Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Fentanyl citrate

Proprietary Product Name: Fentora

Sponsor: Orphan Australia Pty Ltd

April 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- 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.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
λz	Apparent plasma terminal elimination rate constant
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Around-the-clock
$AUC_{0-\infty}$	Area under the plasma drug concentration-versus-time curve from time 0 to infinity after study drug administration
AUC_{0-24}	Area under the plasma drug concentration-versus-time curve from time 0 to 24 hours after study drug administration
AUC_{0-72}	Area under the plasma drug concentration-versus-time curve from time 0 to 72 hours after study drug administration
BMI	Body mass index
BPI-7S	7-item Interference Subscale of the Brief Pain Inventory–Short Form
BPI-SF	Brief Pain Inventory-Short Form
Bpm	Beats per minute
BTP	Breakthrough pain
BUN	Blood urea nitrogen
CAPF	Clinician Assessment of Patient Function
CGIC	Clinical Global Impression of Change
CL	Total plasma clearance
CL/F	Apparent total plasma clearance normalised for systemic bioavailability
C_{max}	maximum observed serum drug concentration
CNS	Central nervous system

Abbreviation	Meaning
COAD	Chronic obstructive airways disease
CSR	Clinical Study Report
CYP	Cytochrome P450
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EU	European Union
FDA	Food and Drug Administration (USA)
FEBT	Fentanyl effervescent buccal tablet
F_{OVF}	Absolute bioavailability of transmucosal Oravescent FEBT
GAS	Goal Attainment Scale
GMPA	Global medication performance assessment
IV	Intravenous
Kel	Terminal elimination rate constant
LLOQ	Lower limit of quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MPA	Medication performance assessment
M-PEM	Modified Prescription-Event Monitoring
MPI	Multidimensional Pain Inventory
NA	Not applicable
NAV	Not available
NOS	Not otherwise specified
OTFC	Oral transmucosal fentanyl citrate
OVF	Oravescent fentanyl (citrate) = FEBT
PADER	Periodic Adverse Drug Experience Reports

Abbreviation	Meaning
PAF	Patient Assessment of Function
PASS	Pain Anxiety Symptoms Scale
PFTS	Pain Flare Treatment Satisfaction
PGIC	Patient Global Impression of Change
PI	Product Information
PI	Pain intensity
PID	Pain intensity difference
POMS	Profile of Mood States
PSUR	Periodic Safety Update Report
RBC	Red blood cell
RMP	Risk Management Plan
SD	Standard deviation
SE	Standard error
SF-36	Short Form Health Survey-36
SI	International System of Units
SPID	Sum of pain intensity differences
$SPID_{30}$	SPID up to 30 minutes after the start of study drug administration
$SPID_{60}$	SPID up to 60 minutes after the start of study drug administration
SpO_2	oxyhaemoglobin saturation
SQ	Sleep questionnaire
T½	Elimination half-life
T_{max}	Time to maximum observed plasma drug concentration
TOTPAR	Total pain relief
U	Unknown (missing)
UK	United Kingdom

Abbreviation	Meaning
ULN	Upper limit of normal
USP	United States Pharmacopeia
V	Volume of distribution
V/F	Apparent volume of distribution normalised for systemic bioavailability
WBC	White blood cell
WHO	World Health Organization
WHO	Drug World Health Organization (WHO) drug dictionary
WPAI	Work Productivity and Activity Impairment Questionnaires
y, yr	Year(s)

I. Introduction to product submission

Submission details

Type of submission:	New dose form and new route (buccal) of administration
Decision:	Approved
Date of decision:	5 February 2015
Active ingredient:	Fentanyl citrate
Product name:	Fentora
Sponsor's name and address:	Orphan Australia Pty Ltd 34-36 Chandos Street St Leonards NSW 2065
Dose form:	Orally Disintegrating Tablets
Strengths:	100 µg, 200 µg, 400 µg, 600 µg and 800 µg
Container:	Blister packs
Pack sizes:	4's and 28's
Approved therapeutic use:	*The treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.*
Route of administration:	Buccal
Dosage:	Fentora should be individually titrated to an 'effective' dose that provides adequate analgesia and minimises undesirable effects. In clinical studies, the effective dose of Fentora for breakthrough time (BTP) was not predictable from the daily maintenance dose of opioid. Patients should be carefully monitored until an effective dose is reached. See Product Information details.
ARTG numbers:	218433, 218434, 218435, 218436 and 218437

Product background

This AusPAR describes the application by the sponsor, Orphan Australia Pty Ltd, to register a new route of administration and new formulation of fentanyl citrate, (Fentora); an effervescent, immediate release orally disintegrating tablet, for the treatment of breakthrough pain in adult cancer patients.

Fentanyl citrate is a synthetic opioid analgesic related to pethidine. Currently fentanyl lozenges, patches, solutions for injection and nasal spray formulations are registered in Australia (see *Regulatory status* below).

A buccal fentanyl citrate formulation (a lozenge), Actiq® (sponsor also Orphan Australia Pty Ltd), is already registered in Australia but Fentora facilitates rapid delivery and enhanced absorption of fentanyl. The maximum single dose is 800 µg fentanyl base compared to 1600 µg fentanyl base for Actiq®. The maximum number of doses/day is 4 and this is the same as that recommended for Actiq®.

Treatment should be initiated by and remain under the guidance of a physician experienced in the management of opioid therapy in cancer patients. Patients should be instructed not to use two different formulations of fentanyl concurrently for the treatment of breakthrough pain and to dispose of any fentanyl product prescribed for breakthrough pain (BTP) when switching to Fentora.

Due to different absorption profiles, switching must not be done at a 1:1 ratio. If switching from another oral fentanyl citrate product, independent dose titration with Fentora is required as bioavailability between products differs significantly.

Regulatory status

This new dose form has not been previously registered on the Australian Register of Therapeutic Goods (ARTG).

Fentanyl citrate is currently registered on the ARTG in the following dosage forms and strengths (Table 1):

Table 1: Registered dosage forms of fentanyl in Australia

Dosage form	Dose / strength	Trade name
Lozenges	200, 400, 600, 800, 1200, 1600 µg	Actiq
Patches	12, 25, 50, 75, 100 µg	Durogesic
Solution for injection	50 µg/mL	Sublimaze
Nasal Spray	100 and 400 µg 50, 100 and 200 µg	PecFent Instanyl

The approved indications for the above dosage forms are:

Durogesic patch is indicated for the management of chronic pain requiring opioid analgesia.

Sublimaze solution for injection is indicated for analgesic action of short duration during anaesthetic periods, premedication, induction and maintenance, and in the immediate post-operatic period (recovery room) as the need arises; use as a narcotic analgesic supplement in general and regional anaesthesia; administration with a neuroleptic such as droperidol injection as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia.

Actiq lozenge 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.

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

Instanyl nasal spray is indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain.

Many generic products are also available.

The table (Table 2) below reveals the overseas regulatory status of this product.

Table 2: International regulatory status

Country	Approval date	Approved Indication
EU	04/04/2008	Treatment of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.
USA	25/09/2006	Management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
Canada	14/06/2013	Management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain.
Switzerland	28/06/2011	Treatment of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

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 <https://www.tga.gov.au/product-information-pi>.

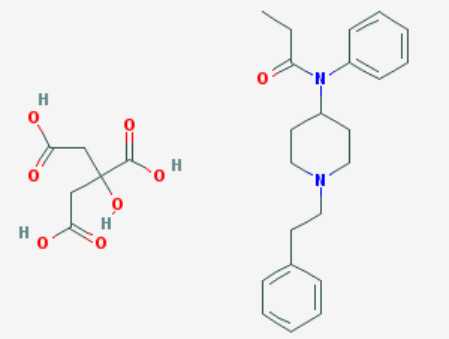
II. Quality findings

Drug substance (active ingredient)

Fentora (fentanyl citrate) is a synthetic, 1:1 citric acid salt of the opioid analgesic fentanyl related to pethidine and with similar properties to morphine.

Fentanyl citrate is a white, crystalline powder with a molecular weight of 528.6 and the molecular formula C22H28N20, C6H807. Its chemical name is N-(I-Phenethy1-4--piperidyl) propionanilide dihydrogen citrate. The chemical structure is depicted below (Figure 1).

Figure 1: Chemical structure of fentanyl citrate



Fentanyl citrate is the subject of monographs in the European Pharmacopeia (Ph Eur; 01/2013:1103), British Pharmacopeia (BP) (Ph Eur monograph 1103) and US Pharmacopeia (USP).

The drug substance has no chiral centres or potential for any geometric isomerism.

The citrate salt is sparingly soluble to soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; and soluble to freely soluble in methyl alcohol.

Drug product

Fentora, orally disintegrating tablets are available in five unit strengths equivalent to 100, 200, 400, 600 and 800 µg of fentanyl base. The excipients include mannitol, sodium starch glycollate type A, sodium hydrogen carbonate, sodium carbonate anhydrous, anhydrous citric acid and magnesium stearate.

Each of the finished products is described as a white to off-white flat-faced, round, bevelled tablet, debossed with 'C' on one side', with the 100 µg, 200 µg, 400 µg, 600 µg and 800 µg tablets being debossed with '1', '2', '4', '6' and '8' (respectively) on the other side.

The products are to be presented packaged in moisture-resistant, physically protective, child resistant blister cards in a 2 x 2 configuration with perforations between each tablet pocket .The blister cards are packaged in an outer cardboard carton (4 or 28 tablets per carton).

The stability of the product has been investigated under accelerated and normal storage conditions. Provided the results were generated from tablets packaged in blisters proposed for Australia, these support a shelf life of 36 months stored below 25°C for the 100 µg and 800 µg orally disintegrating tablets with the limits currently applied. However, these limits only support the allocation of shelf lives of 24 months to the 200 µg and 400 µg tablets, and of 30 months to the 600 µg tablets. A shelf life of 36 months stored below 25°C in the original packaging could be allocated to the 200 µg, 400 µg and 600 µg orally disintegrating tablets if the tighter lower release limits identified are applied to the a*ssay*.

Although not supported by the photostability study results, the results from validation of the *Assay* and *Related Substances* methods clearly suggest the tablets are thermo and photolabile, and are also susceptible to oxidation. However, the blister packaging appears to be adequate protection against such degradation, making additional warning statements on the labelling and in the PI/Consumer Medicine Information (CMI) unnecessary.

Quality summary and conclusions

There are no objections to registration from a quality and biopharmaceutics perspective. The following details relate to this submission:

1. A shelf life of 24 months when stored below 25°C in the original packaging has been assigned to the orally disintegrating tablets packaged in Polyvinyl chloride (PVC)/aluminium/polyamide/PVC/ paper/polyester/aluminium blisters.
2. The (revised) Product Information document is acceptable from the perspective of the Pharmaceutical Sub Committee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).
3. The blister foil 100 µg; 200 µg; 400 µg); 600 µg; 800 µg and carton labels for the 4 tablet 100 µg; 200 µg; 400 µg; 600 µg; 800 µg and 28 tablet presentations 100 µg; 200 µg; 400 µg; 600 µg; 800 µg are acceptable.
4. The provisional ARTG records have been checked by the applicant, and their accuracy has been confirmed.
5. Current evidence of acceptable Good Manufacturing Practice (GMP) has been submitted for the sites nominated for the manufacture of the active ingredient and finished products.
6. Acceptable composite release and composite expiry specifications have been submitted for the finished products.
7. The following bioavailability/bioequivalence studies were presented in support of the submission to register the orally disintegrating tablets:
    a. Absolute and Relative Bioavailability Study C25608/1028/BA/US, in which the relative bioavailability of a single 400 µg transmucosal dose of Oravescent fentanyl (as citrate) when compared to a single 800 µg oral dose of Oravescent fentanyl (as citrate)[1] and a single 800 µg transmucosal dose of Actiq fentanyl (as citrate) lozenge was evaluated, as well as the absolute bioavailability of these formulations was compared with an intravenous infusion of 400 µg fentanyl as assessed by area under the plasma concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$).
    b. Bioequivalence Study C25608/1026/BE/US, in which the bioequivalence of 4 x 100 µg Oravescent fentanyl (as citrate) orally disintegrating tablets *vs* 1 x 400 µg Oravescent fentanyl (as citrate) orally disintegrating tablet was established, and the pharmacokinetics (from arterial and venous blood samples) of 1 x 400 µg Oravescent fentanyl (as citrate) orally disintegrating tablet were assessed.
    c. Study C25608/1043/BE/US, in which the bioequivalence of 1 x 400 µg Oravescent fentanyl (as citrate) orally disintegrating tablet (ODT) placed buccally versus sublingually was established.

III. Nonclinical findings

Introduction

The aim of the drug development program for Fentora was to develop an effervescent tablet for buccal administration to facilitate transmucosal absorption in order to achieve therapeutically effective plasma fentanyl levels with lower drug doses than those of Actiq®, an oral transmucosal formulation (lozenge) already approved in Australia.

