Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for fentanyl citrate

Proprietary Product Name: Abstral

Sponsor: A. Menarini Australia Pty Ltd

October 2013

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 <http://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

I. Introduction to product submission

Submission details

Type of submission	Major variation (new dosage form)
Decision:	Approved
Date of decision:	12 August 2013
Active ingredient:	Fentanyl citrate
Product name:	Abstral
Sponsor's name and address:	A. Menarini Australia Pty Ltd Level 8, 67 Albert Avenue Chatswood NSW 2067
Dose form:	Sublingual tablet
Strengths:	100, 200 and 400 µg
Containers:	Polyamide/aluminium/ PVC/ Paper /Polyester/ Aluminium Blisters
Pack sizes:	10 or 30 sublingual tablets
Approved therapeutic use:	Abstral is indicated for the management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain.
Route of administration:	Sublingual
Dosage:	Recommended initial dose is 100 µg sublingually, with dose titration to a maximum of 800 µg per dose, 4 doses in a day (that is, 3.2 mg per day).
ARTG numbers:	193332 (100 µg) 193335 (200 µg) 193336 (400 µg)

Product background

This AusPAR describes a submission by the sponsor, A. Menarini Australia Pty Ltd, to register a new dose form (Abstral sublingual tablets) containing 100 µg, 200 µg and 400 µg fentanyl citrate.

Fentanyl is a synthetic µ-opioid agonist registered in solution for injection, oral, oromucosal and transdermal dose forms. In this submission, it is proposed to register a new dose form for sublingual administration. The proposed indication of Abstral is:

Abstral is indicated for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain.

The dose is to be titrated to individual response and the product is not interchangeable with any other fentanyl product indicated for management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain.

There are 2 other mucosally absorbed products containing fentanyl indicated for management of breakthrough pain in adult patients using opioid therapy for cancer pain. These are Actiq and Pecfent.

Regulatory status

Abstral sublingual fentanyl tablets have been registered in a range of European Union (EU) countries (under various trade names including Rapinyl and Lunaldin) since late 2008, in the US[1] and Canada since early 2011. Abstral was approved in the EU prior to the final report of the pivotal efficacy and safety study (En3267-005), however, the European Medicines Agency (EMA) had access to an interim report of that study.

Product Information

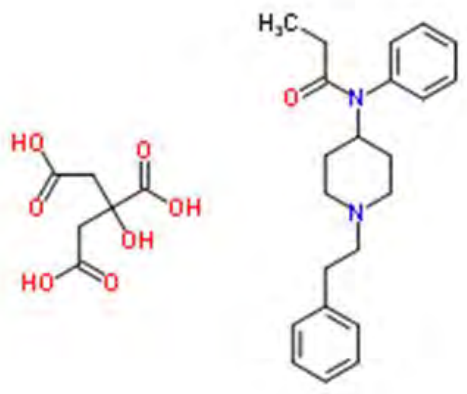
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

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

Figure 1: Chemical structure of fentanyl citrate.



[1] In the US, supply of Abstral is available only through a restricted program called the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access program.

Drug product

The drug products are white, flat faced, bevel edged immediate release sublingual tablets containing fentanyl (as citrate) 100 µg, 200 µg and 400 µg, and having a round, oval or "arc diamond" shape, respectively. The sublingual tablets will be packaged in OPA/aluminium foil/PVC/paper/polyester/aluminium foil blisters (10 or 30 sublingual tablets).

The excipients are commonly present in formulations of other finished products for oral administration.

A dissolution test is not included in the finished product specifications. This was justified on the grounds that the finished products were formulated to maximise dissolution of the active in very small volumes (~1-2 mL) of saliva in the sublingual cavity and that a traditional dissolution procedure is therefore inappropriate. Further, dissolution was >85% within 5 minutes across the product range under all conditions investigated during product development indicating that the rate limiting step in drug absorption is more closely related to disintegration than to dissolution time. This has been accepted without requesting an application for exemption.

The stability data support a shelf life of 36 months stored below 25°C in the blisters proposed for Australia.

The finished product expiry specifications included in the submission were not fully satisfactory in relation to compliance with TGO 78, and ongoing intransigence on the part of the Swedish manufacturer has necessitated the local sponsor providing an assurance that Australia specific stand alone finished product specifications compliant with TGO 78 will be generated locally and submitted to the TGA before conclusion of the evaluation process. This was accepted as an interim measure.

Biopharmaceutics

Study SuF-003 compared fentanyl bioavailability from the formulation used in the Phase III study (Lot D05008) and two other formulations (Lots D05010 and D05012) with that from the main formulation used in Phase I studies (Lot D05011) under fasting conditions and naltrexone blockade.

The report concluded that all three test formulations were bioequivalent to the reference formulation in terms of all three parameters based on the 90% confidence intervals (CIs) falling between 0.80 and 1.25 for area under the plasma concentration-time curve (AUC) and between 0.75 and 1.33 for C_{max} (maximum plasma drug concentration). The 90% CIs were expanded for C_{max} due to a higher variability than observed for AUC, which is in accord with International Conference of Harmonisation (ICH) and Food and Drug Administration (FDA) guidelines for highly variable drugs; however, this was not in accord with the Study protocol (in which C_{max} was only designated secondary variable status). That said, the 90% CIs for two of the three comparisons for C_{max} fell within the tighter range of 0.80-1.25 normally used for the assessment of bioequivalence; only the comparison of C versus D was outside this range (found: 0.7714-0.9925).

Quality summary and conclusions

- A number of questions have been raised with the sponsor concerning the quality/biopharmaceutics data to which satisfactory responses were provided for most. Registration approval cannot be recommended until satisfactory responses are provided to the matters identified as **Recommendations 2.1, 2.2 and 2.3** in the MS5R2 quality/biopharmaceutics evaluation report.

- The opinion of the Pharmaceutical Subcommittee (PSC) to be sought regarding the acceptability of the company's limit for D (v,0.9) in the API (≤ 15 µm), given that the value reported for the API batch used to manufacture the sublingual tablet batches used in the pivotal bioavailability study SuF-003 was only 3 µm.

III. Nonclinical findings

Introduction

The sponsor submitted an application to register a new dose form of fentanyl citrate, Abstral, to be supplied in the form of a sublingual tablet (available in strengths of 100, 200 and 400 µg) for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain. The sponsor submitted the following supporting nonclinical studies:

- one safety pharmacology study;
- two pharmacokinetics studies conducted in rats and dogs;
- one single dose toxicity study in dogs; and
- two local tolerance studies conducted in guinea pigs and hamsters.

All submitted nonclinical studies were direct translations of international study reports. Some of the text was thereby difficult to understand and follow, and some critical aspects of the studies were difficult to locate in the reports provided (for example, route of administration used, placebo formulations). All studies complied with Good Laboratory Practice (GLP) standards.

Pharmacology

Safety pharmacology

The submitted safety pharmacology study examined the cardiovascular and respiratory effects of fentanyl citrate in conscious beagle dogs. Fentanyl citrate was administered intravenously (IV)[2] at three doses (0.003, 0.01, 0.03 mg/kg). The changes observed (monitored by telemetry) included decrease in heart rate (HR) (though no change to blood pressure [BP]) and corresponding increase in the RR intervals, an increase in QRS duration and an increase in QT intervals with the high dose. There was also a decrease in arterial blood pH in both mid and high dose groups (consistent with the known respiratory depressant effects of fentanyl), although no change to absolute respiratory rate was seen. A previous evaluation of a fentanyl product cited a number of published studies that found decreases in blood pressure and heart rates in anaesthetised mongrel dogs. Although the investigators of the study undertaken in conscious dogs did not perform a specific central nervous system (CNS) safety pharmacology study, they did report on the general condition of the treated dogs, noting clinical signs related to CNS depressant actions of fentanyl (sedation, astasia, reduced muscle tone and bradypnea).

