the overall submission, as to the adequacy of the information presented in the proposed Australian PI to inform of and minimise the risks associated with the use of PecFent in the Australian market.

A response from the sponsor concerning the RMP evaluation report has been reviewed. The RMP evaluator then wrote:

The sponsor has provided some clarifications around the change in the wording of the indication, in response to comments noted in the RMP evaluation report. No other error of fact or material omission in the RMP evaluation report has been identified in the sponsor's correspondence. In summary, the OPR's concern regarding the proposed PecFent indication as stated in the PI has been adequately addressed.

The following matter pertaining to the specific precaution on the PecFent excipient propylhydroxybenzoate, as stated the RMP evaluation report is referred to the Delegate for a final decision:

- Specific precaution on the PecFent excipient propylhydroxybenzoate (E216), which "may cause allergic reactions (possibly delayed) and, exceptionally, bronchospasm (if the product is not correctly administered)" is included in the EU SmPC (Annex I of Module 1.13.1: EU RMP Version 4.0, p.77). This precaution is not

included in the Australian PI, although it is acknowledged that the PI contains a statement to contraindicate the use in individuals who are hypersensitive to any components of PecFent. The inclusion of the precautionary statement in the PI on the possible delayed allergic reactions if administered incorrectly may also be useful information to minimise the risks in susceptible individuals, who may not otherwise be specifically identified.

In the event that this application was successful, the OPR recommended the implementation of the EU RMP Version 4.0 with the Australian-specific Annex (dated January 2012), and any subsequent updated versions be implemented as a condition of registration. This recommendation was made pending that there is no additional safety concern(s) identified in the clinical evaluation report that will require changes to the RMP.

Risk-benefit analysis

Delegate considerations

The Delegate agreed with all four evaluators not to raise objection to the registration of PecFent which definitely has a clinical role in the management of breakthrough pain in cancer patients, although current evidence is limited to 18 years or older.

The CE has recommended modifications to the draft PI:

- While patients should not take more than 4 doses per day, patients must wait at least 4 h and not 2 h before treating another episode of breakthrough pain with PecFent. The latter is in line with the evaluated data showing evidence for fentanyl accumulation when administered at 1 or 2 hourly intervals.
- Having considered the sponsor's response to the evaluator's concern regarding the PK study CP048/07 on the use of PecFent in patients with pollen-induced seasonal allergic rhinitis being treated with oxymetazoline, the Delegate reasoned with the sponsor's suggestion that the reference to nasally administered oxymetazoline in the *'Interactions with other medicines'* section of the pPI be maintained, in order not to create a safety concern for patients who may be concomitantly using oxymetazoline. A modified statement could be *'Constant use of nasally administered oxymetazoline may possibly affect (decrease) the absorption of PecFent'* thereby eliminating reference to the inconclusive study proposed for exclusion from the *Pharmacology section* of the draft PI.

The RMP evaluator has recommended modifications to the draft PI:

- Inclusion of a precautionary statement to the effect that "PecFent excipient propylhydroxybenzoate may cause allergic reaction (possibly delayed) and, exceptionally, bronchospasm (if the product is not correctly administered)". That precautionary statement is included in the EU SmPC and EU RMP.

The RMP evaluator has also recommended that the sponsor implements the EU RMP Version 4.0 with the Australian specific Annex (dated January, 2012), and any subsequent updated versions as a condition of registration.

The nonclinical evaluator has recommended amendments to the pPI and the sponsor has agreed to their full implementation.

The quality evaluator referred the submission to the Pharmaceutical Subcommittee of the ACPM. At its 144th (2012/02) meeting held 19 March 2012, the Pharmaceutical Subcommittee (PSC) made the following recommendation to the Advisory Committee on Prescription Medicines (ACPM):

Recommendation No 2255

1. The PSC endorsed all the questions raised by the TGA in relation to pharmaceutical and biopharmaceutical aspects of the submission by ERA Consulting Pty Ltd to register PecFent nasal sprays containing 0.1% w/v and 0.4% w/v of fentanyl (as citrate). Each presentation delivers 100 µl of solution containing 100 µg and 400 µg of fentanyl per actuation for the 0.1% w/v and 0.4% w/v strengths respectively.
2. The Committee advised that any outstanding issues should be addressed to the satisfaction of the TGA.
3. In the Product Information (PI)

The “Description” section should be amended to include the octanol/water partition coefficient or log P, pKa and solubility of the drug substance at relevant physiological pH.

This document should be amended to include an instruction on the disposal of unused product.
4. There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the Advisory Committee on Prescription Medicines (ACPM).