[1] Cephalon's Fentora was known as Oravescent in Studies C25608/1028/BA/US and C25608/1026/BE/US.

Although the sponsor may have chosen to conduct initial pharmacokinetic studies in nonclinical species to compare the pharmacokinetic profiles of Actiq® and Fentora®, it is acceptable that pharmacokinetic studies were conducted directly in humans.

Much of the nonclinical data used to support approval of the Actiq® buccal formulation (evaluation dated 2002) can be used to support the safety of the new formulation, although these data were below current standards and the nonclinical evaluator noted that '*Most of the preclinical data were derived from published papers describing animal experiments performed with other routes of administration. These were mainly non-GLP compliant and, in most instances, were inadequately described. Preclinical data to support the use of fentanyl for long periods (>30 days) remain deficient in that limited repeat dose toxicity studies have been conducted.*' However, it was also noted that '*In the available [repeat dose toxicity] studies, all toxicities observed with fentanyl were generally predictable from the pharmacological effects of the drug or were not of major concern…*', and data for the repeat dose toxicity studies submitted with the current application are consistent with this statement. Further, there is extensive clinical experience with fentanyl (including by the buccal route) and fentanyl has a very well-known pharmaco-toxicological profile. Additionally, the current application contained a number of studies which addressed some of the deficiencies of the Actiq® application.

There is no reason to expect the new formulation to produce a new toxicity as it is to be used similarly to the previous Actiq® formulations (same route, comparable treatment protocol and lower maximum dose).

The sponsor provided an adequate review of available pharmacology/toxicity information and an assessment of whether these data support the proposed clinical use of the new formulation. Data from the submitted studies and the studies discussed in this review support the conclusion that the main risk associated with the use of fentanyl, when given at high doses, is respiratory depression followed by a reduction in heart rate, although these will be of less concern in the target opioid-tolerant population compared to an opioid-naïve population.

Local tolerance is another issue that warrants investigation with a new formulation (for further discussion see '*Local Tolerance*' below).

Pharmacology

Primary pharmacology

Since breakthrough pain is severe and achieves peak intensity in 3 to 5 min, with the median duration of an episode being 30 min[2], fentanyl is well suited to managing pain due to its high potency, fast onset of action and short duration of action. The median number of episodes of breakthrough pain is 4 per day.[2,3] Thus, breakthrough pain would normally be adequately controlled with the proposed dosing schedule.

Secondary pharmacodynamics and safety pharmacology

Core safety pharmacology studies, all Good Laboratory Practice (GLP) compliant, were submitted: central nervous system (CNS) (Irwin test[4]) and respiratory studies in rats, and

[2] Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 1999;(81):129-34

[3] Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. Pain 1990;41(3):273-81

[4] The Irwin observation test is commonly used to evaluate the effects of a new substance on behaviour and physiological function. The results of the Irwin test are used to determine potential toxicity and to select doses for specific therapeutic activity.

a cardiovascular study in conscious telemetered dogs. In the Irwin test in rats, CNS effects were observed at all doses (≥0.003 mg/kg subcutaneously (SC)), but mainly at the high dose (HD) (0.3 mg/kg) which elicited generalised CNS depression (such as catalepsy, decreased alertness, motor activity, touch and startle responses, fearfulness, body tone, grip strength and reflexes, and slowed respiration) and a reduction in body temperature. CNS clinical signs were also a consistent feature of the toxicity studies. In the respiratory study which examined the effects of fentanyl on respiration rate and tidal volume in rats, doses of 0.003 and 0.03 mg/kg SC were without effect but 0.3 mg/kg SC significantly reduced both parameters. CNS clinical signs and respiratory depression are known effects of fentanyl and are consistent with an exaggerated pharmacological response. Assuming comparable bioavailability of the SC dose in rats and the effervescent tablet in humans, the 0.3 mg/kg dose in rats (1.8 mg/m^2; 1.1 mg/m^2 base) is 2.7 fold the maximum human dose of 11.4 µg/kg (800/70) (0.42 mg/m^2), while the 0.03 mg/kg dose in rats is 0.3 fold the maximum human dose.

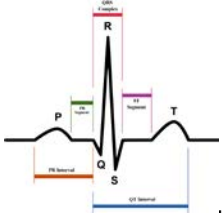
In the cardiovascular study in dogs, significant reductions in heart rate (HR) and associated increases in PR, RR and QT intervals and QRS duration[5] were observed at some time points following a dose of 0.01 mg/kg SC (QTcF and QTcQ were not significantly changed[6]). At 0.05 mg/kg, similar findings were observed, but additionally QTcF and QTcQ were both significantly increased at 120 min post dose and significant increases in systolic and mean arterial blood pressure were observed. Decreased heart rate is a known effect of fentanyl in dogs[7,8,9,10] and fentanyl is known to have the potential to cause bradycardia clinically. Literature studies have generally reported decreases in blood pressure[7,8,10] and fentanyl is known to have the potential to cause hypotension. Decreased HR was observed at 0.2 mg/m^2, below the maximum human dose of 0.42 mg/m^2. QTcF and QTcQ increases (only at one time point) were observed at 1 mg/m^2, giving a margin of safety of 2.5.

Fentanyl and other µ-receptor agonists are also known to dose-dependently increase the tone and decrease the contractions of the gastrointestinal smooth muscle, which results in prolongation of gastrointestinal transit time and constipation.[11]

Pharmacokinetics

Fentanyl is highly lipophilic and can be absorbed very rapidly through the oral mucosa and more slowly by the conventional gastrointestinal route. It is subject to extensive first-pass hepatic and intestinal metabolism and the metabolites make little or no contribution

[5] Schematic representation of normal ECG trace (sinus rhythm), with waves, segments, and intervals labelled.



[6] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like Torsades de pointes and a risk factor for sudden death.

[7] Laubie M, Schmitt H, Canellas J et al. Centrally mediated bradycardia and hypotension induced by narcotic analgesics: dextromoramide and fentanyl. Eur J Pharmacol 1974; 28:66-75.

[8] Hunter JM, Jones RS, Utting E. Effect of anaesthesia with nitrous oxide in oxygen and fentanyl on renal function in the artificially ventilated dog. Br J Anaesth 1980;52:343-8.

[9] Arndt JO, Mikat M, Parasher C. Fentanyl's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. Anesthesiology 1984;61:355-61.

[10] De Hert SG. Study on the effects of six intravenous anesthetic agents on regional ventricular function in dogs (thiopental, etomidate, propofol, fentanyl, sufentanil, alfentanil). Acta Anaesthesiol Belg 1991;42:3-39.

[11] Physicians Desk Reference (2005) 59th ed. Thomson P.D.R., Montvale, NJ, p. 1122

to fentanyl's therapeutic effects. Following administration of Fentora, fentanyl is rapidly absorbed, with a time to peak plasma concentration (T_{max}) of approximately 50 min in the fasted state, and plasma concentrations reaching 80% of the peak plasma concentration (C_{max}) within 25 min. Rapid buccal absorption minimises the proportion of the drug that is swallowed and therefore minimises the first pass effect observed after oral administration. A larger proportion of the fentanyl dose is buccally absorbed after the administration of Fentora than after the administration of Actiq®, resulting in a higher absolute bioavailability for the Fentora formulation (65% compared to 50%). Thus, the Fentora formulation has pharmacokinetic advantages over the currently registered Actiq® formulation for the treatment of breakthrough pain.

According to the Actiq® PI, C_{max} ranges from 0.39 to 2.51 ng/mL in healthy adult subjects after administration of Actiq® (200 µg to 1600 µg). C_{max} values following administration of Fentora (100 µg to 800 µg) were 0.25 to 1.59 ng/mL (Study C25608/1027/PK/US), below those for Actiq®. An AUC of 898 ng.min/mL (approximately 14.97 ng.h/mL) was observed for a dose of Actiq® in the range 1023 to 1275 µg, so a dose of 1600 µg might be expected to result in an AUC of about 10.4 ng.h/mL which is above the $AUC_{0-\infty}$ of 9.05 ng.h/mL observed in Study C25608/1027/PK/US following a dose of 800 µg Fentora base or the estimated 15.2 ng.h/mL based on twice the $AUC_{0-\tau}$ of 7.59 ng.h/mL observed following administration of multiple doses of 400 µg Fentora base in Study C25608/1029/PK/US (note that dose proportionality across the available range of dosages over the range 100 to 800 µg of Fentora has been demonstrated).

Submitted toxicokinetic data (carcinogenicity range-finding studies, carcinogenicity studies and reproductive toxicity studies) suggested broadly dose-proportional increases in plasma fentanyl concentrations and AUC values (mice, rats and rabbits). There was no consistent evidence of a gender difference in plasma fentanyl concentrations/AUC values. In general, there was little evidence of accumulation with repeated dosing over time.

Evidence from incubation of human liver microsomes with specific CYP inhibitors, from correlation analyses of norfentanyl formation rates with CYP activities in individual human liver microsomes, and from incubations with individual recombinant human CYP isozymes all suggested that CYP3A4 is the main isozyme catalysing the formation of norfentanyl from fentanyl, with little, if any, contribution from other CYP isozymes.

Toxicology

Acute toxicity

Fifty percent lethal dose (LD_{50}) values have been estimated in a number of species using a number of routes (in studies not submitted with this application), although oral LD_{50} values were estimated only in mice and rats (120 and 18 mg/kg, respectively). These values suggest that fentanyl is of moderate to low acute toxicity. Respiratory depression was an important cause of deaths.

Repeat-dose toxicity

The repeat dose toxicity studies submitted (4 week dermal study in FVB type mice and 13 week SC study in Sprague Dawley (SD) rats) were conducted as range-finding studies for subsequent carcinogenicity studies and were GLP compliant. The studies were adequately conducted and formed an appropriate basis for dose selection in the carcinogenicity studies.

At dermal doses of up to 5 µg/day in mice, the main findings were CNS clinical signs (mainly at the mid dose (MD) and HD) and small body weight losses associated with reduced food consumption at the HD. No skin irritation was observed.

At SC doses of 50 to 250 µg/kg/day in rats, mortalities (dose-dependent incidence) were observed at the MD and HD, probably associated with respiratory arrest, although this was not clear from the study report. A number of CNS clinical signs were observed, with decreased activity at all dose levels. A decrease in body weight gain in HD males was associated with reduced food consumption. A dose-dependent incidence of granulomatous inflammation in the lungs was observed, and the No Observable Adverse Effect Level (NOAEL) was <50 µg/kg/day. The granulomatous inflammation in the lungs was considered by the authors to be a secondary effect caused by aspiration of feed material, associated, in turn, with the marked and prolonged sedation which caused the MD and HD rats to lie motionless for extended periods of time. This evaluator concurs with this explanation. Testicular seminiferous tubular degradation was increased in incidence (dose-dependent) in MD and HD males, and testicular weight was decreased in HD males. Epididymides were examined only in control and HD males but aspermia and luminal cellular debris were observed only in the HD animals. Thymus weights were reduced in HD animals, a finding commonly observed in stressed animals.

Relative exposure

Exposure ratios (ERs) have been calculated based on animal: human plasma AUC, using single (800 µg) and multiple (800 µg x 4/day) dose values for humans, or C_{max} values (Table 3). For the single dose in humans, the ERs were acceptable in the dose range-finding studies but low in the carcinogenicity studies. For the multiple dosing in humans, ERs were low.

