PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Finasteride Apotex 5 mg, film-coated tablets
Apopex Europe BV, 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/910/001/MR
Registration number in the Netherlands: RVG 33578

Date of first publication: 12 March 2009
Last revision: 20 October 2011

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Concerned Member States: Mutual recognition procedure with CZ, PL and UK (withdrawn on 9-11-2010)
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 Apotex 5 mg, film-coated tablets from Apotex Europe BV. 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.

Finasteride 5 mg tablets should be administered in patients with an enlarged prostate (prostate volume above ca. 40 ml).

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 hyperplastic 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 MAH 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, 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/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. The MAH committed to submit an updated EDMF, via a type II variation. See variation NL/H/0910/001/II/008.

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.

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°C 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 Apotex 5 mg, film-coated tablets contain as active ingredient 5 mg of finasteride.

The Finasteride Apotex 5 mg 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 Apotex 5 mg 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 drug 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 Apotex 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 Apotex 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 pre-dose 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$</th>
<th>AUC$_{0-\infty}$</th>
<th>C$_{\text{max}}$</th>
<th>t$_{\text{max}}$</th>
<th>t$_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=35</td>
<td>ng.h/ml</td>
<td>ng.h/ml</td>
<td>ng/ml</td>
<td>h</td>
<td>h</td>
</tr>
<tr>
<td>Test</td>
<td>294 ± 82</td>
<td>304 ± 84</td>
<td>44 ± 10</td>
<td>1.3 (0.5-3.0)</td>
<td>5.3 ± 1.3</td>
</tr>
<tr>
<td>Reference</td>
<td>290 ± 85</td>
<td>299 ± 86</td>
<td>46 ± 10</td>
<td>1.3 (1.0–5.0)</td>
<td>5.3 ± 1.2</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.02 (0.97-1.06)</td>
<td>1.02 (0.97-1.06)</td>
<td>0.97 (0.92-1.02)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td>11</td>
<td>10</td>
<td>12</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C$_{\text{max}}$ maximum plasma concentration
t$_{\text{max}}$ 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$_{\text{max}}$ 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 Apotex 5 mg tablet and the German reference Proscar 5 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfill 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. See variation NL/H/0910/001/II/007 in table ‘Steps taken after finalisation of the initial procedure’.

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 Apotex 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 Apotex 5 mg was authorised in the
Netherlands on 22 June 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written
procedure. The concerned member states, on the basis of the data submitted, considered that
bioequivalence has been demonstrated for Finasteride Apotex 5 mg film-coated tablets with the reference
product, and have therefore granted a marketing authorisation. This mutual recognition procedure was
finished on 21 December 2006.

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 (fulfilled post-approval, see
table on page 9, NL/H/0910/001/II/003).

**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 (fulfilled post-approval, see table on page 9, NL/H/0910/001/II/007).
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
- **Cmax**: 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_{1/2}**: Half-life
- **t_{max}**: Time for maximum concentration
- **TSE**: Transmissible Spongiform Encephalopathy
- **USP**: Pharmacopoeia in the United States
<table>
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<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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<tr>
<td>Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place.</td>
<td>NL/H/0910/001/IA/001</td>
<td>IA</td>
<td>16-2-2007</td>
<td>2-3-2007</td>
<td>Approval</td>
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<td>21-6-2007</td>
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<td>NL/H/0910/001/II/003</td>
<td>II</td>
<td>7-9-2007</td>
<td>27-2-2008</td>
<td>Approval</td>
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<td>18-9-2007</td>
<td>2-10-2007</td>
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<td>NL/H/0910/001/IA/005</td>
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<td>24-10-2007</td>
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<td>10-10-2007</td>
<td>9-11-2007</td>
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<td>20-6-2008</td>
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<td>Submission of the DDQ route DMF (version February 2008) of the active substance manufacturer.</td>
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<td>II</td>
<td>2-6-2008</td>
<td>7-8-2008</td>
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<td>27-7-2009</td>
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<td>9-7-2010</td>
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<td>R</td>
<td>7-1-2011</td>
<td>29-4-2010</td>
<td>Approval</td>
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<td>Withdrawal of the Marketing Authorisation in the UK.</td>
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<td>Withdrawal</td>
<td>---</td>
<td>9-11-2010</td>
<td>---</td>
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<td>Deletion of manufacturing sites (including for an active substance, intermediate, or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place or supplier of a starting material, reagent or excipient (when mentioned in the dossier). Change within the range of the currently approved pack sizes.</td>
<td>NL/H/0910/001/IA/012/G</td>
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<td>20-6-2011</td>
<td>20-7-2011</td>
<td>Approval</td>
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Annex I - Renewal of the marketing authorisation

I RECOMMENDATION

Based on the review of the data submitted for this renewal application, the member states are of the opinion that the renewal can be granted with 5 years validity for Finasteride Apotex NL/H/0910/001/R/001 in view on the unresolved safety issue of male breast cancer. The 5-year renewal may be issued provided that the MAH takes into account the requirements made in this report.

