LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Abstral, sublingual tablet
50, 100, 200, 300, 400, 600 and 800 µg

(Fentanyl citrate)

SE/H/575/01-07/DC

This module reflects the scientific discussion for the approval of Abstral. The procedure was finalised at 20080229. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Prostrakan Ltd has applied for a marketing authorisation for Abstral, sublingual tablet, 50, 100, 200, 300, 400, 600 and 800 µg. The active substance is fentanyl citrate. Fentanyl is a synthetic short acting strong analgesic of the opioid type, belonging to the phenylpiperidine group. It is well-known and widely used in the treatment of patients with severe pain.
For approved indications, see the Summary of Product Characteristics.

Potential serious risk to public health was raised by several concerned member states as the presented bridging strategy was not found sufficient and therefore not acceptable. As a consequence, additional efficacy and safety data for Abstral for the management of breakthrough pain in the target population were required before these member states considered that an appropriate assessment of the product could be performed. Agreement was not reached in CMD and thus, the procedure was referred to CHMP. At this stage of the procedure, the RMS decided to approve Abstral nationally.
Eventually, following the arbitration procedure, a positive opinion was adopted on 26 June 2008 by the CHMP and was converted into a decision by the European Commission on 11 September 2008. For further information regarding the CHMP referral procedure, visit the EMEA website (please refer to Rapinyl).

II. QUALITY ASPECTS

II.1 Introduction

Abstral is presented in the form of sublingual tablets containing 78.55, 157.1, 314.2, 471.3, 628.4, 942.6 or 1257 µg of fentanyl citrate, which corresponds to 50, 100, 200, 300, 400, 600 or 800 µg of fentanyl. The excipients are mannitol, silicified microcrystalline cellulose, croscarmellose sodium and magnesium stearate. The tablets are packed in Al-blisters consisting of aluminium, PVC and polyamide.

II.2 Drug Substance

Fentanyl citrate has a monograph in the Ph Eur.
Fentanyl citrate is a white or almost white powder which is freely soluble in organic solvents and sparingly soluble in water. The structure of fentanyl citrate has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.
The active substance specification includes relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.
Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Abstral, sublingual tablet is formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility and hygroscopic properties.
The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.
The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 25°C and in the original blister package in order to protect the product from moisture.

III. NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of fentanyl citrate are well known. As fentanyl is a widely used and a well-characterised active substance, local tolerance and the level of systemic exposure were the main aspects in safety assessment of Abstral.

The Applicant submitted, in support of this application, new pharmacokinetic, safety pharmacology, single dose toxicity and local tolerance studies. The submitted studies did not add any new knowledge regarding fentanyl.

The Applicant had in the bioequivalence clinical programme conducted with Abstral and Actiq® shown similar exposure between these two products at one-half the dose of Abstral. Thus, from a preclinical point of view, since the exposure in humans after the highest dose of Abstral (800 μg) dose did not exceed the exposure after the highest dose of Actiq® (1600 μg), no reassessment of the safety of Abstral was necessary from a preclinical point of view.

The local tolerance was not adequately evaluated in the submitted dossier. In one study, the tablets tested did not contain fentanyl/citrate, and the other study was of 4 days duration only. Clinically, application site irritation and dermatitis was reported in 5 (2.3%) and 4 (1.8%) out of 221 volunteers, respectively. In the study including 41 patients, no one experienced any local irritation. To conclude, the preclinical programme failed to evaluate the local tolerance of Abstral. However, there were few reports on adverse local tolerance effects in volunteers and patients, and fentanyl citrate in oral mucosal formulation has previously been approved (Actiq®). Further, the excipients are well known and tested for local tolerance for 4 weeks in Syrian hamster. It was therefore considered that further animal studies would not add any useful information regarding this issue.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application concerns a well known active substance and pharmacokinetic data concerning the actual formulation applied for has been produced to complement the published literature on clinical pharmacology, efficacy and safety concerning fentanyl. The pharmacokinetic characterisation following treatment with Abstral and pharmacokinetic comparisons of Abstral versus Actiq®, an authorised transmucosally administerd fenatanyl on demand, was used as a basis for bridging to the extensive published data regarding clinical efficacy and safety data for authorized fentanyl products. Thus, only limited clinical data have been generated for the use of Abstral.

IV.2 Pharmacokinetics

Abstral exhibits roughly dose-proportional pharmacokinetics and the pharmacokinetics characteristics are similar in patients as compared with healthy volunteers. Comparable systemic exposure of fentanyl has been demonstrated following administration of Actiq® and Abstral (at the 100 and 800 µg doses), Abstral given as half the Actiq® dose. Further, the intra-individual variability in overall exposure (AUC) has been shown to be low (approximately 12%). Accordingly, it has been demonstrated that treatment with Abstral employing individual dose titration in the proposed dose strengths, will result in a range of plasma concentrations expected to be safe and efficacious.

The dosing recommendations have been satisfactorily changed to take care of the potential risks associated with Abstral, i.e. inability to terminate administration in case of side-effects, risk of overexposure if a patient changes treatment from Actiq® to Abstral, risk of increased exposure in mouth wounds and the importance of moistening mouth in cases of dry mouth.

