



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for fentanyl (as citrate)

Proprietary Product Name: Pecfent

Sponsor: AstraZeneca Pty Ltd

May 2014

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- 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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Contents

List of the most common abbreviations used in this AusPAR	4
I. Introduction to product submission	5
Submission details	5
Product background	6
Regulatory status	6
Product Information	6
II. Quality	6
Rate and extent of absorption	6
Metabolism and distribution	7
Mode, route and rate of elimination	7
Active entity	7
Effects of gender	7
Effects of genetic polymorphism	7
Administrative information	8
Quality summary and conclusions	12
III. Nonclinical findings	13
IV. Clinical findings	13
V. Pharmacovigilance findings	13
VI. Overall conclusion and risk/benefit assessment	13
Quality	13
Nonclinical	14
Clinical	14
Risk management plan	14
Risk-benefit analysis	14
Outcome	17
Attachment 1. Product Information	18

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
PK	Pharmacokinetics
PD	Pharmacodynamics
PI	Product Information
CMI	Consumer Medicine Information
ARTG	Australian Register of Therapeutic Goods
BTP	Breakthrough pain
TGA	Therapeutic Goods Administration
OTFC	Oral transmucosal fentanyl citrate
T _{max}	Time to maximum concentration
C _{max}	Concentration maximum
CYP	Cytochrome P450
GCRP	Good clinical research practice
FCNS	Fentanyl citrate nasal spray
LOQ	Level of quantification
QC	Quality control
AUC	Area under the curve
ANOVA	Analysis of variance
CI	Confidence Interval

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Major Variation
<i>Decision:</i>	Withdrawn
<i>Date of decision:</i>	3 March 2014
<i>Active ingredient:</i>	Fentanyl (as citrate)
<i>Product name:</i>	Pecfent
<i>Sponsor's name and address:</i>	AstraZeneca Pty Ltd PO Box 131 North Ryde NSW 1670
<i>Dose form:</i>	Nasal spray solution
<i>Strength:</i>	100 µg
<i>Container:</i>	Metered dose pump
<i>Pack size:</i>	4 doses
<i>Approved therapeutic use:</i>	Not applicable
<i>Route of administration:</i>	Nasal
<i>Dosage:</i>	Proposed: To allow either 4 actuations (2 in each nostril) of the 100 µg/ actuation strength OR the current titration step.
<i>ARTG numbers:</i>	185934, 185935

Product background

This AusPAR describes the application by the sponsor for an alternative dose titration regime for Pecfent.

Pecfent is a nasal spray solution containing fentanyl citrate in two dose strengths (100 µg/ actuation and 400 µg/ actuation).

It was registered in August 2012 for the management of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic pain. It had not been marketed when this submission was lodged.

The maximum dose that is recommended for administration as a single dose is 800 µg, administered as a 400 µg actuation in each nostril. Each bottle contains 1.55 mL ensuring delivery of 8 full sprays. Bottles in their child resistant containers are supplied in cartons containing 1 or 4 bottles.

With this submission the sponsor seeks approval for an alternative dose titration regimen for the 400 µg dose.

The current titration is to replace a single 200 µg dose given in one nostril (2 actuations of 100µ) with a single 400 µg dose given in one nostril. The proposed alternative titration step is for 4 actuations of 100 µg given as two actuations in each nostril. This proposed dose regimen is intended to increase patient convenience. The sponsor has contended that the current titration step is less than optimal in clinical practice because it requires a patient who demonstrates a need for a dose of more than 200 µg to return to their physician to receive a new prescription for the 400 µg product before being able to upward-titrate.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) in August 2012.

At the time the TGA considered this application, a similar application had been submitted in the United States (Food and Drug Administration) and the European Union (European Medicines Agency) for amending the 400 µg titration step in November 2012. At the time this application was considered neither of these agencies had approved the proposed alternative titration step. It has not been proposed in other countries where Pecfent is approved for marketing.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as 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>>.