Table 3: Relative exposure for fentanyl in repeat-dose range-finding studies and carcinogenicity studies (data are for males and females combined unless otherwise specified)

Species		Study duration	Dose µg/day (mice); µg/kg/day (rats)	AUC or C_{max}	AUC ng·h/mL* or C_{max} ng/mL	Exposure ratio$	Exposure ratio&
Mouse	FVB/N	4 weeks	1	AUC	4.0	0.3	0.1
			5		17.1	1.4	0.3
			50		256	21	4
			1	C_{max}	0.568	0.3	0.2
			5		2.36	1.2	0.7
			50		33.1	17	9
	Tg.AC trans-genic	26 weeks carcinog-enicity	5	C_{max}@	1.68	0.9	0.5
			15		3.58	1.8	1.0
			50		6.53	3.3	1.8
Rat (SD)		3 months	50	AUC	18.1	1.5	0.3
			100		36.2	3.0	0.6

Species	Study duration	Dose µg/day (mice); µg/kg/day (rats)	AUC or C_{max}	AUC ng·h/mL* or C_{max} ng/mL	Exposure ratio$	Exposure ratio&
		up to 250		105.5	9	1.7
	2 years carcinog-enicity	12.5 (males only)	AUC	5.34	0.4	0.1
		25		10.7	0.9	0.2
		50		20.5	1.7	0.3
		100 (females only)		37.5	3.1	0.6
Human (healthy volunteers)	single dose / steady state	[800 µg]	NA	AUC 12.24 ng.h/mL^/C_{max} 1.968 ng/mL# for a single dose and AUC 60.72 ng.h/mL♦/C_{max} 3.54 ng/mL^^ for multiple daily doses	-	-

* AUC0-24 h for animals (mean data for relevant time points) and AUC0-∞ for humans; $ ER based on a single human dose of 800 µg (pooled data from Studies 11, 18, 1026, 1027, 1028, 1029, 1037 and 1043); & ER based on AUC0–τ (scaled from a 400 µg dose to an 800 µg dose) or Cmax (scaled from a 400 µg dose to an 800 µg dose) following administration in humans every 6 h over a 24 h period (Study C25608/1029/PK/US); ^ 8 x AUC normalised to 100 µg dose (8 x 1.53 ng.h/mL); # 8 x Cmax normalised to 100 µg dose (8 x 0.246 ng.h/mL) (pooled data from Studies 11, 18, 1026, 1027, 1028, 1029, 1037 and 1043); ♦ 4 x 2 x 7.59 ng.h/mL (Study C25608/1029/PK/US); ^^ 2 x 1.77 ng/mL (Study C25608/1029/PK/US); @ 2 h plasma concentrations (that is, the Cmax after dermal administration); NA = not applicable

There was a large (5 fold) difference in the ER (based on C_{max}) calculated for the dose of 50 µg/day in the mouse range-finding study and the ER (based on C_{max}) calculated for the same dose in the carcinogenicity study which was probably due to variability (the difference between the two studies at the 5 µg/day dose level was only 33%). This difference suggests that the ER of 3.3 at 50 µg/day in the carcinogenicity study may have been an underestimate.

Genotoxicity

A compilation of GLP compliant genotoxicity studies comprising a reverse mutation study in *S. typhimurium* and *E. coli* strains, a forward mutation study at the thymidine kinase locus in mouse lymphoma L5178Y cells and an in vivo mouse micronucleus assay, were submitted. As the same studies have been evaluated previously (Actiq®), they were not re-evaluated. The studies were adequately conducted and there was no evidence from any of the studies that fentanyl was genotoxic.

Carcinogenicity

Carcinogenicity studies are not required for the indication currently sought (in cancer patients) but the studies were conducted to support a non-cancer indication in the USA and are evaluated here as they are relevant for the Product Information and for possible future applications to the TGA.

Carcinogenicity studies conducted were a 26 week dermal study in the Tg.AC transgenic mouse and a standard 104 week SC study in rats (both were GLP compliant). The submitted studies were consistent with the relevant guideline[12] which recommends that a carcinogenicity package should consist of two long-term rodent carcinogenicity studies or one long-term study (preferably in the rat) and one short or medium-term in vivo rodent test system providing insight into carcinogenic endpoints and having the potential to contribute information valuable to the overall 'weight of evidence' for the assessment of carcinogenic potential, which may include models using transgenic rodents. The guideline notes that the rationale for the choice of this test system should be documented and a discussion should be provided on the strengths and weaknesses of the chosen method. The justification given by the study authors was that Tg.AC mice are recommended for identification of dermally applied carcinogens, which is not specifically relevant for the current application (possibly more relevant to fentanyl patch formulations). No discussion on the strengths and weaknesses of the chosen method was provided.

Studies were GLP compliant and study designs (including species, route, animal numbers and duration) were adequate. The SC route was justified as giving a pharmacokinetic profile that most closely resembles the profile following buccal delivery of fentanyl by effervescent tablets, which seems reasonable. The mouse carcinogenicity study included a positive control group which elicited the expected significant increase in the incidence of dermal papillomas at the site of application, with all positive control animals reaching ≥20 papillomas and therefore being euthanised prior to the completion of the study. While this positive control provided some validation of the study methodology, the relevant EU guideline[13] noted that the Tg.AC model reacted inconsistently and incompletely to known human carcinogens, but is useful for screening the properties of dermally-administered pharmaceuticals.

Based on the results of the dose range-finding study, the dermal doses chosen for the mouse study (5, 15 and 50 µg/day) were appropriate. Note that the FVB/N strain used in the dose-range finding study and as toxicokinetic animals in the main study is the genetic background for the Tg.AC mouse. There was no evidence of a carcinogenic effect of fentanyl in the mouse study as there was no significant increase in the number of animals bearing papillomas in the treated groups. There were also no other treatment-related neoplastic lesions.

Based on the results of the range-finding study, the selection of 50/100 µg/kg/day SC as the HD in the rat carcinogenicity study was appropriate. There were no treatment-related neoplastic lesions in this study. Overall, fentanyl showed no evidence of carcinogenic potential in these studies.

ERs achieved at the HD in the mouse carcinogenicity study were about 3 (although this value may be an underestimate; see above), and in the rat study about 1.7 (males) and about 3 (females), for a single human dose, providing a small margin of safety. There was little or no margin of safety for multiple daily doses. However, maximal doses in both mice and rats were limited by toxicity (effects of fentanyl on body weight gain).

[12] ICH Guidance S1B: Carcinogenicity: Testing for Carcinogenicity in Pharmaceuticals.
[13] CPMP/ICH/299/95 CHMP SWP Conclusions and Recommendations on the Use of Genetically Modified Animal Models for Carcinogenicity Assessment

As in the range-finding study, non-neoplastic lesions in rats included granulomatous inflammation in the lungs. Testicular/epididymal changes were not observed in the carcinogenicity study where the HD in males was 50 µg/kg/day, as opposed to 250 µg/kg/day in the range-finding study. Initially, the study report did not note any unusual histological findings in the brain; however, the slides were re-examined in the light of findings of brain lesions in a separate 2 year SC rat carcinogenicity study with fentanyl hydrochloride (ALZA Corporation study TR-02-5715-021), including mineralisation/ necrosis in the brain of 12/65 (18%) male and 3/65 (5%) female rats treated with 100 µg/kg/day. Following slide re-examination for the current fentanyl citrate SC study, brain lesions (most notably areas of mineralisation) were observed in 4 males and one female at 50 µg/kg/day and in one female at 100 µg/kg/day (this dose was not tested in males). Additionally, minimal focal necrosis (1 male at 50 µg/kg/day) and minimal focal spongiosis (1 female at 50 µg/kg/day) were reported. These lesions were observed at low incidence and minimal severity, and were not observed in the 3 month dose range-finding study. In a follow-up study (AB11800) in rats treated with fentanyl citrate twice daily SC for 2 or 6 weeks (the latter animals showing some evidence of tolerance), there was no evidence of treatment-related brain histopathology or necrosis. These data suggest that the brain lesions may be related to long term treatment but not opioid tolerance. In the sponsor's response to TGA's request for further information, the sponsor cited similar previous findings in rats given high opioid doses[14,15] suggestive of a treatment-related class effect. In any event, the brain findings in rats are not considered to be of particular concern for the proposed patient population (cancer patients) because of their low incidence and severity and the possibly long period of administration prior to their appearance/detection.

Reproductive toxicity

A full package of reproductive toxicity studies (all GLP compliant) was submitted, including a fertility study in rats (treated males were mated with untreated females and vice versa), embryofetal development studies in rats and rabbits and a pre and postnatal development study in rats. While these studies are not all required for the indication currently sought, they are fully evaluated here, as they are relevant for the Product Information and for possible future applications.

All studies were GLP compliant and were adequately conducted (including appropriate doses and dosing periods, and adequate animal numbers and parameters investigated). All studies used the SC route which, as noted above, was selected to most closely resemble the pharmacokinetic profile following buccal administration of the effervescent tablet. Although pilot rabbit embryofetal development and rat pre and postnatal studies were conducted, doses were relatively low, with the HD selected for the main studies being higher than the HD in the pilot studies, and the 13 week repeat-dose study was used as the basis for dose selection in the pre and postnatal study. The HD groups in the fertility and pre and postnatal studies were initiated at a later date compared to the groups in the original study but time-matched controls were included and this alteration in study design did not detract from the data. However, these additional high doses were excessively toxic, causing substantial mortalities.

There was clear evidence from the fertility study of an effect on male fertility, with significant changes observed at the HD (300 µg/kg/day). These included reductions in fertility indices in the untreated females/treated males; there was also a slight reduction in mating for the untreated females/treated males. Uterine weights in untreated females

[14] Kofke WA, Garman RH, Stiller RL et al. Opioid neurotoxicity: fentanyl dose-response effects in rats. Anesth Analg 1996;83:1298-1306.
[15] Kofke WA, Garman RH, Tom WC et al. Alfentanil-induced hypermetabolism, seizure, and histopathology in rat brain. Anesth Analg 1992;75:953-964.

were reduced which was likely to be male mediated due to reduced viable fetuses. A reduction in implantation sites and an increase in pre-implantation loss were also observed in untreated females. This reduction in male fertility was associated with significant changes in sperm parameters at the HD (reductions in % motility and sperm concentration, and increases in % abnormal sperm). Weights of organs of the male reproductive tract (testes, epididymides, prostate and seminal vesicles) were also reduced at the HD. However, the HD was a lethal dose, with 14/25 HD males succumbing (probably from respiratory depression) over the first 51 days of the study. These effects on male fertility are consistent with the effects seen in testes (degeneration of the seminiferous tubules) and associated effects in the epididymides (aspermia and luminal cellular debris) in the 13-week rat study. The authors/sponsor's nonclinical expert hypothesised that the effect on sperm was an indirect effect due to sedation causing the rats to lie down for long periods, thus resulting in the testes being pushed into the inguinal canal and increasing their temperature. Whilst this is a feasible explanation, it was difficult to substantiate and a possible direct effect of fentanyl cannot be eliminated as reductions in the weights of organs of the wider male reproductive tract were observed at the HD. No toxicokinetic data were provided for the fertility study but an estimate can be made from the toxicokinetic data from the 3 month rat study (mean day 19 data in males). Thus, extrapolating linearly from the 250 µg/kg/day AUC value (103.2 ng.h/mL) gives an $AUC_{0\text{-}24h}$ of 124 ng.h/mL for a dose of 300 µg/kg/day, which gives ERs of 10 and 2 based on a single dose or multiple doses, respectively. The NOAEL for male fertility was 100 µg/kg/day, although sperm motility was reduced at this dose (NOAEL 25 µg/kg/day)). The $AUC_{0\text{-}24h}$ at 100 µg/kg/day was 38.9 ng.h/mL (ERs of 3 and 0.6 based on a single human dose or multiple doses, respectively). There was little effect on female fertility, although at the HD oestrous cycling was affected and uterine weights were reduced.

There was no evidence from the submitted rat or rabbit embryofetal development studies of an embryofetotoxic (including teratogenic) effect of fentanyl, except for a reduction in fetal weights at the HD (100 µg/kg/day) in rats, a dose which was maternotoxic (clinical signs and reductions in food consumption and body weight gain); dose-related maternotoxicity was also seen in the rabbits. The sponsor's nonclinical expert noted that some embryofetotoxic effects had been reported following administration of fentanyl under some experimental conditions (for examples see published PI documents for other fentanyl products); however, teratogenic activity has not been observed in mice[16] or in rats or rabbits[17,18,19].

In the pre and postnatal development study at the HD (400 µg/kg/day) there were reductions in pup birth weight, and growth and development were inhibited (reductions in body weight gain and viability and lactation indices, clinical signs, delays in physical development and sexual maturation, as well as minor changes in motor activity and a reduction in implantation sites/female during reproduction of the F_1 generation[20]). The second mid dose (MD2) (100 µg/kg/day) was also associated with inhibited pup growth and reduced day 21 survival (lactation index), although to a lesser extent. Both the HD and the MD2 were lethal doses with approximately 60% of the F_0 females[20] dying at these doses. The NOAEL for F_1 developmental toxicity was the MD1 (50 µg/kg/day). Increased postnatal pup mortality in rats has been previously reported in similar fentanyl studies (PI documents for other fentanyl products).

[16] Martin LVH and Jurand A. The absence of teratogenic effects of some analgesics used in anaesthesia: additional evidence from a mouse model. Anaesthesia 1992;47:473-6.
[17] Fujinaga M, Stevenson JB, Mazze RI. Reproductive and teratogenic effects of fentanyl in Sprague-Dawley rats. Teratology 1986;345;1-57
[18] Mazze RI, Fujinaga M, Baden JM. Reproductive and teratogenic effects of nitrous oxide, fentanyl and their combination in Sprague-Dawley rats. Br J Anaesth 1987;59:1291-7.
[19] PI documents for other fentanyl products
[20] F1 is the first filial generation of offspring of parental types (F0).