Next PSUR
For finasteride a yearly PSUR cycle is mandatory. Next PSUR covering the period 1 September 2010 - August 2011 is expected within 60 days of data lock point.

Proposed common renewal date
The proposed common renewal date is set to 30 April 2011.

II SCIENTIFIC DISCUSSION

II.1 Introduction

Finasteride Apotex is a testosteron-5α-reductase-inhibitor indicated the treatment and control of benign prostatic hyperplasia (BPH) in patients with enlarged benign prostatic hyperplasia (BPH) in patients with an enlarged prostate (prostate volume above ca. 40 ml) for the improvement of their urinary flow and the symptoms associated with BHP, to decrease the incidence of acute urinary retention and lessen the need of surgery.

Finasteride has been approved in the EU through the MRP NL/H/0910/001/R/001 with the Netherlands as RMS. In the Netherlands registration date is 22 June 2006.
For this product Sweden acts as P-RMS within the EU PSUR work-sharing with a harmonised birthdate of April 1998. The next data lock point (DLP) is August 2011. The conclusions of this FAR have been taken into account during current assessment.

For current renewal the MAH submitted the following documents:
- PSUR 2, covering the period 1 September 2007– 31 August 2010, dated 19 October 2010, and signed.
- Summary Bridging Report (SBR) covering the period 31 August 2004– 31 August 2010, dated 19 October 2010, and signed.

The first PSUR, covering the period 31 August 2004 – 31 August 2007, was submitted and assessed previously. That assessment has been taken into account during this renewal procedure.

II.2 Module 1/GMP compliance statements

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

The following documents were submitted
- GMP compliance statements for all manufacturers listed in the application form beside the manufacturers of the active substance
- Declaration of the qualified person as regards the manufacturer of the active substance
- Contact person for pharmacovigilance
- Contact person with the overall responsibility for product defects and recalls
- Contact person for scientific service in charge of information about the medicinal product
II.3 Quality

A chronological list of all post-authorisation submissions since grant of the Marketing authorisation or last renewal: a list of all approved or pending Type IA/IB and Type II variations, Extensions, Art 61(3) Notifications, USR, giving the procedure number (where applicable), date of submission, date of approval (if approved) and brief description of the change. Refer to the table on page 9 for an overview of variations.

Day 55 comments (PL)

3.2.P.5.1
The MAH confirmed that the manufacturing site has implemented the harmonized microbiological requirements and methods in line with Ph. Eur. General Chapters 5.1.4, 2.6.12, 2.6.13 valid from 1st January 2009. The information is adequate. The withdrawal of a batch control site was noticed. The variation is awaited no later than July 2011.

II.4 Clinical efficacy and safety

II.4.1 Clinical Efficacy

No new clinical data have become available during the previous period.

II.4.2 Clinical Safety

II.4.2.1 Summary of Cumulative Experience
N/A

II.4.2.2 Report of Post Marketing Experience 1 August 2004 to 31 August 2010

Worldwide Marketing Authorisation Status
Finasteride Apotex is approved for marketing in 6 European countries and is launched in 5 countries.

Update of regulatory authority or MAH actions taken for safety reasons
The risk of male breast cancer has been discussed at the PhVWP in April 2009, July 2009 and in October 2009. The PhVWP recognised the limitations of the available data but considered that it could not rule out that there was a weak signal of an increased risk of male breast cancer associated with finasteride and that the product information should be updated to reflect the reported cases. The PhVWP also considered the proposals that had been made by the innovator's Marketing Authorisation Holder to further evaluate this issue. The discussions resulted in the recommended wordings concerning breast cancer in section 4.4 and section 4.8.

Due to an ongoing discussion at EU level of possible causal relationship between risk for male breast cancer and use of finasteride, a renewal may be granted for a limited period of 5 years. In addition the FDA requested a SPC update concerning the warning on effects on PSA and prostate cancer detection. The above-mentioned issues are sufficiently covered in the proposed SPC (version October 2010).

