COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Finasteride Aristo 5 mg, film-coated tablets (finasteride)

NL/H/5516/001/DC

Date: 9 April 2024

This module reflects the scientific discussion for the approval of Finasteride Aristo 5 mg film-coated tablets. The procedure was finalised on 14 May 2023. 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
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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Finasteride Aristo 5 mg, film-coated tablets, from Aristo Pharma GmbH.

The product is indicated for the treatment and control of benign prostatic hyperplasia (BPH). To reduce the incidence of acute urinary retention and reduce need for surgery including transurethral resection of the prostate (TURP) and prostatectomy. The product should only be administered in patients with an enlarged prostate (prostate volume above ca. 40 ml).

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator (reference) product Proscar 5 mg, film-coated tablets which has been registered in the Netherlands via national procedure (RVG 15482) since 1992.

The concerned member states (CMS) involved in this procedure were Austria, Czechia, Germany, Italy, Spain and Portugal. During the clock-stop the application has been withdrawn in CMSs Denmark, Norway and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Finasteride Aristo is a film-coated tablet. It is a blue colour, round shaped tablet with a diameter of 6.5 mm, debossed with 'H' on one side and '37' on the other side. One tablet contains 5 mg of finasteride.

The excipients are:
Tablet core - lactose monohydrate (E460), microcrystalline cellulose (PH 102), maize starch, (pregelatinised, 1500), sodium starch glycolate (Type A), docusate sodium and magnesium stearate (E572).
Film-coating - hypromellose (type 2910 6cP, E464), titanium dioxide (E171), indigo carmine aluminium lake (E132), talc (E553b) and iron oxide yellow (E172).

The film-coated tablets are packed in aluminium-polyvinyl chloride/polyethylene/polyvinylidene chloride (Alu-PVC/PE/PVDC) blisters.

II.2 Drug Substance

The active substance is finasteride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white, or almost white crystalline powder. Finasteride is practically insoluble in water, and freely soluble in methanol and methylene chloride.

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 and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for nine full-scaled batches.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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 MAH has performed a bioequivalence study with one batch of the proposed drug product against one batch of the same strength of the reference product. The biobatches used for the bioequivalence study are acceptable. Comparative dissolution profiles in buffer at three different pH and in the QC dissolution method demonstrate that the *in vitro* dissolution of both proposed and reference products is similar.

Manufacturing process

The manufacturing process consists of preparing a dry mix with pre-weighted, sifted drug substance and excipients, followed by granulation, drying, milling, (pre-)lubrication, compression, coating and packing. The narrative of the manufacturing has been adequately described. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing. Process

validation data on the product have been presented for two commercial batches of the minimum and the maximum commercial size batches in accordance with the relevant European guidelines. All results are found within the proposed limits. A protocol for the validation of the remaining commercial batch sizes has been included and is acceptable. The proposed holding time of the bulk capsules is acceptable in view of the data provided

Control of excipients
The excipients comply with Ph.Eur. requirements. 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 mass, water content, uniformity of dosage unit, dissolution, assay, related substances, identification of colourants and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial batches of the minimum and maximum batch sizes 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 for three commercial scaled batches of the minimum batch size stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guideline. Photostability studies were performed as per ICH Q1B on one commercial batch demonstrating that the product is stable when exposed to light. The crystalline form 1 has been found to be stable and well maintained in the active substance and the drug product subjected to long-term stability condition. On the basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Finasteride Aristo 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 Finasteride Aristo is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Proscar which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Finasteride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one BE study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Finasteride Aristo 5 mg, film-coated tablets (Aristo Pharma GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Proscar 5 mg, film-coated tablets (N.V. Organon, Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. Comparative dissolution profiles in 0.1 HCl, 4,5 pH acetate buffer and 6.8 pH phosphate buffer, and in the QC dissolution method demonstrate that the *in vitro* dissolution of both proposed and reference products is similar. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover open-label bioequivalence study was carried out under fasted conditions in 26healthy male subjects, aged 19-38 years. Each subject received a single dose (5 mg) of one of the two finasteride formulations. The tablet was orally administered with 240 mL water after overnight fasting of at least 10 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24 and 36 hours after administration of the products.

The design of the study is acceptable.

Finasteride may be taken 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."

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

28 subjects enrolled in the study. Two subjects did not report in period II before dosing. 26 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of finasteride, 5 mg under fasted conditions.

Treatment N=26	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	351.69 ± 76.64	368.11 ± 87.56	43.57 ± 7.68	2.5 (1.0-4.5)
Reference	376.33 ± 105.34	395.80 ± 127.72	45.32 ± 8.10	2.5 (1.0-4.5)
***Ratio (90% CI)**	0.95 (0.91 – 0.98)	0.95 (0.91 – 0.98)	0.96 (0.92 – 1.00)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Finasteride Aristo 5 mg is considered bioequivalent with Proscar 5 mg.

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 Finasteride Aristo.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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 Proscar. 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 language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Finasteride Aristo 5 mg, has a proven chemical-pharmaceutical quality and is a generic form of Proscar 5 mg. 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 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 Finasteride Aristo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 May 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5516/001/IB/001	**Type IB: C.I.z** Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products	Yes	16-01-2024	Approved	N/A