Overall, these observed changes were consistent with the known effects of fentanyl on the cardiovascular and respiratory system, and appropriate precautionary statements are provided in PI documents of other fentanyl products (as well as in the proposed PI for

[2] Sublingual administration was mentioned in the text but no data were provided using this route.

Abstral) advising on the potential of fentanyl to induce bradyarrhythmias in some patients and the risk for respiratory depression.

The other core safety pharmacology tests were not performed but reference was made in the Nonclinical Overview/Summary to the well known effects of opioids on the gastrointestinal (GI) system (reduced motility, prolonged gastric emptying, nausea, and vomiting). Given the extensive clinical experience with fentanyl, this is acceptable.

Pharmacokinetics

Two pharmacokinetic studies using the sublingual, oral and IV route in rats and dogs were provided to ascertain the absorption profile of fentanyl citrate with the Abstral sublingual formulation. Again, because of the difficulties associated with the translated version of foreign reports, details concerning the method of analyses were difficult to locate in the documents. Nevertheless, in the study in rats both males and females were tested for the sublingual route, there was a slight differences seen in absorption parameters (slower absorption in females and lower C_{max}) which did not affect overall plasma exposure and bioavailability. Bioavailability for the sublingual route was predictably[3] greater than the oral route at 73% for 0.01 mg/kg, although this tended to be variable when higher doses were used (this may have resulted from the use of a solution for sublingual administration).

In the study in dogs, only males were used. Absorption via the sublingual route was rapid (T_{max} [time to reach maximum plasma concentration following drug administration] for dogs ~10 min compared with rats ~30-50 min) and linear relative to dose. Both oral and sublingual bioavailability was substantially higher in dogs than in rats, appearing to be complete for sublingual administration (>95%) and even appearing to be in excess of IV exposure at the highest tested dose (~120% for 0.4 µg tablet dose). Bioavailability was extrapolated from IV area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) values at 0.04 mg/kg where it was assumed that exposure would follow a linear relationship at higher IV doses in order to ascertain relative bioavailability. In a previous evaluation report for Actiq, a published study on the kinetic profile of an oral transmucosal fentanyl preparation (800 µg/kg) given to dogs showed that the bioavailability was no more than 50% and this only when pH was increased (to 7.7) in the oro buccal environment. No information was available on whether pH was adjusted in the current study in dogs to account for the high bioavailability. However, using the buccal route may also include some absorption through the oral route and thus the consequent first pass metabolism may account for the considerably lower overall bioavailability of a fentanyl preparation administered via the oro buccal route.

Toxicology

Acute toxicity

The sponsor submitted one single dose toxicity study using beagle dogs that examined the effects of fentanyl citrate (using a formulation intended for absorption by the oral mucosa) and at a single dose only (35 mg/kg oral administration [PO]). The purpose of this study was to determine if there were likely to be any toxic effects encountered if the sublingual formulation was mistakenly swallowed. Although there were no deaths and the observed toxicities were anticipated class effects (bradypnea, postural abnormalities, flaccid muscle

[3] Because of well known first pass effects with PO administration.

tone) or were transient in nature (weight loss that resolved by the end of the 14 day treatment period), the significance and usefulness of the findings from this study remain unclear. Observations were carried out on two male dogs only in which there was considerable variation in plasma fentanyl measurements: [C_{max} (ng/mL) – Dog 1: 39.1, Dog 2: 1490.0; $AUC_{0\text{-}48h}$ (ng.h/mL) – Dog 1: 230; Dog 2: 5880; T_{max} (h) – 0.5 (both dogs)], limiting any definitive linking of the observed toxicities to systemic exposure to fentanyl or human exposures. Nevertheless, the acute toxicity profile of fentanyl is well known and clinical experience already exists with a related route of administration (Actiq lozenges, which are available in strengths up to 1600 µg, four times the maximum strength of Abstral). Information on the acute toxicity of fentanyl documented in previous evaluation reports was made available from published literature reports, which, although scant in details, reported deaths in multiple species, when administered by various routes, that were predominantly caused by respiratory depression.

Relative exposure

The submission did not include repeat dose toxicity studies with fentanyl administered sublingually and incorporating measurements of systemic exposure to compare with clinical exposure following use of Abstral. Given that the systemic toxicity of fentanyl is well established, the focus of the current submission was the local tolerance of the product. As a point of interest, the pharmacokinetic data in dogs when compared with clinical exposure showed low animal/human exposure ratios (Table 4), but these relative exposures do not impact on the risk assessment of the product.

Table 4: Summary of exposure measurements in dog (beagle) studies and relative exposures.

Study details	Dose	C_{max} (ng/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	Exposure ratio*
Single dose PK study Study no.: 04-054 Beagle dogs (n = 3) 12 sampling intervals	0.01 mg/kg SL [0.1 mg/body]	2.4±0.5	2.8±0.2	0.1
	0.02 mg/kg SL [0.2 mg/body]	5.0±1.1	5.8±1.4	0.2
	0.04 mg/kg SL [0.4 mg/body]	9.6±2.1	13.9±1.8	0.5
Single dose toxicity study Study no.: SBL26-84 Beagle dogs (n = 2)	35 mg/kg, PO	39.1 and 1490	230 and 5880	8.6 and 220
Human (healthy volunteers)	800 µg 3200 µg *	1.25 -	6.66 26.64*	-

* MRHD 800 µg x 4 doses/day; AUC extrapolated from measurements made using 800 µg formulation
# = animal:human plasma $AUC_{0\text{-}\infty}$

With regard to systemic exposure to fentanyl from the use of Abstral, it is appropriate to compare the clinical exposure to the opioid at the recommended dose of Abstral to the clinical exposure to fentanyl at the recommended doses of other fentanyl products, as potential exposure to fentanyl (from the use of Abstral) greater than exposures previously determined acceptable with other fentanyl products could have implications for risk assessment.

Table 5: Fentanyl clinical exposure with various fentanyl products.

Fentanyl product	C_{max} (ng/mL)	AUC (ng.h/mL)
Pecfent® nasal spray	0.35 - 2.8 (100 - 800 µg	2.5 - 17 (100 - 800 µg dose)

Fentanyl product	C_{max} (ng/mL)	AUC (ng.h/mL)
[MRHD 3200 µg/day]	dose)	
Actiq® lozenge [MRHD 6400 µg /day]	0.4 - 2.5 (200 - 1600 µg dose)	
Durogesic® transdermal patch [MRHD 300 µg/h)	1.9 - 3.8 (100 µg/h)	
Abstral® sublingual tablets [MRHD 3200 µg/day]	0.19 – 1.25 (100 – 800 □g single dose)	

^ From the sponsor's Clinical Overview [Study EN3267-001]

The tabulated exposure (C_{max}, AUC) data from other fentanyl containing products indicate that fentanyl exposure from the Maximum Recommended Human Dose (MRHD) of Abstral is similar to or less than corresponding exposure achieved with the other products.

Local tolerance

Both local tolerance studies were GLP compliant. In the study in guinea pigs (Study No. 1-2019), the investigators tested a similar formulation of fentanyl citrate sublingual tablets to that proposed for registration (400 µg, administered 4 times per day for 4 consecutive days) against a placebo formulation, as well as against positive and negative controls. Irritation was observed only in the positive control group. There was a significant reduction in weight gain in the fentanyl test group (between Days 0-4) which resolved upon cessation of treatment (Days 4-6), though there was no recording of food consumption to determine whether the fentanyl sublingual tablets affected palatability to account for the attenuation of weight gain during the treatment period. Sedation, mydriasis and tremor were reported in all groups ruling out fentanyl as a cause for these effects.

