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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Finasteride Tiefenbacher 5 mg, film-coated tablets
Alfred Tiefenbacher (GmbH & Co. KG), Germany

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/905/01/MR
Registration number in the Netherlands: RVG 33573

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Pharmacotherapeutic group:	Drugs used in benign prostatic hypertrophy, testosterone-5-alpha reductase inhibitors
ATC code:	G04CB01
Route of administration:	oral
Therapeutic indication:	treatment and control of benign prostatic hyperplasia (BPH) to cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH, reduce the incidence of acute urinary retention and reduce need for surgery.
Prescription status:	prescription only
Date of authorisation in NL:	22 June 2006
Concerned Member States:	Mutual recognition procedure with DE (withdrawn on 14-5-09), DK, FI (withdrawn on 18-9-07), FR, IT (withdrawn on 17-4-07), LU, NO, PL, SE and UK (withdrawn on 22-8-07)
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 concerned member states have granted a marketing authorisation for Finasteride Tiefenbacher 5 mg, film-coated tablets from Alfred Tiefenbacher (GmbH & Co. KG), Germany. The date of authorisation was on 22 June 2006 in the Netherlands.

The product is indicated for the treatment and control of benign prostatic hyperplasia (BPH) to:
- cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH,
- reduce the incidence of acute urinary retention and reduce need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

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

Finasteride is a synthetic 4-azasteroid, a specific competitive inhibitor of the intracellular enzyme Type-II-5a-reductase. The enzyme converts testosterone into the more potent androgen dihydrotestosterone (DHT). The prostate gland and, consequently, also the hyperplasic prostate tissue are dependent on the conversion, of testosterone to DHT for their normal function and growth. Finasteride has no affinity for the androgen receptor.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Proscar® 5 mg, film-coated tablets. The innovator product has been registered in the Netherlands by Merck Sharp & Dohme / NL since 28 July 1992 (NL License RVG 15482). In addition, reference is made to Proscar 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 applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Proscar 5 mg film-coated tablets by Merck Sharp & Dohme / NL registered in Germany. 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.

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 drug substance is a white or almost white crystalline powder, freely soluble in chloroform and ethanol.

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. The MAH committed to submit an updated EDMF, via a type II variation. See variation NL/H/0905/001/II/002.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is based on the Ph.Eur. monograph, and extended with in-house specifications for polymorph identity, particle size, bulk density and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

CMD referral
During the mutual recognition procedure a concern was raised regarding the amount of selenium present in the active substance and the possibility of formation of diphenyl diselenide (DDS) during synthesis. Therefore, a CMD(h) referral was started. Agreement was reached before the CMD(h) meeting of 23-24 April 2007. The MAH provided additional batch data on the amount of selenium in the active substance, and the validation of the method of analysis. Furthermore, a specification was set.

Stability of drug substance
Stability data on the active substance have been provided for 4 batches in accordance with applicable European guidelines, demonstrating the stability of the active substance over 18 months. Based on these results, a retest period was granted of one year, when stored below 25 ºC in the original packaging.

** 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 Tiefenbacher 5 mg film-coated tablets contain as active ingredient 5 mg of finasteride.
The Finasteride Tiefenbacher tablets are blue, round biconvex, 7 mm with "F5" marking on one side.
The tablets are supplied in blisters and in HDPE containers with LDPE screw cap.

The excipients are:
tablet core: lactose monohydrate, microcrystalline cellulose, pregelatinised maize starch, lauroyl macrogolglycerides, sodium starch glycolate (type A), magnesium stearate (E572).
film coating: hypromellose, titanium dioxide (E171), indigo carmine (E132), macrogol 6000.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packagings are usual and suitable for the product.

The objective was to develop a product that would be essentially similar with respect to bioavailability and in-vitro characteristics (but not in shape: Proscar is hexagonal and Finasteride Tiefenbacher is round) to brand leader Proscar 5 mg, marketed by Merck Sharp & Dohme BV.

Excipients
The excipients used are common in the manufacture of tablets. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs, except for the colouring agent indigo carmine blue lake, which is not described in the Ph.Eur. This pigment complies with the US Food and Drug Administration (FDA) standards and with Directive 95/45/EC of 26 July 1995, laying down specific purity criteria for colours for use in foodstuffs. It is also approved for use in medicinal products in Directive 78/25/EEC. An adequate FDA certificate was submitted.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 2 pilot-scale batches in accordance with the relevant European guidelines. The MAH committed to provide validation data on commercial-scale batches.

Quality control of medicinal product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications are based on the monograph for tablets in the Ph.Eur. and include tests for appearance, identification, uniformity of mass, content uniformity, average mass, disintegration time, resistance to crushing, assay, related substances, dissolution rate and microbiological purity. Limits in the specifications 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 for 3 pilot-scale batches have been provided, demonstrating compliance with the specifications.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches stored at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH, in accordance with applicable European guidelines. Based on the data submitted, a shelf life of 3 years could be granted. No specific storage conditions need to be included in the SPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Proscar, 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 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 one bioequivalence study in which the pharmacokinetic profile of the test product Finasteride Tiefenbacher 5 mg is compared with the reference product Proscar 5 mg under fasted conditions. The choice of the reference product 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.