Relative exposure – fentanyl

Table 4: Exposure ratios in animals

Species	Study	Dose (µg/kg/day)	AUC_{0-24h}* (ng·h/mL)	Exposure ratio$	Exposure ratio^
Rat (SD)	Embryofetal development	25	5.53	0.5	0.1
		50	13.2	1.1	0.2
		100	32.8	2.7	0.5
	Pre-/postnatal development	25	5.41	0.4	0.1
		50	11.4	0.9	0.2
		100	29.1	2.4	0.5
		400	140.6	11	2.3
Rabbit (NZW)	Embryofetal development	50	11.5	0.9	0.2
		100	23.1	1.9	0.4
		250	63.7	5.2	1.0
Human (healthy volunteers)	steady state	[800 mg]	12.24 for single dose/60.72 for multiple doses	-	-

* AUC0-24h for animals and AUC0-∞ for humans; $ ER based on 8 x AUC normalised to 100 µg dose (12.24 (8 x 1.53) ng.h/mL) (pooled data from Studies 11, 18, 1026, 1027, 1028, 1029, 1037 and 1043); ^ ER based on AUC (scaled to an 800 µg dose) following administration in humans every 6 h over a 24 h period (60.72 (4 x 2 x 7.59 ng.h/mL)) (Study C25608/1029/PK/US)

The ERs achieved at the HD in the pre and postnatal development study were acceptable (but this was a lethal dose). Other ERs achieved were low-adequate but were limited by fatal respiratory depression, as well as reductions in body weight gain. At the NOAEL for pup developmental toxicity (50 µg/kg/day), the ERs were approximately 1 and 0.2 based on a single human dose or multiple doses, respectively.

Substantial excretion of fentanyl, and to a lesser extent, norfentanyl, in milk was demonstrated in lactating rats (postnatal day (PND) 12) following SC administration of fentanyl at 25 to 50 µg/kg/day. Milk: plasma ratios were about 6 for fentanyl and about 2-3 for norfentanyl. No studies on placental transfer of fentanyl were submitted, however, in published studies, fentanyl has been reported to cross the placental barrier in both rabbits[21] and sheep[22]. The concentrations of fentanyl in umbilical vein perfusate in rabbits were approximately 25% of those in maternal arterial blood and fetal plasma levels in sheep were approximately 40% of those in maternal *plasma.

[21] Vella LM, Knott C, Reynolds F. Transfer of fentanyl across the rabbit placenta. Effect of umbilical flow and concurrent drug administration. Br J Anaesth 1986;58:49-54.
[22] Craft JB, Coaldrake LA, Bolan J, Mondino M, Mazel P, Gilman RM et al. Placental passage and uterine effects of fentanyl. Anesth Analg 1983; 62: 894-8.

Pregnancy classification

The sponsor has proposed Pregnancy Category C[23] which is the category for all other fentanyl formulations, and is acceptable.

Local tolerance

While the excipients in the Fentora formulation would not be expected to elicit local irritation in the buccal cavity, no specific nonclinical local tolerance studies with the Fentora formulation were submitted. The sponsor's nonclinical expert noted that a visual assessment of local buccal tolerance was made in the pharmacokinetic study in dogs (Study RD/FC/97/007) and that no visual irritation was observed for any of the 6 test formulations in any dog. The study was a pharmacokinetic investigation and the submitted results made no mention of the results of visual assessment of the buccal cavity, although the protocol stated 'Effects on the oral mucosal tissue (colour change, obvious irritation) will be determined by visual examination.' There was certainly no histological examination of the buccal mucosa and the formulations used in the study were not specifically relevant to the effervescent tablet. Given the limited nonclinical local tolerance evaluation of the product as required by the relevant guideline[24], it is important that adequate clinical monitoring of the buccal cavity during clinical development of Fentora has been conducted.

Impurities

The sponsor's quality expert noted that the potential known and unknown impurities in fentanyl citrate comply with the Ph.Eur according to the Certificate of Suitability No. R1-CEP 2005-104, with the additional requirement that any unspecified impurity not mentioned in the Ph Eur is limited to not more than 0.1%. Final stage solvents are each limited to not more than 0.5% and the catalyst is limited to not more than 50 parts per million (ppm).

Paediatric use

Fentanyl is not proposed for paediatric use and no specific juvenile animal studies were submitted.

Nonclinical summary and conclusions

- The main newly submitted studies were core safety pharmacology, carcinogenicity (including range-finding) and reproductive toxicity studies, all using the SC route except for the mouse carcinogenicity study. All studies were GLP compliant and adequately conducted. Carcinogenicity studies and a full package of reproductive toxicity studies were not required for the proposed indication but the studies were not conducted specifically for this application
- The safety pharmacology studies did not reveal any unknown activities of fentanyl. Respiratory depression, bradycardia and CNS findings were the main observations

[23] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
[24] CPMP/SWP/2145/00, January 2002: Note for guidance on non-clinical local tolerance testing of medicinal products.

- No pharmacokinetic data in nonclinical species were generated for the effervescent buccal tablet formulation. AUC and C_{max} values of fentanyl at the maximum clinical dose of Fentora were below those at the maximum clinical dose of Actiq®
- The 3 month range-finding study for the rat carcinogenicity study revealed granulomatous inflammation in the lungs, likely to be due to a secondary effect (feed aspiration) due to sedation, and testicular degeneration and aspermia in males (possibly also secondary to sedation)
- Genotoxicity studies (a reverse mutation study, a forward mutation study in mouse lymphoma L5178Y cells and a mouse micronucleus assay) had been submitted previously and all were negative
- Carcinogenicity studies (2 year study in rats with doses up to 50 μg/kg/day SC in males and 100 μg/kg/day SC in females, and 6-month study in transgenic Tg.AC mice with dermal doses up to 50 μg/day) did not reveal any carcinogenic potential of fentanyl. Some histological changes (including mineralisation and 1 case of necrosis) were observed at low incidence and severity in the brain in rats given ≥50 μg/kg/day, and are not considered of relevance to the proposed patient population. Exposure ratios at the HD were about 3 in mice and 2 to 3 in rats (based on a single daily dose)
- A full suite of reproductive toxicity studies was submitted. In a fertility and embryofetal development study in rats, male (but not female) fertility was impaired, with most findings (including reduced sperm motility and concentration, increased abnormal sperm, and reduced fertility index and viable fetuses) at the HD (300 μg/kg/day SC), but this dose was highly toxic (associated with mortalities). Exposure ratio at the NOAEL was about 3 (based on a single daily dose). There were no adverse findings in rat or rabbit embryofetal development studies. In a pre and postnatal development study in rats, growth/development of F_1 pups was impaired at the higher, toxic doses (100, 400 μg/kg/day); the exposure ratio at the NOAEL was about 1 (based on a single daily dose)
- No local tolerance study was conducted with the buccal tablet in nonclinical species.

Nonclinical conclusions and recommendation

- This nonclinical evaluation did not raise any issues of concern regarding the use of Fentora for the proposed indication and there no nonclinical objections to the registration of Fentora for the proposed indication
- Given the limited nonclinical local tolerance data, it is important that adequate clinical monitoring of the buccal cavity during clinical development of Fentora has been conducted
- The nonclinical evaluator recommended amendments to the draft Product Information document but the details of 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

The major clinical pharmacology studies and the efficacy and safety studies were all conducted using the Generation III formulation. The only difference between Generation

III and the Commercial formulation is that the colorant was removed from the Commercial formulation. No bioequivalence studies were conducted as the full pharmacology program and efficacy and safety studies were conducted using Generation III and the change to Commercial formulation is not expected to make any difference to its performance.

Clinical rationale

The ability to achieve a rapid analgesic effect is important in the management of pain for patients with cancer who, despite continuous background analgesia often experience recurrent episodes of acute transitory pain otherwise known as BTP. Opioid analgesics are standard treatment for patients with cancer pain and there are a number of marketed opioid drugs in a range of formulations used for the management of both background pain and BTP. However, the effectiveness of currently available products used in the management of BTP is limited by their mode of administration, lag time to adequate analgesia and long duration of action.

The prevalence of BTP is high, with 64% to 89% of patients with chronic cancer pain experiencing such events. BTP is usually severe and achieves peak intensity in 3 to 5 minutes and the median duration is 30 minutes. Patients with BTP are usually treated with short acting or normal release opioid analgesics. In contrast, background pain is continuous throughout the day (≥12 hours/day) and is managed with around the clock (ATC) medication, usually in the form of long acting or sustained release opioid formulations.

For patients taking opioids as their ATC medication, it is recommended that they also take opioids for BTP. The method of determining the most effective dose of an opioid remains an inexact science, with little correlation between the dose of daily ATC opioid and the opioid dose needed for BTP. Episodes of BTP vary in cause, severity and duration and thus, medication to manage BTP should be titrated individually in a fashion similar to that used for opioid medications given for continuous background pain.

Fentanyl is suited for the management of BTP for the following reasons: greater potency than morphine, shorter duration of action, lack of ceiling effect on analgesia, analgesic effects related to blood levels and rapid buccal absorption avoiding extensive first pass metabolism. FEBT was developed using proprietary technology for efficient delivery with the aim of enhanced rate and extent of absorption.

Guidance

The TGA has adopted the EU Guidance *Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain*[25]. This is a general guide for all types of nociceptive pain and does not provide specific guidance for breakthrough cancer pain. It is noted that no specific pain scale is recommended and no specific endpoints are recommended.

Contents of the clinical dossier

The objective of the initial drug development program was to develop a buccal dosage form of fentanyl citrate using effervescence in the tablet to facilitate absorption transmucosally in order to achieve therapeutically effective blood levels with lower doses of fentanyl than those in Actiq®, an oral transmucosal fentanyl citrate drug product, which is approved in a number of countries worldwide. The fentanyl buccal tablet was designed to disintegrate in the buccal cavity at approximately the same rate as Actiq®. However, due to the differences in PK profiles observed between the fentanyl effervescent buccal tablet

[25] CPMP/EWP/612/00

(FEBT) and Actiq® it was decided that clinical efficacy and safety studies should be conducted and the objective was no longer to show bioequivalence. As a result a number of studies with the earlier formulations were included in the submission for completeness but have not been evaluated as part of this report.

The submission contained the following clinical information:

- 16 clinical pharmacology studies, including 15 that provided pharmacokinetic data and 1 that provided pharmacodynamic data
- 2 pivotal efficacy/safety studies
- 2 other efficacy/safety studies
- 7 studies of efficacy/safety in other indications which are not the indication being sought in this submission. These studies have been reviewed for safety but not evaluated for efficacy
- 14 (other including 13 Periodic Safety Update Reports (PSURs) and 1 drug utilisation study)

Paediatric data

The submission did not include paediatric data. No information was provided 1 on paediatric data.

Good clinical practice

The study reports state that all studies were conducted in full accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH) and any applicable national and local laws and regulations (for example in USA - Title 21, Code of Federal Regulations [21 CFR] Parts 50, 54, 56, 312, and 314). Before the studies were initiated, the protocol was submitted to the Institutional Review Board (IRB) according to national or local regulations and written informed consent was obtained from each subject before any procedures or assessments were done and after the aims, methods, anticipated benefits and potential hazards were explained.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 shows the studies relating to each pharmacokinetic topic.

Table 5: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	General PK - Single dose	1029	PK
	- Multi-dose	1029	PK
		099-20	PK
	Dose proportionality (single dose)	099-18	PK
		1027	PK
		1037	PK
		1052	PK
		099-19	PK Japanese
		1054	PK Japanese
	Bioavailability		
	absolute and relative	1028	BA
	comparison of strengths	099-21	BA
	Bioequivalence		
	Different strengths	1026	BE
	Buccal vs sublingual	1043	BE
	Oravescent vs Actiq	099-11	BE
	Different strengths	1053	BE
PK in special populations	Target population § - Single dose	099-16	PK
	- Multi-dose		

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
BE=Bioequivalence; BA=Bioavailability

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The PK studies for FEBT were consistent with the known information for fentanyl. The submission contained the necessary studies to document those aspects of the PK of FEBT that were expected to be unique given its novel formulation.

Fentanyl formulated as FEBT is readily absorbed, with an absolute bioavailability of 65% following buccal administration. The absorption profile is largely the result of initial rapid absorption from the buccal mucosa, with peak plasma concentration attained at approximately 50 minutes in the fasted state. The mean PK profile based on the pooled data demonstrates that within 25 minutes, plasma concentrations reach approximately 80% of the C_{max} and are maintained through 2 to 3 hours after the start of administration. Approximately 50% of the total dose administered is absorbed across the buccal mucosa and rapidly becomes systemically available. The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract. Following absorption, fentanyl formulated as FEBT exhibits an apparent bioexponential or triexponential decline from peak plasma concentration. The metabolism and excretion are as expected for fentanyl.

Multiple studies were conducted to demonstrate that fentanyl formulated as FEBT exhibits linear pharmacokinetics. Dose proportionality was not found in all the studies, which is explained in some of the study reports as being due to low numbers and in others to be due to decreased absorption due to taking multiple tablets to achieve the highest doses. There appears to be dose proportionality at doses from 100 to 800 µg and likely up to 1000 µg. Above this dose (1000 µg) the largest study demonstrated dose proportionality up to 1300 µg. The lack of dose proportionality, if it exists, is unlikely to create problems as the results approximate dose proportionality and all patients should be individually titrated to the effective dose.