The study in hamsters (Study No. 59259) investigated the effects of a sublingual form of zolpidem against placebo. This was relevant to the current Abstral submission only with regard to potential local intolerance of the excipients, which according to the nonclinical overview, are common to both formulations. No histological effects of note were reported in the placebo treated groups. The observed irritant effects did not surpass the very slight erythema stage (score 1). Relative to untreated cheek pouches, placebo did not have any effects in males, although there were more placebo treated females given a score of 1 compared to untreated females. Details of the composition of the placebo formulation of the tablet used in this study were provided only in the Nonclinical Overview.

In a Section 31 request, the sponsor was asked to: 'Please confirm the exact compositional details of the test articles used in these two (local tolerance) animal studies' which was addressed as follows:

> *'For Study #1-2019 Certificates of Analysis and Clinical Trial Formulas for both fentanyl tablets and placebo are included as Appendix 3a, 3b, 3c and 3d. For Study #59259 please note that this study was performed on the investigational product OX22 and not on Rapinyl/Abstral. The actual composition of the test article is different from Rapinyl/Abstral and therefore should not bear any relevance in this context.'*

This statement did not sufficiently address the uncertainties concerning the composition of the placebo used in Study 1-2019 to confirm that it was relevant to the potential local effects of excipients in Abstral. Nevertheless, on the assumption that the composition of the test articles used in the two local tolerance studies were listed accurately in the Nonclinical Overview (as summarised in Table 6), it appears that the formulation of the placebo used in the study in hamsters contains the same constituents as the intended Abstral formulation, and at higher levels. Thus, based on the minimal irritant effects exerted by this placebo formulation, it is unlikely that the intended Abstral formulation, with its lower excipient content, will evoke significant local intolerance.

Table 6: Comparison of the composition of fentanyl and excipient test articles used in local tolerance studies.

Tablet Composition (Amounts in grams)	ABSTRAL® 400 µg	Local tolerance test article* Guinea Pig study (Study: 59259)	Local tolerance test article** Hamster study (Study: 1-2019)
Fentanyl citrate	0.628	0.625	-
Mannitol	58.96	58.9	70
Silicified microcrystalline	9.35	7	15
Croscarmellose sodium	0.73	-	3.2
Magnesium stearate veg.	0.35	0.4	0.7
Crospovidone	-	3	-
Saccharin sodium	-	-	5.0
Silicon dioxide, colloidal	-	-	1.1

* Rapinyl tablet formulation (400 µg); ** Excipient formulation

Nonclinical summary and conclusions

Summary

- The sponsor submitted an application to register a sublingual tablet formulation of fentanyl citrate (Abstral) indicated for the treatment of breakthrough pain in cancer patients. The nonclinical data provided with the submission were adequate although, at times, difficult to follow (all submitted studies were direct translations of foreign reports which affected the clarity of the data).
- A cardiovascular/respiratory safety pharmacology study showed anticipated respiratory depressant effects in conscious dogs. Electrocardiograph (ECG) changes included increases in RR intervals (consistent with observed bradycardia) and prolonged QT intervals that were associated with high dose fentanyl (0.03 mg/kg, IV only).
- In single dose pharmacokinetic studies in rats and dogs, the bioavailability of sublingual fentanyl was 37-73% and 95-100%, respectively. Absorption was more rapid in dogs (T_{max} 9-11 min) compared with rats (30-50 min).
- The single dose toxicity study in 2 dogs did not reveal any critical/unexpected effects that could arise if Abstral is accidentally ingested rather than absorbed sublingually, although C_{max} and AUC were highly variable. The maximum strength of Abstral sublingual tablet (400 µg) was much lower than that of a registered fentanyl lozenge (Actiq, up to 1600 µg).
- Neither of the local tolerance (oral irritation) studies identified any significant local effects with either a fentanyl citrate tablet or a tablet containing the excipients. Local tolerance of Abstral under human clinical conditions will still need to be confirmed.

Conclusion and recommendation

- Despite the noted limitations in the nonclinical data that was provided, there were no immediate issues identified to raise nonclinical objections about the registration of Abstral for the proposed indication. Clinical data may provide more certainty on whether the product has an acceptable local tolerance profile. The established clinical use of fentanyl citrate by various methods of delivery, however, does provide some assurance on the expected clinical outcomes of using Abstral.

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 following clinical information was presented for evaluation:

- 14 pharmacokinetic studies (7 in opioid naïve healthy subjects, 1 in opioid tolerant patients with cancer pain);
- 1 study of the effect of acidic and basic food/beverages on oral pH;
- 1 placebo controlled pharmacodynamic (dose exploration) study in opioid tolerant patients with cancer pain;
- 1 placebo controlled efficacy/safety study in opioid tolerant patients with cancer pain;
- 1 uncontrolled, open label, long term safety study in opioid tolerant patients with cancer pain;
- Literature references.

Pharmacokinetics

The pharmacokinetics of fentanyl, after the administration of Abstral, has been satisfactorily elucidated in the submitted studies or by reference to the published literature.

Pharmacodynamics

The submitted PD study (SuF-002) provides evidence that Abstral Formulation 1 (and thus the bioequivalent Formulation A that is proposed for registration) should be capable of significantly relieving acute breakthrough cancer pain (BTcP), with a sufficiently rapid onset of action, provided that an adequate dose is used for the individual patient.

Study SuF-002 also indicated that 100 µg would be a reasonable starting dose of Abstral in subsequent efficacy studies (on the basis that it did not appear to be associated with excessive adverse effects and may provide adequate pain relief in some individuals), and that subsequent efficacy studies should provide for titration of the Abstral dose up to at least 400 µg.

Study SuF-002 only measured pain severity for 30 minutes after the dose and did not, by itself, show that the duration of action of Abstral is sufficient to treat BTcP. Being a single dose study, the pharmacodynamic study also did not examine whether the therapeutic and adverse effects of Abstral remained consistent across successive episodes of BTcP.

Efficacy

The design and analysis of Study EN3267-005 mean that it will have exaggerated the population benefit of Abstral compared to placebo and did not permit an unbiased assessment of the number needed to treat (NNT). Nevertheless, the study demonstrates that there is a large subpopulation of BTcP sufferers who can be identified via a process of dose titration as responders to Abstral and that the response to Abstral in those individuals is greater than the "placebo effect".

Study SuF-002 provided only limited supporting efficacy data that involved the treatment of only a single BTcP episode with placebo and with each dose level of Abstral, which did not cover the full dose range of Abstral as proposed in the PI.

Study EN3267-007 did not provide meaningful efficacy data due to the lack of a control group.

The Abstral dose range examined in the submitted studies, now proposed for approval in Australia, appears to reflect a mistaken belief that the bioavailability of Abstral is double that of Actiq and therefore that the starting dose, titration steps, and maximum doses of Abstral should be half those that are approved for Actiq. The recommended Abstral starting dose, titration steps and maximum dose may therefore be unduly conservative. However, it would be unwise to change the Abstral starting dose, titration steps and maximum dose to higher ones that have not been studied in any clinical trial. The more conservative titration steps are also advisable for another reason: unlike an Actiq lozenge which can be easily removed from the mouth, it is less feasible to terminate absorption from a rapidly disintegrating and mucosally adherent Abstral sublingual tablet should excessive opioid side effects start to develop.

Safety

In the submitted studies, Abstral was associated with typical opioid type adverse effects, the most common being gastrointestinal effects such as nausea and vomiting, and effects reflecting the CNS depressant action of fentanyl, such as somnolence, fatigue and asthenia. A small percentage of patients had adverse events that could represent local effects of Abstral at or near the application site. Hypersensitivity/allergic reactions and rashes were also seen in a small percentage of patients. Overall, the types of adverse events are what one would expect for a sublingually administered fentanyl product.