In summary, the presented pharmacokinetic documentation together with the recommendation of strict individual dose titration is sufficient for an approval and the pharmacokinetic information is sufficient for bridging published safety and efficacy data from authorised fentanyl products.

IV.3 Pharmacodynamics

IV.4 Clinical efficacy

Due to the limited number of cancer patients in the submitted main clinical study, the study was insufficient by itself for demonstrating a consistent therapeutic effect. However, the systemic exposure of fentanyl following administration of Abstral was demonstrated to be similar as that obtained following treatment with the fentanyl lozenge Actiq® when doses are adjusted, at least when volunteers take the whole nominal dose of this lozenge. Actiq® has a short but a recognised record of clinical effectiveness and the pharmacokinetic information have been considered sufficient for bridging published efficacy data from authorised fentanyl products. Thus, the submitted clinical Abstral study was solely supportive.

Breakthrough pain contains a wide spectrum of pain intensities and sensitiveness to opioid substances. The optimal dose of rescue medication is highly individual and must, in clinical practice, always be individually titrated. In the present cross-over study, including 23 patients, a significant improvement in pain scores were reported for Abstral 400 µg compared with placebo.

The lowest strength of many fentanyl transdermal patches releases 25 µg/h, corresponding to a daily delivered dose of 600 µg. The recommended initial dose to start the individual titration is 100 µg. If the regular background dose is below 100 mg oral morphine equivalents daily the starting dose may be lower.

IV.5 Clinical safety

The applied indication for Abstral is breakthrough pain in cancer patients already treated with a base dose of an opioid. Targeting this special population instead of patients with acute non-malignant pain or for breakthrough pain in patients not treated with a base opioid, some safety (i.e. abuse potential) aspects are less relevant.

The well known side effects of fentanyl are reported also in the Abstral studies. Two organ systems specifically affected in the intended population were the nervous system and the gastrointestinal system. Dizziness is to be expected in this population but there is also a high reported frequency of headache. Nausea and vomiting dominate the AEs for the gastrointestinal system. However, for effective ambulatory treating of breakthrough pain there is presently no other drug class or any opioid formulation with fewer side effects.

The optimal dose must be carefully titrated, which is stated in the SPC. If patients are switched from another fentanyl containing product for transmucosal administration, a new dose titration with Abstral is required.

Accidental overdosing with eventually fatal respiratory depression is a clearly identified risk with this formulation especially with off-label use by opioid naïve persons.

The drug is delivered in a child proof package.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a nonclinical point of view, no concerns were raised with regard to local tolerance and the level of systemic exposure.
Treatment of breakthrough in patients with malignant diseases is still a therapeutic challenge. The treatment options vary depending on the pain aetiology and its temporal aspects. Often this pain is related to some kind of event, e.g. standing, position in bed or defecation. The patient with breakthrough pain has usually some kind of “basic” pain medication in which an opioid often is included and the breakthrough pain is in most cases known to be sensitive to opioids or could be tested for that. If sensitive to opioids, oral transmucosal fentanyl citrate has been found to be a good compromise between a possibility for self-treatment with rapid onset and an analgetic duration covering the pain peak. Abstral is a new formulation of fentanyl citrate, which by itself is well-known drug. When used under standardised condition in healthy volunteers, the nominal Abstral dose should be half the nominal dose of the lozenge Actiq® to give similar serum concentrations of fentanyl. For patients in real life, additional concerns such as mouth dryness, amount of saliva swallowed and amount of the lozenge used must be considered. The two products are *not* directly interchangeable. The analgetic response after adequate titration combined with the side effect profile determines if transmucosal fentanyl treatment has a place in the therapy of the individual patient or not.

The side effects of fentanyl are well-known. For a patient with a malignant disease and already treated with opioids the additional burden of a short period of dizziness or nausea but effective pain alleviation should be acceptable. If the pain is not/poorly responsive to an opioid analgetic, an upward titration of fentanyl citrate may cause problems, sometime serious.
For the target population as defined in the indication the benefit/risk for the treatment with Abstral is considered favourable as long as the initial titration dose is considered safe.

The misuse or accidental unintended use of the drug may be fatal.
Abstral could have a high abuse potential, higher than for Actiq® because of the greater bioavailability and smaller size of the drug.

The Clinical conclusion was that the submitted pharmacokinetics, efficacy and safety documentation together with the proposed bridging strategy combined with the information

given in the SPC and the proposed Risk Management Plan constituted a sufficient basis for an approval of Abstral.

User testing of the package leaflet has been performed.

The risk/benefit ratio was considered positive and Abstral, sublingual tablet, 50, 100, 200, 300, 400, 600 and 800 µg was recommended for approval.

VI. APPROVAL

Abstral, sublingual tablet, 50, 100, 200, 300, 400, 600 and 800 µg was nationally approved on 2008-02-29. After a referral to the CHMP, a positive opinion was adopted on 26 June 2008 and was then converted into a decision by the European Commission on 11 September 2008.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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