The rate and extent of fentanyl absorption of FEBT are not affected by the dwell time and there is no difference in the PK profile between buccal and sublingual placement of the tablet.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 6 shows the studies relating to each pharmacodynamic (PD) topic.

Table 6: Submitted PD studies.

PD Topic	Subtopic	Study ID	Primary aim
Primary Pharmacology	Effect on analgesic potency	1046	PD

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Only one PD study (Study 1046) of FEBT was submitted. Analgesic efficacy was tested in healthy volunteers with thermally induced hyperalgesia. The primary PD variable was the $SPID_{60}$ (sum of pain intensity scores averaged for each temperature at each time point over the first hour). The criteria for significance were not met for this variable. The study

utilised an experimental pain model in healthy subjects rather than in patients with chronic pain. There was no significant difference from placebo following the 43°C and 46°C thermal applications, which resulted in a lack of significant effect when averaging the responses from all 3 temperatures. Pain intensity difference (PID) and pupil diameter measurements 60 minutes following the 49°C thermal application showed comparable relative potency.

The implications of the results of this study are limited and it is noted that there is no discussion of the PD in the sponsor's summaries. Additionally, the results of this study are limited to the studied dose range and cannot be extrapolated to higher doses. The results of the efficacy studies found that the efficacy of FEBT was not influenced by age, sex, race, weight or BTP pathophysiology.

Dosage selection for the pivotal studies

In selecting FEBT dose strengths for the clinical efficacy studies, results from Study 099-011 indicated that lower doses of FEBT (approximately 50%) were required to achieve a similar effect to the of the oral transmucosal fentanyl lozenge (Actiq®). Results from Study 1028 indicated that the dose of fentanyl from FEBT should be approximately 70% of that in an Actiq unit in order to obtain comparable plasma concentrations rather than the 50% predicted from the earlier study. No standard dose was selected for the efficacy studies and all patients were individually titrated from a starting dose of 100 µg to an individual effective dose. The effective dose was then used in the pivotal studies for the double blind comparison to placebo. No patient received more than 800 µg.

Efficacy

Studies providing efficacy data

Two pivotal efficacy/safety studies and two other efficacy/safety studies were submitted. See Attachment 2 for further details.

Evaluator's conclusions on efficacy

The efficacy is based on two pivotal studies (placebo controlled) and two open label studies. The two pivotal studies were of moderate size but similar design. The inclusion criteria were similar with the patients enrolled being typical of opioid tolerant adult men and women with cancer related background pain and BTP. They all were using ATC opioid therapy for their background pain and additional opioid therapy as rescue medication for their BTP. Both trials used a within patient control design which is necessary to minimise the risk of patients being treated with placebo.

The efficacy results from both pivotal studies showed a consistent positive effect for FEBT compared to placebo across the standard measures of pain (pain intensity, pain relief and use of rescue medication) and time points (15, 30, 45, and 60 minutes). At both the 30 and 60 minute time points a patient was twice as likely to achieve at least a 33% or 50% decrease in pain intensity with FEBT compared to placebo.

No active comparator trials have been conducted which is disappointing as a comparison to oral transmucosal fentanyl would have been useful to clinicians but the final decision will probably rest with patient preference.

All studies included a dose titration period and the comparison between starting doses of 100 µg and 200 µg indicated that a starting dose of the lower dose (100 µg) was the most

appropriate. If patients could not determine an effective dose they did not continue in the studies.

The non-pivotal studies, which were open label non comparative studies provided some long term data demonstrating that the efficacy is maintained for up to 12 months.

Safety

Patient exposure - studies providing safety data

The primary safety analysis set is made up of the following studies:

- Pivotal double blind, placebo controlled studies - Studies 099-14 and 3039
- Open label study – Study 099-15

An additional study (4027) was included in the submission. It is included in the sponsor's Summary of Clinical Safety but the data for this trial was not integrated with the other data. It is presented separately as 'supportive safety data'. Data from the studies in non-cancer pain is only referenced where relevant.

Table 7: Exposure to FEBT and comparators in clinical studies.

Study type / Indication	FEBT			Total FEBT
Clinical pharmacology Single dose Multiple dose	596 35			596 35
	Controlled studies		Uncontrolled studies	
Indication BTP	FEBT	Placebo	FEBT	
Pivotal				
099-14				
titration	123	123		123
post titration	77	77		77
3039				
titration	125	125		125
post titration	86	86		86
Other				
099-15				
titration			115	115

Study type / Indication	FEBT			Total FEBT
post titration			197	197
4027				
titration			312	312
post titration			223	223
TOTAL				
titration	248	248	670	1306
post titration	163	163	462	1214

Table 8: Exposure to FEBT in clinical Studies 099-14, 3039 and 099-15 according to dose

Variable Category	Number (%) of patients (N=358)
Successful dose (µg)	
None	113 (32)
100	23 (6)
200	33 (9)
400	54 (15)
600	59 (16)
800	76 (21)
Maximum dose (µg)	
100	38 (11)
200	33 (9)
400	62 (17)
600	57 (16)
800	168 (47)
Average dose per BTP episode (µg)[a]	
<200	49 (14)

Variable Category	Number (%) of patients (N=358)
≥200-<400	91 (25)
≥400-<600	100 (28)
≥600-<800	79 (22)
≥800	18 (5)
Missing	21 (6)
Average daily dose (µg)[a]	206 (58)
≤800 µg	
>800-≤1600 µg	54 (15)
>1600-≤2400 µg	27 (8)
>2400-≤3200 µg	47 (13)
>3200 µg	21 (6)
Missing	3 (<1)

a The average dose per BTP episode and the average daily dose were calculated for the titration and post titration periods combined. BTP=breakthrough pain.

Table 9: Average Study Drug Dose per Breakthrough Pain Episode by Weeks or Months of Exposure in Patients with Cancer and Breakthrough Pain (Studies 099-14, 3039, 099-15)

Length of exposure	Number (%) of patients by average dose per BTP episode (mcg)						
	<200 (N=49)	≥200-<400 (N=91)	≥400-<600 (N=100)	≥600-<800 (N=79)	≥800 (N=18)	Missing[a] (N=21)	Total (N=358)
≥1 day	49 (100)	91 (100)	100 (100)	79 (100)	18 (100)	21 (100)	358 (100)
≥1 week	27 (55)	69 (76)	75 (75)	79 (100)	17 (94)	4 (19)	271 (76)
≥2 weeks	19 (39)	54 (59)	63 (63)	74 (94)	16 (89)	2 (10)	228 (64)
≥1 month	17 (35)	35 (38)	53 (53)	67 (85)	16 (89)	1 (5)	189 (53)
≥3 months	7 (14)	24 (26)	38 (38)	53 (67)	12 (67)	0	134 (37)
≥6 months	3 (6)	15 (16)	18 (18)	33 (42)	11 (61)	0	80 (22)
≥9 months	2 (4)	12 (13)	12 (12)	20 (25)	8 (44)	0	54 (15)

Length of exposure	Number (%) of patients by average dose per BTP episode (mcg)						
	<200 (N=49)	≥200-<400 (N=91)	≥400-<600 (N=100)	≥600-<800 (N=79)	≥800 (N=18)	Missing[a] (N=21)	Total (N=358)
≥12 months*	2 (4)	10 (11)	8 (8)	14 (18)	5 (28)	0	39 (11)
≥15 months	1 (2)	6 (7)	4 (4)	8 (10)	2 (11)	0	21 (6)
≥18 months	1 (2)	1 (1)	3 (3)	4 (5)	1 (6)	0	10 (3)

a Average dose per day cannot be calculated due to incomplete diary data. BTP=breakthrough pain.

Table 10: Extent of exposure to the study drug in Study 4027

Variable	Titration period			Treatment period	Continuation period	All periods
	100 µg (N=145)	200 µg (N=167)	Total (N=312)	Overall (N=223)	Overall (N=87)	Overall (N=223)
Duration of treatment (days)						
N	144	162	306	219	87	223
Mean	5.5	5.5	5.5	4.8	204.2	90.6
SD	2.02	1.97	1.99	1.89	198.66	158.26
SE of mean	0.17	0.15	0.11	0.13	21.30	10.60
Median	6.5	6.0	6.0	4.0	115.0	14.0
Min, max	1, 10	1, 12	1, 12	1, 12	1, 684	1, 688
Total dose (mcg)						
n	144	16*7	311	222	—	—
Mean	2995.8	3620.4	3331.2	2552.7	—	—
SD	3207.77	3107.75	3164.75	1918.65	—	—
SE of mean	267.31	240.49	179.46	128.77	—	—
Median	1950.0	2700.0	2400.0	1600.0	—	—
Min, max	100, 20800	200, 17000	100, 20800	0, 12000	—	—

Variable	Titration period			Treatment period	Continuation period	All periods
	100 µg (N=145)	200 µg (N=167)	Total (N=312)	Overall (N=223)	Overall (N=87)	Overall (N=223)
Average dose per episode (µg)						
n	144	167	311	222	—	—
Mean	250.1	330.3	293.1	309.5	—	—
SD	152.70	157.04	159.90	196.00	—	—
SE of mean	12.73	12.15	9.07	13.15	—	—
Median	200.0	300.0	230.8	200.0	—	—
Min, max	100, 743	100, 757	100, 757	0, 800	—	—

NOTES: The titration safety analysis set is presented by randomized treatment group. The average dose per episode is the total dose divided by the number of episodes in the titration/treatment period. Max=maximum; min=minimum; n=number of patients with a response; SD=standard deviation; SE=standard error.

Safety issues with the potential for major regulatory impact

Overdose

There was one report of overdose in the studies in patients with cancer and BTP (in Study 4027). The overdose occurred during the titration phase of the study and it is unknown if the overdose was accidental or intentional. The patient was recorded as non-compliant with the study drug due to taking study drug more frequently than every 4 hours for 3 days. The patient was discontinued from the study because of the overdose and because of progression of cancer.

In the non-cancer studies there were 12 cases of overdose reported. No event was fatal. Three events were intentional, occurring in the context of suicide attempts and in another the study drug was used in combination with alcohol. In three other cases the patients had medical factors (pneumonia, head trauma and drug interaction) that were considered to have contributed to the overdose. Four patients had overdoses that were considered accidental and for one patient the exact circumstances were not known. A final case related to the overdose death of the partner of a study participant. The patient reported that the partner had taken the patients study drug (800 µg) as 12 to 18 tablets were missing and autopsy reported that the patient's partner died from fentanyl overdose.

Dependence, rebound phenomena, abuse, tolerance

Physical dependence is a known characteristic with fentanyl treatment, as with other opioids. The potential for developing dependence is difficult to assess in an opioid tolerant patient population. In the clinical program FEBT was used on an as needed basis by patients with an average of 1 to 4 BTP episodes per day and who were already taking ATC opioids. The short term studies allowed only one tablet per episode and in the long term study a maximum of two tablets was permitted per BTP episode. Consequently no specific evaluations have been made of the potential for withdrawal and/or rebound effects with FEBT.

Fentanyl has a significant well documented abuse potential. FEBT may be attractive for abuse because of the rapid rise of fentanyl blood levels although the peak plasma concentration and the time to reach the peak are notably lower than after intravenous administration. Although the risk of extraction of fentanyl from the tablets is present, manipulation (such as crushing) of the tablet is not likely to substantially alter the absorption characteristics of the medication when administered buccally or orally. Although intranasal and intravenous administration of a crushed tablet is possible, the risk of such is not considered to be any greater for FEBT than for any other strong μ-opioid drugs such as oxycodone, hydromorphone or morphine.

Evaluator's conclusions on safety

The total patient numbers in the safety assessment is low but fentanyl is a well know substance and the new dosage form and route of administration is not significantly different to other approved products. There is some concern of the paucity of long term data; nearly half the patients received the drug for less than one month but this may be representative of the patients likely to be prescribed the product.

No new safety issues emerged in the clinical studies. The most common AEs reported with FEBT treatment were characteristic of fentanyl products, namely nausea, dizziness, constipation, fatigue, headache and vomiting. The incidence and types of adverse events did not appear to be dose related. Further the rapid absorption of FEBT did not appear to affect the type or severity of the AEs reported.

Approximately 10% of patients experienced AEs that could be considered to be related to the tablet application site; for example, application site pain, ulcer or burning. In the majority of patients these AEs were mild to moderate and resolved without treatment interruption. Women appeared to be at greater risk for application site events. Application site AEs could be reduced if the patient is advised to alternate the placement of the tablet in the right and left buccal mucosa or to administer the tablet sublingually.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Fentora in the proposed usage are:

- FEBT at a range of individually titrated doses (from 100 to 800 μg) was superior to placebo in relieving BTP in cancer patients on maintenance ATC opioid therapy as measured by a range of pain measures including pain intensity, pain relief, rescue medication used and global medication performance.
- Most patients were able to achieve a successful dose with a simple titration schedule starting at 100 μg.