Long term safety data were relatively limited, being available from only 170 patients (72 in EN3267-005 and 98 in EN3267-007). However, no unexpected safety issues were identified and the systemic safety profile of Abstral is expected to be broadly similar to that of Actiq (based on the similarity of fentanyl plasma concentrations during use of the two products).

The Abstral studies did not reveal any major problems in relation to adverse events at or near the application site, but the database is limited. Given the underlying frequency with which oral adverse events occur in the general population and in patients with cancer, it is unlikely that preregistration studies will be able to either detect or exclude, with a satisfactory degree of confidence, an increased risk of such events in users of Abstral. Rather, if Abstral use is associated with oral adverse effects, then this would only become apparent after marketing and consequent usage in a much larger number of patients (as was the case, for example, with Actiq).

The sponsor's proposal to not register the 300 µg, 600 µg and 800 µg tablet strengths in Australia means that some patients will be titrated to doses that can only be achieved by using two different strength tablets, with a consequent risk of administration error that could be avoided if these tablet strengths were available. In addition, the need to take two tablets instead of one (for titration and also to achieve doses above 400 µg) may have an

adverse impact on compliance which could be avoided if the sponsor were to market in Australia all of the strengths that are available overseas.

As expected, the incidence of opioid type adverse events, including respiratory depression, was relatively high amongst non opioid tolerant healthy subjects in the clinical pharmacology studies. This serves to underline the recommendation that Abstral should only be used in patients who are opioid tolerant.

List of questions

The Periodic Safety Update Reports (PSURs) included in the submission are now 2 years old. The sponsor should provide up to date PSURs for review before authorisation.

The sponsor should be asked to comment on the gender difference in Sum of Pain Intensity Differences (SPID), particularly at 60 minutes after the dose, in the pivotal Study EN3267-005.

As noted in the Clinical Pharmacology Study Summaries, a few minor issues could be addressed if the Sponsor were to make available certain appendices to the study reports that were omitted from the material provided to the TGA. However, these minor issues would not affect the registration decision, so it is not necessary to obtain or evaluate the data.

Clinical summary and conclusions

First round benefit-risk assessment

The design and analysis of Study EN3267-005 mean that it will have exaggerated the population benefit of Abstral compared to placebo, and it did not permit an unbiased assessment of the NNT. Nevertheless, the study demonstrates that there is a large subpopulation of BTcP sufferers who can be identified, via a process of dose titration, as responders to Abstral, and that the response to Abstral in those individuals is greater than the "placebo effect". The dose-titration process by which responders are identified is associated with AEs, so that some individuals who start Abstral will therefore experience AEs without eventually gaining any benefit from the drug. However, treatment related adverse events during the titration period were generally minor and transient and, overall, the benefit-risk balance is considered to be favourable.

First round recommendation regarding authorisation

Authorisation of Abstral is recommended, provided that:

- The PI and Consumer Medicine Information (CMI) are revised to more accurately reflect the available information.
- The sponsor provides satisfactory responses to the clinical questions.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) 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 7.

Table 7: Ongoing Safety Concerns for fentanyl citrate.

Important Identified Risks	• Respiratory depression
Important Potential Risks	• Abuse or diversion potential • Naïve (opioid-intolerant) use (accidental or iatrogenic) • Overdose (accidental or intentional) • Inappropriate switching from other oral transmucosal fentanyl compounds (OTFCs)
Important Missing Information	• Nil

OPR reviewer comment

The specified list of Ongoing Safety Concerns is consistent with similar products and is satisfactory.

Pharmacovigilance plan

Proposed pharmacovigilance activities

According to the Australian Specific Annex (ASA), routine pharmacovigilance is proposed to monitor all the specified risks (Table 8).

Table 8: Proposed pharmacovigilance activities for fentanyl citrate.

Important Identified Risks	
• Respiratory Depression	• Routine pharmacovigilance
Important Potential Risks	
• Abuse or diversion potential	• Routine pharmacovigilance
• Naïve (opioid-intolerant) use (accidental or iatrogenic)	• Routine pharmacovigilance
• Overdose (accidental/intentional)	• Routine pharmacovigilance
• Inappropriate switching from other OTFCs	• Routine pharmacovigilance

In regards to "routine pharmacovigilance", the ASA states:

> *"Reports involving (the safety concerns) will be subject to additional scrutiny. Such reports will be discussed in the PSUR in the context of whether the PI, or other forms of risk communication or distribution controls, need reinforcement or strengthening, and the current proposed Risk Management Plan will be critically reviewed and/or amended as appropriate".*

The EU-RMP describes "active surveillance" of some safety concerns which according to the sponsor involves "monitoring of appropriate registries". Appendix 5 of the EU-RMP lists several overseas sources for such information with organisations such as the European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA) and the UK National Poisons Information Service. Further information was sought from the sponsor as to the nature of "active surveillance" as it applies to Australia. In the subsequently supplied ASA, the sponsor states:

> *All of the safety concerns identified in the EU-RMP are relevant for patients in Australia. Within the EU, Prostrakan and its partners have committed to address/monitor safety concerns via "active surveillance" by monitoring several EU_UK registries (shown as Appendix 5 in EU-RMP). Menarini believes such active surveillance of registries will not be effective or possible in Australia. Instead, as*

mentioned in previous section, and described in detail below, Menarini will be addressing safety concerns by HCP Educational tools.

Furthermore, prescription controls imposed as part of PBS Section 100 listing (Palliative Care Schedule) will limit use of Abstral.

Therefore, it is considered that routine pharmacovigilance only is proposed for Australia.

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

The evaluator does not accept that routine pharmacovigilance is sufficient to monitor the safety concerns for this product. Furthermore risk minimisation activities (such as the proposed Section 100 mechanism) cannot be a surrogate for an adequate pharmacovigilance plan.

In particular the clinical evaluator's concerns regarding the important potential risk of 'abuse or diversion potential' have not been appropriately addressed in the ASA. Therefore, it is recommended that at minimum an active surveillance program (for example a post authorisation safety study and a drug utilisation study) which appropriately characterises the risks of abuse and diversion as well the occurrence of off label use should be undertaken, ideally in Australia. The details of such a study program should be agreed with the TGA prior to marketing and included in an update to the ASA. As the sponsor has not proposed any active pharmacovigilance measures, the Delegate may wish to make this requirement a condition of registration.

It is additionally recommended that post marketing assessment of abuse or diversion should be detailed separately in the PSUR. This would include interim results of related studies (as described above).

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities:

According to the ASA, the sponsor has concluded that additional risk minimisation in addition to product labelling is required to mitigate the safety concerns associated with Abstral.

OPR evaluator comment

The evaluator agrees that additional risk minimisation activities are necessary for the safe use of Abstral in Australia.

Potential for medication errors

The potential for medication errors is not foreseen to be any different in Australia versus that characterised in the EU-RMP. This is based upon similar patient demographics and treatment practice. Furthermore, the pack sizes and packaging will be the same as that provided in the EU.

OPR evaluator comment

As the clinical evaluator has pointed out, the sponsor is not proposing to register the 300 µg, 600 µg and 800 µg tablet strengths which are available in the EU. The sponsor should provide comment in the ASA regarding the potential for medication errors in the context that some patients will be titrated to doses that could use two different strength tablets or two tablets of the same dose because of the unavailability of alternative dose tablets.

