COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dailiport 0.5 mg, 1 mg, 2 mg, 3 mg and 5 mg, prolonged release hard capsules

(tacrolimus monohydrate)

NL/H/4508/001-005/DC

Date: 30 December 2019

This module reflects the scientific discussion for the approval Dailiport 0.5 mg, 1 mg, 2 mg, 3 mg and 5 mg, prolonged release hard capsules. The procedure was finalised at 18 September 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Dailiport 0.5 mg, 1 mg, 2 mg, 3 mg and 5 mg, prolonged release hard capsules, from Sandoz B.V.

The product is indicated for:

- Prophylaxis of transplant rejection in adult kidney or liver allograft recipients
- Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients

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

This decentralised procedure concerns a generic application [article 10(1)] claiming essential similarity with the innovator product Advagraf 0.5 mg, 1 mg, 3 mg and 5 mg prolonged release hard capsules registered in the EEA by Astellas Pharma GmbH since 23 April 2017 via a centralised procedure (EMEA/H/C/000712).
As the innovator product does not consist as 2 mg strength, the MAH applies for the registration of this newly proposed formulation/strength 2 mg capsules via a hybrid application [article 10(3)].

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic (not for the 2 mg strength), Denmark, Estonia, Finland, Germany, Ireland, Iceland, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovak Republic (not for the 2 mg strength) and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) and 10(3) (a hybrid application as the innovator product is not available as a 2 mg strength prolonged release hard capsule) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

- Dailiport 0.5 mg is a prolonged-release hard capsule with a light brown body and a light yellow cap, imprinted in black with “0.5 mg”, containing a white to yellowish powder or compacted powder. Each capsule contains 0.5 mg tacrolimus.
- Dailiport 1 mg is a prolonged-release hard capsule with a light brown body and a white cap, imprinted in black with “1 mg”, containing a white to yellowish powder or compacted powder. Each capsule contains 1 mg tacrolimus.

- Dailiport 2 mg is a prolonged-release hard capsule with a light brown body and a dark green cap, imprinted in black with “2 mg”, containing a white to yellowish powder or compacted powder. Each capsule contains 2 mg tacrolimus.
- Dailiport 3 mg is a prolonged-release hard capsule with a light brown body and a light orange cap, imprinted in black with “3”, containing a white to yellowish powder or compacted powder. Each capsule contains 3 mg tacrolimus.
- Dailiport 5 mg is a prolonged-release hard capsule with a light brown body and a pink cap, imprinted in black with “5 mg”, containing a white to yellowish powder or compacted powder. Each capsule contains 5 mg tacrolimus.

The prolonged release hard capsules are packed in PVC/PVDC//aluminium blisters with a desiccant sealed in an aluminium bag.

The excipients are:
Capsule content – ethyl cellulose, hypromellose, lactose monohydrate and magnesium stearate
Capsule shell – brilliant blue FCF (E133), allura red AC (E129), titanium dioxide (E171), gelatin, sunset yellow FCF (E110), and tartrazine (E102) for only the 0.5 mg and 2 mg strengths and erythrosine (E127) for only the 5 mg strength.
Printing ink - shellac glaze, allura red AC aluminium lake (E129), brilliant blue FCF aluminium lake (E133), sunset yellow FCF aluminium lake (E110), propylene glycol (E1520), lecithin (soya) and simethicone

II.2 Drug Substance

The active substance tacrolimus monohydrate, an established active substance, is described in the European Pharmacopoeia (Ph.Eur.). Tacrolimus is a white to almost white crystalline powder. It is non-hygroscopic and practically insoluble in water, soluble in ethanol (96%) and practically insoluble in heptane. Tacrolimus exists in the cis amide conformation only; the polymorphic form is in line with that presented in the literature and does not change during storage.

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.

<u>Manufacturing process</u>
The manufacturing process has been described in sufficient detail. All critical manufacturing steps have been validated in line with the requirement as set in the applicable ICH guideline.

An exhaustive characterisation has been performed. Potential impurities are addressed, including residual solvents, in line with the European guidelines.

Quality control of drug substance

The active substance specification has been established in-house by the ASMF holder, based on the Ph.Eur and United States Pharmacopeia monographs for tacrolimus. The specification is considered adequate to control the quality and meets the requirements of the monographs and various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for eight full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for a total of four batches in accordance with applicable European guidelines demonstrating the stability of the active substance. Based on the data submitted, a retest period could be granted of 36 months when stored in an airtight container, protected from light.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The target release profile of the product and the system chosen to achieve it, have been discussed in view of the prolonged release nature of the product. The dissolution profile of the biobatch has been compared with that of the reference product and found to be satisfactorily similar. The chosen biobatch is acceptable from a chemical-pharmaceutical point of view.