II. Quality

Rate and extent of absorption

In a pharmacokinetic study comparing PecFent (100, 200, 400 and 800 µg) with oral transmucosal fentanyl citrate (OTFC), fentanyl was shown to be rapidly absorbed following single dose intranasal administration of PecFent, with median Tmax ranging

from 15 to 21 minutes while T_{max} for OTFC was approximately 90 minutes. The variability of the pharmacokinetics of fentanyl was considerable following treatment with both PecFent and OTFC. Relative bioavailability of fentanyl from PecFent compared to the 200 µg OTFC was appropriately 120%.

Metabolism and distribution

Fentanyl is highly lipophilic and is well distributed beyond the vascular system, with a large apparent volume of distribution. Animal data have shown that, following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80 to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis.

The metabolic pathways following nasal administration of PecFent have not been characterised in clinical studies, but fentanyl is metabolised in the liver to norfentanyl by cytochrome CYP3A4 isoform. Norfentanyl is not pharmacologically active in animal studies. It is more than 90% eliminated by biotransformation to inactive N-dealkylated and hydroxylated metabolites.

Mode, route and rate of elimination

Disposition of fentanyl following intranasal administration of PecFent has not been characterised in a mass balance study. Less than 7% of an intranasal administered dose of fentanyl is excreted unchanged in the urine and only about 1% is excreted unchanged in the faeces. The metabolites are mainly excreted in the urine, while faecal excretion is less important.

Active entity

Fentanyl.

Dose response proportionality

Plasma concentrations increased linearly in a dose-dependent manner within the concentration range 100 µg to 800 µg following oral transmucosal or intranasal administration.

Effects of gender

No clinically important pharmacokinetic difference due to gender or ethnicity has been identified.

Effects of genetic polymorphism

No effects of genetic polymorphism have been mentioned for fentanyl citrate. However as fentanyl is metabolised in the liver and in the intestinal mucosa to norfentanyl by the specific enzyme CYP3A4 isoform, genetic polymorphism would be expected to have effects on the pharmacokinetics of Fentanyl Nasal Spray products.

Administrative information**Study title**

A Cross-over Trial to Describe the Pharmacokinetics of Four Sprays of 100 mcg as Part of the Titration Regimen for Fentanyl Citrate Nasal Spray (FCNS-Lazanda/PecFent).

Dates of trial

31 October to 21 December 2011.

Site for clinical aspects of trial

Texas, United States.

Ethics committee approval

The study was conducted in accordance with GCRP and with the approval of an ethical review board.

Treatments compared and batch data

There were three Fentanyl Citrate Nasal Spray (FCNS) treatments (per 100 µL):

- Treatment A: 4 x 100 µg (2 into each nostril [left, right, left, then right without delay]).
- Treatment B: 2 x 100 µg (1 into each nostril [left, then right without delay]).
- Treatment C: 1 x 400 µg.

Both products were identical to the products registered in Australia.

All subjects received FCNS under a naltrexone block. Naltrexone is a specific antagonist of the centrally mediated effects of opioid analgesics.

Comparative dissolution data

Not applicable.

Study design

This was an open-label, single-centre, 3 way, cross over study in which subjects were randomly assigned to 1 of 3 FCNS treatment sequences. Each subject received each of the 3 treatments in a randomly assigned sequence separated by at least a 72 hour wash out period.

The primary objective of this study was to assess the pharmacokinetic (PK) profile and bioavailability (BA) of a 400 µg dose of Fentanyl Citrate Nasal Spray (FCNS) administered as 4 sprays of 100 µg/100 µL solution in alternating nostrils.

The secondary objectives of this study were to compare the:

- BA of a 400 µg dose of FCNS administered as 4 sprays of 100 µg/100 µL solution in alternating nostrils with the BA of a 200 µg dose of FCNS administered as 2 sprays of 100 µg/100 µL solution in alternating nostrils;
- BA of a 400 µg dose of FCNS administered as 4 sprays of 100 µg/100 µL solution in alternating nostrils with the BA of a 400 µg dose of FCNS administered as 1 spray of 400 µg/100 µL solution in 1 nostril.