Summary of recommendations

The evaluator considers the RMP is currently **not satisfactory** with respect to the recommendations below. The OPR provides these recommendations in the context that the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration:

- It is recommended that the sponsor should provide a summary of the key differences between version 2 and version 3 of the EU-RMP.
- The safety specification of the RMP and/or ASA should be amended as recommended by the clinical evaluator.
- It is recommended that at minimum an active surveillance program (for example, a post authorisation safety study and a drug utilisation study) which appropriately characterises the risks of abuse and diversion as well the occurrence of off label use should be undertaken, ideally in Australia. The details of such a study program should be agreed with the TGA and included in an update to the ASA. As the sponsor has not proposed any active pharmacovigilance measures, the Delegate may wish to make this requirement a condition of registration.
- It is recommended that any post marketing assessment of abuse or diversion should be detailed separately in the PSUR. This would include interim results of related studies (as described above).
- The sponsor should provide comment in the ASA regarding the potential for medication errors in the context that some patients will be titrated to doses that could use two different strength tablets or two tablets of the same dose because of the unavailability of alternative dose tablets in Australia.
- It is recommended that the sponsor should outline in the ASA how they propose to facilitate systematic return of unused medicine.
- It is recommended that the sponsor provide further information regarding the education program. Specifically the sponsor should provide a distribution plan (eg. who will receive the education materials and how will they receive them) as well as a clear plan of how the effectiveness of the program will be assessed in Australia and communicated to the TGA. These details should be included in an update to the ASA.
- Changes are recommended to the 'prescriber guide' and the 'patient and carer' guide.
- Changes are recommended to the draft PI and CMI documents.
- It is recommended that the CMI is included in every package of Abstral to ensure that patients have direct access to this information.

VI. Overall conclusion and risk/benefit assessment

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

Quality

This submission was discussed by the PSC on 25 March 2013. There are no objections to registration from a quality and biopharmaceutics perspective.

The drug substance is a potent μ-opioid analgesic with rapid onset of analgesia and short duration of action. It is achiral. The chemistry, manufacture, quality control and stability of fentanyl citrate used in these products are covered by the EDQM issued CEP. It is the

subject of Ph Eur, British Pharmacopoeia (BP) and US Pharmacopoeia (USP) monographs. There are no USP or BP monographs for the drug product.

All the excipients comply with relevant European Pharmacopiea specifications. The stability data provided support the proposed shelf life of 3 years when stored below 25°C in the nominated container.

The drug products are immediate release sublingual tablets containing fentanyl (as citrate) 100 µg, 200 µg and 400 µg. The sublingual tablets will be packaged in OPA/aluminium foil/PVC//paper/polyester/aluminium foil blisters (10 or 30 sublingual tablets). The excipients are commonly present in formulations of other finished products for oral administration.

Nonclinical

There were no nonclinical issues that would preclude registration. The nonclinical data provided with the submission were adequate.

The nonclinical evaluator noted that neither of the local tolerance (oral irritation) studies identified any significant local effects with either a fentanyl citrate tablet or a tablet containing the excipients. Local tolerance of Abstral under clinical conditions requires confirmation.

Clinical

Pharmacology

The pharmacokinetics of fentanyl after the administration of single doses of Abstral was investigated for several formulations, for doses ranging from 50 µg to 800 µg, in healthy subjects and in patients with cancer pain. Abstral is intended to be placed under the tongue where it adheres to the buccal mucosa then dissolves, releasing fentanyl which is systemically absorbed via three potential mechanisms:

- direct passage from the adherent tablet into the buccal mucosa;
- dissolution into saliva, followed by absorption across the buccal mucosa; and
- dissolution into saliva, followed by swallowing and gastrointestinal absorption.

The sponsor asserts that oral absorption plays a minimal role and that absorption is predominantly via the transmucosal route.

When dose adjusted the 200 µg and 400 µg tablet strengths proposed for registration are bio equivalent, two x 200 µg tablets given at the same time are bioequivalent to the 400 µg tablet. The bioavailability of Abstral was compared to that of (US marketed) Actiq in three studies. Results of those comparisons were variable and dependent on the method of administration of Actiq. The studies varied in how completely Actiq was dissolved in the mouth and the time period for complete dissolution. However, it appears that broadly similar quantities of fentanyl reach systemic circulation from the same quantity of fentanyl from either product. The absolute bioavailability of fentanyl from Abstral tablets was 50% in Study EN3267-012 and “about 50%” from Actiq (as stated in the Actiq PI).

Mean *in vivo* tablet dissolution times for Abstral ranged from 5 to 16 minutes with the mean around 7 minutes in most studies. The median Tmax across pharmacokinetic studies is shown in Table 9.

Table 9: Median T_{max} (min) after single and multiple doses of Abstral in healthy subjects.

Formulation/ Study	Gender	Dose comp.	Dose schedule	Abstral dose 50 µg	100 µg	200 µg	400 µg	2×400 µg
Formulation A 2246-EU-005	M+F	PG	single dose	-	30	52	60	30
			q6h, 13 doses	-	30	60	120	90
Formulation 1 2246-EU-002	M+F	-	single dose	30	-	-	-	-
			q4h, 12 doses	30	-	-	-	-

Dose comp. = Type of comparison between different dose levels in that study (PG = parallel group).

For formulation A at the dose strengths proposed for registration the median T_{max} was between 30 to 60 minutes after single doses and between 30 to 120 minutes after multiple doses given at 6 hourly intervals. The effect of food or oral liquids on absorption has not been assessed and it is recommended that Abstral not be taken with food or liquids. Patients with a dry mouth may moisten the product. The effect of acid and basic beverages (and by extension foods) on oral pH was minimal and it has been assumed that food or drink taken prior to an Abstral dose will have minimal effect on the rate or extent of absorption of fentanyl.

During repeated 6 hourly dosing with Abstral at doses of 100 to 800 µg, peak plasma fentanyl concentrations rose to about 1.5 to 2 times the peak concentration after a single dose while fentanyl exposure over the dose interval rose to about 2 to 2.5 times the amount after a single dose. The mean accumulation ratios were broadly similar across the range of doses.

There were no studies assessing the pharmacokinetics of fentanyl from Abstral in patients with hepatic or renal impairment and no interaction studies however the metabolism and interaction potential of fentanyl is known, having been identified in the development of other products. Fentanyl is predominantly eliminated by hepatic metabolism to norfentanyl and other inactive metabolites, with only about 10% of a dose excreted as unchanged drug in the urine. Fentanyl is metabolised by CYP3A4 in the liver and intestinal wall. Grapefruit juice and drugs that inhibit CYP3A4 – such as macrolide antibiotics (for example, erythromycin), azole antifungal agents (for example, ketoconazole and itraconazole), certain protease inhibitors (for example, ritonavir) – would be expected to increase the bioavailability of any fentanyl that is swallowed during Abstral administration and would also slow the elimination of fentanyl, with resultant increased or prolonged opioid effects. Conversely, inducers of CYP3A4 would be expected to increase both the intestinal and hepatic metabolism of fentanyl, leading to reduced efficacy.

Efficacy

The submission contained one adequate, well controlled efficacy study (EN3267-005). This was a randomised, double blind, multiple crossover study comparing Abstral and placebo for the treatment of BTcP in opioid tolerant cancer patients.

Study EN3267-005 enrolled patients aged ≥17 with cancer related pain. The most important entry criteria were:

- Receiving a stable, fixed schedule oral opioid regimen equivalent to 60 to 1000 mg of oral morphine per day or transdermal fentanyl equivalent to 50 to 300 µg/h. The fixed dose opioid regimen must have been taken for at least 14 days before screening, and must have been expected to remain unchanged for the duration of the open label titration and double blind treatment phases of the study (that is, up to approximately 4 weeks);
- On a stable dose of opioid for relief of BTcP. This drug/dose combination was to be used, if required, as rescue medication during the course of the study.
- Experiencing 1 to 4 episodes of BTcP per day.