Changes to the Reference Safety Information
The Summary of Product Characteristics (SPC) dated 24 January 2007 is used as the Reference Safety Information (RSI) for listing of cases processed prior to 1 January 2010. No changes were performed to the RSI during the period of this report.
The Core Safety Profile (CSP) dated 9 March 2010 is used as the Reference Safety Information (RSI) for listing of cases processed from 1 January 2010 on. This CSP includes the information on male breast cancer. No changes to that RSI were performed during the period January 2010 - August 2010.

**Patient exposure**

Based on sales data and a DDD of 5 mg: patient exposure amounts up to 4.04 million patient days over the period covered by this review period. In PSUR 1: 317,830 patient days and in PSUR 2: 3,725,972 patient days.

No patients were exposed in studies sponsored by the MAH.

**RMS comment:**

_Since this substance has been marketed by many other MAHs in clinical practice the patient exposure is larger. This has been taken into account during current assessment and applies especially concerning the literature._

**Adverse events**

In the period covered by this review report, a total of 10 adverse drug reactions from Health Care Professionals (HCPs) were received.

Of these reactions, seven were serious unlisted, two were serious listed and one was non-serious unlisted. The MAH did not receive any medically unconfirmed case reports.

**Pancreatitis** was identified as an issue for close monitoring following assessment of PSUR 1, based on one publication in the literature including 4 cases¹. However in the period covered by PSUR 2 no further reports concerning pancreatitis were received. The MAH wants to continue close monitoring of pancreatitis.

**Intraoperative floppy-iris syndrome (IFIS)**

During current review period there were 3 cases of IFIS: two reported through the MHRA and one through the literature.

- **Case reference number 2010AP000053** is a case reported through MHRA pertaining to an 81-year old male who experienced fall, hallucinations, lack of coordination and memory loss while using finasteride. Medical history included enlarged prostate, myocardial infarction since 2004, Parkinson’s disease since 2001 and urinary tract infection since 2009. Concomitant medications included Aspirin® (acetylsalicylic acid) for the treatment of post myocardial infarction syndrome since 2004, lansoprazole since 2004, Madopar® (benserazide hydrochloride + levodopa) for the treatment of Parkinson’s disease, ramipril for the treatment of post myocardial infarction syndrome since 2004, simvastatin for the treatment of post myocardial infarction syndrome since 2004 and Neupro® (rotigotine) for the treatment of Parkinson’s disease since 2008. In Nov 2009, the patient was started on finasteride 10mg daily orally for the treatment of enlarged prostate. On an unknown date he experienced fall, hallucinations, lack of coordination and memory loss. The drug was discontinued on unknown date. The events resolved after three days.

- **Case reference number 2009AP001334** is a literature case report received through MHRA pertaining to a 77-year old male who experienced floppy iris syndrome while using finasteride. Medical history included benign prostatic hyperplasia, hypertension, asthma, and gout and cataract surgery. Concomitant medications included atropine 1% topical, bendroflumethiazide for the treatment of hypertension, losartan for the treatment of hypertension, phenylephrine 10% and salbutamol for the treatment of asthma and amiodipine. On unknown date the patient was started on finasteride 5mg daily orally for the treatment of benign prostatic hyperplasia (BPH). Phacoemulsification was performed in the right eye in September 2006. The surgeon anticipated Intraoperative Floppy Iris Syndrome (IFIS) and ordered topical preoperative 10% phenylephrine and 1% atropine. Although the pupil was adequately dilated preoperatively the iris was significantly floppy during the surgery and there was iris prolapse toward the main corneal section and side port. However there were no significant complications. Phacoemulsification was performed in the left eye two months later. Atropine and phenylephrine were used preoperatively but the pupil was significantly

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small (4.5mm) and iris hooks were used. The iris was very floppy intraoperatively but there was no iris prolapse. It was unknown if the drug was discontinued and the event was resolved.

- Case reference number 2009AP001545 is a literature case report received through MHRA pertaining to an 81-year old male who developed intraoperative floppy iris syndrome while receiving finasteride. Medical history included bilateral cataracts, ocular hypertension, myocardial infarction, mild ventricular dysfunction and asthma. Concomitant medication included lisinopril, acetylsalycylic acid, simvastatin and beclometasone. The patient was being treated with finasteride 5mg once a day, for benign prostatic hyperplasia. He was scheduled for cataract surgery. Preoperatively, the visual acuity was 6/12 and the intraocular pressure was increased in both eyes.

