CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Tacrolimus Sandoz 0.5 mg, 1 mg and 5 mg, capsules, hard
Sandoz B.V., the Netherlands

tacrolimus (as monohydrate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1341/001-003/DC
Registration number in the Netherlands: RVG 102096-102098

1 February 2010

Pharmacotherapeutic group:	immunosuppressants; calcineurin inhibitors
ATC code:	L04AD02
Route of administration:	oral
Therapeutic indication:	prophylaxis of transplant rejection in liver, kidney or heart allograft recipients; allograft rejection resistant to treatment with other immunosuppressive medicinal products.
Prescription status:	prescription only
Date of authorisation in NL:	22 December 2009
Concerned Member States:	Decentralised procedure with AT, DE, LU
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Tacrolimus Sandoz 0.5 mg, 1 mg and 5 mg, capsules, hard, from Sandoz B.V. The date of authorisation was on 22 December 2009 in the Netherlands.

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 SPC.

Tacrolimus belongs to the pharmacotherapeutic group of macrolide immunosuppressants, and to the subgroup of calcineurin inhibitors. At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of lymphokine genes.
Tacrolimus is a potent immunosuppressive agent and has proven activity in both *in vitro* and *in vivo* experiments. In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Prograft 0.5 mg, 1 mg and 5 mg capsules (NL License RVG 22236, 18107 and 18108, respectively) which have been registered in the Netherlands by Astellas Pharma B.V. since 1996 (1 and 5 mg) and 1998 (0.5 mg). In addition, reference is made to Prograft authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profiles of the 0.5 mg and 5 mg products are compared with the pharmacokinetic profiles of the reference products Prograft 0.5 mg and Prograft 5 mg capsules, registered in Ireland. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is tacrolimus monohydrate, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia. 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/EMEA 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
Satisfactory details on the manufacturing process have been provided. Information on potential impurities has been provided. The analytical methods used to detect each of the likely impurities have been described and relevant chromatograms have been provided. The description of the process validation and the manufacturing process is considered to be acceptable.

Quality control of drug substance
The drug substance specification has been established in-house by the 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 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were adequately stored. During the accelerated and long-term studies no out of specification data or trends were observed. A retest period of 36 months was granted. The storage conditions *'protect from light'* are applicable.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Tacrolimus Sandoz 0.5 mg is an opaque white and ivory hard gelatin capsule containing white to off-white powder.
Tacrolimus Sandoz 1 mg is an opaque white and light brown hard gelatin capsule containing white to off-white powder.
Tacrolimus Sandoz 5 mg is an opaque white and orange hard gelatin capsule containing white to off-white powder.

The hard capsules are packed in PVC/PE/PVdC/Aluminium blisters with dessicant in a triple laminated aluminium bag containing a Molecular sieve packet in order to capture the moisture from the air.

The excipients are:
Capsule contents - hypromellose (Methocel E6 LV), lactose monohydrate, croscarmellose sodium, magnesium stearate.
Hard gelatine capsule - gelatin, titanium dioxide (E 171), sodium laurilsulfate, sorbitan laureate.
0.5 and 1 mg: yellow iron oxide (E 172). 1 mg and 5 mg: red iron oxide (E 172), 1 mg only: black iron oxide (E 172)
Printing ink - shellac, black iron oxide, potassium hydroxide.

The 1 mg and 5 mg capsules are dose proportional; the 0.5 mg capsule is not.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients comply with the Ph.Eur. These specifications are acceptable. Tacrolimus Capsule was manufactured using the same excipients as that of the innovator. The following development studies have been performed: HPMC Grade selection, lactose grade selection, selection of solvent and selection of lubricant. Comparative dissolution studies have been performed in three different media with the developed product and EU originator products. The method used in release testing was the same as the one with which the dissolution profile demonstrated a complete release of Tacrolimus. The dissolution profiles of the reference product and test-product are considered to be comparable. Furthermore, the dissolution profiles of the 0.5 mg, 1.0 mg and 5.0 mg are also comparable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of the following steps: manufacture of solid dispersion granules, manufacture of final capsule blend, capsule filling and packing of filled capsules. The formulation development has been adequately described and is considered to be acceptable. Process validation data on the product has been presented for three full-scale solid dispersion granule batches and three full-scale batches per strength. The MAH committed to perform process validation for full-scale batches post authorisation.

Quality control of drug product
The product specification includes tests for appearance, identity, uniformity of dosage units, content uniformity, dissolution, water content, loss on drying, related substances, assay, residual solvents and microbial contamination. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two full-scale batches per strength stored at 25°C/60% RH (24 months), 30°/65% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PE/PVdC/Al blisters in a triple laminated aluminium bag containing a Molecular Sieve Packet 3.0 g. Based on the data available, a shelf-life of 2 years could be granted.
The MAH committed to conduct stability studies on the first three industrial-scale batches of the finished product. These studies will be continued at least until the end of the applied shelf-life.

