

Public Assessment Report

Scientific discussion

**Dutasteride Apotex 0.5 mg capsules, soft
(dutasteride)**

NL/H/2957/001/DC

Date: 1 June 2015

This module reflects the scientific discussion for the approval of Dutasteride Apotex 0.5 mg capsules, soft. The procedure was finalised on 25 September 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Dutasteride Apotex 0.5 mg capsules, soft from Apotex Europe B.V.

The product is indicated for:

- treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).
- reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.

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

Dutasteride reduces circulating levels of dihydrotestosterone (DHT) by inhibiting both type 1 and type 2, 5 α -reductase isoenzymes which are responsible for the conversion of testosterone to DHT.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Avodart 0.5 mg, soft capsules, which has been registered in Sweden by Glaxo Group Ltd since 19 July 2002. In the Netherlands Avodart 0.5 mg, soft capsules (NL License RVG 28317) were authorised by GlaxoSmithKline on 16 December 2002 through mutual recognition procedure SE/H/0304/001.

The concerned member states (CMS) involved in this application were Belgium, Czech Republic, Luxembourg, Poland and Spain.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Dutasteride Apotex 0.5 mg is a pale yellow, oblong gelatin capsule marked on one side "APO", opposing side "D 0.5", containing an oily, colourless to pale yellow liquid.

The capsules are packed in PVC/PVdC/Al blister packs.

The excipients are:

Capsule contents - glycerol monocaprylocaprate, butylhydroxytoluene (E321)

Capsule shell - gelatin, glycerol, titanium dioxide (E171), iron oxide yellow (E172), titanium dioxide (E171), Opacode red ink.

II.2 Drug Substance

The active substance is dutasteride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or pale yellow powder, which is soluble in methanol and absolute ethanol, but is insoluble in water. Dutasteride incorporates seven chiral centres and shows isomerism. Dutasteride is produced as anhydrous crystalline Form-1.

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 manufacturing process consists of eight steps. No class 1 organic solvents are used in the process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. dutasteride monograph with a tighter limit for assay and with additional tests for identity by HPLC, specific optical rotation, related substances, residual solvents, loss on drying, heavy metals, particle size distribution and polymorphic identity. 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 full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for at least three full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). No trends or changes were seen at both storage conditions. Photostability of the drug substances was confirmed. Based on the results of the stability studies, the claimed retest period of 3 years without any special storage requirements is justified.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described and the choice of excipients is justified and their functions explained. The main development studies concerned the characterisation of the reference product and the performance of comparative dissolution studies. The excipients are well known. The choice of the packaging and manufacturing process are justified. A bioequivalence study has been performed for the drug product versus the reference product Avodart 0.5 mg soft capsules. The test batch used in the bioequivalence study was manufactured according to the finalized composition and process. Sufficient comparative dissolution data have been provided. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps in the manufacturing process are the preparation of the fill material and preparation of the gelatin solution, the encapsulation and the finished product operations. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data have been presented for three full-scale batches of drug product.

Control of excipients

The excipients comply and are tested in accordance with their Ph.Eur. monographs or according to in-house specifications. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, water content, uniformity of dosage units, assay, dissolution, related substances, disintegration, residual solvents and microbial limits. Except for water content and assay the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on five full-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for two full-scale batches 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 batches were stored in PVC-PVdC/Al-blisters. Except for an increase in water content at both storage conditions and a decrease in butylhydroxytoluene after 24 months storage at long-term conditions, no trends or changes were seen in any of the tested parameters. All parameters were within the specified limits. The proposed shelf-life of 24 months and storage conditions 'Store below 30°C' and 'Store in the original package in order to protect from light' is justified. Results from a formal photostability study showed a decrease in butylhydroxytoluene content after direct exposure to light. The blister pack was shown to protect the drug product from light degradation.

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

The only excipient of animal origin in the product is gelatin. For the gelatin used in the drug product 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 confirmed.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dutasteride Apotex 0.5 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dutasteride Apotex is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Avodart 0.5 mg, soft capsules, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Dutasteride Apotex 0.5 mg (Apotex Europe B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Avodart 0.5 mg, soft capsules (GlaxoSmithKline Limited, UK).

The choice of the reference product from the UK in the bioequivalence study has been justified.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy male subjects, aged 18-43 years. Each subject received a single dose (0.5 mg) of one of the 2 dutasteride formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 45 days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.5, 4, 5, 6, 7, 9, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence for dutasteride is considered adequate as the bioavailability of dutasteride is not affected by food. Dutasteride can be taken with or without food, as stated in the SmPC. The wash-out period is justified taking into account the very long half-life of the active substance.

Analytical/statistical methods

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

Dutasteride has a very long elimination half-life (about 65 h) and in accordance with the guideline, AUC_{0-72h} was taken as main variable for the extent of absorption.

Results

Three subjects dropped out: two subjects were withdrawn in Period II because of adverse events and one subject in Period II for protocol violation. Thirty-one subjects completed the study and were included in the analysis.

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

Treatment N=31	AUC _{0-72h} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	72.4 ± 34.0	137.6 ± 99.5	3.27 ± 1.21	3.04 ± 1.15	64 ± 38
Reference	73.6 ± 32.1	141.4 ± 88.8	3.33 ± 1.16	2.87 ± 1.21	65 ± 32
*Ratio (90% CI)	0.99 (0.92 - 1.05)	0.99 (0.90 - 1.09)	0.99 (0.92 - 1.05)	--	--
CV (%)	15.3	21.9	15.6	--	--
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC₀₋₇₂ area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration t_{max} time for maximum concentration t_{1/2} half-life					

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Dutasteride Apotex 0.5 mg is considered bioequivalent with Avodart 0.5 mg, soft capsules.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Dutasteride Apotex.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> • Sexual adverse events-altered (decreased libido, impotence, ejaculation disorders, that may persist after discontinuation of drugs) • Breast disorders (enlargement and tenderness) • Allergic reactions, including rash, pruritus, urticarial localized edema and angioedema • Cardiac failure • Depressed mood
Important potential risks	<ul style="list-style-type: none"> • Cardiovascular events other than cardiac failure • Male breast cancer • High-grade prostate cancer • Interference with formation of external male genitalia in the foetus
Important missing information	<ul style="list-style-type: none"> • Safety of dutasteride therapy in men with severe hepatic impairment • Safety of dutasteride therapy in men with unstable medical conditions

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

The MAH will closely monitor the following topics:

- penile and scrotal disorders. A cumulative review is expected in the next PSUR.
- Stevens Johnson Syndrome (SJS) or Severe Cutaneous Adverse Reaction (SCAR). A discussion is expected in the next PSUR.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Avodart 0.5 mg, soft capsules. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The MAH selected men only, which is accepted in view of the indication.

The PL reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively. The layout and design of the leaflet are also considered acceptable. The readability of the leaflet has been assessed in an appropriate way, using methodology in line with the readability guideline.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dutasteride Apotex 0.5 mg capsules, soft has a proven chemical-pharmaceutical quality and is a generic form of Avodart 0.5 mg, soft capsules. Avodart 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 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 Dutasteride Apotex 0.5 mg capsules, soft with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 September 2014.

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