A bioequivalence study has been performed with the 5 mg strength. For the four lower strengths a biowaiver has been claimed. Comparative dissolution data has been provided for all lower strengths in pH 1.2 without enzyme, acetate buffer pH 4.5, and phosphate buffer 6.8. All f_2 values were between 50 and 100 indicating similarity of the dissolution profiles. Overall, the pharmaceutical development is acceptable.

Manufacturing process

The manufacturing process consist of three steps: wet granulation, blending and encapsulation. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial batches for the strengths 0.5 mg, 1 mg, 5 mg and one batch for the 2 mg and 3 mg strengths in accordance with the relevant European guidelines. As the final encapsulation blend can be used to produce capsules of the different strengths, the bracketing approach is acceptable. The quantity and size of validated batches are appropriate. The product is manufactured using conventional manufacturing techniques.

Control of excipients

All excipients, except for the excipients of the capsules and ink comply with the respective Ph. Eur. monographs and are considered acceptable. For the capsules and ink, composition,

specifications, description of analytical methods and exemplary Certificates of Analysis are provided. The specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, related substances, dissolution, uniformity of dosage units, residual solvents, water activity, and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of the 0.5 mg, 1 mg and 5 mg strengths and one batch of the 2 mg and 3 mg strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches of the 0.5 mg, 1 mg and 5 mg strengths and one batch of the 2 mg and 3 mg strengths stored at 25°C/60% RH (up to 12 months) and 40°C/75% RH (up to 6 months). Additional transportation (up to 50°C, one month), freeze-thaw cycles and in-use stability (open pouch) studies have been performed. Photostability studies were performed in accordance with ICH recommendations and showed that the product is sensible to light. In-use stability after opening of the pouch has been shown for up to one year. The available results show no trends or significant change in results, at all tested conditions. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are 'store in the original package in order to protect from light and moisture'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dailiport 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 Dailiport 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 generic and, for one strength, hybrid formulation of Advagraf 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.

For this generic application, the MAH has submitted four bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Dailiport 5 mg, prolonged release hard capsules (Sandoz B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Advagraf 5 mg, prolonged release hard capsules (Astellas Pharma GmbH, Germany) under single-dose fed and fasted and multiple-dose fasted conditions.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver has been accepted for the lower strengths (0.5 mg, 1 mg, 2 mg and 3 mg) based on the following criteria:

- The pharmaceutical products are manufactured by the same manufacturer and process:
- The drug input has been shown to be linear over the therapeutic dose range
- The qualitative composition of the different strengths is the same
- The composition of the strengths are quantitatively proportional
- The dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study

Bioequivalence studies

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the whole blood samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – Single-dose under fasting conditions.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 120 healthy male and female subjects, aged 19-55 years. Each subject received a single dose (5 mg) of one of the 2 tacrolimus formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected at pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, and 120 hours after administration of the products.
The design of the study is acceptable

Results

Six subjects discontinued the study prior to the second period and one subject was excluded from statistical analysis due to very low whole blood concentrations of tacrolimus for the reference product. 114 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tacrolimus under fasted conditions.

Treatment N=114	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	196.7 ± 81.4	215.4 ± 91.2	9.8 ± 3.8	1.75 (0.67-6.0)

Reference	189.2 ± 86.7	207.3 ± 96.7	10.4 ± 4.5	1.58 (0.67-6.0)
***Ratio (90% CI)**	1.06 (1.02-1.10)	1.06 (1.02-1.10)	0.95 (0.91-1.00)	--
CV (%)	17	16	23	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Bioequivalence study II – Single-dose under fed conditions.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, monocentric crossover bioequivalence study was carried out under fasted conditions in 72 healthy male and female subjects, aged 19-55 years. Each subject received a single dose (5 mg) of one of the 2 tacrolimus formulations. The tablet was orally administered with 240 ml water after a high-fat, high-calorie breakfast.(consisting of eggs, butter, whole wheat toast, hash brown potatoes, milk and chicken bacon) There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected at pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, and 120 hours after administration of the products.