The study initially consisted of screening followed by an open label titration phase then a double blind treatment phase and an open label, long term extension phase. Part way through the study an "observed test dose" was added prior to subjects commencing the titration phase and patients not tolerating that dose were not continued. During the titration phase if pain relief was unsatisfactory 30 minutes after taking a dose of Abstral, patients were to take rescue medication (that is, their previously prescribed drug/dose of BTcP medication). Patients were to wait at least 2 h after the treatment of one BTcP episode before treating the next episode. The titration phase continued for up to 2 weeks. Patients who were unable to titrate to a satisfactory and stable dose (for example, because of lack of efficacy, adverse effects or unstable dose requirements) or who did not continue to have 1-4 episodes of BTcP per day were withdrawn from the study and excluded from the efficacy analyses.

In the double blind phase patients had 10 blinded doses of study medication taken as 7 doses of the Abstral dose each patient had stabilised on in the titration phase and 3 placebo doses. This phase was to continue until the 10 doses had been consumed. The same criteria for use of rescue doses of BTcP medication and waiting at least 2 h between episodes were applied. Patients then continued in the open phase using Abstral doses up to 800 µg per dose for up to 6 episodes daily.

The primary efficacy endpoint was the SPID from baseline to 30 minutes after dosing. This is the same primary endpoint used in assessment of Actiq. For each patient the pain intensity differences from baseline in each of the 7 BTcP episodes treated with Abstral were averaged into one value and the 3 episodes treated with placebo were averaged into one value and then used in the analysis. The primary efficacy analysis was Intent To Treat (ITT), defined as all randomly assigned patients who received at least one dose of double blind study medication and provided baseline and at least one post baseline pain intensity score during the double blind treatment Phase. Missing baseline values were imputed with Last Observation Carried Forward (LOCF).

A total of 136 patients were assessed for eligibility and 131 entered the open label titration phase. Of these, 53 (40%) were discontinued. Of the 78 patients satisfactorily titrated to Abstral, 66 entered the double blind phase with the remaining 12 proceeding directly to the open phase. An interim analysis (primary analysis; presented to the EMA) that included 63 patients and an end of study (secondary) efficacy analysis of all 66 patients given blinded treatment were performed. Six patients discontinued during the blinded treatment phase so efficacy data from the blinded treatment phase were available for 50% (66/131) of patients entering the study.

During the blinded treatment phase 379/393 (96.4%) episodes treated with Abstral were evaluable and 156/168 episodes (92.9%) treated with placebo were evaluable. The main reasons BTcP episodes were considered not evaluable was the use of rescue medication sooner than 30 minutes after the dose of study medication and the use of study medication <2 h after treatment of an earlier episode. For the primary analysis the median time to reach a stable Abstral dose was 7 days and the median dose was 400 µg (median 496.8 µg). A total of 29/63 doses were for >400 µg fentanyl. The mean SPID at 30 minutes during the blinded phase was 49.5 when patients took Abstral and 36.6 when they took placebo, Least Squares (LS) mean difference was 14.08 (95%CI: 6.515, 21.637; p=0.0004).

Statistical superiority of Abstral over placebo was also demonstrated for the secondary analysis, the PP population and for the major secondary endpoints of SPID at 60 minutes, PID at each time point assessed from 10 minutes post dose, total pain intensity difference and BTcP intensity reduction of ≥30% from baseline. Similar results were seen for the end of study (secondary analysis).

Patients who completed the blinded phase were generally satisfied or very satisfied with study treatment and those patients who remained on treatment during the open phase had even higher levels of satisfaction.

Safety

Abstral was associated with typical opioid type adverse effects, the most common were gastrointestinal effects such as nausea and vomiting, and effects reflecting the CNS depressant action of fentanyl, such as somnolence, fatigue and asthenia. A few patients had adverse events that could represent local effects of Abstral at or near the application site. Hypersensitivity/allergic reactions and rashes were also seen in a few patients. Overall, the types of adverse events are what one would expect for a sublingually administered fentanyl product.

Long term safety data were relatively limited and were available from only 170 patients: 72 from Study EN3267-005 and 98 from Study EN3267-007. No unexpected safety issues were identified and the systemic safety profile of Abstral is expected to be broadly similar to that of Actiq (based on the similarity of fentanyl plasma concentrations during use of the two products).

Respiratory depression associated with sublingual fentanyl was reported in pharmacology studies in non opioid tolerant healthy volunteers.

Risk management plan

The following risks were identified as Ongoing Safety Concerns:

- Respiratory depression;
- Abuse or diversion potential;
- Naïve (opioid intolerant) use (accidental or iatrogenic);
- Overdose (accidental or intentional); and
- Inappropriate switching from other oral transmucosal fentanyl compounds.

The RMP evaluator has noted these Ongoing Safety Concerns are consistent with similar products.

The sponsor did not initially submit an RMP for Australia but subsequently did so. Neither the Safety Specification nor the Risk Minimisation Plan in the current RMP are satisfactory to the RMP evaluator and revisions as discussed in the RMP evaluation have been recommended.

The FDA disclosed that a number of significant adverse events including deaths due to incorrect usage have been reported for oral transmucosal fentanyl products marketed in the US. As a result particularly stringent controls have been imposed by the FDA on the prescribing and dispensing of Abstral and other oral transmucosal fentanyl products in the US.

Routine pharmacovigilance has been proposed for Australia. The sponsor was of the view that prescription controls imposed as part of PBS Section 100 listing (Palliative Care Schedule) will limit off label use of Abstral. The evaluator recommended that at minimum, an active surveillance program (for example a post authorisation safety study and a drug utilisation study) which appropriately characterises the risks of abuse and diversion as well the occurrence of off label use should be undertaken, ideally in Australia. The details of such a study program should be agreed with the TGA and included in an update RMP. Other active pharmacovigilance activities were also proposed as was the inclusion of the CMI with the packaging. Risk-benefit analysis

Delegate considerations

The clinical trial data have convincingly demonstrated that patients obtain more pain relief from Abstral than from placebo. Although the AUC for the same strength of fentanyl in Abstral and Actiq are similar, the maximum proposed dose of Abstral is only half that approved for Actiq.

There have been no direct comparisons of efficacy between Abstral and any other active treatment for BTcP. Abstral cannot be considered interchangeable with other opioid products and titration will be required on commencement of treatment or on switching from another BTcP treatment to Abstral. Duration of titration will be dependent on the frequency of BTcP episodes and up to 50% of patients with BTcP will not be successfully titrated to a stable dose of Abstral. Of the patients who are successfully stabilised, about half are likely to require two tablets per dose. These limitations to efficacy and use should be clearly described in the PI. Time to titration, lack of ease of interchangeability, and a substantial proportion of patients not able to be stabilised on Abstral are the major efficacy concerns with this product for its intended indication.

The clinical evaluator has noted that the study design was intended to detect statistically significant rather than clinically meaningful differences in pain between Abstral and placebo, however it appears that the differences were also clinically meaningful as there was a high level of patient satisfaction with the treatment for those patients who opted to continue treatment. The reporting of adverse events would have under estimated the likely frequency and severity of opioid related events because patients who were intolerant of the "observed test dose" were excluded from further participation in the pivotal efficacy and safety study for this submission.

The Delegate considers the major safety concerns are:

- Potential for abuse and misuse. The short T_{max} and high bioavailability relative to other forms of fentanyl suggests this product would be preferred by individuals likely to abuse opioids. Potential for accidental overdose – either by patients or others.
- "Off label" use of Abstral. This is likely to occur in patients with chronic pain who may also experience periodic acute exacerbations of pain and would place those patients at high risk of development of dependency. The sponsor has proposed that Section 100 prescribing would limit off label use however this seems very unlikely given the possibility of private prescribing. In addition, the Delegate does not consider potential patient rebates on purchase of a medicine to be an acceptable way to manage risk of abuse or misuse.