Subject selection and demographics

Twenty two subjects (16 male, 6 female) aged 23 to 54 years were enrolled; twenty subjects completed the study.

Restrictions on subjects

Appropriate inclusion and exclusion criteria were applied.

Subject dropouts and withdrawals

Two subjects were discontinued after receiving only one treatment, due to nicotine use and a positive urine drug screen test.

Blood sampling times

Blood samples (5 mL) for the determination of plasma fentanyl concentrations were collected at 0, 2, 5, 10, 15, 20, 30, and 45 minutes, and at 1 (plus/minus 1 minute up to and including the 1 hour sample), 1.5, 2, 3, 4, 6, 8, 12, and 24 hours (plus/minus 5 minutes up to and including the 24 hour sample) post dose.

Assay procedure***Fluids analysed***

Plasma (lithium heparinised).

Entities assayed

Fentanyl.

Assay method

HPLC-MS/MS using a C18 column eluted with acetonitrile/2 mM ammonium formate, pH 4.0 (3:1).

Preparation of samples for analysis

Aliquots of human plasma (200 µL) are fortified with 50.0 µL of the working internal standard (1000 pg/mL Fentanyl-d₅ in 1:1 (v:v) methanol:water) in microcentrifuge tubes. A 0.100 mL aliquot of 1:1 (v:v) methanol:water and 1.00 mL of 2% orthophosphoric acid are added. The samples are then mixed and centrifuged at 13000 rpm for 5 minutes. Samples are transferred to a Water Oasis® HLB Extraction Plate (30 mg) that has been conditioned with 1.00 mL of methanol followed by 1.00 mL water. The wells are washed with 1.00 mL water followed by 1.00 mL 20% methanol before elution into a clean 96-well plate with 0.800 mL methanol. The extracts are evaporated to dryness at approximately 50°C under a stream of nitrogen, reconstituted with 150 µL of mobile phase (75:25 (v:v) acetonitrile:2mM ammonium formate, pH 4.0), and vortex mixed. Ten (10) microliters are injected onto the LC/MS/MS system.

Samples were stored at -20°C prior to analysis.

Internal standard used in assay procedure

Fentanyl d-5 (deuterated on the N-phenyl ring).

Concentrations of daily calibration standards

Seven standards in the range 20 to 4000 pg/mL.

Claimed LOQ(s)

20.0 pg/mL.

Pre-study validation of assay procedure

Specificity

Four out of six lots of blank human plasma showed a peak at the retention time of fentanyl. In two of those lots, the interfering peak was greater than 20% of the level of quantification (LOQ) of fentanyl. Therefore, all lots of plasma used in the study were screened for absence of this interfering peak prior to use. This begs the question of whether study participants would have had an interfering peak, but given the high specificity of the method of detection (MS-MS) the matter is not considered critical.

Matrix effects

Matrix effects were determined using six lots of blank human plasma. A mean matrix effect of 0.81 (range 0.78-0.84) was observed, indicating ion suppression. However, the internal standard normalised matrix factor was 1.00 (range 0.98 to 1.02) indicating that the matrix effect is consistent for the analyte and internal standard (as expected when the internal standard is a stable isotope of the analyte).

Linearity

Linearity, with $r^2 > 0.9994$, was established over the concentration range 20 to 4000 pg/mL. Calibration curves were fitted with $1/x^2$ weighting.

Precision and accuracy

Satisfactory over the calibration range. Also satisfactory for samples at 20,000 pg/mL diluted 10 fold.

Recovery

About 84 to 90%.

LOQ

Precision and accuracy were satisfactory (2.7% and 5.5%, respectively) at the defined LOQ (20 pg/mL). Signal to noise ratio was greater than 5.0.

Stability

Satisfactory stability data were provided for fentanyl in whole blood and plasma, including 8 days' storage in plasma at -20°C. Stability studies were ongoing at -20°C and -70°C. Data have been evaluated previously, showing that fentanyl is stable in plasma for 109 days at -20°C.

Assessment of the validation data

Satisfactory. The validation was also repeated in the presence of naltrexone, and satisfactory results were obtained.