Proposed action

The Delegate proposed that consideration be given to the approval of the application to register a new dose form of a previously approved active substance (fentanyl) as Pecfent (fentanyl nasal spray) for the proposed indication: *‘Management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain’*. The recommendation is subject to resolving issues arising from the ACPM deliberations and to the finalisation of matters pertaining to the pPI and RMP to the satisfaction of the TGA.

Submitted to the ACPM for advice.

Response from Sponsor

Archimedes has two comments on the *Request for ACPM’s Advice* (dated 24 April 2012) for the application to register PecFent in Australia; the first regards the dosing interval and the second concerns the inclusion of excipients in the ARTG. Archimedes respectfully requests that the Delegate considers these comments when the PecFent application is discussed at the ACPM.

1. Dosing interval

The Request for ACPM’s Advice recommended that, *‘patients must wait at least 4 h and not 2 h before treating another episode of breakthrough pain with PecFent. The later is in line with the evaluated data showing evidence for fentanyl accumulation when administration at 1 or 2 hrly intervals.’*

While the sponsor would agree that re-administration of PecFent while there is still a circulating level of fentanyl would lead to an increased C_{max} and AUC relative to the initial dose, the sponsor disagrees that re-administration at 2 h versus 4 h has a different benefit-risk assessment given the variability of these data. Further, if a patient were to experience an episode of BTPc 2 h after the previous episode and required analgesia, it would be better for the patient to re-administer PecFent to relieve their pain than to add another rescue opioid with a less certain and uncharacterised pharmacodynamic additive effect with PecFent.

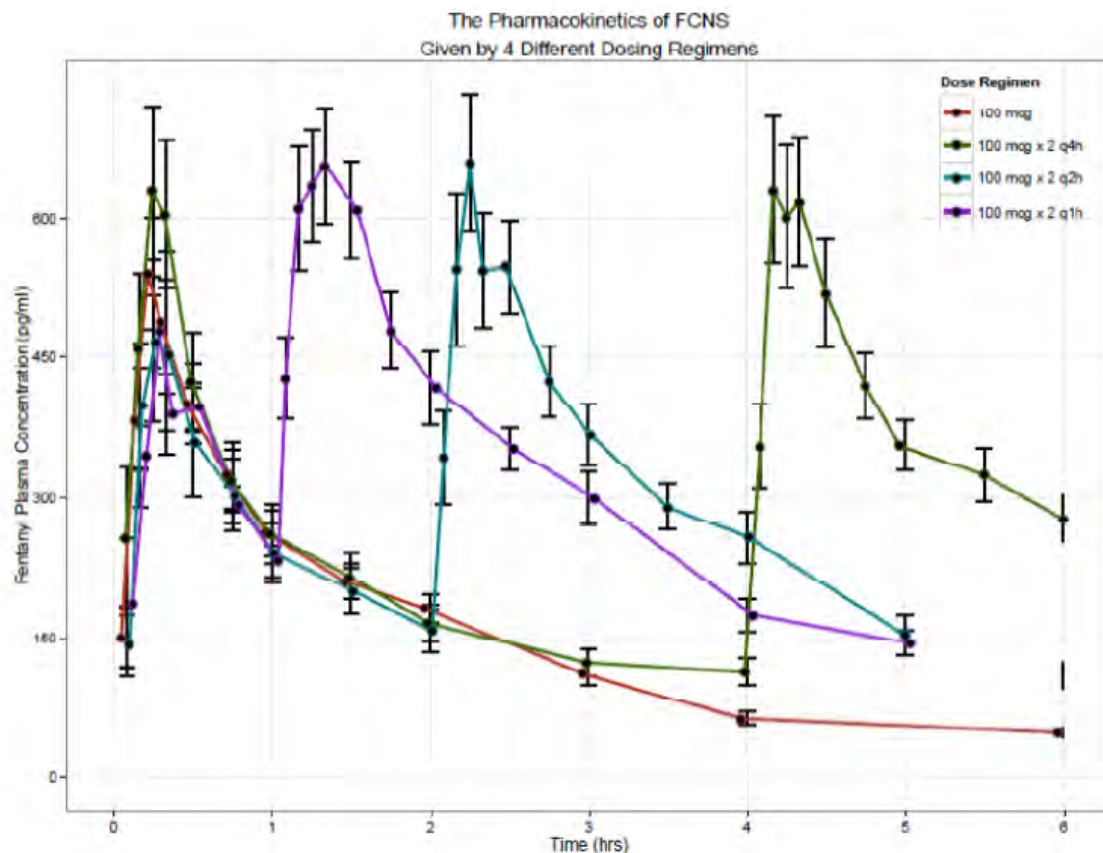
In making the determination as to whether the window for re-administration of PecFent should be 2 or 4 h after the previous dose, the sponsor believes the best assessment is to compare the C_{max} of a second dose at 2 h with the C_{max} of a second dose at 4 h.