The absence of agreement on additional risk mitigation, or even of an agreement to identify the extent of use is of particular concern. This product could not be approved without risk mitigation strategies satisfactory to the TGA being in place.

Assuming that a satisfactory RMP will be negotiated, this product could be an addition to the available opioid treatments for BTcP, though switching to Abstral from other BTcP treatments will require quite prolonged dose titration. In addition a significant proportion of eligible patients are unlikely to benefit due to tolerance issues.

Based on current information, the Delegate proposes to approve Abstral sublingual tablets containing 100 µg, 200 µg, and 400 µg fentanyl citrate subject to satisfactory negotiation of the RMP, PI and CMI.

The general advice of the Advisory Committee on Prescription Medicines (ACPM) is requested. The Committee is also requested to provide advice on the following specific issues:

1. The proposed indication does not restrict use to patients receiving maintenance opioid therapy. The Delegate proposes amending the indication to be consistent with

other immediate release fentanyl products intended for treatment of breakthrough pain in patients with cancer. Does the Committee agree that the indication should be amended to: *the management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain?* Note: the Delegate does not object to the inclusion of the additional definition of breakthrough pain proposed by the sponsor to be included in the indication.

2. The Delegate proposes that Abstral be contraindicated in *patients not receiving opioid maintenance therapy for cancer-related pain unless under the immediate supervision of healthcare professionals such as in a hospital or in-patient clinic*. Does the Committee consider this is an appropriate contraindication? If not, could the Committee propose an alternative method of restricting use of this product and similar patient controlled immediate release opioid products?
3. Does the Committee consider the controls proposed by the sponsor would adequately manage the risks of inappropriate prescribing, development of dependency, misuse, abuse and diversion?

Response from sponsor

Clinical evaluation

"…Time to titration, lack of ease of interchangeability, and a substantial proportion of patients are not able to be stabilised on Abstral are the major efficacy concerns with this product for its intended indication."

Response

Clinical need for a range of Immediate Release (IR) fentanyl presentations[4]

Patients with chronic cancer pain will be receiving long term, around the clock analgesia for ongoing pain management. Patients can also experience episodes of BTcP, which is a transient exacerbation of otherwise controlled chronic background pain. Episodes of BTcP are severe, rapid in their onset (2 to 3 minutes) and relatively short in duration (median of 60 minutes). This pain profile requires an immediate acting analgesic with sufficient efficacy to provide pain relief for the duration of the BTcP episode. The most commonly used agents for BTcP in Australia are IR oxycodone and morphine, whose pharmacokinetic profiles are not commensurate with the span of most BTcP episodes. With onset of analgesia at 30 minutes, and time to maximal plasma concentration over an hour, coupled with extensive first pass metabolism and consequent low bioavailability, these preparations are poorly suited for use as effective controllers of BTcP. At present, fentanyl, a μ-opioid receptor antagonist with both anaesthetic and analgesic properties, is the only compound that displays the required pharmacokinetic profile to provide adequate relief for BTcP.

It might be assumed that control of BTcP can be achieved with increasing the dose of the background opioid medication. Increasing the dosage of these medications, however, increases the opioid levels present in the blood at all times, thereby increasing the likelihood of opioid side effects. Thus, a difficulty with treating BTCP is that often the doses required to control this pain can produce unacceptable adverse effects in a minority of patients, when the patient is at rest or pain stops spontaneously.

Currently available fentanyl treatments in Australia for BTcP include an oral transmucosal fentanyl citrate (OTFC) lozenge (Actiq), as well as an intranasal fentanyl spray (INFS)

[4] Howard S. (2012) A comprehensive review of rapid-onset opioids for breakthrough pain. *CNS Drugs* 26: 509-535.

preparation (PecFent). As indicated in the TGA Delegate's overview for Abstral, a third product, also an INFS, has also recently been approved for use by the TGA.

The choice of administration route is heavily dependent on individual patient characteristics, including their clinical stability in terms of their underlying disease, likely adherence to medication regimens, the characteristics of their BTcP (onset, predictability, severity and duration) and formulation preferences. For example, some patients may find it difficult or uncomfortable to use a medication that requires inhalation, while individuals with severe dysphagia may prefer not to use oral formulations. Patients may also express preference for certain administration routes for BTcP medications. These are taken into account up front by the treating physician when BTcP is diagnosed, and the best match between the patient and the fentanyl presentation is made. Switching between presentations is not at all common and all of them require titration of the patient to an effective dose.

Actiq was first approved in the US in 1998 and was essentially the first in class product for the treatment of BTcP. Limitations associated with this product include the relatively long administration time of approximately 15 minutes, the loss of approximately 50% of the administered dose to first pass metabolism, the burden of self administration for chronically ill patients, the potential for dental problems with prolonged use, the perceived appearance as 'childish', and the inability in some patients to produce sufficient saliva to correctly administer the full dose.

The introduction of intranasal preparations delivered a rapid administration, and hence rapid onset opioid (ROO) product with a higher bioavailability than OTFC preparations. INFS preparations were suitable for patients with dry mouth and could be administered by a treating clinician or family member. INFS preparations, however, are also not without limitations in certain patient populations. For example the potential emergence of side effects (for example, nasal irritation, unpleasant taste, nausea) and where patients have issues associated with their nasal mucosa, such as colds and influenza or disease pathology. This preparation also relies on the patient being in an upright position to ensure effective drug delivery, while oral preparations do not.

Buccal preparations are also available in the US and EU, however not yet in Australia and will therefore not be discussed further here. Suffice to say that current reviews indicate that the safety and efficacy of such preparations is similar to the OTFC and INFS preparations described above.

Abstral is a sublingual fentanyl (SLF) tablet that offers the patient an alternative oral preparation with a higher bioavailability than OTFC preparations. This is due to the absorption of fentanyl being predominantly via the transmucosal route, with minimal oral absorption. Importantly, there are no new limitations to this product when compared with existing products already available for this indication in Australia.

In summary, it is likely that factors such as disease characteristics, patients' preference and ease of administration will continue to be key determinants in deciding the most appropriate formulation for individual patients.

Duration of titration

The time to titration is not expected to be of significant duration in routine use (recent postmarketing data suggest that the mean time to successful titration is 5.5 days, median 3.5 days[5]). It is expected that this would be similar for the other fentanyl BTcP products.

[5] Abstral BTcP Registry (UK), 29 February 2012.

In clinical studies, the time to titration is typically protocol driven (that is, allowing up to 2 weeks for Abstral Study EN3267-005) and not reflective of real world practice. It is unlikely that the time to titration would be clinically prohibitive to the use of Abstral.

Up to 50% of patients BTcP will not be successfully titrated to a stable dose of Abstral

Patients with BTcP are predominantly but not exclusively later stage metastatic cancer patients who are already receiving an opioid for their background pain control. Patients with BTcP experience greater pain intensity and less overall pain control than patients without BTcP.

In a cross sectional survey of inpatients with cancer conducted by Portenoy and colleagues,[6] patients with BTcP experience more intense background pain than patients without BTcP. On the pain interference scale of the BPI (Brief Pain Index), patients with BTcP had scores more indicative of greater functional impairment on all items compared to patients with controlled background pain and no BTcP. Similarly, BTcP was associated with relatively worse scores on the measures of affective disturbance.

While total freedom from pain is an objective, it is not an achievable goal; rather adequate pain control is hoped to be achieved. No other opioid product or combination of products has achieved results better than those seen with Abstral.

