CBG MEB

Public Assessment Report

Scientific discussion

Adport 2 mg and 0.75 mg, capsules, hard (tacrolimus)

NL/H/1340/004-005/DC

Date: 15 December 2014

This module reflects the scientific discussion for the approval of Adport 2 mg and 0.75 mg, capsules, hard. The procedure was finalised on 5 June 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Adport 2 mg and 0.75 mg, capsules, hard from Sandoz B.V.

The product is indicated for:
- prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
- treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application with reference to the innovator product Prograft 0.5 mg capsules, hard (NL License RVG 22236) which has been registered by Astellas Pharma BV in the Netherlands since 12 June 1998. The reference product is available in the strengths of 0.5 mg, 1 mg and 5 mg, but not in the proposed strengths of 0.75 mg and 2 mg. With this application the strengths of 0.75 mg and 2 mg are introduced to allow accurate dose adjustments.
The application is a line extension to Adport 0.5 mg, 1 mg and 5 mg, capsules for which Sandoz B.V. obtained a registration in 2009 (procedure NL/H/1340/001-003/DC). The Public Assessment Report for this procedure is available on http://mri.medagencies.org/download/NL_H_1340_001_PAR.pdf.

The concerned member states (CMS) involved in this procedure were Austria (only 2 mg), Belgium, Czech Republic, Denmark, Finland, France (only 2 mg), Germany, Italy, Norway, Portugal, Slovenia, Spain (only 2 mg), Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application.

II. QUALITY ASPECTS

II.1 Introduction

Adport 2 mg is a dark green opaque capsule, imprinted in black with 2 mg on the cap, containing white to off-white powder.
Adport 0.75 mg is a light green opaque hard gelatin capsule, imprinted in black with 0.75 mg on the cap, containing white to off-white powder.

The capsules are packed in PVC/PE/PVdC/Aluminium blisters with dessicant in Aluminium bag.

The excipients are:
Capsule contents – hypromellose (E464), lactose monohydrate, croscarmellose sodium (E468), magnesium stearate (E572).
Hard gelatine capsule – gelatin, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172) (2 mg only), FD&C Blue 1 (E133), shellac (E904), propylene glycol (E1520), potassium hydroxide (E525), black iron oxide (E172).

The proposed 0.75 mg strength is dose proportional to the approved Adport 0.5 mg strength and the proposed 2 mg strength is dose proportional to the approved Adport 1 mg and 5 mg strengths.

II.2 Drug Substance

The active substance is tacrolimus monohydrate, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white, crystalline powder. Tacrolimus is insoluble in water, sparingly soluble in hexane and petroleum ether, and soluble in chloroform, methanol, acetone, ethanol, ethyl acetate and ethyl ether. No polymorphic forms of tacrolimus are known. Tacrolimus exists in a solution as a mixture of 2 isomers.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Tacrolimus is produced by a fermentation process. Satisfactory details on the manufacturing process have been provided. Information on potential impurities has been provided. The description of the process validation and the manufacturing process is considered acceptable.

Quality control of drug substance
The drug substance specification has been established in-house by the ASMF holder and MAH. All methods and criteria included in the drug substance specification are acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial-scale batches of the original manufacturing process and of three commercial-scale batches of the optimized process. The MAH provided batch analysis data of two batches demonstrating compliance with the drug product specification.