Phacoemulsification and posterior chamber intraocular lens (IOL) implantation were performed in the right eye in April 2005. The iris was remarkably floppy during the entire procedure, and there was significant iris prolapse through the main corneal section. A small pupil was observed preoperatively and there was significant iris prolapsed through the main corneal section. The postoperative period was uneventful. In July 2006, phacoemulsification was performed in the left eye. The pupil was very small at the start of the procedure so the surgeon used iris hooks. Postoperative visual acuity improved to 6/6 in the left eye and the intraocular pressure was in normal range for both eyes.

**RMS comment:**
*In line with the conclusions within the PSUR worksharing project the MAH should closely monitor reports of intraoperative floppy iris syndrome (IFIS). In next PSUR the MAH should provide a cumulative overview of the reported cases and present a literature overview.*

Increased creatine phosphokinase level/myalgia.
Case reference number 2009AP000758 is a literature case report pertaining to a 30-year old male who experienced myalgia and increased serum creatine phosphokinase associated with finasteride use. The patient had been taking finasteride 5mg/day for 12 years for male pattern baldness, and had an approximate 10-year history of muscle pain in the legs, thigh and arms which worsened with exercise. The muscle pains worsened in intensity, prompting a visit to his physician; he was found to have an elevated serum creatine kinase level of 10,117 IU/L. Finasteride was discontinued and four weeks later his creatine kinase levels had decreased. About two months later his muscle pains persisted but were less severe. Nerve conduction studies, electromyography and muscle biopsy found no abnormalities. One month later his muscle pains had completely resolved and his creatine kinase (CK) level was 250 IU/L. The author commented: "The temporal relationship between the exposure and response to finasteride withdrawal and the symptom and serum CK resolution implicated finasteride as the cause of the reversible myopathy."

**RMS comment:**
The positive dechallenge and the temporal relationship support possible causality between CK increase and finasteride. However the large patient exposure should be taken into account. Therefore it is considered sufficient that, in line with the conclusions within the PSUR work-sharing project, the MAH should closely monitor reports of elevated CPK and myalgia/rhabdomyolysis and discuss new case reports in next PSUR.

Psychiatric disorders
- Case reference number 2009AP003260 is a case report received through MHRA pertaining to a 56-year old male who experienced aggressive behavior, loss of libido, lack of motivation, and persistent hot flushes while receiving finasteride. Medical history included benign prostatic hyperplasia for which he was treated with tamsulosin hydrochloride from 05-Mar-2009 to 19-Mar-2009. On 08-Apr-2009, the patient was started on finasteride 5mg orally for the treatment of benign prostatic hyperplasia. On 15-Apr-2009 he experienced loss of libido, loss of motivation and aggressive behavior treated with fluoxetine. On an unknown date, he developed persistent hot flushes. On 26 May 2009 the
drug was discontinued. There was an improvement in the mood swings but total loss of libido although otherwise normal sexual functioning. On 26-May-2009, the drug was discontinued. The lack of motivation and hot flushes were not resolved.

The MHRA’s single patient anonymized report mentioned: “The patient will be given a trial of injectable testosterone.”

- Case reference number 2009AP003463 is a case report received from MHRA, pertaining to a 64-year old male who developed unspecified depression while receiving finasteride.

Medical history included unspecified coronary artery disease and benign prostatic hyperplasia. Concomitant medications included Aspirin® (acetylsalicylic acid), diltiazem and simvastatin; all for unspecified coronary disease. On 01-Jan-2009 the patient was started on finasteride 5mg tablets orally once daily for benign prostatic hyperplasia. On 01-Jan-2009 he developed unspecified depression which was treated with citalopram. The drug was discontinued in May-2009 and the event resolved on 30-Jun-2009.

- Rahimi-Ardabili B, Pourandarjani R, Habibollahi P, Mualeki A (2006). Finasteride induced repression: a prospective study. BMC Clin Pharmacol. 2006 Oct 7; 6:7. This study was aimed to examine whether depressive symptoms or anxiety might be induced by finasteride administration. It involved 128 male patients with an average of 25.8 (SD = 4.4) years age suffering from androgenetic alopecia and treated with finasteride 1 mg daily. Depressed mood and anxiety were measured owing to the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS). The mean BDI and HADS depression scores of the patients treated with finasteride increased statistically significantly. Comparative trend was observed for HADS anxiety scores, however the difference was not statistically significant (p = 0.061).

According to the reporter the study confirmed the causal relationship between finasteride and depressive symptoms.


Abstract: The 5-alpha-reductase inhibitor finasteride is used for the treatment of androgenic alopecia, benign prostate hyperplasia and prostate cancer. Besides inhibiting the conversion of testosterone to the biologically more active 5alpha-dihydrotestosterone, it also inhibits the production of neurosteroids. Decreased neurosteroid levels are postulated to be involved in the pathophysiology of psychiatric disorders such as depression. As neurosteroids metabolized by 5-alpha-reductase influence neural plasticity, we investigated whether finasteride treatment alters adult hippocampal neurogenesis, implicated in the pathophysiology of depression. METHODS: Male C57BL/6N mice were treated subchronically (7 days) with finasteride or vehicle. Adult neurogenesis was assessed at two different time points after treatment (day 1; day 35) using immunohistochemistry. RESULTS: Finasteride treatment led to a significant decrease in brain 5alpha-dihydrotestosterone levels and induced a reversible reduction in the number of newborn cells and young neurons in the hippocampus. 35 days after the last finasteride injection, neurogenesis had returned to normal. DISCUSSION: These data indicate that inhibition of 5-alpha-reductase activity by finasteride treatment influences neuronal plasticity on a structural level. These changes might contribute to the pathophysiology of depressive episodes observed after finasteride treatment.

RMS comment:
Taking into account the large worldwide patient exposure of this substance and the very limited case reports received it is considered sufficient that the MAH should closely monitor reports of depression and related events. In the next PSUR the MAH should provide a cumulative overview of the reported cases. This request is in line with the conclusions within the PSUR work-sharing project.

Infertility

This article reported three cases of finasteride-associated male infertility. Case 1 concerns a 31-year-old male patient who had a varicocele diagnosed ten years ago. He had been using finasteride 1mg/day for 2 years for androgenetic alopecia (AGA). His seminal analysis showed 8.2 million sperm/ml with 70% mobility and 7% normal shaped spermatozoa. Before a varicocele repair he was asked to stop finasteride for 4 months. After that period his seminal analysis showed 50 million sperm/ml with 70% mobility and 19% normal shape.

Case 2 concerns a 33-year-old male patient who had small cysts in the head of the epididymis bilaterally and moderate sized left varicocele. For 1 year the patient was taking finasteride 1mg/day for AGA. His seminal analysis showed 30 million sperm/ml with 20% mobility and 15% normal shaped spermatozoa. Following an interruption of finasteride therapy for 3 months his seminal analysis showed 43 million sperm/ml with 42% mobility and 17% normal shape. Case 3 concerns a 32-year-old obese male patient who had been on finasteride 1mg/day for AGA for more than a year. His seminal analysis showed 970,000 sperm/ml, with 30% mobility and 16% normal shaped spermatozoa. Finasteride therapy was interrupted and after 3 months his seminal analysis showed 10 million sperm/ml, 60% mobility and 22% normal shape. Six months after finasteride interruption the analysis showed 7.2 million sperm/ml, with 50% mobility and 22% normal shape.

The authors stressed that 2 patients had varicocele and one patient was obese. They therefore hypothesize that perhaps finasteride does not dramatically change spermatogenesis in healthy men, but in patients with other problems contributing to infertility, the negative influence of finasteride may be amplified.

**RMS comment:**

The proposed SPC (version October 2010) includes impotence, decreased volume of ejaculate, ejaculation disorder and decreased libido as possible ADRs, thus this issue is considered to be sufficiently covered.

In line with the conclusions within the PSUR worksharing project the MAH should perform close monitoring of persistence of erectile dysfunction, infertility or decreased fertility and discuss the new case reports in next PSUR.

Aphalangia possibly linked to unintended use of finasteride during early pregnancy


Case reference number 2009AP003727 is a literature case report pertaining to a female neonate who developed phalangeal agenesis due to transplacental exposure to finasteride. The neonate’s mother was seeing a dermatologist due to male pattern alopecia after her last delivery. Finasteride 1mg was prescribed, and she was warned against pregnancy. However, she did not use contraception because she was breastfeeding and thought she would not become pregnant. Unfortunately, pregnancy was confirmed after a history of six weeks of amenorrhea. Finasteride was stopped immediately. She had six previous healthy children and was not known to have any chronic medical illnesses. The family history was unremarkable for congenital anomalies or genetic diseases. She used no medication other than finasteride and there was no history of radiation exposure. She was counseled about its general and specific teratogenic effects of finasteride during the current pregnancy. Ultrasound examination was performed at 12 weeks of gestation and was unremarkable. A detailed anatomy ultrasound scan at 18 and 26 weeks of gestation found no anomalies. Because the fetus was a female, the mother was reassured. For the rest of her antenatal care, the pregnancy was uneventful. At term, she delivered a baby girl with a normal birth weight. The baby was found to have deformities in the right hand in the form of a small hand with short fingers and absent phalangial bones in all five fingers (aphalangia) and in the left foot in the form of short second and third toes with absent distal phalanges. Two cafe au lait spots were also seen on the back. No other abnormalities could be identified. X-ray examinations of upper and lower limbs confirmed the clinical findings. Abdominal ultrasound examination was unremarkable.
Author Comment: To our knowledge, this is the first case report of finasteride use during pregnancy in a human. It is not clear if these deformities are related to finasteride use in pregnancy, but it is worthwhile to document a possible association and focus attention on the possibility of limb deformities in such cases.

RMS comment:
The proposed SPC (version October 2010) includes pregnancy as contra-indication. In line with the conclusions within the PSUR work-sharing project the MAH should perform close monitoring of case reports concerning the use during pregnancy and their outcomes or events in the SOC Congenital and familial and genetic disorders and present a cumulative overview in next PSUR.

Additionally, in line with the conclusions within the PSUR work-sharing project, the MAH should perform close monitoring of reports of male breast cancer as well as cardiac disorders and discuss new cases in next PSUR.

No other relevant safety or efficacy related information was revealed in the submitted documents.

II.4.2.3 Conclusion on Clinical Safety

The benefit-risk remains positive. Based on the submitted data and/or in line with previous assessment within the PSUR worksharing the MAH should closely monitor:
- persistence of erectile dysfunction, infertility or decreased fertility: discussion of new case reports in next PSUR
- reports of depression and related events: cumulative overview in next PSUR.
- reports of intraoperative floppy iris syndrome (IFIS): cumulative overview of reported cases and literature overview in next PSUR.
- reports of elevated CPK and myalgia/rhabdomyolysis and discuss new case reports in next PSUR
- reports of male breast cancer: discuss new cases in next PSUR.
- reports of cardiac disorders and discuss these cases in next PSUR.
- reports concerning the use during pregnancy and their outcomes or events in the SOC Congenital and familial and genetic disorders: cumulative overview in next PSUR.

II.5 Product information

II.5.1 Summary of Product Characteristics

The proposed SmPC (version October 2010) is in line with the CSP and is adequate. See the separately enclosed PI.

II.5.2 Package leaflet and user testing

Package Leaflet
Some changes are included as suggested by the RMS.

Assessment of User Testing
A user test has been performed during the initial application.

II.6 REMAINING POST-APPROVAL COMMITMENTS TO BE FULFILLED BY THE MAH

The following post-approval commitments are still outstanding:

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### Pharmacovigilance

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<td>The next PSUR (period 1 September 2010 - August 2011) should also be submitted to Swedish regulatory authority (P-RMS).</td>
<td>October 2011</td>
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<td>The following safety issues should be monitored:</td>
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<td>- persistence of erectile dysfunction, infertility or decreased fertility</td>
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<td>- reports of depression and related events:</td>
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<td>- reports of intraoperative floppy iris syndrome (IFIS):</td>
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<td>- use during pregnancy and their outcomes or events in the SOC Congenital and familial and genetic disorders: cumulative overview</td>
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### Quality

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<td>Withdrawal of One specific batch control site</td>
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### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The benefit-risk remains positive. The proposed SPC (version October 2010) is adequate. The RMS accepted the renewal with 5 years validity for Finasteride Apotex NL/H/0910/001/R/001 in view on the unresolved safety issue of male breast cancer. The 5-year renewal may be issued provided that the MAH takes into account the requirements made in this assessment report.

Finasteride participates in the EU PSUR Work-sharing project of the Heads of Medicines Agencies (SE/H/PSUR/0002/004). Within this scheme the PSUR submission is currently yearly due to assessment of the safety issues as indicated in this assessment report.

The next allocated data lock point is August 2011. The next PSUR should be prepared using this data lock point and should be submitted within two months after data lock point. The MAH is requested to participate in this project.