COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dutasteride Sandoz 0.5 mg, soft capsules (dutasteride)

NL/H/5237/001/DC

Date: 21 August 2025

This module reflects the scientific discussion for the approval of Dutasteride Sandoz 0.5 mg, soft capsules The procedure was finalised at 27 July 2016 in Malta (MT/H/0190/001/DC). After a transfer on 23 June 2020, the current RMS is the Netherlands. For information on changes after the finalisation 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 Dutasteride Sandoz 0.5 mg, soft capsules, from Sandoz 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. For information on effects of treatment and patient populations studied in clinical trials, please see section 5.1 of the SmPC*.*

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

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

II. QUALITY ASPECTS

II.1 Introduction

Pharmaceutical form:	*Capsules, soft*
Formulation:	*Active Ingredient:* Dutasteride *Capsule contents:* Butylhydroxytoluene (E321) Glycerol monocaprylocaprate (type I) *Capsule shell:* gelatin glycerol titanium dioxide (E171), yellow iron oxide (E172), *Other ingredients:* triglycerides,medium chain lecithin (may contain soya oil) (E322) water, purified
Container system*:*	White opaque PVC/PVDC – Aluminium blisters containing 10, 30, 40, 50, 60, 80, 90, 100 or 120 capsules.

II.2 Drug Substance

The active substance, Dutasteride, is an established active substance which is now described in the European Pharmacopoeia. A European Pharmacopoeia monograph for dutasteride has

been implemented in the 8th edition of the Ph. Eur. in January 2014. The drug substance is practically insoluble in water, freely soluble in methylene chloride and soluble of sparingly soluble in anhydrous ethanol.

II.3 Medicinal Product

Pharmaceutical development
The development of Dutasteride Sandoz was aimed to develop a generic pharmaceutical product of a 0.5 mg soft capsule of dutasteride as drug substance essentially similar, in terms of physico-chemical characteristics and bioavailability, to the reference product Avodart 0.5 mg soft capsules by GlaxoSmithKline UK Limited registered in the UK since 17 January 2003 (PL 19494/0006).

The drug product is a soft gelatin capsule presented as oblong soft gelatine capsules, opaque, yellow, containing an oily and yellowish liquid. The excipients and packaging materials used for the drug product are well known. The development of the product has been described, the choice of excipients is justified and their functions explained.

Manufacturing process
Given the low content of drug substance, the finished product is considered a specialised dose form and the manufacturing process is considered non-standard. Manufacturing process validation data on three production scale batches have been provided. The manufacturing process is considered to be validated.

Quality control of drug product
The finished product specifications control the quality of the product. Batch analysis data has been provided and CoA's have been provided for batches of finished product manufactured by the finished product manufacturing sites.

Stability of drug product
The stability data provided support the proposed shelf life of 36 months.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to the finished product are of sufficient quality in view of the present European regulatory requirements.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of dutasteride are well known. As Dutasteride is a well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Dutasteride Sandoz 0.5 mg, soft capsules 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.3 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data has been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dutasteride is a well-known active substance and since this product has been shown to be essentially similar and refer to a product approved based on a full application, no additional clinical data is need. Thus, the submitted overview based on scientific literature is acceptable. For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

This was a single dose crossover comparative oral bioavailability study to establish comparative bioequivalence of Dutasteride Sandoz 0.5 mg, soft capsules (Sandoz B.V., the Netherlands) vs Avodart 0.5mg capsules (Catalent France Beinheim SA France) in 24 healthy, adult, male human subjects (aged between 18-55 years) under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Dutasteride 0.5mg.

The results are shown below in Table 1 and 2.

Table 1 Summary of Assessment bioequivalence studies (1)

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	2653.52	37.5	2576.16	37.3
ln (C_{max})	7.8200	4.6	7.7861	4.9
T_{max} (hours) *	2.00	42.1	2.33	31.5
AUC_{0-72} (pg·h/mL)	45990.77	53.1	47480.38	53.7
ln (AUC_{0-72})	10.6065	5.0	10.6408	4.8
AUC_{∞} (pg·h/mL)	72926.55	88.4	73863.29	79.5
ln (AUC_{∞})	10.9420	6.4	10.9648	6.4
$AUC_{0-72/\infty}$ (%)	71.26	18.5	72.69	18.3
K_{el} (hours^{-1})	0.0170	44.9	0.0173	38.0
$T_{½el}$ (hours)	48.54	44.5	46.58	42.7

* median is presented

Table 2 Summary of Assessment bioequivalence studies (2)

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	14.1	2487.03	2413.35	103.05	95.95	110.68
AUC_{0-72}	6.6	40238.75	41911.56	96.01	92.86	99.26

* units are pg/mL for C_{max} and pg·h/mL for AUC_{0-72}

The 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters, AUC0-72 and Cmax were within 80-125% acceptance range for Dutasteride. This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **).