Stability of drug substance
Stability data on the active substance have been provided for commercial batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). No significant changes or trends were observed. Based on forced degradation studies, it is concluded that the drug substance is not photostable. The proposed retest period of 36 months and storage condition "Store in an airtight container, protected from light" is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The manufacturing process of the proposed strengths is identical to that of the approved strengths. The MAH provided comparative dissolution profiles of the dose-proportional strengths of the test product (1 mg, 2 mg, 5 mg/0.5 mg, 0.75 mg) and of the approved strengths of the test and reference product (0.5 mg, 1 mg, 5 mg) in pH 1.2, pH 4.5 and pH 6.8 buffers without surfactant and in the QC medium (phosphate buffer pH 7.0 with 0.1% sodium lauryl sulphate). As expected, dissolution was not complete in the media without surfactant. Dissolution of the proposed strengths was similar to that of the relevant approved strengths in the media with surfactant. The comparative dissolution data of the approved strengths of the test and reference product show that drug release is drug substance rather than formulation related. Dissolution of the approved strengths was also similar in the media with surfactant. In all cases, dissolution exceeded 85% in 15 minutes in the QC medium. Based on the provided comparative dissolution data, the biowaiver is acceptable from a chemical pharmaceutical point of view. Reference can be made to the bioequivalence studies with the 0.5 mg and 5 mg capsules as approved in procedure NL/H/1340/001-003/DC.

Manufacturing process
The manufacturing process includes manufacture of solid dispersion granules, manufacture of final capsule blend, capsule filling and packing of filled capsules. Due to the low drug load, the drug product is considered as specialised pharmaceutical dose form requiring process validation data at production scale. Process validation data were provided for two full-scale batches of the solid dispersion granules and of the capsules of each strength. All predefined acceptance criteria were met. The process validation data are considered sufficient in view of the experience of the MAH with the approved strengths which are manufactured by the same process at the same scale.

Control of excipients

Excipients of the capsule blend comply with the Ph.Eur. Additional in house requirements were defined for hypromellose and lactose monohydrate. An in-house specification was set up for the hard gelatin capsules. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of tacrolimus, uniformity of dosage units by content uniformity, dissolution, water content, related substances, assay, residual solvents, and microbial contamination.
Analytical methods have been adequately described and validated. The stability indicating nature of the HPLC methods for assay and related substances was shown by forced degradation studies.
Batch analytical data from the proposed production site have been provided on two full-scale batches of each strength demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on two full-scale batches of each strength stored at 25°C/60% RH (12 months), 30°/75% RH (12 months) and 40°C/75% RH (six months). The long term and accelerated storage conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PE/PVdC/Al blisters in triple laminated aluminium bags containing a molecular sieve packet 3.0 g. Stability data of the approved strength covering 24 months at long term conditions were provided as well.
The MAH claims a shelf life of 24 months and storage condition “Do not store above 30°C. Store in the original package in order to protect from moisture”. This is considered acceptable based on the provided stability data.
In-use stability studies were initiated with opened bags of all batches. Samples were stored up to 12 months at long term conditions. The provided in use stability data support an in use shelf life of 12 months and storage condition “Do not store above 25°C.” Photostability is considered to be covered by the in-use stability studies which appear to include exposure to light during use by patients. The in-use stability studies will be repeated with batches which have been stored for 12 months at long term conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-athies
Copies of the Certificates of Suitability of all suppliers of gelatin are provided. The supplier of lactose monohydrate certifies that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption. No other ruminant materials than milk and calf rennet are used. The product of calf rennet complies with Regulation 999/2001 as amended and other applicable EU legislation. Magnesium stearate is of vegetable source.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Adport 2 mg and 0.75 mg capsules has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Adport is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Prograf, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-

clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tacrolimus is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver
The application is based on a biowaiver for additional strengths, referring to the previously submitted bioequivalence studies supporting registration of the 0.5 mg strength and the study supporting registration of the 5 mg strength.

Registration of the 0.75 mg tacrolimus strength was requested based on the studies with the 0.5 mg strength. For granting this biowaiver the following was noted:

- Based on results from the bioequivalence studies submitted for the 0.5 mg (2 studies) and 5 mg strength (1 study), tacrolimus pharmacokinetics appears reasonably linear between a 0.5 mg and 5 mg dose.
- The 0.5 mg and 0.75 mg strengths are manufactured by the same manufacturer and manufacturing process.
- The contents of the 0.5 mg and 0.75 mg capsules have the same qualitative composition, and the same ratio between active substance and excipients.