First round assessment of risks

The risks of Fentora in the proposed usage are:

- Known AEs to fentanyl; nausea and vomiting, dizziness, constipation, fatigue and headache
- Respiratory depression
- Dependency and abuse, but less likely in the indication being sought.

First round assessment of benefit-risk balance

The benefit-risk balance of Fentora, given the proposed usage, is favourable.

First round recommendation regarding authorisation

Based on the clinical data submitted it is recommended that Fentora be approved.

Clinical questions

No clinical questions were raised by the clinical evaluator.

Second round evaluation of clinical data submitted in response to questions

As there were no clinical questions raised by the clinical evaluator, no second round clinical evaluation was conducted.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 3.0 (dated 19 June 2014, data lock point (DLP) 30 April 2014) and Australian Specific Annex Version 3 (dated September 2014) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 11.

Table 11. Ongoing safety concerns provided by the sponsor in their RMP submission.

Important identified risks	• Drug abuse • Drug diversion • Pharmacodependence • Drug misuse • Off-label use • Accidental exposure • Medication errors • Overdose • Respiratory depression (new) • Hypersensitivity and anaphylaxis (new) • Local tolerability (including dental disorders) (new)
Important potential risks	• Cardiovascular/circulatory depression (new) • Occurrence of brain lesions in form of multifocal neuronal mineralisation/necrosis following repeated application of high doses of fentanyl in rats. Relevance to human is unknown. • Suicide (new)
Important potential interaction	• Potential drug interaction with serotonergic drugs leading to serotonin syndrome
Missing information	Fentanyl was not studied in • Pregnant, breastfeeding women • Paediatric population • Patients with renal or hepatic dysfunction (new) • Long-term use (new)

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all ongoing safety concerns and additional pharmacovigilance activities for some important identified risks.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for all ongoing safety concerns and additional risk minimisation activities for most important identified risks.

Reconciliation of issues outlined in the RMP report

Table 12 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the TGA's evaluation of the sponsor's responses.

Table 12: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	*'Please note that safety considerations have not been raised in the nonclinical and clinical section 31 request. The PCS have however requested changes that relate to safety to the PI, and subsequently CMI. These have been updated together with the OPR's recommendation below.'*	The sponsor's response has been noted.
The sponsor should make available the details of the planned survey of pharmacists, once available.	*'Confirmation is provided that the details of the planned survey of pharmacists will be made available to the TGA, once available.'*	This is considered acceptable.
The sponsor should make available the final study report of the conducted PASS, once available.	*'Confirmation is provided that the final study report will be made available to the TGA, once available.'*	This is considered acceptable.
The sponsor should add the planned Canadian Drug Utilisation Study to the pharmacovigilance plan.	*'Canadian Drug Utilisation Study is taken into consideration as part of additional pharmacovigilance obligation and is mentioned in the EU-RMP; however it is not included as specific obligation in Part III of the EU-RMP since it is not an EU requirement. Data on study results will be provided in the future EU-RMP, and therefore available to the TGA.'*	The sponsor's response has been noted. Whether an additional pharmacovigilance activity is an EU requirement or not, is not considered relevant in the context of Australian regulation and will be evaluated on a case-by-case basis. Post-authorisation drug utilisation data is necessary in the context of this application. Normally, a local drug utilisation study would be required. However, a study in a jurisdiction with comparable demographics may be acceptable. It was noted that the sponsor is

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
		already conducting such a study and could add this to the pharmacovigilance plan in the ASA with negligible effort. However, if the sponsor insists on not adding the existing Canadian study to the pharmacovigilance plan, a proposed Australian drug utilisation study should be proposed. The recommendation remains: the sponsor should add the planned Canadian Drug Utilisation Study to the pharmacovigilance plan, update the ASA accordingly, and provide updates in PSURs, or, alternatively propose a Drug Utilisation Study to be conducted in Australia.
The sponsor should commit to assigning the additional pharmacovigilance activities conducted outside Australia to the ASA.	*'The ASA has been updated to include the additional pharmacovigilance activities outside Australia, as noted in Table 3 of the Risk Management Plan Evaluation Report.'*	This is considered acceptable.
The sponsor should outline how they wish to assess local tolerability issues in patients taking Fentora.	*'As indicated in the EU-RMP Part IV, the risk of local tolerbility [sic] is assessed via post-market monitoring. Potential increase in the relevant cases for this risk will be measured by the PRR (proportional reporting ratio) signal detection method. Results will be used to assess the need for further risk minimisation activities updates. To date, no signals have arised related to this risk, and therefore it is considered that routine risk minimisation measures are sufficient for this risk (please refer to the responses to Questions 15 and 28).'*	This is considered acceptable in the context of this application.
The CMI document should include the patient information leaflet as an attachment.	*'We would like to provide clarification that the leaflet referred [sic] in the application is*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	the CMI. A separate patient information leaflet have not been developed. *However, to address rule based and action based medication errors, it is proposed to include the 'Patient guide for FENTORA' as a leaflet as an attachment to the CMI. The document forms part of the patient educational material, and includes dosing and administration information in detail.* *Please find the draft CMI and Patient guide for FENTORA enclosed in Module 1.3.1.3.'*	
The CMI should be contained as a package insert.	*'The CMI is intended to be included as a package insert.'*	This is considered acceptable.
A separate patient dosing card should be developed.	*'A separate patient dosing card is incorporated in the Patient guide for FENTORA leaflet insert immediately following the CMI. Please refer to the proposed leaflet in Module 1.3.1.3 and annex 3 of the ASA.'*	It is noted that the flowchart contains the trade name 'EFFENTORA' rather than 'FENTORA' (the proposed trade name for Australia). The sponsor should amend this. The flowchart content is considered acceptable, subject to approval by the Delegate.
Tick-boxes should be present on the packaging (or an equivalent risk mitigation measure) to enable patients to record the number of tablets taken.	*'Due to the limited amount of space on the packaging, an equivalent tick-boxes table is proposed to be included in the Patient guide for FENTORA leaflet insert immediately following the CMI. This will also enable patient the flexibility to carry only the necessary number of tablets rather than the entire box of tablets. In addition as the smaller pack sizes of 4's will generally be used during the initial titration process and the large pack size of 30's used during maintenance dose, by including the tick-boxes table in the leaflet allows the patient to record the number of tablets taken in one location rather than on multiple cartons, thereby increasing compliance.'*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
The sponsor should advise whether Fentora is supplied in child-proof packaging, or provide a compelling justification.	*'We provide confirmation that Fentora is supplied in child - proof packaging.'*	This is considered acceptable.
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to accommodate the changes made to the product information document.	*'The draft CMI document is updated to align with the changes made to the PI document.'*	This is considered acceptable, subject to approval by the Delegate.
The sponsor should commit to providing updates on the effectiveness measurement of additional risk minimisation activities in PSURs.	*'Orphan Australia commits to providing updates on the effectiveness measurement of additional risk minimisation activities in PSURs.'*	This is considered acceptable.
The sponsor should provide the TGA with the following details of the Australian specific education materials for agreement, and update the ASA accordingly: All draft education materials (including a patient dosing card); A clear distribution plan.	*'Educational materials:* *The Australian specific draft education materials for healthcare professionals and patients have been developed based on the materials developed for EU. The patient dosing table is included in the Patient's guide for Fentora which will be included as a leaflet in the product carton. The updated CMI and Patient's guide for Fentora is also included.* *Distribution plan:* *-Educational materials will be distributed via the field representatives to the healthcare professionals, available in both hard copies and electronically via a QR code on the label.* *- Patients can access also access the educational materials through their healthcare professional or via the QR codes. The CMI and 'Patient's guide for Fentora' are contained in the product box as leaflets.* *Please note that QR code will be included on the product carton upon approval from the OPR of the above plan.'*	The sponsor's response has been noted. The OPR evaluator has not been provided with the actual content to which the proposed QR code links. Notwithstanding any of the OPR evaluator comments regarding the content of the provided education materials, the sponsor is reminded that any education material must not be promotional in any way, or be considered to be advertising of a prescription medicine to the general public. The sponsor should ensure that any content to which the QR code links is in compliance with relevant legislation.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
Local tolerability issues may occur with the buccal/sublingual dosage form and should also be addressed by and assigned to the additional risk minimisation activities.	*'Orphan Australia is aware of local tolerability with the buccal/sublingual dosage forms. As per TGA's advice a precautionary statement regarding patients with mucositis and local toerability [sic] issues has been added to the 'Precautions' section in the PI.* *Based on post-marketing data no signals have arised for Fentora related to this risk.* *Therefore, it is considered that routine risk minimisation measures are sufficient for this risk and no additional risk minimisation measures are warranted at this stage.'*	This is considered acceptable in the context of this application.
The additional risk minimisation activity materials should be finalised before approval, and not developed post-approval. Furthermore, all materials should be annexed to an updated ASA.	*'Please find the updated ASA enclosed in Module 1.13.1'*	The sponsor's response has been noted. There are no definite objections to the provided materials. However, the sponsor should review the proposed materials for errors (including the use of trade names not proposed for Australia) and ensure internal consistency (for example. the statement *'The educational material for patients shall consist of the following <u>three</u> items'* is only followed by two items).

CMI=consumer medicine information

Summary of recommendations

It is considered that the sponsor's response to the TGA s request for further information has adequately addressed most of the issues identified in the RMP evaluation report. There are outstanding issues.

Summary of outstanding issues

Recommendations in regard to content of the submission

1. The sponsor should review the proposed materials for errors (including the use of trade names not proposed for Australia and ASA version labelling) and ensure internal and external consistency. It is noted that the dose titration flowchart contains the trade name 'Effentora' rather than 'Fentora' (the proposed trade name for Australia). The sponsor should amend this.

Recommendations in regard to pharmacovigilance activities

2. The sponsor should add the planned Canadian Drug Utilisation Study to the pharmacovigilance plan, update the ASA accordingly, and provide updates in PSURs, or, alternatively propose a Drug Utilisation Study to be conducted in Australia.

Recommendations in regard to risk minimisation activities

3. The sponsor should ensure that any content to which the QR code links is in compliance with relevant legislation.
4. In the submitted RMP, the sponsor has not outlined how they plan to facilitate the systematic return of unused and used products (other than CMI pack inserts). Further details should be made available to outline how the sponsor proposes to facilitate the systematic return of unused and partially used products. This should be outlined in an amended ASA.

Key changes to the updated RMP

EU-RMP Version 3.0 (dated 19 June 2014, DLP 30 April 2014) remains unchanged. Australian Specific Annex Version 2.0 (dated June 2014) has been superseded by: Australian Specific Annex Version 3 (dated September 2014) (but still labelled as Australian Specific Annex Version 2.0 (dated June 2014)).

Table 13: Summary of key changes to ASA versions 2.0 and 3.0

Summary of key changes between ASA Version 2.0 and ASA Version 3	
Safety specification	No change.
Pharmacovigilance activities	PASS study (France) added.
Risk minimisation activities	Educational materials to HCPs and patients added.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> Implement EU-RMP Version 3.0 (dated 19 June 2014, DLP 30 April 2014) and Australian Specific Annex Version 3 (dated September 2014)[26], and future updates, where approved by the TGA, as a condition of registration.

[26] The sponsor submitted an Australian Specific Annex Version 4 (dated November 2014) with their pre ACPM response.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The evaluator stated that:

- There are no objections to registration from a quality and biopharmaceutics perspective.

Nonclinical

- This evaluation did not raise any issues of concern regarding the use of Fentora for the proposed indication, and there no nonclinical objections to the registration of Fentora for the proposed indication.
- Given the limited nonclinical local tolerance data, it is important that adequate clinical monitoring of the buccal cavity during clinical development of Fentora has been conducted.
- The nonclinical evaluator also recommended amendments to the draft Product Information document.

See also *Nonclinical summary and conclusions* above for further details of the nonclinical evaluation.

Clinical

The clinical evaluator noted that in the submission, several different names and abbreviations are used for the product intended to be marketed in Australia. Oravescent, which is used in many of the study reports, appears to be a trade name for the buccal effervescent fentanyl citrate tablet. It is also referred to as the fentanyl buccal tablet (FBT) and the fentanyl effervescent buccal tablet (FEBT) which are identical. In the clinical evaluation report, the product is called Oravescent when that is used in the study reports and FEBT when no trade name is given.

Pivotal

Study 099-14

This was a double blind, randomised, placebo controlled study to determine the clinical efficacy of Oravescent fentanyl when used to relieve breakthrough pain (BTP) in opioid tolerant patients with cancer who are receiving maintenance opioids.