Finasteride Tiefenbacher 5 mg can be taken once daily without reference to food intake. From the literature it is known that food does not interact with the absorption of finasteride. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioequivalence study
A randomised, open-label, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 36 healthy male volunteers, aged 18-32 years. Each subject received after an overnight fast of at least 10 hours a single dose (5 mg) of one of the 2 finasteride formulations. The tablets were administered with 240 ml water. For each subject there were 2 dosing periods, separated by a washout period 14 days. Blood samples were taken predose and at 0.5, 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours after administration of the products.

The analytical method is adequately validated and 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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of finasteride under fasted conditions

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	294 ± 82	304 ± 84	44 ± 10	1.3 (0.5-3.0)	5.3 ± 1.3
Reference	290 ± 85	299 ± 86	46 ± 10	1.3 (1.0–5.0)	5.3 ± 1.2

***Ratio (90% CI)**	1.02 (0.97-1.06)	1.02 (0.97-1.06)	0.97 (0.92-1.02)	---	---
CV (%)	11	10	12	---	---

$AUC_{0-\infty}$	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 within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters of finasteride under fasted conditions, it can be concluded that test Finasteride Tiefenbacher 5 mg tablet and the German reference Proscar 5 mg tablet 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 studies have 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 post-authorisation, 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 Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the mutual recognition procedure is harmonised with the SPC from procedure FI/H/358-364/01 (finasteride 5 mg film-coated tablets). The MAH committed to adopt section 4.6 of the SPC (Package leaflet: section 2) depending on the outcome of the decision of Pharmacovigilance Working Party, regarding the necessity of a "*condom warning*" (CMD-discussion for referral procedure SE/H/0636 (EMEA/CMDh/431795/2006) , via a type II variation.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test was performed with 20 participants. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Finasteride Tiefenbacher 5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Proscar. 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. The content of the SPC approved during the mutual recognition procedure is harmonised with the SPC from procedure FI/H/358-364/01 (finasteride 5 mg film-coated tablets).

The Board followed the advice of the assessors. Finasteride Tiefenbacher 5 mg was authorised in the Netherlands on 22 June 2006.

During the mutual recognition procedure a concern was raised regarding the amount of selenium present in the active substance and the possibility of formation of diphenyl diselenide (DDS) during synthesis. Therefore, a CMD(h) referral was started. Agreement was reached before the CMD(h) meeting of 23-24 April 2007. The MAH provided additional batch data on the amount of selenium in the active substance, and the validation of the method of analysis. Furthermore, a specification was set.

The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Finasteride Tiefenbacher 5 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. This mutual recognition procedure was finished on 16 March 2007.

A European harmonised birth date has been allocated (17 April 1998) and subsequently the first data lock point for finasteride is August 2007. The first PSUR is therefore expected in August 2007, after which a PSUR should be submitted every 3 years.

The date for the first renewal will be 21 December 2011.

The following post-approval commitments were made during the procedure:

Quality – active substance

- The MAH committed to submit an updated EDMF, via a type II variation (see table on page 9, NL/H/0905/001/II/002).

Product information

- The MAH committed to adopt section 4.6 of the SPC (Package leaflet: section 2) depending on the outcome of the decision of Pharmacovigilance Working Party, regarding the necessity of a "*condom warning*" (CMD-discussion for referral procedure SE/H/0636 (EMEA/CMDh/431795/2006) , via a type II variation.

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
PL	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
Change to batch release arrangements and quality control testing of the finished product. Replacement or adidtion of a site where batch control/testing takes place.	NL/H/0905 /001/IA/ 001	IA	28-3-2007	11-4-2007	Approval	N
Withdrawal of the marketing authorisation in Italy.	NL/H/0905 /001/MR	Withdrawal	---	17-4-2007	---	N
Withdrawal of the marketing authorisation in the UK.	NL/H/0905 /001/MR	Withdrawal	---	22-8-2007	---	N
Withdrawal of the marketing authorisation in Finland.	NL/H/0905 /001/MR	Withdrawal	---	18-9-2007	---	N
Update of the DMF of the active substance manufacturer	NL/H/0905 /001/II/002	II	14-5-2007	21-12-2007	Approval	N
Change in batch size of the finished product. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation.	NL/H/0905 /001/IA/ 003	IA	14-1-2008	28-1-2008	Approval	N
Minor change in the manufacture of the finished product	NL/H/0905 /001/IB/ 004	IB	14-1-2008	13-2-2008	Approval	N
Change in the name of the medicinal product in NL, FR and DE due to change in MA holder.	NL/H/0905 /001/IB/ 005	IB	14-1-2008	21-2-2008	Approval	N
Submission of the DDQ route DMF of the active substance	NL/H/0905 /001/II/ 006	II	17-4-2008	24-9-2008	Approval	N
Change in the name of the medicinal product in France.	NL/H/0905 /001/IB/ 007	IB	6-4-2009	6-5-2009	Approval	N
Withdrawal of the marketing authorisation in the Germany.	NL/H/0905 /001/MR	Withdrawal	---	14-5-2009	---	N