In all measures of pain relief, Abstral gave better results than placebo. In the phase 3 trial with Abstral, significantly greater pain relief was associated with fentanyl sublingual tablet (FST) from 10 minutes through 60 minutes compared with placebo ($P \leq 0.049$). The mean patient global evaluation of medicine (PGEM) for FST was 3.1, compared with 3.6 for placebo ($P = 0.0006$). At the study's completion, 29.7% of patients were very satisfied and 17.2% were satisfied with FST. The percentage of responders to FST was 86.9%, compared with 64.9% of those who had been treated with placebo. The use of rescue medications was significantly lower for BTcP episodes treated with FST (11.2%) compared with 27.4% of episodes treated with placebo.

Analysis of the end of study ITT population (n = 64) confirmed the primary analysis with significantly better SPID for FST at 30 and 60 minutes compared with placebo ($P \leq 0.0004$). Mean PID and pain relief scores were also significantly higher for patients treated with FST compared with placebo at 10, 15, 30, and 60 minutes following administration of each dose ($P \leq 0.0054$ for mean PID and ≤ 0.027 for pain relief comparing FST with placebo).

Furthermore, the observed rate of successfully titrated patients was 75%, as documented in the above mentioned post marketing study.[7]

These results are in line with those observed with other fentanyl IR formulations.[8]

Lack of interchangeability

As stated above, the decision as to which formulation would best suit a patient is made by the treating physician on review of the patient's pain control, based on various factors. It is therefore not anticipated that patients will switch between the formulations. Also, every product requires that patients be titrated up to a suitable dose, and hence the issue of interchangeability is not a relevant one in this clinical setting.

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[6] Portenoy RK, Hagen HA. (1990) Breakthrough pain: definition, prevalence and characteristics. Pain 41: 273-281.
[7] Abstral BTcP Registry (UK), 29 February 2012.
[8] Davis MP. (2011) Fentanyl for breakthrough pain: a systematic review. *Espert Rev. Neurother.* 11: 1197-1216; Howard S. (2012) A comprehensive review of rapid-onset opioids for breakthrough pain. *CNS Drugs* 26: 509-535.

While it is not anticipated that switching between products will be a common occurrence, several products already registered in the EU specifically advise that no switching is allowed. This is a common instruction for opioid titration. Abstral has been on sale in the EU for over 5 years and there has been no evidence to suggest that the advice on switching has been restrictive to the use of this product. In addition, post marketing data also suggest that there has been no evidence of cases of death or opioid related adverse reactions in reported cases of switching with Abstral.

RMP

"Routine pharmacovigilance has been proposed for Australia. The sponsor was of the view that prescription controls imposed as part of PBS Section 100 listing (Palliative Care Schedule) will limit off label use of Abstral. The evaluator recommended that at minimum, an active surveillance program which appropriately characterises the risks of abuse and diversion as well the occurrence of off label use should be undertaken, ideally in Australia. Other active pharmacovigilance activities were also proposed as was the inclusion of the CMI with the packaging.

The Delegate considers the major safety concerns are:

- *Potential for abuse and misuse…*
- *"Off-label" use of Abstral…*

The absence of agreement on additional risk mitigation, or even of an agreement to identify the extent of use is of particular concern. This product could not be approved without risk mitigation strategies satisfactory to the TGA being in place."

Response

The sponsor intends to address the TGA safety concerns in two ways:

1. By establishing a robust education program targeting the key prescribers for this product/indication
2. By adopting a post market surveillance program to identify the extent of use

Education program

While a high proportion of specialists in this area of prescribing are quite familiar with the use of fentanyl, an education program will be put in place that will reiterate to the prescribing physician the importance of appropriate patient selection according to the approved indications, as well as providing appropriate instructions to the patients. Educational material will also be provided to the pharmacists, patients and their carers highlighting the importance with regard to potential abuse/misuse/diversion, risks to opioid naïve persons, the importance of avoiding inappropriate patient switching and risks of respiratory depression.

The finer details of the proposed education program have yet to be elucidated, however it is proposed that the program will include the follow key attributes:

- The program will provide both physicians and patients with educational materials.
- Educational materials will focus on managing the risks associated with prescribing and using Abstral, including advice on appropriate patient selection.
- Having successfully completed the educational component, selective access to now 'certified and/or registered' physicians and pharmacists can be implemented.
- At the point of ordering stock the wholesaler will be restricted to supplying Abstral only to 'certified' pharmacists.

It is expected that Australian sponsors for other IR fentanyl products recently approved by the TGA have, or are in the process, of implementing a similar education program. The

sponsor is therefore happy to work with the TGA to confirm the details of the proposed education program in line with the requirements for similar products.

Ensuring the effectiveness of educational activities

The effectiveness of risk communications with respect to respiratory depression, abuse/dependence/diversion, naïve use, intentional overdose, and inappropriate switching from other OTFCs, will be monitored following implementation of the aforementioned education program.

Feedback via an agreed 'audit' program will be obtained from willing participants regarding the effectiveness of the education program and the educational materials provided. Initial and subsequent (if required) results will be provided to the TGA.

Post market surveillance program

Given the safety concerns associated with substance abuse, it has become increasingly more important to monitor the use of IR fentanyl products in the post market setting. In light of this, the sponsor proposes to establish a post market surveillance program for Abstral in Australia.

The National Drug and Alcohol Research Centre (NDARC) recently published data in relation to "Trends in fentanyl prescriptions and fentanyl related mortality in Australia". These data appear to suggest appropriate controls need to be in place to ensure restricted prescribing, which the sponsor would address via their Education Program. It is the sponsor's intention to initiate a similar monitoring program or to collaborate with existing researchers in this area to monitor the use of Abstral in the clinic.

Again the sponsor is happy to work with the TGA to ensure that any post market surveillance program implemented for Abstral is in line with what has been agreed for similar, recently approved IR fentanyl products. There are no reasons apparent to the sponsor that would justify applying any more restrictive measures towards Abstral than what has been/will be applied for other IR fentanyl products.

The exact nature of the post market surveillance program would be documented and provided to the TGA OPR for agreement prior to implementation and prior to product launch.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Abstral sublingual tablets containing fentanyl citrate to have an overall positive benefit-risk profile for the amended indications:

> *Abstral is indicated for the management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain.*

Conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory negotiation of the RMP, to provide additional risk mitigation and identify the extent and type of use
- Negotiation of PI and CMI to the satisfaction of the TGA, specifically to reflect the RMP issues raised.

Proposed PI/CMI amendments

The ACPM agreed with the Delegate on the proposed amendments to the PI and CMI.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Abstral fentanyl (as citrate) 100 µg, 200 µg and 400 µg sublingual tablet blister pack for the indication:

> *Abstral is indicated for the management of breakthrough pain in adults with cancer who are already receiving maintenance opoid therapy for chronic pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain.*

Specific conditions of registration applying to these therapeutic goods

1. The Abstral fentanyl citrate Risk Management Plan (RMP), included with submission PM-2011-03151-3-1 is ***not satisfactory*** to the TGA and requires ongoing negotiation with the OPR. *Acceptance of a RMP satisfactory to OPR is a condition of registration.*

An obligatory component of RMPs is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval. No fewer than three annual reports is required. The reports are to at least meet the requirements for PSURs as described in the EMA's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes".[9] Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to the TGA no later than 15 calendar months after the date of this approval. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval.

The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

Attachment 1. Product Information

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

[9] European Medicines Agency, "Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report (Rev 1) (EMA/816292/2011 Rev 1)", 19 April 2013, Web, accessed 13 September 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/ 2012/06/WC500129136.pdf>.

Attachment 2. Extract from the Clinical Evaluation Report

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