For inclusion, male or female (non-childbearing potential) patients, at least 18 years old with a histologically documented diagnosis of a malignant solid tumour or a haematological malignancy causing cancer-related pain and an Eastern Cooperative Oncology group (ECOG) status[27] of ≤2; and who had been receiving 60 to 100 mg of morphine/day or 50 to 300 μg of transdermal fentanyl or an oral morphine equivalent

[27] These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. 0=fully active to 5= dead.

dose for at least a week for cancer related pain and was experiencing on average, but not necessarily every day, 1 to 4 episodes of BTP per day that were adequately controlled with a stable dose of standard rescue medication, typically a fast acting opioid were eligible.

The study has an open-label dose titration component which enrolled 123 patients (mean age = 58 years, range 27 to 87 years.). In the open label phase of the study which lasted for 21 days, patients started titration with a single tablet of the lowest dosage strength of Oravescent fentanyl, 100µg, placed buccally to treat an episode of BTP. The patient treated each episode with an escalating dose until they achieved a successful dose which was defined as the dose strength that provided adequate analgesia (sufficient pain relief within 30 minutes after placing a single tablet of that dose strength in the buccal cavity for each of 2 consecutive episodes of BTP that occurred at least 4 hours apart) without unacceptable adverse events. Two tablets each of 100 µg, 200 µg, 400 µg, 600 µg and 800 µg Oravescent fentanyl strengths were provided.

Seventy two (72) patients were evaluable in the randomised double-blind treatment period of the study (up to 21 days). Patients received 10 blinded study drug treatments (7 Oravescent fentanyl tablets at the successful dose and 3 matching placebo tablets). During the double-blind treatment period of the study, patients served as their own controls by the requirement to take all the 10 blinded study drug treatments. Patients were introduced to take only one tablet of study drug for each BTP episode and not to administer additional study drug within 4 hours following any study drug administration. Patients were asked to refrain from using rescue medication for at least 30 minutes after study drug administration. All 10 doses were to be taken within a 21 day period.

The rescue medication was not specified but was described as the 'patient's standard rescue medication'. The rescue medication used included oxycodone/acetaminophen (24%), hydrocodone/acetaminophen (21%), morphine (17%) and hydromorphone 11%).

The *primary efficacy outcome* was the SPID through 30 minutes after the start of administration of study drug used for an episode of BTP during the double blind period ($SPID_{30}$).

$SPID_{30}$ was calculated as the sum of the PID at both 15 and 30 minutes after administration of study drug for each BTP episode as follows: $SPID_{30} = PID_{15}+PID_{30}$.

Other efficacy outcomes included:

- SPID at each additional time point: $SPID_{15}$, $SPID_{45}$ and $SPID_{60}$
- Pain intensity difference (PID) value at each time point:- PID_{15}, PID_{30}, PID_{45}, PID_{60}
- Pain relief (PR) score at each time point: PR_{15}, PR_{30}, PR_{45}, PR_{60}
- Total PR (TOTPAR) value at each time point: $TOTPAR_{15}$, $TOTPAR_{30}$, $TOTPAR_{45}$, $TOTPAR_{60}$
- Global medication performance assessment at 30 and 60 minutes after administration of study drug
- Proportion of BTP episodes for which rescue medication was used, time from start of administration of study drug to use of rescue medication and relative risk of requiring rescue medication.

Note: The PID and SPID were based on patients' visual analogue scales [1 (no pain) to 10 (worst pain)] via patients' pain intensity (PI) of each BTP episode before taking study drug and at 15, 30, 45 and 60 minutes after study drug administration. A PID was calculated for each of the time points after administration of study drug by subtracting the PI at 15, 30, 45, and 60 minutes after administration of study drug from the PI at 0 minutes (PID_{15}, PID_{30}, PID_{45}, and PID_{60}, respectively).

Patients rated PR at 15, 30, 45, and 60 minutes after administration of study drug using a 5-point visual scale (0=none, 1=slight, 2=moderate, 3=lots, 4=complete).

TOTPAR was derived from PR scores. TOTPAR was calculated for each episode as the sum of PR scores at each quarter-hour assessment of PR until 60 minutes after administration of study drug, as follows: $TOTPARi=TOTPARi_{-15}+PRi$, where $i=30$, 45, and 60, and $TOTPAR_{15}=PR_{15}$.

A patient global medication performance assessment (0=poor, 1=fair, 2=good, 3=very good, 4=excellent) was also made at 30 and 60 minutes after administration of study drug.

Analyses included: Intent-to-treat (ITT), modified ITT and evaluate sets. For sample size, estimation was based on approximately 63 patients to evaluate efficacy during the double blind period. This would provide over 95% power to detect a treatment difference of 1.4 between study drug and placebo in the primary efficacy variable, $SPID_{30}$, with a standard deviation of the within-patient difference not exceeding 3.00.

The primary efficacy outcome was tested using an analysis of variance (ANOVA) with treatment and centre as fixed effects and patient as a random effect. The statistical test was two-tailed using $\alpha=0.05$. The consistency of treatment effects over different centres was evaluated by a separate ANOVA with treatment, centre, patient and treatment-by-centre as factors. If there was evidence of a treatment-by-centre interaction (p-value ≤0.10), a descriptive summary of treatment differences for each centre was used to identify the nature of the interaction and the data were analysed as appropriate. In this case, the p-value reported was from a model with the interaction term included. The final model for the primary efficacy analysis was also the model for the secondary variables SPID and TOTPAR. No separate treatment by covariate interaction or treatment-by-centre interaction was tested for any of these secondary variables. A one-sample Wilcoxon signed rank test was used for the analyses of the secondary variables PID, PR score and global medication performance assessment. All statistical testing was two-tailed using $\alpha=0.05$.

Study C25608/3039/BP/US

Double blind, randomised, placebo controlled study to evaluate the efficacy, safety and tolerability of Oravescent fentanyl citrate in opioid tolerant patients with cancer and breakthrough pain. As in *Study 099-14*, there was an initial open label titration period and similar inclusion criteria: male and female (non-childbearing potential) patients, aged 18 to 80 years who had histologically documented diagnosis of malignant solid tumour or a haematological malignancy causing cancer related pain. Patients had to be opioid tolerant with an average PI score, over the prior 24 hours, of <7 (on 10 point scales) for their persistent cancer pain and were experiencing, on average 1 to 4 BTP episodes per day while taking ATC opioid therapy and obtained at least partial relief from rescue opioid therapy. Patients had a life expectancy of at least 2 months.

There were 129 patients (mean age 54.9 years, range 29 to 79 years.) in the open label phase of the study and 75 patients completed the double blind treatment phase and as in Study 099-14, the patients were randomised to a sequence of 10 blinded study drug treatments (7 Oravescent fentanyl tablets at the successful dose and 3 matching placebo tablets in a prespecified sequence).

The analgesics used most commonly as rescue medication were oxycodone/acetaminophen (31 patients, 25%), hydrocodone/acetaminophen (25 patients, 20%), and oxycodone (23 patients, 18%). At baseline, the mean oral morphine equivalent dose per day taken as ATC medication was 279.2 mg (range 60 to 3198 mg), and the mean oral morphine equivalent dose per day taken as rescue medication for BTP was 24.7 mg (range 4 to 480 mg) per episode.

The *primary efficacy outcome* was the $SPID_{60}$ for each BTP episode during the double-blind treatment period.

The $SPID_{60}$ was calculated using the data collected on the patient's diary and was derived from the time-weighted sum of the PID scores recorded at 5, 10, 15, 30, 45, and 60 minutes after the administration of study drug.

PI scores were assessed by the patient on an 11 point numerical rating scale (0=no pain to 10=worst pain) immediately prior to the administration of study drug and at 5, 10, 15, 30, 45 and 60 minutes after the administration of study drug for each episode of BTP and were recorded in the patient's electronic diary.

The PID is the difference between the PI scores immediately prior to and at 5, 10, 15, 30, 45 and 60 minutes after the administration of study drug.

Other efficacy outcomes included:

- Sum of the Pain Intensity Differences: The $SPID_{30}$, $SPID_{90}$, and $SPID_{120}$ scores were calculated as the sum of the PID scores from 5 through 30 minutes, 5 through 90 minutes, and 5 through 120 minutes, respectively, after the administration of study drug
- Pain Intensity Difference: The PID was calculated for 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug. The PID was calculated as the patients' ratings of PI at each of these time points minus the rating of PI immediately before the administration of study drug
- Pain Relief: The PR scores at 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug were recorded on the patient's diary. The PR scores were assessed using a 5 point Likert scale (0=none to 4=complete)
- Total Pain Relief : The $TOTPAR_{60}$, $TOTPAR_{90}$, and $TOTPAR_{120}$ scores were calculated as the sum of PR scores recorded 5 through 60 minutes, 5 through 90 minutes, and 5 through 120 minutes, respectively, after the administration of study drug
- Time to Meaningful Pain Relief: The time in minutes to when meaningful pain relief was achieved after the administration of study drug was recorded in the patient's diary
- Global Medication Performance Assessment: The global medication performance assessment was recorded in the patient's diary at 60 and 120 minutes after the administration of study drug (and immediately before the use of any rescue medication for any episode of BTP for which rescue medication was used). Patients rated how well each dose of study drug performed in controlling BTP using a 5 point scale (0=poor through 4=excellent)
- Use of Standard Rescue Medication: Any use of standard rescue medication after the administration of study drug was recorded in the patient's diary.

The technical aspects of patients' and efficacy analyses were as for Study 099-14.

Other

Study C25608/4027/BP/EU

This was a European multicentre open label study of breakthrough cancer pain. Assessment of fentanyl buccal tablets (FBT) titration and treatment in opioid tolerant patients.

The study included an open label titration period in which patients were randomised to receive a starting dose of 100 µg (Group A) or 200 µg (Group B). Patients were then individually titrated to an effective FBT dose. Once the effective dose had been identified the patients entered an open label treatment period in which each patient treated 8 episodes of BTP. Once patients completed the 8 episodes they had the option to continue

treatment in an open label continuation period which continued until the product became commercially available.

Some 330 patients (Group A (GpA)= 156, mean age 59.5 years, Group B (GpB)= 174, mean age 60.1 years) were enrolled; 218 patients completed the treatment phase and 166 patients entered the continuation phase. For enrolment, patients must have histologically documented diagnosis of cancer and experiencing up to 4 BTP episodes per 24 hours (on average) with a stable background pain on opioid treatment of at least 60 mg of oral morphine/day or at least 25 µg of transdermal fentanyl/hour or at least 30 mg of oxycodone/day or at least 8 mg of hydromorphone/day or an equianalgesic dose of another opioid for a week or longer before administration of the first dose of study drug.

The *primary efficacy outcome* was the percentage of patients reaching an effective FBT dose when titration was initiated by 100 µg (GpA) compared to 200 µg (GpB).

Other efficacy outcomes included:

- Time to meaningful pain relief
- Use of standard rescue medication
- Medication performance enhancement
- Quality of life of the patient
- Global assessment by the patient.

Regarding *statistical methods*, it is stated in the clinical evaluation report that given the titration success rate of 65% seen in previous studies, a total of 880 patients (440 per group) were needed to have 80% power to demonstrate the non-inferiority of starting with a 200 µg dose rather than a 100 µg dose (based on the large sample normal approximation test of proportions with a one sided 0.05 significance level).

The primary efficacy variable, namely achieving an effective dose, was analysed by estimating the effective dose rate (that is, number of patients reaching an effective dose divided by the total number of patients in the titration group) in each randomised titration group and comparing the confidence interval (CI) for the difference, calculated as 100 µg to 200 µg, with the non-inferiority margin. In order to assess if non-inferiority was met (that is, whether the null hypothesis was rejected), a two-sided 90% CI equivalent to a one-sided 95% CI was calculated. Non-inferiority was established if the upper bound of the two-sided CI was less than 8%. Kaplan-Meier analysis was used to estimate the distribution of time to meaningful pain relief overall (the total number of episodes) and average (taken to be the average time for each patient to achieve meaningful pain relief). Secondary efficacy data were summarised with descriptive statistics.

Study 099-15

This was a multicentre, open label, long term study of Oravescent fentanyl citrate for the treatment of breakthrough pain in opioid tolerant cancer patients.

Some 232 patients (mean age 55.3 years, range 24 to 95 years) entered the study. Of the 232 patients, 120 patients were from Studies 099-14 and 3039 post completion of the double blind phase while 112 patients were newly enrolled after completing the mandatory open label titration period to determine the individual effective dose. The newly enrolled patients had the same inclusion criteria as for those in Studies 099-14 and 3039. All patients were treated with their individual effective dose for 12 months (patients were dispensed sufficient quantity of the effective dose of Oravescent for 1 month's treatment and then returned to the clinic monthly for assessment and new Oravescent supplies) after which, they could continue in the study for ongoing treatment until November 2006 when the product became commercially available in the USA. The mean duration of exposure overall was 158.4 days with a median of 99 days.

At baseline, the ATC opioids used most frequently (10% or more of patients) were transdermal fentanyl (38%), oxycodone (31%) and morphine (21%). The rescue medications used most frequently were hydrocodone/acetaminophen (24%), oxycodone (22%), morphine (15%), oxycodone/acetaminophen (14%) and hydromorphone (12%).