Investigators' criteria for accepting assay results

Standard acceptance criteria were applied.

Quality control (QC) of sample assays

QC samples at the following concentrations were used: 60, 750 and 3000 pg/mL. All QC results were satisfactory.

Reported pharmacokinetic parameters and statistical analyses

The reported data (median for T_{max}, area under the curve (AUC) arithmetic mean plus/minus SD for other parameters) are summarised below.

Table 1. Reported Data

	Tmax (h)	Cmax (pg/mL)	AUC _{0-1h} (pg.h/mL)	AUC _t (pg.h/mL)
A: 4 x 100 µg Range:	0.25 0.17-0.83	1750 ± 770 570 to 3700	1010 ± 370 350 to 1710	4870 ± 1550 1960 to 7470
B: 2 x 100 µg Range:	0.25 0.17 to 0.5	1050 ± 470 490 to 2060	660 ± 260 290 to 1160	2990 ± 1050 1080 to 5020
C: 1 x 400 µg Range:	0.5 0.25 to 1.0	1490 ± 650 640 to 2650	940 ± 400 410 to 1640	5120 ± 1460 2610 to 8280
Statistical analysis:		ratio (%)	ratio (%)	ratio (%)
A vs. C Estimate		121.4%	112.5%	98.5%
90% CI		102 to 144%	95 to 134%	89 to 110%
A versus B* Estimate		81.5%	75.6%	80.4%
90% CI		69 to 97%	64 to 90%	72 to 89%

*Dose-normalised

Evaluator's recalculations of pharmacokinetic parameters and statistics

The company's mean results (above) were obtained using all subjects who were administered a particular treatment. The evaluator's results (below) were based only on those subjects who completed all three treatment phases. In addition, the company excluded subject R105 treatment B results and subjects R104 and R110 treatment C results on the basis that the pharmacokinetic profiles obtained were not consistent with other observed data. This is not considered appropriate for subjects R105 and R110, whose pharmacokinetic profiles were not sufficiently different from those of other subjects. In accordance with the CHMP Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1) exclusion of subject R104 is accepted on the basis that the AUC obtained for treatment C was well below 5% of the mean AUC across all subjects. Hence, the evaluator's analyses are based on the results for 19 subjects (excluding subject R101 who only received treatment C, subject R119 who only received treatment A and subject R104).

The analysis of variance (ANOVA) performed by the evaluator showed significant subject and treatment effects for both AUC and Cmax, but no significant period effects. The results obtained are shown below.

Table 2. Evaluator's data

	Tmax (h)	Cmax (pg/mL)	AUCt (pg.h/mL)
A: 4 x 100 µg	0.25	1790 ± 770	4980 ± 1460
Range:	0.17 to 0.83	570 to 3700	2160 to 7470
B: 2 x 100 µg	0.25	1030 ± 490	3040 ± 980
Range:	0.17 to 0.50	280 to 2060	1590 to 5020
C: 1 x 400 µg	0.50	1460 ± 690	4990 ± 1700
Range:	0.25 to 1.5	170 to 2650	1040 to 8280

	Cmax	AUCt
Statistical analysis:	ratio (%)	ratio (%)
A versus C Estimate	130%	103%
90% Confidence Interval (CI)	106 to 160%	91 to 117%
A versus B* Estimate	89%	82%
90% CI	72 to 109%	73 to 93%

*Dose-normalised

On the basis of these results, the following conclusions may be drawn:

- The extent of absorption of fentanyl from 4 x 100 µg sprays is equivalent to that from 1 x 400 µg spray.
- Fentanyl is absorbed more rapidly after 4 x 100 µg sprays, with a shorter Tmax and a 30% higher Cmax compared to 1 x 400 µg spray. This is not unexpected given that the 100 µg sprays are given in both nostrils so there is twice the nasal surface area available for drug absorption. A Wilcoxon signed rank test showed that the Tmax for treatment C is significantly longer than for the other treatments.
- There is less than a proportional increase in AUC, and possibly Cmax, when the dose is increased from 2 x 100 µg sprays to 4 x 100 µg sprays.
- The most significant difference between the results calculated by the company and the evaluator is that the evaluator estimated a 30% higher Cmax for 4 x 100 µg sprays compared to 1 x 400 µg spray whereas the company estimated a 21.4% higher Cmax. The Delegate should assess whether the 30% higher Cmax represents a safety concern.

