CBG MEB

Public Assessment Report

Scientific discussion

Dutasteride Strides 0.5 mg capsules, soft

(dutasteride)

NL/H/3249/001/DC

Date: 17 May 2016

This module reflects the scientific discussion for the approval of Dutasteride Strides 0.5 mg capsules, soft. The procedure was finalised on 18 August 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
PSUR	Periodic Safety Update Report
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP-NF	United States Pharmacopoeia – National Formulary

I. INTRODUCTION

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

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 Spain, France, Italy 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 Strides is a yellow to pale yellow coloured, oblong shaped soft gelatine capsules containing clear oily liquid, with red imprint “0.5”. Each capsule contains as active substance 0.5 mg of dutasteride.

The soft capsule is packed in opaque PVC/PVDC-Aluminium blisters packs and HDPE bottle packs with polypropylene closure.

The excipients are:

Capsule contents
- Glycerol monocaprylocaprate
- Butylhydroxytoluene (E321)

Capsule shell
- Gelatine
- Glycerol
- Glycine
- Citric acid anhydrous
- Titanium dioxide (E171)
- Iron oxide yellow (E172)

Imprinting ink
- Propylene glycol (E1520)
- Iron oxide red (E172)
- Polyvinyl acetate phthalate
- Macrogol 400
- Ammonium hydroxide (E527)

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 slightly hygroscopic, white to off white coloured powder, which is soluble in methanol and absolute ethanol, but is insoluble in water. Dutasteride is polymorphic and has seven chiral centres. The anhydrous crystalline Form-1 is produced. Polymorphism and particle size distribution do not affect the *in vivo* bioavailability since the drug substance is dissolved during the manufacturing process of the drug product.

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 synthesis of dutasteride involves eight stages. The manufacturing process is sufficiently described in the ASMF and the process controls are considered adequate.

Quality control of drug substance
The drug substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three commercial lower and higher scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 8 batches stored at 25°C/60% RH and 40°C/75% RH in accordance with applicable European guidelines. Based on the data submitted, a retest of 4 years, stored not above 25°C, in well closed containers is acceptable.

II.3 Medicinal Product

Pharmaceutical development
The product is a novel pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The excipients are well-known for the manufacture of soft gelatine capsules and present in the innovator product or recently approved generic products. Their function has been explained. The packagings are usual and suitable for oral soft capsules. The pharmaceutical development has been adequately described.
The MAH demonstrated that dutasteride hardly dissolves in aqueous media without surfactant. Dissolution profiles of the test and reference batch have been compared in three aqueous media with surfactant sodium lauryl sulphate. Results were comparable.
A bioequivalence study has been performed using Dutasteride Strides 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 finalized composition and process.

Manufacturing process
The manufacturing process consists of preparation of the capsule fill, preparation of the gelatine paste, encapsulation, drying, wiping, capsule sorting and printing of the capsules before inspection and packaging. in view of the low concentration of active substance, the manufacturing process is considered a non-standard production process. Process validation data on the product have been presented for two batches in accordance with the relevant European guidelines.

Control of excipients
All excipients are controlled in accordance with Ph.Eur. monographs, except iron oxide and the printing ink. The iron oxide is controlled according to the USP-NF monograph and the printing ink has an in-house specification. The quality control of the Opacode WB Red ink is acceptable. The individual components comply with Ph.Eur. or NF where applicable. The specifications are acceptable.

Quality control of drug product
The product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for identification, uniformity, microbial limits, loss on drying of the shell, moisture content, disintegration time, dissolution, related substances, assay and residual solvent. 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 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided from two batches at long term (25°C/60% RH; 36 months) and accelerated conditions (40°C/75% RH; 6 months) in accordance with applicable European guidelines. The capsules were packed in both PVC/PVDC/Al blisters and HDPE tablet containers. As the product concerns a conventional dosage form (immediate release solid dosage form) and the active substance is known to be stable, stability testing with two batches is sufficient for approval. Photostability studies demonstrated that the active substance is not photosensitive. On basis of the data submitted, a shelf life was granted of 3 years, when not stored above 30°C.

Results of a 90-day in-use stability study showed no difference in stability between the closed- and in-use products; therefore an in-use shelf-life is not required.

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 Strides 0.5 mg capsules, soft 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 Strides 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 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Dutasteride Strides 0.5 mg capsules, soft (Strides Arcolab International Ltd, UK) is compared with the pharmacokinetic profile of the reference product Avodart 0.5 mg soft capsules (GlaxoSmithKline, Hungary).

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
An open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, comparative bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 30-44 years. Each subject received a single dose (0.5 mg) of one of the 2 dutasteride formulations. The capsules were orally administered in solid form 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 0.33, 0.67, 1, 1.33, 1.67, 2.0, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 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
Three subjects were withdrawn due to adverse events. One subject was withdrawn due to elevated plasma concentrations in Period II. 40 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=40	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	47.7 ± 25.1	2.64 ± 0.89	2.33 (1.0 – 4.5)
Reference	50.7 ± 26.1	2.74 ± 1.03	2.0 (1.0 – 5.0)
***Ratio (90% CI)**	0.94 (0.90 – 0.97)	0.98 (0.92 - 1.04)	--

CV (%)	10.1	17.0	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

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

Summary table of safety concerns as approved in RMP:

Important identified risks	• Sexual adverse events of altered [decreased] libido, impotence, ejaculation disorders) that may persist after drug discontinuation • Breast disorders (enlargement and tenderness) • Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema • Cardiac failure • Depressed mood
	• 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	Safety of dutasteride therapy in: • 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.

The MAH will closely monitor the following topics:

- male breast cancer. A discussion of this topic, especially with focus on the duration of exposure to dutasteride in relation to occurrence of breast cancer is expected in the next PSUR.
- 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 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 4 participants, followed by two rounds with 10 participants each. The questionnaire contained 16 questions specific to Dutasteride Strides and 3 specific to the format of the package leaflet. The questions addressed all the key safety issues and concerns of Dutasteride Strides. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dutasteride Strides 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 Strides soft capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 August 2015.

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
Submission of a new Ph.Eur. certificate of suitability from an already approved manufacturer	NL/H/3249/ 001/IA/001	IA	17-2-2016	7-3-2016	Approval	No