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study, Dutasteride Sandoz 0.5 mg, soft capsules is considered bioequivalent with Avodart 0.5mg capsules.

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 Sandoz 0.5 mg, soft capsules.

- Summary table of safety concerns as approved in RMP

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

Routine PhV is enough to manage the risks of dutasteride. No additional risk minimisation measures are proposed by the applicant.

V. USER CONSULTATION

A full readability testing results were submitted in Seq000, Module 1.3.4 for the leaflet of Dutasteride Sandoz 0.5 mg, soft capsules (Lead procedure: MT/H/0170/001/DC). The full Patient Information Leaflet (PIL) user testing was performed by a hired company, Altiex Life s.r.o. (Nám. 14. října 2/1307, 150 00 Prague 5, Czech Republic) on behalf of the Applicant (Sandoz B.V., the Netherlands). The performed user testing was successful and considered approvable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Dutasteride Sandoz 0.5 mg, soft capsules contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

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
MT/H/0190/001/IB/001/G	Change in the (invented) name of the medicinal product for Nationally Authorised Products Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use • Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	Yes No	15-4-2017	Approved	N.A.
MT/H/0190/001/IA/002	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site	No	15-5-2017	Approved	N.A.
MT/H/0190/001/IB/003	Change in the (invented) name of the medicinal product for Nationally Authorised Products	Yes	15-5-2017	Approved	N.A.
MT/H/0190/001/II/004	Other variation	No	7-3-2019	Approved	N.A.
MT/H/0190/001/IB/005	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient	No	28-6-2019	Approved	N.A.

	European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph: • Updated certificate from an already approved manufacturer				
MT/H/0190/001/II/006	Change in the batch size (including batch size ranges) of the finished product • The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	No	21-5-2020	Approved	N.A.
NL/H/5237/001/IB/007	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product • Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	18-11-2020	Approved	N.A.
NL/H/5237/001/R/001	Renewal	No	31-12-2020	Approved	N.A.
NL/H/5237/001/IB/008	Change in test procedure for the finished product • Other changes to a test procedure (including replacement or addition): Addition of conditions to a test procedure.	No	11-2-2021	Approved	N.A.
NL/H/5237/001/IB/009	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of	No	11-2-2021	Approved	N.A.

	Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient • New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer				
NL/H/5237/001 /IA/010	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer	No	20-3-2021	Approved	N.A.
NL/H/5237/001 /IA/012	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer	Yes	1-6-2021	Approved	N.A.

	responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)).				
NL/H/5237/001 /IA/011	Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a manufacturer responsible for importation and/or batch release: Not including batch control/testing	Yes	10-6-2021	Approved	N.A.
NL/H/5237/001 /IA/013/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • Updated certificate from an already approved manufacturer European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient • New certificate for a	No	20-2-2022	Approved	N.A.

	starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer				
NL/H/5237/001 /IA/014/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site • Primary packaging site Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a manufacturer responsible for importation and/or batch release: Not including batch control/testing	No Yes	10-10-2023	Approved	N.A.
NL/H/5237/001 /IA/015	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient • Updated certificate from an already	No	2-11-2023	Approved	N.A.

	approved manufacturer				
NL/H/5237/001 /IA/017/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site	No	1-7-2024	Approved	N.A.
NL/H/5237/001 /IA/019	Change to importer, batch release arrangements and quality control testing of the finished product Replacement or addition of a site where batch control/testing takes place	No	30-9-2024	Approved	N.A.
NL/H/5237/001 /IA/018/G	Change in the name and/or address of the marketing authorisation holder	Yes	30-10-2024	Approved	N.A.
NL/H/5237/001 /WS/020	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products. Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a site where batch control/testing takes place	No No	8-1-2025	Approved	N.A.
NL/H/5237/001 /IA/022/G	Change in the specification parameters and/or limits of the immediate packaging of the finished product Deletion of a non-significant specification parameter (e.g.	No	27-1-2025	Approved	N.A.

	deletion of an obsolete parameter)				
NL/H/5237/001 /IA/021	Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a manufacturer responsible for importation and/or batch release: Including batch control/testing	Yes	3-2-2025	Approved	N.A.
NL/H/5237/001 /IA/023/G	Change in the name and/or address of the marketing authorisation holder	Yes	17-3-2025	Approved	N.A.
NL/H/5237/001 /WS/024	Change in description and composition of the Finished Product • Other variation: correction of typographical errors in product information	Yes	26-6-2025	Approved	N.A.