CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Finasteride Aurobindo 5 mg, film-coated tablets Aurobindo Pharma Limited, UK

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/1005/001/DC
Registration number in the Netherlands: RVG 35032

14 August 2008

Pharmacotherapeutic group:	Testosteron 5 α-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 including transurethral resection of the prostate (TURP) and prostatectomy. Finasteride Aurobindo should be administered in patients with an enlarged prostate (prostate volume above ca. 40 ml).
Prescription status:	prescription only
Date of first authorisation in NL:	14 August 2008
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)
Concerned Member States:	AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LV, NO, PL, PT, SI, SK, SE, and UK

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 RMS has granted a marketing authorisation for Finasteride Aurobindo 5 mg from Aurobindo Pharma Limited, UK. The first date of authorisation was on 14 August 2008 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 the symptoms associated with BPH, and to reduce the incidence of acute urinary retention and the need for surgery. Finasteride Aurobindo 5 mg, film-coated tablets should be administered to patients with an enlarged prostate (prostatic volume more than about 40 ml).

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

Finasteride, a synthetic 4-azasteroid, is a specific and selective inhibitor of Type-II-5-α-reductase, that converts testosterone to the more potent androgen receptor agonist dihydrotestosterone (DHT), especially prominant in prostate tissue. Finasteride's inhibition of 5 alpha-reductase is competitive with testosterone. A single dose of finasteride suppresses serum DHT levels for up to 4 days, i.e. longer than would be expected from the serum terminal elimination half-life (~6-8 hours) probably due to the high affinity of finasteride for the enzyme.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Proscar® 5 mg film-coated tablets, which has been registered in the Netherlands (NL License RVG 15482) by Merck Sharpe & Dohme since 28 July 1992 (original product). In addition, reference is made to Proscar 5 mg film-coated tablets 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, registered in United Kingdom. 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 preclinical and clinical studies were conducted, which is acceptable for this abridged application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The RMS 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 and excipients

The active substance is finasteride, an established active substance described in the European Pharmacopoeia. The active substance is practically insoluble in water.

The ASMF-procedure is used.
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.

Stability data on the active substance have been provided for three full scale batches stored at 30ºC/65%RH (12 months) and 40ºC/75%RH (6 months). The proposed retest period of 24 months and storage condition 'no additional storage condition' are justified.

The excipients, except for the colouring agent Opadry blue, comply with the Ph. Eur. In house specifications are set for Opadry blue. These specifications are acceptable.

Medicinal Product

Composition

The drug product concerns blue coloured, circular, biconvex, beveled edged film-coated tablets debossed with 'E' on one side and '61' on the other side containing 5 mg finasteride. The excipients used are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, pregelatinised starch, docusate sodium and magnesium stearate. The coating consists of opadry blue. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained.

The applicant had produced different batches with different excipients. The initial concentrations of excipients were based on experience and desired function. Three entirely different formulations are tested for the drug product. Hardness, disintegration and dissolution were tested with reference to the dissolution of the innovator product.

The developed formulation was optimized for all excipients separately by analyzing hardness, disintegration time and dissolution profile of three batches with different concentrations for the excipient at issue. The formulation development has been sufficiently described.

Manufacturing process and quality control of the medicinal product

The tablets for registration are manufactured by wet granulation, followed by mixing of dry components, followed by compression in to tablets and coating of the tablets.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two batches. Process validation for full scaled batches will be performed post authorisation.

Stability tests on the finished product

Stability data on the product has been provided for two batches full scale batches stored at 30ºC/65%RH (12 months) and 40ºC/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-Alu foil blister pack (market pack) and LDPE bag in triple laminated bag (simulated bulk pack). The batches stored in the simulated bulk pack are only tested at long term conditions.

No significant changes were observed for any of the parameters after 6 months of accelerated stability testing. A change in disintegration time and water content is observed in the beginning of stability testing, but these changes stabilized during further testing.

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

Except for lactose monohydrate none of the excipients is derived from animal origin, thus no TSE/BSE risk is present. Magnesium stearate is of vegetable origin. Lactose monohydrate is derived from the milk of healthy animals. Supplier's certificates are presented for all excipients stating that the material at issue is TSE/BSE free.

II.2 Non clinical aspects

Good Laboratory Practice

The RMS has been assured that the non-clinical studies have been conducted in accordance with acceptable standards of Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Finasteride Aurobindo 5 mg is a generic formulation of Proscar® 5 mg 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.

The content of the SPC approved during the decentralised procedure is in accordance with the SPC approved for procedure NL/H/1105-1106/001/MR.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Finasteride Aurobindo 5 mg film-coated is compared with the pharmacokinetic profile of the reference product Proscar® 5 mg film-coated tablet.

This was a single-dose, 2-way cross-over study. Twenty-four (+ 2 stand by) healthy male subjects, aged 19 - 36 years, were included in this study. Four subjects were smokers (less than 3 cigarettes per day). Each subject received a single dose (5 mg; 1 x 5 mg tablet) of both the test and reference finasteride formulations. The tablets were administered in solid form with a sufficient amount of water after an overnight fast of at least 10h. For each subject there were 2 dosing periods, separated by a washout period of 9 days. Data obtained from 22 subjects were taken into account (table 1).

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range).

Treatment n=22	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	438 ± 134	468 ± 158	49 ± 9	2.38	7.6 ± 2.2
Reference	433 ± 151	460 ± 176	45 ± 11	2.63	7.4 ± 2.1
***Ratio (90% CI)**	1.03 (0.95 – 1.11)	1.03 (0.95 – 1.12)	1.10 (1.01 – 1.19)		
CV (%)	14.9 %	15.9 %	16.5 %		

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

**ln-transformed values*

Based on the pharmacokinetic parameters of finasteride, the reference and test are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC(0-t), AUC(0-inf) and Cmax of finasteride were inside the normal range of acceptability (0.80 – 1.25).

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 of finasteride is identical to the formula proposed for marketing.

The RMS 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).

Readability test
The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test has been adequately performed. The test process involved two rounds in a sufficient number of participants.

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.

PSUR cyclus and renewal date
The PSUR submission cycle is 3 years European harmonised birth date has been allocated (17 April 1998) and subsequently the first data lock point for finasteride is August 2010.The 1st PSUR will cover the period until August 2010.

The proposed date for the first renewal is agreed to be 18 August 2012.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Finasteride Aurobindo 5 mg is a generic form of Proscar® 5 mg film-coated tablets. Proscar® 5 mg film-coated tablets are a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the European guidance documents. The SPC is consistent with that of the reference product.

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. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. The concerned member states, on the basis of the data submitted, considered that Aurobindo Pharma Limited has demonstrated bioequivalence for Finasteride Aurobindo 5 mg film-coated tablets with the reference product and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between the concerned member states was reached during a written procedure.

The following post-approval commitments were made during the procedure:
Process validation for full scaled batches will be performed post authorisation.

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