Quality summary and conclusions

The extent of absorption of fentanyl from 4 x 100 µg sprays is equivalent to that from 1 x 400 µg spray, but the rate of absorption from 4 x 100 µg sprays is greater, resulting in a 30% higher Cmax. The Delegate should assess whether the 30% higher Cmax represents a safety concern.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

There was no requirement for a clinical evaluation in a submission of this type.

V. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan for this application.

VI. Overall conclusion and risk/benefit assessment

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

Quality

A single crossover study was submitted to support the proposed alternative titration step. This study is described in the quality evaluation report. It was an open, 3 way, cross over study in which subjects were randomly assigned to 1 of 3 Fentanyl Citrate Nasal Spray (FCNS) treatment sequences. Each subject received each of the 3 treatments in a randomly assigned sequence separated by at least a 72 hour wash out period.

The primary objective of this study was to assess the pharmacokinetic (PK) profile and bioavailability (BA) of a 400 µg dose of FCNS administered as 4 sprays of 100 µg/100 µL solution in alternating nostrils. The sponsor's results are below. While overall AUC_t is bioequivalent for the 2 proposed titration regimens C_{max} is not, with a mean increase in C_{max} of 21%. In addition mean T_{max} is reduced from 30 minutes to 15 minutes.

	T _{max} (h)	C _{max} (pg/mL)	AUC _{0-1h} (pg.h/mL)	AUC _t (pg.h/mL)
A: 4 x 100 µg Range:	0.25 0.17 to 0.83	1750 ± 770 570 to 3700	1010 ± 370 350 to 1710	4870 ± 1550 1960 to 7470
B: 2 x 100 µg Range:	0.25 0.17 to 0.5	1050 ± 470 490 to 2060	660 ± 260 290 to 1160	2990 ± 1050 1080 to 5020
C: 1 x 400 µg Range:	0.5 0.25 to 1.0	1490 ± 650 640 to 2650	940 ± 400 410 to 1640	5120 ± 1460 2610 to 8280

	Tmax (h)	Cmax (pg/mL)	AUC _{0-1 h} (pg.h/mL)	AUC _t (pg.h/mL)
Statistical analysis:		ratio (%)	ratio (%)	ratio (%)
A versus C Estimate		121.4%	112.5%	98.5%
90% CI		102 to 144%	95 to 134%	89 to 110%
A versus B* Estimate		81.5%	75.6%	80.4%
90% CI		69 to 97%	64 to 90%	72 to 89%

The PC evaluator conducted an additional analysis that included subjects that had been excluded from the sponsor's analysis. The results of that analysis were similar.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The BE study was evaluated by the pharmaceutical chemistry section and there were no other clinical data.

Risk management plan

No RMP was submitted.

Risk-benefit analysis

Delegate's considerations

That Cmax would be increased and Tmax reduced with the proposed alternative titration step could be predicted from the difference in method of administration of the proposed new titration regimen. The nasal mucosal surface area over which fentanyl is presented for absorption is doubled.

The issue of concern is whether safety of the product will be compromised by use of this new regimen compared to the current regimen. The sponsor has contended the major reason for its proposal is to allow patients to up titrate without the need to visit their treating doctor to obtain a new prescription. The Delegate does not consider this to be an advantage but rather an opportunity to increase the risk of unintentional overdose to patients who may consider they are able to up-titrate without discussion with their treating doctor. Pecfent is approved to be supplied in bottles containing 8 doses. It is intended that patients be carefully monitored during the titration period and the prescription of small quantities during this phase would be expected. Excess supply of the 100 µg strength product should not be an issue for patients.