In-use stability
An in-use stability study was conducted on three full-scale batches of each strength. The drug product was stored for one year at 25°C/60% RH and opened. The data for a storage time after opening up to 12 months have been included. No change in the parameters was observed. An in-use shelf-life of 12 months could be granted
During stress testing a photostability test has been conducted, demonstrating that the drug product is photostable. Therefore, the proposed storage condition '*store in the original packaging in order to protect*

from moisture' and packaging material are considered to be acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin from different suppliers is used. All of these suppliers have a TSE certificate of suitability. The lactose is derived from milk sourced from healthy animals in the same conditions as milk collected for human consumption. The lactose is prepared without the use of other ruminant materials than milk and calf rennet. The used magnesium stearate is of vegetable origin.
With respect to the drug substance a TSE statement which applies to all materials used in the production of tacrolimus was provided, including all components used during the fermentation process.

II.2 Non clinical aspects

This product is a generic formulation of Prograft, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of tacrolimus released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Tacrolimus is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Tacrolimus Sandoz 0.5 mg and 5 mg capsules (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products Prograft 0.5 mg and 5 mg capsules (Astellas Pharma Ireland Co, Ltd., Ireland), respectively. Both reference products

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

Bioequivalence study I – 0.5 mg capsules
Design
An open-label, single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 46 healthy male subjects, aged 19-43 years. Each subject received a single dose (0.5 mg) of one of the 2 tacrolimus formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. No fluid except for the 240 ml given with drug administration was allowed from 1 hour pre-dose to 2 hours post-dose. The subjects were instructed not to lie down for the first three hours after dosing. There were 2 dosing periods, separated by a washout period of 26 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 6.0, 8.0, 24, 48, 72, 96, 120, 144 and 168 hours after administration of the products.

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

Results
One subject was withdrawn prior to period 2 due to protocol violation, one subject discontinued on his own request after period 2, and one subject was withdrawn due to emesis after period 1. The remaining 43 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=43	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	34.3 ± 18.6	37.2 ± 19.1	3.25 ± 1.19	1.25 (0.75-3.5)	36 ± 8
Reference	32.2 ± 19.6	35.5 ± 20.2	3.21 ± 1.27	1.5 (0.75-2.67)	35 ± 4
***Ratio (90% CI)**	1.10 (1.01-1.19)	1.06 (1.00-1.14)	1.03 (0.94-1.11)	-	-
CV (%)	22.7	19.3	23.3	-	-

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of tacrolimus under fasted conditions, it can be concluded that Tacrolimus Sandoz 0.5 mg capsules and Prograft 0.5 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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).

Bioequivalence study II – 5 mg capsules
Design
An open-label, single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 46 healthy male subjects, aged 19-43 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 of 10 hours. No fluid except for the 240 ml given with drug administration was allowed from 1 hour pre-dose to 2 hours post-dose. The subjects were instructed not to lie down for the first three hours after dosing. There were 2 dosing periods, separated by a washout period of 27 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 6.0, 8.0, 24, 48, 72, 96, 120, 144 and 168 hours after administration of the products.

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

Results
Three subjects were withdrawn prior to period 2 due to protocol violation and one subject was discontinued on medical grounds in period 1. The remaining 42 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 fasted conditions.

Treatment N=42	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	402 ± 211	424 ± 219	39.2 ± 13.5	1.5 (0.75-3.0)	34 ± 7
Reference	388 ± 207	410 ± 214	39.3 ± 14.5	1.75 (0.75-6.0)	36 ± 8
***Ratio (90% CI)**	1.05 (0.99-1.11)	1.04 (0.99-1.10)	1.01 (0.92-1.11)	-	-
CV (%)	15.2	14.0	27.0	-	-

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of tacrolimus under fasted conditions, it can be concluded that Tacrolimus Sandoz 5 mg capsules and Prograft 5 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Upon request, the MAH has provided compelling argumentation why the 0.80-1.25 acceptance criteria are adequate for this application, and the use of narrowed acceptance criteria for tacrolimus is not deemed necessary. The same criteria were applied by the innovator company demonstrating bioequivalence between the 0.5 mg and 1 mg Prograf[1]. The RMS and CMSs consider the 0.80-1.25 acceptance interval appropriate.

The advice is to administer the capsules on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption. Therefore a food interaction study is not deemed to be necessary.

Extrapolation to 1 mg strength
A biowaiver was requested for the 1 mg strength, based on the provided data for the 5 mg strength. Extrapolation of the results of the bioequivalence study performed with the 5 mg capsules is acceptable, as all requirements as led down in the *Note for Guidance on the Investigation of Bioavailability and Bio-Equivalence* are met and the capsules are made by the same manufacturer.

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).

[1] Bekersky I, Dressler D, Boswell GW, Fergen B, Tracewell W and Mekki Q. Bioequivalence of new strength Tacrolimus capsule under development; Transplantation proceeding, 30 1457-1459 (1998)

CMD(h) Referral for NL/H/1340/001-003/DC
During DCP NL/H/1340/001-003, for which an identical dossier was submitted, several CMSs did not approve of the bioequivalence studies performed in the acceptance interval 0.80-1.25, because they consider tacrolimus a "critical dose drug" with a narrow therapeutic index. In their view the acceptance range should be 0.90-1.11. Furthermore, the lack of bioequivalence for the 0.5 mg capsules further impacts on the 1 mg and 5 mg capsules, as the lack of 0.5 mg capsules means that dose titration is not possible with only two strengths. During the decentralised procedure, consensus on these issues could not be reached. The procedure was referred to the CMD(h).

In response to the questions raised, the MAH provided a new bioequivalence study with an acceptance range of 0.90-1.11, performed with the 0.5 mg strength. The calculated 90% CI for AUC_{0-t}, AUC_{inf} and C_{max} for tacrolimus were within the predefined 0.90-1.11 acceptance range. Therefore, bioequivalence with respect to the rate and extent of absorption of tacrolimus was sufficiently demonstrated for the 0.5 mg strength. All CMSs endorsed this conclusion.
As the dossier for the procedure at issue is identical to the one submitted for NL/H/1340/001-003/DC, the bioequivalence results in the acceptance range of 0.90-1.11 also apply to Tacrolimus Sandoz 0.5 mg, 1 mg and 5 mg, capsules, hard. For more information on the discussion and bioequivalence study, refer to the Public Assessment Report for NL/H/1340/001-003/DC.

Dosing errors
During the CMD discussion, one of the CMSs pointed out that for the innovator products Prograft and Advagraf serious dosing errors occurred. Up to 14 November 2008, 50 cases of medication errors have been reported involving confusion between Advagraf (prolonged release formulation of tacrolimus to be taken once daily) and Prograft (immediate release formulation of tacrolimus to be taken twice daily). Therefore, warnings have been included in the product information to prevent inadvertent, unintentional or unsupervised switching of immediate or prolonged release formulations of tacrolimus.
It was agreed upon that the MAH should provide Risk Minimisation Activities to prevent the same occurring for Tacrolimus Sandoz. In response the MAH provided a new labelling proposal and an updated Risk Management System. On the outer labeling the following sentence was added: *Warning: This medicine should be taken twice a day.*
As it concerns an identical product, the labelling texts for NL/H/1341/001-003/DC will be adapted accordingly through a variation.

Risk management plan
Tacrolimus was first approved in 1993, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of tacrolimus can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
To harmonise the different nationally approved SPCs, Prograft capsules underwent a company-initiated Article 30 referral in 2006 and then was converted into the SPC of the MRP product (IE/H/0165/001-002-003/MR). The SPC proposed for Tacrolimus Sandoz is in line with the SPC for Prograft.

Readability test
The MAH provided a bridging rationale. The parent PIL 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 proposed PIL fulfils all conditions set out in the guidance concerning '*Consultation with target patient groups – meeting the requirements of article 59(3) without the need for a full test – recommendations for bridging'*(CMDh, Oct. 2007). Although the daughter PIL contains additional information, analogy of key

messages and application of the user-tested Sandoz house style providing clearly structured texts are substantial arguments for maintained readability within the daughter PIL. Parent PIL and daughter PIL have the same layout and style. Furthermore, the content/wording of additional text in the daughter PIL is derived from the originator Prograft PIL, which was harmonized according to Article 30 of Directive 2001/83/EC in the referral procedure CHMP/85997/06. Where different wording is used in the daughter PIL, all recommendations of the Readability guideline are fulfilled.
For these reasons, a readability test for the PIL at issue is not necessary.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Tacrolimus Sandoz 0.5 mg, 1 mg and 5 mg, capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Prograft 0.5 mg, 1 mg and 5 mg capsules. Prograft 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is in general consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates. Through a variation, the following warning will be included in the labelling texts: *Warning: This medicine should be taken twice a day.*

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 Tacrolimus Sandoz 0.5 mg, 1 mg and 5 mg, capsules, hard with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 26 July 2009. Tacrolimus Sandoz 0.5 mg, 1 mg and 5 mg, capsules, hard were authorised in the Netherlands on 22 December 2009.

A European harmonised birth date has been allocated (2 April 1993) and subsequently the first data lock point for tacrolimus is March 2010. The first PSUR will cover the period from July 2009 to September 2009, after which the PSUR submission cycle is 6 months.

The date for the first renewal will be: May 2014.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to conduct process validation on the first three commercial-scale batches.
- The MAH committed to conduct stability studies on the first three industrial-scale batches of the finished product.
- The MAH committed to perform stability testing on the first three production batches of the finished product; the stability study will be continued at least until the end of the applied shelf-life.
- The MAH committed to perform a transportation validation study for the products Tacrolimus 0.5 mg and 5 mg in order to examine the efficacy of the primary packaging material to ensure quality, safety and efficacy along the distribution chain from the production site to the customer.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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
Deletion of imprinting and logo from the capsule shell	NL/H/1341/ 001/IA/ 001	IA	7-10-2009	21-10-2009	Approval	N
Deletion of imprinting and logo from the capsule shell	NL/H/1341/ 002/IA/ 002	IA	8-10-2009	22-10-2009	Approval	N
Deletion of imprinting and logo from the capsule shell	NL/H/1341/ 003/IA/ 003	IA	8-10-2009	22-10-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for batch release; not including batch control/testing.	NL/H/1341/ 001-003/IA/ 004	IA	13-10-2009	27-10-2009	Approval	N