This comparison of fentanyl pharmacokinetics after nasal administration of PecFent has been well described in Study CP047 (which was included in the original submission). In this study, a second dose of 100 µg was administered at varying intervals (1, 2 and 4 h) after the initial dose of 100 µg. Figure 1 demonstrates the pharmacokinetic profiles, the interpretive data are reported in Table 11. From those data, the sponsor draws the following conclusions:

- For a second dose after a 4 h interval, the C_{max} is approximately 25% higher than the mean C_{max} of the 4 averaged initial doses.
- For a second dose after a 2 h interval, the C_{max} is approximately 23% higher than the mean C_{max} of the 4 averaged initial doses.
- Therefore, the C_{max} for a second dose after a 2 h interval is no different from the C_{max} for a second dose after a 4 h interval.

The ability to re-administer PecFent at 2 h (rather than at 4 h) would offer the patient a good opportunity to relieve pain when the alternative would be to use a different opioid. Additional reassurance comes from the US experience in which re-dosing is allowed after 2 h and where no additional safety concerns or risks have been identified. Finally, it is the sponsor's intent to submit a variation in the EU to change the interval to 2 h.

Figure 1. Pharmacokinetic profiles



Mean±SE of fentanyl concentration versus time given by 4 different dose regimens (CP047).

Table 11. Pharmacokinetic parameters

Treatment	100 mcg NasalFent	100 mcg NasalFent 4 hr apart	100 mcg NasalFent 2 hr apart	100 mcg NasalFent 1 hr apart
C _{max} (pg/mL) 1 st dose	572.098 ± 297	642.506 ± 263.887	511.463 ± 245.872	513.324 ± 124.966
C _{max} (pg/mL) 2 nd dose	NA	698.905 ± 245.973	687.458 ± 217.247	742.671 ± 177.795
T _{max} (hr) 1 st dose	0.3 (0.18 - 0.50)	0.267 (0.17 - 0.78)	0.333 (0.25 - 0.75)	0.25 (0.08 - 0.50)
T _{max} (hr) 1 st dose	NA	0.25 (0.17 - 0.75)	0.25 (0.17 - 0.53)	0.333 (0.17 - 0.62)
K (hr ⁻¹)	0.21646 ± 0.12248	0.10619 ± 0.05056	0.11856 ± 0.0426	0.10893 ± 0.0374
AUC _{0-τ} (pgx _{hr} /mL)	1132.4 ± 453.5	2835.4 ± 1061.1	2509.9 ± 821.3	2776 ± 794.6
AUC ₀₋₂₄ (pgx _{hr} /mL)	1264.8 ± 466.1	2847.4 ± 942	2596.6 ± 731.1	2823.2 ± 698.3

2. Inclusion of excipients in the Australian Register of Therapeutic Goods (ARTG)

In Archimedes' response to the TGA's Evaluation Reports (dated 21 March 2012), a request was made to remove hydrochloric acid from the provisional ARTG register because it is only present in the PecFent formulation if it has been required for pH adjustment. However, in the Request for ACPM's Advice the Clinical Delegate responded that it is routine practice to include pH-adjusting excipients in the formulation details even if they are not always used in a particular batch.

Therefore Archimedes would like to request that sodium hydroxide is added to the ARTG register, as it is also an excipient that may be used for pH adjustment.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered these products to have an overall positive benefit-risk profile for the following indication:

Management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain.

The ACPM advised that the minimum interval between dosing should be long enough for the patient to experience the peak effect of the opioid before being able to administer a further dose. The ACPM therefore recommended that from a pharmacokinetic perspective and from established use of other immediate release opioids, the sponsor's proposed minimum interval between doses of two hours is acceptable for safety.

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and advised that specific reference to the dosage interval of two hours to be included.

The ACPM agreed with the Delegate that full implementation of the RMP is an appropriate condition of registration.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of PecFent Fentanyl (as citrate) 100 or 400 µg per actuation nasal spray solution with metered dose pump, indicated for:

The management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain.

Specific conditions applying to these therapeutic goods:

1. The implementation in Australia of the EU RMP version 4.0 for PecFent Fentanyl (as fentanyl citrate) with the Australian-specific Annex (dated January 2012) and any subsequent updated versions included with submission PM-2011-00911-3-1, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

<http://www.tga.gov.au>

Reference/Publication #