There are no clinical data from which to assess the likelihood of adverse events consistent with overdose events from patient initiated up-titration using the proposed method. Particularly there are no clinical trial data to demonstrate whether respiratory depression events would be increased using the proposed titration step (from 200 µg to 4 x 100 µg) rather than the step that was used in clinical trials on which initial approval was based.

Based on currently available information the Delegate does not intend to approve the proposed revision of the dosing instructions. The advice of the committee is requested.

Proposed action

The Delegate is not in a position to say, at this time, that the application for Pecfent should be approved.

Request for ACPM advice

The committee is requested to provide advice on the following issues:

- The proposed alternative titration step of 4 x 100 µg actuations of Pecfent (2 actuations in each nostril) results in an exposure to fentanyl that is not bioequivalent to the current titration step of 1 x 400 µg actuation in one nostril. The mean C_{max} is 30% higher and T_{max} 50% faster with the proposed alternative dose regimen. The AUC is similar. Advice is requested on the clinical implications of a faster onset and higher C_{max}. Specifically is the margin of increase in C_{max} likely to cause clinically significant respiratory depression in patients who had been able to tolerate a single 200 µg actuation?
- Given the slower onset of action and lower C_{max} associated with the single dose should a down titration step be required for patients who are successfully titrated to the 4 x 100 µg dose prior to switching to a 1 x 400 µg dose?
- The sponsor has proposed this alternative regimen in order to allow patients to up-titrate from 200 µg to 400 µg doses without the need to purchase a 400µg actuator initially. This will allow up titration without assessment by the treating doctor or by a pharmacist. Does the committee consider this appropriate? Should the PI be amended to include a statement that medical advice should be obtained prior to increasing the dose?
- The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor agrees that variances in certain PK parameters (for example, C_{max} and AUC) are observed between the 1 x 400 µg and 4 x 100 µg regimens. However, it is the sponsor's contention that these variances do not represent any negative clinical implications to the patient population for which PecFent is indicated. The sponsor believes that given the observed variability in PK with fentanyl (up to approximately 40%) documented in the PK studies included in the original dossier, and that the use of PecFent is restricted to individuals who are opioid tolerant, these differences would not be associated with safety concerns, including any likelihood of respiratory depression.

In relation to the specific comments of the Delegate in the request for ACPM advice, the sponsor offers the following observations:

Discussion

- The proposed alternative titration step of 4 x 100 µg actuations of Pecfent (2 actuations in each nostril) results in an exposure to fentanyl that is not bioequivalent

to the current titration step of 1 x 400 µg actuation in one nostril. The mean C_{max} is 30% higher and T_{max} 50% faster with the proposed alternative dose regimen. The AUC is similar. Advice is requested on the clinical implications of a faster onset and higher C_{max}. Specifically is the margin of increase in C_{max} likely to cause clinically significant respiratory depression in patients who had been able to tolerate a single 200 µg actuation?

Table 1 provides the key PK parameters (C_{max}, T_{max} and AUC_t) from all of the conducted PK studies with PecFent. The table is organised to bring together the arms from each study that has the same dose.

Table 3. Key PK parameters for all conducted PK studies with PecFent

Dose	1x100 µg				2x100 µg		400 µg		800 µg	
Study	CP037	CP047	CP048	CP048	CP063	CP037	CP063	CP063	CP037	CP037
Schedule	1x100	1x100	100 (Reference Arm)	100 (Rhinitis - no Rx)	2x100	2x100	1x400	1x400	4x100	2x400
C _{max} (pg/mL)	351 (51)	572 (230)	420 (213)	462 (222.93)	1030 (470)	780 (48)	1490 (650)	1552 (26)	1750 (770)	2844 (36.0)
T _{max} (h)	0.33 (0.08-1.5)	0.30 (0.18-0.5)	0.25 (0.17-1.0)	0.33 (0.08-2.0)	0.25 (0.17-0.5)	0.25 (0.17-1.6)	0.5 (0.25-1.0)	0.35 (0.25-0.75)	0.25 (0.17-0.83)	0.34 (0.17-3.0)
AUC _t (pg.h/mL)	2460 (17.9)	1132 (43)	1038 (415)	1108.40 (411.72)	2990 (1030)	4359 (29.8)	5120 (1460)	7513 (26.7)	4870 (1550)	17272 (48.9)

In the development program (which included 523 opioid tolerant patients treated for up to 3 years), 1 non-serious case of respiratory depression was reported and considered unrelated to PecFent by the investigator.