For the 2 mg tacrolimus strength the biowaiver was requested based on the studies with the 5 mg strength. For granting this biowaiver the following was noted:

- Based on results from the bioequivalence studies submitted for the 0.5 mg (2 studies) and 5 mg strength (1 study), tacrolimus pharmacokinetics appears reasonably linear between a 0.5 mg and 5 mg dose.
- The 2 mg and 5 mg strengths are manufactured by the same manufacturer and manufacturing process.
- The contents of the 2 and 5 mg capsules have the same qualitative composition, and the same ratio between active substance and excipients.

The MAH sufficiently demonstrated that dissolution of the proposed strengths was similar to that of the relevant approved strengths. Based on all data provided, the biowaiver for the 0.75 mg and 2 mg can be granted.

IV.3 Clinical efficacy and safety

The recommended initial dosages for tacrolimus are intended solely as a guideline. Tacrolimus dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring. The applied tacrolimus 0.75 and 2 mg strengths are in the range between the already approved strengths of tacrolimus. Given the need for an individual titration of the doses for an optimal balance between efficacy and toxicity, additional strengths providing the possibility of an even more accurate dosing for each patients, are welcomed. The applied strengths make dosing intervals of 0.25 mg instead of 0.5 mg feasible, which may be an advantage considering the narrow therapeutic index of tacrolimus. With the additional strengths if necessary combined with the already approved strengths, the recommended dosage can be reached

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Adport capsules.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Medication error due to switching of prolonged release (once daily) to immediate-release (twice daily) formulations (or vice versa) resulting in incorrect dosage. • Medication error due to switching between tacrolimus brands. • Blood cell changes • Cardiac arrhythmias • Cardiomyopathias/Ventricular hypertrophy • Coagulopathies • Diabetogenicity • Diarrhoea • Electrolyte changes • Galactose-intolerance • Hepatic and renal dysfunction • Hypertension • Lactation • Neoplasms • Neurological and visual disorders • Pregnancy • Serious infections and reactivation of pre-existinginfections • Pure red cell aplasia (PRCA) • QT interval prolongation
Important potential risks	• Interaction with MMF • Hypersensitivity reactions: allergic & anaphylactoid reactions
Missing information	• None

To prevent medication errors, the following statement is included on the label: 'Warning: This medicine in the formulation on hand should be taken twice a day'. The MAH should have follow up questionnaires in place to collect more information in case of medication error, and thus enable further root cause analyses and facilitate the identification of the need for possible further risk minimisation measures.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Prograf. No new clinical studies were conducted. The MAH did not conduct any new bioequivalence studies, but referred to the previous studies with Adport 0.5 mg and 5 mg capsules. A biowaiver was granted for the new strengths. Risk management is adequately addressed.

V. USER CONSULTATION

For procedure NL/H/1340/001-003/DC the MAH provided a bridging rationale. The parent package leaflet (PL) to which is bridged is Mycophenolate 250 mg capsules for which a readability test was performed in registration procedure UK/H/0886/001/DC.
The package leaflet of Adport 0.75 mg and 2 mg hard capsules is identical with the package leaflet of the 0.5 mg, 1 mg and 5 mg strengths, which was assessed in the bridging study approved to be

compliant with Article 59(3) of Directive 2001/83/EC. Thus, an additional user test is not deemed necessary.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Adport 0.75 mg and 2 mg capsules, hard have a proven chemical-pharmaceutical quality and are hybrid forms of Prograf 0.5 mg, 1 mg and 5 mg. Prograf is a well-known medicinal product with an established favourable efficacy and safety profile.

Based on bridging to the studies performed with Adport 0.5 mg and 5 mg, bioequivalence is considered demonstrated.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that similarity to the existing strengths of Adport and Prograf has been demonstrated for Adport 0.75 mg and 2 mg capsules, and have therefore granted a marketing authorisation. The proposed new strengths are considered appropriate to facilitate individual dose titration. The decentralised procedure was finalised with a positive outcome on 5 June 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached