

Public Assessment Report

Scientific discussion

Dutasteride Aurobindo 0.5 mg, soft capsules (dutasteride)

NL/H/3792/001/DC

Date: 19 September 2017

This module reflects the scientific discussion for the approval of Dutasteride Aurobindo 0.5 mg, soft capsules. The procedure was finalised on 30 March 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

BPH	Benign Prostatic Hyperplasia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SLS	Sodium Lauryl Sulphate
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

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

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 procedure were Belgium, France, Italy, Portugal, Romania, Spain and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Dutasteride Aurobindo is a dull yellow, opaque, oblong shaped, soft gelatin capsule containing clear colourless to pale yellow viscous oil. Each capsule contains as active substance 0.5 mg of dutasteride.

The soft capsules are packed in clear PVC/PVdC–Aluminium foil blister packs and white opaque HDPE bottle packs with polypropylene closure.

The excipients are:

Capsule contents - Glycerol Monocaprylocaprate (Type I) and Butylated Hydroxy Toluene (E321)

Capsule shell - Gelatin (Gelatin 160 Bloom), Glycerol, Titanium Dioxide (E171) and Iron oxide yellow (E172)

II.2 Drug Substance

The active substance is dutasteride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Dutasteride is a white or pale yellow powder. The active substance is freely soluble in methylene chloride, sparingly soluble in anhydrous ethanol and practically insoluble in water. Polymorphic form is not seen as a critical parameter as the drug substance is dissolved.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. It meets the requirements of the monograph in the Ph.Eur. and an additional limit for residual solvents. In addition an in-house method to control residual solvents has been provided. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (six months) and 40°C/75% RH (six months). No significant trends or changes were observed. On the basis of the provided stability data, the claimed retest period of 12 months can be granted.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The same excipients as in the reference product were selected. Pharmaceutical development has been adequately performed.

One bioequivalence study has been performed using Dutasteride Aurobindo 0.5 mg and the originator Avodart 0.5 mg soft capsules. The test batch used in the bioequivalence study was manufactured according to the finalised composition and process. Dissolution profiles of the test and reference batch have been compared in three aqueous media with surfactant sodium lauryl sulphate (SLS). The provided dissolution profiles of the test and reference product batches at three different pH and in the medium proposed for routine dissolution testing (0.1N HCl with pepsin +0.5% SLS) were comparable and support bioequivalence. Dutasteride hardly dissolves in aqueous media without surfactant. The use of enzymes in the dissolution medium has also been adequately justified. In addition the results of the *in vitro* dissolution study with the test and reference product batches used in the bioequivalence study in the different media without a surfactant have been provided and are found to be comparable.

Manufacturing process

The manufacturing process consists of medicament preparation, gelatin mass preparation, encapsulation, drying, polishing and packing. The manufacturing process has been described in sufficient detail. The process is considered to be a non-standard manufacturing process. Process validation of the drug product has been presented for three production scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with their respective Ph.Eur. monographs, except for iron oxide yellow (E172), which complies with the United States National Formulary (USNF) and Regulation 231/2012. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average fill mass, dissolution, uniformity of dosage units, assay, related substances, residual solvents, content of butylated hydroxy toluene, loss on drying, disintegration, identification of titanium dioxide, identification of colourant iron oxide yellow and microbial contamination. Limits in the specification 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 from three commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the drug product has been provided for three full scale batches stored at 25°C/60% RH (12 months), 30°C/65% RH (12 months) and 40°C/75% RH (six months).

When the drug product is stored under accelerated conditions, the dissolution results are discontinued after three months due to significant changes observed for the capsules stored in the HDPE containers, where the batches failed to comply with the proposed limits for dissolution. Therefore a stability study at intermediate conditions has been performed. For the drug product stored in the

proposed packaging at intermediate conditions and long term conditions no significant changes or trends were observed for the tested parameters. When the drug product is stored in HDPE containers under intermediate conditions and long term conditions no significant changes or trends were observed for the tested parameters.

The drug product was shown to be photostable, as no significant changes were observed in the tested parameters when one submission batch was directly exposed to UV and fluorescent light.

The results of the in-use stability study demonstrate the suitability of the drug product in the HDPE containers during actual use. No significant changes or trends were observed in the currently available in-use stability data, comparable results are seen as for the unopened HDPE containers. On the basis of the provided in-use stability data a separate shelf-life after opening is not deemed necessary.

On the basis of the provided stability data, a shelf-life of 24 months when stored below 30°C, store in the original package, can be granted.

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

Gelatine is the only excipient of animal origin used in the drug product. A certificate of suitability issued by the EDQM has 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dutasteride Aurobindo 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 Aurobindo 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 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study

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

The choice of the reference product

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

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

Design

A single-dose, open-label, randomised, two-treatment, two-sequence, two-period cross-over bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 31-45 years. Each subject received a single dose (0.5 mg) of one of the two dutasteride formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 30 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study under fasting conditions to assess bioequivalence for dutasteride is considered adequate. Dutasteride can be taken with or without food, according to the SmPC.

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.

Results

One subject did not show up for period II and was considered a drop-out. Therefore 59 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=59	AUC _{0-t} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	65.5 \pm 31.1	3.57 \pm 1.15	2.0 1.0 - 6.0	76.9 \pm 37.1
Reference	67.1 \pm 31.6	3.67 \pm 1.20	2.0 (1.0 - 5.0)	91.4 \pm 70.9
*Ratio (90% CI)	0.99 (0.94 - 1.04)	0.98 (0.93 - 1.04)	--	--
AUC _{0-t}	area under the plasma concentration-time curve from time zero to t hours			
C _{max}	maximum plasma concentration			
t _{max}	time for maximum concentration			
t _{1/2}	half-life			

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Dutasteride Aurobindo is considered bioequivalent with Avodart.

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 Aurobindo.

Summary table of safety concerns as approved in RMP:

Important identified risks	<ul style="list-style-type: none"> Sexual adverse events of altered (decreased] libido, impotence, ejaculation disorders) and breast disorders (enlargement and tenderness) Allergic reactions, including rash, pruritus, urticaria, localised oedema, 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
Missing information	<p>Safety of dutasteride therapy in:</p> <ul style="list-style-type: none"> Men with severe hepatic impairment Men with unstable medical conditions such as recent myocardial infarction, coronary bypass surgery, unstable angina, cardiac arrhythmias, clinically evident congestive heart failure, or cerebrovascular accident, cancer, or uncontrolled diabetes or peptic ulcer disease.

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Avodart. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Dutasteride Teva 0.5 mg Soft Capsules (Parent PIL-Text) which was approved through a decentralised procedure (EE/H/177-178/DC/001). Another bridging is submitted to compare the lay-out of Dutasteride Aurobindo 0.5 mg, soft capsules with Metoprolol Aurobindo 50 mg and 100 mg film-coated tablets which was assessed and approved during decentralised procedure SE/H/120/001-002/DC. The differences between the PL's were shown to have no significant impact on readability.

The bridging reports submitted by the MAH have been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dutasteride Aurobindo 0.5 mg, soft capsules 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 Aurobindo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 March 2017.

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