During routine clinical use since PecFent has been on the market (estimated exposure = 2,800,471* patient days calculated based on patient days = Total µg sold/600 (DDD)), there have been very rare reports of 'respiratory depression'. The majority of these were associated with an accidental overdose of PecFent and/or occurred in a setting in which PecFent was used in opioid naïve patients rather than within the approved indication of opioid tolerance.

* Cut-off data to 30 April 2013, PSUR (No. 05) PecFent

- Given the slower onset of action and lower C_{max} associated with the single dose should a down titration step be required for patients who are successfully titrated to the 4 x 100 µg dose prior to switching to a 1 x 400 µg dose?

The sponsor considers the 4 x 100 µg dose and the 1 x 400 µg dose to be clinically equivalent; therefore a down titration should not be required. However, this would be at the discretion of the treating physician.

- The sponsor has proposed this alternative regimen in order to allow patients to up-titrate from 200 µg to 400 µg doses without the need to purchase a 400 µg actuator initially. This will allow up titration without assessment by the treating doctor or by a pharmacist.
 - Does the committee consider this appropriate?
 - Should the PI be amended to include a statement that medical advice should be obtained prior to increasing the dose?
 - The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The sponsor would encourage discussion between the patient and treating physician before making changes to the dose administered. It is important to note that the DOSAGE AND ADMINISTRATION section of the current PI already states 'Treatment should be initiated by and remain under the supervision of a physician experienced in the management of opioid therapy in cancer patients' and that 'Patients should be carefully monitored until an

effective dose is reached. AstraZeneca have no objection for a clarifying statement in the PI/CMI to be included if the TGA feel this is necessary.

Conclusion

PecFent has been demonstrated to be a safe and effective treatment for opioid tolerant patients experiencing break-through cancer pain when used in accordance with the PI and CMI. Taken together, the inherent PK variability of fentanyl and the registered indication which specifically restricts the use of PecFent to an opioid tolerant population, the sponsor believes that the difference in PK parameters observed between the 1 x 400 µg and 4 x 100 µg regimens are not clinically relevant. As such, the sponsor believes that this alternative titration schedule would not result in any safety concerns and that the 4 x 100 µg regimen represents a useful alternative titration step that offers benefits to patients who are under close medical supervision during this time.

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 submission seeks to register a major variation (dosage) for a currently registered product.

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Pecfent nasal spray solution containing 100 µg and 200 µg per actuation of Fentanyl (as citrate). The ACPM considered this product to have an overall negative benefit-risk profile for the proposed dosage.

In making this recommendation the ACPM:

- noted that the proposed dosage regimen delivers an exposure to fentanyl that is not bioequivalent to the currently approved titration step.
- This results in the mean C_{max} is 30% higher and T_{max} 50% faster with the proposed alternative dose regimen. The AUC is similar.
- While faster onset of pain relief is generally beneficial and the high (30%) C_{max} is within the variability of inter-patient range (47%) the ACPM expressed considerable concern that there were no clinical data to support the potential efficacy or provide reassurance on safety.
- expressed concern that the proposed change eliminates the potential safety step of the patient, as is currently the case, needing to revisit their doctor for a new prescription for a 400 µg spray. This allows the opportunity for patient review before the increase in dose from 200 µg to 400 µg. Such a necessary safety step would be difficult to build into the product information documents.

In addition, the ACPM recommended consideration of investigating a down titration step for patients could be successfully titrated to the 4 x 100 µg dose prior to switching to a 1 x 400 µg dose.

Outcome

On 3 March 2014 AstraZeneca withdrew the submission proposing to register an alternative dosing regimen.

Attachment 1. Product Information

The Product Information approved for Pecfent 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>.

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