The design of the study is acceptable

Results

Four subjects discontinued the study as one subjects tested positive for THC in urine, one subjects became pregnant, one subjects confiscated a restricted item and one subject withdrew for personal reasons. Therefore, 68 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tacrolimus under fed conditions.

Treatment N=68	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	128 ± 52	135 ± 56	6.0 ± 2.8	6.0 (2.0-10.0)
Reference	127 ± 46	134 ± 50	5.7 ± 2.0	4.8 (2.0-14.0)
***Ratio (90% CI)**	1.00 (0.97-1.03)	1.00 (0.97-1.03)	1.02 (0.96-1.07)	--

CV (%)	11	11	19	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

ln-transformed values

Bioequivalence study III – multiple-dose under fasting conditions.

Design

A single-centre, randomised, two-period, two-treatment, two-sequence, multiple dose crossover bioequivalence study was carried out under fasted conditions in 120 healthy male and female subjects, aged 19-55 years. Each subject received a single (5 mg) of one of the 2 tacrolimus formulations for 10 days. The tablet was orally administered with 240 ml water after an overnight fast. There were 10 successive dosing days, separated by a washout period of 14 days.

Blood samples were collected at pre-dose on days 1, 8, 9 and 10 and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 14, 18 and 24 hours after administration of the products.

The design of the study is acceptable

Results

Eight subjects withdrew the study for personal reasons, three subjects were withdrawn due to protocol deviation and thirteen subjects were withdrawn due to adverse events and two subjects did not show up in the first period. In addition, a subject was excluded from the statistical analyses as no whole blood tacrolimus concentrations were observed after administration of the reference and test product. Therefore, a total of 94 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tacrolimus under fasted conditions.

Treatment N=114	**$AUC_{0-\tau}$** (ng.h/ml)	**$C_{max,ss}$** ng/ml	**$C_{min,ss}$** (ng/ml)	**$t_{max,ss}$** (h)
Test	169.1 ± 62.2	12.6 ± 4.7	4.9 ± 2.0	1.8 (1.0-6.0)
Reference	159.9 ± 58.1	12.4 ± 4.5	4.5 ± 1.9	1.0 (1.0-8.0)
***Ratio (90% CI)**	1.06 (1.03-1.09)	1.01 (0.97-1.06)	1.08 (1.05-1.12)	--
CV (%)	12	18	11	--

$AUC_{0-\tau}$	area under the plasma concentration-time curve during a dosage interval at steady state
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{min,ss}$	concentration at the end of the dosing interval at steady-state **$t_{max,ss}$** time for maximum concentration at steady state
CV	coefficient of variation

ln-transformed values

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for C_{max}, $C_{max,ss}$ and $C_{min,ss}$ are within the bioequivalence acceptance range of 0.80 – 1.25. The 90% confidence intervals calculated for AUC_{0-t} and $AUC_{0-\infty}$ are within the bioequivalence acceptance range of 90.00% – 111.11%. Based on the submitted bioequivalence studies Dailiport is considered bioequivalent with Advagraf.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Dailiport.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	- Medication errors - Hypertension - Torsade de Pointes - Cardiac arrhythmias - Prolonged QT interval - Ventricular hypertrophy - Cardiomyopathies - Neurological and visual disorders - Diabetogenicity - Electrolyte changes - Galactose intolerance - Hepatic dysfunction - Renal dysfunction - Blood cell count changes - Coagulopathies - Use during pregnancy and lactation - Gastrointestinal (GI) perforation - Diarrhoea

	- Neoplasms - Serious infections and reactivation of pre-existing infections - Pure red cell aplasia (PRCA)
Important potential risks	- Interaction with Mycophenolate mofetil (MMF)
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Advagraf. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the content of the PL of Prograf 0.5 mg, 1 mg and 5 mg capsules (NL License RVG 22236, 18107 and 18108, respectively). The MAH's package insert house style design and layout (e.g. print size and type, print colour, arrangement of the text, structure of the headings) to be used in the patient leaflet has been successfully tested in several readability tests for different already approved medicines. This includes, for example, the following procedure numbers: DE/H/717+719/01/MR (clozapine, 2007), EMEA/H/C/1181-1184, (rivastigmine, 2009) and DE/H/3330+3331/01-04/DC (ziprasidone, 2012). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dailiport 0.5 mg, 1 mg, 2 mg, 3 mg and 5 mg, prolonged release hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Advagraf 0.5 mg, 1 mg, 3 mg and 5 mg prolonged release hard capsules. Advagraf is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 essential similarity has been demonstrated for Dailiport with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 September 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse