

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Finasteride Mylan 1 mg, film-coated tablets
Mylan B.V., the Netherlands**

finasteride

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/1258/001/DC
Registration number in the Netherlands: RVG 101374**

23 December 2009

Pharmacotherapeutic group:	Other dermatologicals
ATC code:	D11AX10
Route of administration:	oral
Therapeutic indication:	Early stages of androgenetic alopecia in men
Prescription status:	prescription only
Date of authorisation in NL:	27 May 2009
Concerned Member States:	Decentralised procedure with DE, ES, FI, FR, IT, SE, UK
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 Finasteride Mylan 1 mg film-coated tablets, from Mylan B.V. The date of authorisation was on 27 May 2009 in the Netherlands.

The product is indicated for early stages of androgenetic alopecia in men. In men aged 18-41 years Finasteride Mylan 1 mg film-coated tablets stabilises the process of androgenetic alopecia. Efficacy in bi-temporal recession and hair loss in the end stage has not been established.

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

Finasteride is a 4-azasteroid, which inhibits human type 2 5 α -reductase (present in the hair follicles) with a more than 100-fold selectivity compared with human type 1 5 α -reductase, and blocks the peripheral conversion of testosterone to the androgenic dihydrotestosterone (DHT). In men with male pattern hair loss, the balding scalp contains miniaturised hair follicles and increased concentrations of DHT. Finasteride inhibits the process responsible for miniaturisation of the scalp hair follicles, which can lead to reversal of the balding process.

This decentralised procedure concerns a generic application; the reference product is Proscar 5 mg tablet, which has been registered in the United Kingdom by MSD since 22 May 1992 (NL RVG 15482). Reference is also made to Propecia 1 mg, an additional strength of Proscar 5 mg, which has been registered in the Netherlands by MSD since 28 July 2002 (NL RVG 27397). In addition, reference is made to Propecia 1 mg authorisations in the individual member states.

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 second reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Proscar 1 mg tablets, registered in the UK. 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. This generic product can be used instead of its reference product.

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.

No paediatric development programme has been submitted.

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 this product type 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 finasteride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is practically insoluble in water. Finasteride can exist in two polymorphic forms and has seven chiral centres. It is a steroid derivative. The active substance used is a specific isomer Finasteride exists in two polymorphic forms, form I and form II (Journal of Pharm Sci 2000, 89 910), 1271-1285). The polymorphic form manufactured is Form I. The polymorphic form of every production batch is confirmed by appropriate tests.

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

The drug substance is manufactured in four steps. Crude finasteride is purified and crystallized in suitable solvents to yield finasteride Ph.Eur. In the manufacturing process several class II and class III solvents are used. More details are given in the restricted part of the EDMF. The active substance is adequately characterized and acceptable requirements for the solvents have been adopted in the specification.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur., with additional requirements for particle size, bulk density, selenium content, sulphated ash, heavy metals and residual solvents. The specification is 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 production scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). The batches were stored in double PE bags (colourless inside, black outside), placed within a rigid fibreboard drum. At both storage conditions no changes or trends have been observed. The claimed retest period of 2 years is justified, when stored in the original package to protect from light.

* *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

Finasteride Mylan 1 mg is a brown, round, biconvex film-coated tablet.

The film-coated tablets are packed in PVC/Aluminium blisters packs.

The excipients are:

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Pregelatinised Maize starch
Sodium starch glycollate
Docusate sodium
Magnesium stearate
Povidone

Coating

OPADRY OY-S-36500 brown:
Titanium dioxide (E171)
Yellow and red iron oxide (E172).
Microcrystalline cellulose (E460)
Magnesium stearate (E470b)
Talc (E533b)
Hypromellose (E464)
Hydroxypropylcellulose (E463)
Povidone (E1201)

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. During drug development, the dissolution profiles and impurity profiles of the test and innovator product were compared. Both the test and innovator product have good dissolution characteristics. The impurity profiles are comparable. A study regarding the influence of the particle size distribution on the dissolution profile has been performed. The excipients and packaging are usual for this type of dosage form. Except for Opadry, the excipients comply with the Ph.Eur.. The specifications are acceptable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The product is manufactured by wet granulation. The active substance and several excipients are sieved and blended. The binder solution is prepared using ethanol. It is added to the mixture and the mixture is then granulated. The granules are dried and sieved. The lubricant is added to the granules before tableting. The tablets are coated with Opadry brown. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches.

Quality control of drug product

The product specification includes tests for appearance, identity, uniformity of dosage units, uniformity of mass, average mass, loss on drying, disintegration time, dissolution, assay, related substances and microbial quality. The proposed specification is acceptable. The analytical methods have been adequately described and validated. Batch analysis results from the proposed production site have been provided on three full scaled batches, demonstrating compliance with the release specification.

Stability tests on the finished product

Stability data on the product have been provided for three full scaled batches stored at 25°C/60%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 tablets were stored in PVC/Alu blisters.

At accelerated storage conditions extreme variability in assay values is observed. The MAH has conducted a study and decreased the sampling quantity to reduce the variability in assay.

Stability results of batches stored at the intermediate conditions (30°C/65%RH) have been submitted for one production-scale batch. Results for at least one additional pilot-scale batch are required.

Results of a photostability study according to the NfG on photostability testing are submitted, however the storage conditions are not conform the NfG on photostability testing. Meanwhile the storage condition

“store in the original package to protect from light” is applicable. However, the storage conditions will be re-evaluated when more stability data become available. A shelf life of 2 years could be granted, when stored in the original package to protect from light.

For all 4 post-approval commitments made by the MAH regarding the stability studies, see page 7 of this report.

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.2 Non clinical aspects

This product is a generic formulation of Propecia 1 mg film-coated tablets, 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 finasteride 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Finasteride Mylan 1 mg is compared with the pharmacokinetic profile of the reference product Proscar 1 mg tablets from the UK market.

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results 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

A single-dose, randomized, two-period, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19-45 years. All subjects were non-smokers. Each subject received a single dose (1 mg) of both the test and reference finasteride formulations. The tablet was orally administered with 200 ml water after an overnight fast of at least 10 hours. Fasting was continued for 6 hrs after dosing. For each subject there were 2 dosing periods, separated by a washout period of 21 days. Blood samples were collected pre-dose and at 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours after administration of the products.

One subject dropped out before study medication at Period I. All 27 subjects who completed the study were eligible for pharmacokinetic analysis.

Statistical/analytical methods

Plasma samples were analysed for finasteride using Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS). The method was adequately validated and a validation report was provided.

Finasteride AUC_{0-∞} and AUC_{0-t} were calculated by the linear trapezoidal method. C_{max} and t_{max} were derived directly from concentration-time-curve. Elimination rate constant was estimated from the slope of the regression line using the terminal data points of the semi-logarithmic plasma concentration - time curve. T_{1/2} was calculated as 0.693/k_{el}. The statistical analysis was acceptable.

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

Treatment N=27	AUC_{0-t} ng.h/ml	AUC_{0-∞} ng.h/ml	C_{max} ng/ml	t_{max} h	t_{1/2} h
Test	46.9 \pm 20.1	47.9 \pm 20.2	6.07 \pm 1.87	1.5 (0.667 - 3.0)	5.8 \pm 2.2
Reference	47.8 \pm 21.0	48.9 \pm 21.3	6.45 \pm 2.31	1.5 (0.667 - 4.0)	6.1 \pm 2.5
*Ratio (90% CI)	0.98 (0.89- 1.07)	0.97 (0.88 - 1.07)	0.95 (0.88 -1.02)	-	-
CV (%)	19.7	19.5	15.9	-	-
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 finasteride under fasted conditions, it can be concluded that Finasteride Mylan 1 mg and Proscar 1 mg tablets 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).

Risk management plan

Finasteride was first approved in 1992, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of finasteride 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

Readability test

The MAH has provided acceptable bridging documentation and therefore no separate readability test for the package leaflet of this product was performed. Bridging was carried out to the test results of the 5 mg finasteride tablet. The bridging report shows that the leaflets are sufficiently similar in both content and layout. The differences between the two PILs in both the textual and visual presentation has been outlined and analyzed. These differences have no significant impact on the readability. The readability test on the 5 mg finasteride tablet has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Finasteride Mylan 1mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Proscar 1 mg film-coated tablets. Proscar 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, package leaflet and labelling are in the agreed templates and are in agreement with other finasteride containing products.

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 Finasteride Mylan 1 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 8 February 2009. Finasteride Mylan 1 mg was authorised in the Netherlands on 27 May 2009.

A European harmonised birth date has been allocated (17 April 1998) and subsequently the first data lock point for finasteride is August 2009. The first PSUR will cover the period from February 2009 to August 2009, after which the PSUR submission cycle is 1 year.

The date for the first renewal will be: 8 February 2014

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

Quality - medicinal product

- The MAH should state the amount of lux and W/m² for the lamp used in the photostability study. In the meantime the storage condition "*store in the original package to protect from light*" is applicable.
- The shelf-life limit for any other impurity will be re-evaluated, when more stability data are available.
- The MAH committed to perform a study on polymorphism and isomerism on samples from the 24 months stability point at the end of October 2008. It should be demonstrated that polymorphic form I is still present at the end of shelf-life. Furthermore, the manufactured isomer should not have been changed during storage.
- The MAH committed to submit stability data on the pilot-scale batches at intermediate conditions as soon as completed and will also evaluate the storage conditions at that point.

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 _{1/2}	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