The *primary objective* was to determine the tolerability and safety of Oravescent fentanyl when used long term to relieve pain (BTP) in opioid tolerant patients with cancer.

The *secondary objective* was to assess the effectiveness of Oravescent fentanyl and the development of incremental tolerance when used long term to treat BTP in opioid tolerant patients who were receiving maintenance opioids.

The efficacy outcomes were based on:

- Global medication performance assessment
- Patient responses to study medication assessment questionnaires.

The Global Medication Performance Assessment was assessed on a 5 point scale (0=poor, 1=fair, 2=good, 3=very good, 4=excellent). The patients completed the assessment only once per day.

For *statistical methods*, it is stated in the clinical evaluation report that medication performance assessment is a subjective measure of the effectiveness of the study drug for dealing with the patients' pain. Patients assessed the study drug performance daily during the long-term maintenance treatment period. Average patient responses for each visit were summarised using descriptive statistics. Patients' responses to study medication assessment questionnaires were summarised using descriptive statistics for categorical response.

Clinical evaluator's overall conclusions on efficacy

- The efficacy is based on two pivotal studies (placebo controlled) and two open label studies. The two pivotal studies were of moderate size but similar design. The inclusion criteria were similar with the patients enrolled being typical of opioid tolerant adult men and women with cancer related background pain and breakthrough pain (BTP). They all were using ATC opioid therapy for their background pain and additional opioid therapy as rescue medication for their BTP. Both trials used a within patient control design which is necessary to minimise the risk of patients being treated with placebo
- The efficacy results from both pivotal studies showed a consistent positive effect for FEBT compared to placebo across the standard measures of pain (pain intensity, pain relief and use of rescue medication) and time points (15, 30, 45, and 60 minutes). At both the 30 and 60 minute time points a patient was twice as likely to achieve at least a 33% or 50% decrease in pain intensity with FEBT compared to placebo
- No active comparator trials have been conducted which is disappointing as a comparison to oral transmucosal fentanyl would have been useful to clinicians but the final decision will probably rest with patient preference
- All studies included a dose titration period and the comparison between starting doses of 100 μg and 200 μg indicated that a starting dose of the lower dose (100 μg) was the most appropriate. If patients could not determine an effective dose they did not continue in the studies
- The non-pivotal studies, which were open label and non-comparative studies provided some long term data demonstrating that the efficacy is maintained for up to 12 months.

Regarding the overall conclusions on safety, the clinical evaluator stated that:

- The total patient numbers in the safety assessment is low but fentanyl is a well know substance and the new dosage form and route of administration is not significantly different to other approved products. There is some concern of the paucity of long term data; nearly half the patients received the drug for less than one month but this may be representative of the patients likely to be prescribed the product
- No new safety issues emerged in the clinical studies. The most common AEs reported with FEBT treatment were characteristic of fentanyl products, namely nausea, dizziness, constipation, fatigue, headache and vomiting. The incidence and types of adverse events did not appear to be dose related. Further the rapid absorption of FEBT did not appear to affect the type or severity of the AEs reported
- Approximately 10% of patients experienced AEs that could be considered to be related to the tablet application site, for example application site pain, ulcer or burning. In the majority of patients these AEs were mild to moderate and resolved without treatment interruption. Women appeared to be at greater risk for application site events. Application site AEs could be reduced if the patient is advised to alternate the placement of the tablet in the right and left buccal mucosa or to administer the tablet sublingually.

On postmarketing experience, the clinical evaluator mentioned that:

- FEBT was first registered in the USA in September 2006 and marketed from October 2006. As of September 2011 it was approved in 31 countries and marketed in 10 (USA, Austria, France, Germany, Ireland, Italy, the Netherlands, Poland, Spain and the United Kingdom). Cumulatively through 31 March 2011, worldwide post marketing usage of FEBT is estimated at 18, 538 patient treatment years
- 13 PSURs were included in the submission covering the period September 2006 to April 2012
- Spontaneous reports received have been consistent with the safety profile observed in the clinical trials. The following new AEs have been identified during the post marketing period: loss of consciousness, respiratory arrest and drug tolerance
- The sponsor also submitted a Prescription Event Monitoring Report from the Drug Safety Research Trust, which operates in association with the University of Portsmouth. This drug utilisation study was conducted from March 2009 to June 2011 and included 551 evaluable patients who had been prescribed FEBT as part of normal practice by General Practitioners (GPs) in England. Overall the prescribing was found to be in line with the approved Summary of Product Characteristics (SmPC). The median time from test dose to effective dose was 19.5 days. Where specified (n=201), the most frequent effective dose reported was 100 µg (n=66) as was the dose reported on initiation of maintenance regimen of fentanyl buccal tablets (n=72 of 200 responses). There were four reports of doses in excess of 800 µg for both the effective and maintenance dose; one report of 1,000 µg, two reports of 1,200 µg and one of 3,200 µg. There were no new safety events identified. There were no cases of respiratory failure reported during neither treatment nor obliterative bronchiolitis; however there was one case of respiratory depression reported. There were two cases of opioid withdrawal syndrome reported during treatment with fentanyl buccal tablets and four cases of overdose reported.

Further details on the **efficacy and safety** of the proposed new dosage form, route of administration and indication for fentanyl citrate (Fentora) are described in Attachment 2 Extract from the Clinical Evaluation Report.

Clinical evaluator's recommendation

The clinical evaluator recommended approval.

Risk management plan

See Pharmacovigilance findings above.

Risk-benefit analysis

Delegate's considerations

There is definitely a role for the buccal mucosa route of administration for fentanyl in the management of breakthrough pain in adults with cancer. Such patients are often weak and lethargic as they approach the end of life stage. The availability of a fentanyl formulation, that can be placed inside the cheek will provide for a simple route of analgesic administration, for a relatively pain free exit. None of the evaluators have raised objection to approval of the application.

The draft Product Information needs modifications as suggested by the evaluators. The details of these are however beyond the scope of this AusPAR.

Summary of issues

The PK studies for FEBT were consistent with the known information for fentanyl. The absolute and relative bio availabilities were assessed in Study C25608/1028/BA/US. The relative bioavailability of a single 400 µg transmucosal dose of Oravescent fentanyl (as citrate) was compared to a single 800 µg oral dose of Oravescent fentanyl (as citrate) and a single 800 µg transmucosal dose of Actiq fentanyl (as citrate) lozenge. The absolute bioavailability of these formulations was compared with an intravenous infusion of 400 µg fentanyl as assessed by $AUC_{0-\infty}$.

Two double blind, randomised, placebo controlled studies (099-14 and C25608/3039/BP/US) to determine the clinical efficacy, safety and tolerability of Oravescent fentanyl citrate when used to relieve breakthrough pain (BTP) in opioid tolerant patients with cancer and who, are already receiving maintenance opioids, were submitted.

The efficacy results from both pivotal studies showed a consistent positive effect for fentanyl effervescent buccal tablet (FEBT) compared to placebo, across the standard measures of pain (pain intensity, pain relief and use of rescue medication) and time points (15, 30, 45, and 60 minutes). At both the 30 and 60 minute time points, a patient was twice as likely to achieve at least a 33% or 50% decrease in pain intensity with FEBT compared to placebo.

There were also two non-pivotal studies (C25608/4027/BP/EU and 099-15), which were open label and non-comparative. They provided some long term data demonstrating that the efficacy is maintained for up to 12 months.

No new safety issues emerged from the clinical studies. The most common AEs reported with FEBT treatment were characteristic of fentanyl products, namely nausea, dizziness, constipation, fatigue, headache and vomiting. The incidence and types of AEs did not appear to be dose related. Further, the rapid absorption of FEBT did not appear to affect the type or severity of the AEs reported.

Delegate's proposed action

The Delegate had no reason to say, at this time, that the application to register a new dosage form and route of administration of Fentanyl Citrate (Fentora) should not be

approved subject to resolving issues, arising from the ACPM deliberations and finalisation of matters pertaining to the draft PI and RMP to the satisfaction of the TGA.

Request for ACPM advice

1. In the consideration for approval, the committee is requested to provide advice on any issues that it thinks may be relevant, to a decision not to approve the application.

Response from sponsor

The following appendices have been requested:

1. A tabulation of any serious unexpected adverse drug reactions which are not mentioned in the proposed Australian PI and have not been submitted previously.

Response

There are no additional serious unexpected adverse reactions that have been reported. The information in the proposed Australian PI is accurate and up to date.

2. The updated proposed Australian Product Information and the most up-to date Consumer Product Information.

Response

The PI and CMI were attached.

3. A statement of the current international regulatory status of the drug. This should detail approvals (with indications), deferrals, withdrawals and rejections (with reasons for these three).

Response

The regulatory status information has not changed since the original submission of the Fentora dossier.

4. Where available, the UK, US and Canadian Product Information documents and an English translation of the Swedish Product Information.

Response

The documents were attached. A similar application has not been lodged in Sweden, therefore, the Swedish Product Information is not applicable and has not been included as part of the response. A comparison of the foreign PIs was provided.

5. Please include a copy of the latest PSUR, unless already supplied or unless none is available.

Response

The latest PSUR No. 439/05/14 (data lock point (DLP) 1 May 2013 to 30 April 2014) was attached. In addition, please find our response to the Delegate's questions

Nonclinical and clinical evaluations

a. Summary of toxicological data evaluation as per the evaluator.

Response

The recommended updates to the following sections of the Australian PI have been adopted; *Effects on Fertility, Use in Pregnancy, Genotoxicity* and *Carcinogenicity*.

b. Overview of clinical data evaluation

Response

The recommended updates to the following sections of the Australian Product Information have been adopted; *Pharmacokinetic Properties* and *Adverse effects*.

RMP evaluation

c. The sponsor should review the proposed materials for errors (including the use of trade names not proposed for Australia, and ASA version labelling) and ensure internal and external consistency. It is noted that the dose titration flowchart contains the trade name 'Effentora' rather than 'Fentora' (the proposed trade name for Australia). The sponsor should amend this.

Response

The Australian PI, the CMI and the educational materials attached to the ASA have been reviewed and updated as required.

d. The sponsor should add the planned Canadian Drug Utilisation Study to the pharmacovigilance plan, update the ASA accordingly, and provide updates in PSURs or alternatively propose a Drug Utilisation Study to be conducted in Australia.

Response

The planned Canadian Drug Utilisation Study has been added to the pharmacovigilance plan and the ASA has been updated accordingly.

e. The sponsor should ensure that any content to which the QR code links is in compliance with relevant legislation.

Response

An assurance has been provided in the ASA.

f. In the submitted RMP, the sponsor has not outlined how they plan to facilitate the systematic return of unused and used products (other than CMI pack inserts). Further details should be made available to outline how the sponsor proposes to facilitate the systematic return of unused and partially used products. This should be outlined in an amended ASA.

Response

The ASA has been updated to include an additional risk minimisation activity for 'Special requirements for safe use, storage and disposal' (see attached A3g). The corresponding section in the proposed Australian Prescribing Information, 'Instructions for use, handling and disposal' has been amended.

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 Fentora effervescent tablets containing 100 µg, 200 µg, 400 µg, 600 µg and 800 µg of fentanyl (as citrate) to have an overall positive benefit–risk profile for the indication**;**

> *For the treatment of breakthrough pain (BTP) in adults with cancer, who are already receiving maintenance opioid therapy for chronic cancer pain.*

In making this recommendation the ACPM

- noted the adverse effects reported are typical and as for other mu opioid analgesics
- noted the bioavailability of transmucosal fentanyl products is unpredictable from one patient to another patient. Doses cannot be predicted from other opioid requirements. Individual patient dose titration is necessary
- Expressed some concern that there were no active comparator studies submitted. It would have been clinically helpful to patients and carers to know how Fentora compared with Actiq
- Expressed some concern over the dosage instructions for the need to wait at least 4 hours between treating episodes, which is derived apparently from the PK half-life of the active. However, standard clinical care of breakthrough cancer pain emphasises not making patients wait long periods between breakthrough analgesic doses.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

- Regarding the frequency of dosing for breakthrough, amend the PI and the CMI to state that 'the Fentora dose for breakthrough pain is usually every four hours but that the frequency may be increased under clinical supervision'.
- Review the dose titration section to improve clarity with regard to dosing.

Specific advice

No specific advice was requested

The ACPM advised that 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 these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Fentora, Fentanyl as citrate 100 µg, 200 µg, 400 µg and 600 µg, orally disintegrating tablet blister pack for buccal administration, indicated for:

> *The treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.*

Specific conditions of registration applying to these goods

The Fentora fentanyl (as citrate) EU-Risk Management Plan (RMP), Version 3.0 (dated 19 June 2014, DLP 30 April 2014) and Australian Specific Annex Version 3 (dated September 2014), included with submission PM-2013-03632-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product information

The Product Information approved for main Fentora at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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
https://www.tga.gov.au