

Public Assessment Report

Scientific discussion

**Dutasteride/Tamsulosinehydrochloride Teva 0.5
mg/0.4 mg, hard capsules**

(dutasteride/tamsulosin hydrochloride)

NL/H/4492/001/DC

Date: 24 September 2019

This module reflects the scientific discussion for the approval of Dutasteride/Tamsulosinehydrochloride Teva 0.5 mg/0.4 mg, hard capsules. The procedure was finalised at 31 July 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
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/Tamsulosinehydrochloride Teva 0.5 mg/0.4 mg, hard capsules from Teva 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 Combodart 0.5 mg/0.4 mg, hard capsules (NL licence RVG 104130). Combodart is authorised in the Netherlands by GlaxoSmithKline B.V through DE/H/2251/001/DC since 3 May 2010. Duodart 0.5 mg/0.4 mg hard capsules used for the bioequivalence studies has been registered in Germany by GlaxoSmithKline GmbH & Co.KG since 21 May 2010.

The concerned member states (CMS) involved in this procedure were Spain and Portugal.

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

II. QUALITY ASPECTS

II.1 Introduction

Dutasteride/Tamsulosinehydrochloride Teva is an oblong hard capsule with brown body and orange cap printed with C001 in black ink.

Each capsule contains:

- One oblong soft gelatine capsule of dutasteride of light yellow colour, filled with transparent liquid. The soft gelatin capsule contains as active substance 500 mg of dutasteride.
- Approximately 183.8 mg of modified release tamsulosin pellets with white to off white colour. The tamsulosin hydrochloride amount per capsule is 0.4 mg.

The hard capsules are packed in HDPE bottle with silica gel desiccant contained in the polypropylene cap.

The excipients are:

Hard capsule shell

- Black iron oxide (E172)
- Red iron oxide (E172)
- Titanium dioxide (E171)
- Yellow iron oxide (E172)
- Gelatin
- Black ink (shellac, black iron oxide (E172), propylene glycol, ammonia solution, concentrated, potassium hydroxide)

Content of dutasteride soft capsules

- Propylene glycol monocaprylate, type II
- Butylhydroxytoluene (E321)
- Gelatin
- Glycerol
- Titanium dioxide (E171)
- Triglycerides (medium chain)
- Lecithin (may contain soya oil)

Content of tamsulosin pellets

- Methacrylic acid - ethyl acrylate copolymer 1:1 dispersion 30 per cent (contains sodium laurilsulfate and polysorbate 80)
- Cellulose microcrystalline
- Dibutyl sebacate
- Polysorbate 80
- Silica colloidal hydrated
- Calcium stearate

II.2 Drug Substances

The active substances are dutasteride and tamsulosin hydrochloride, established active substances described in the European Pharmacopoeia (Ph.Eur.). Dutasteride is a white or pale yellow powder. The active substance is practically insoluble in water. The manufacturing process consistently yields the anhydrous form of dutasteride (Form I). Tamsulosin hydrochloride is a white or almost white powder. It is slightly soluble in water. No polymorphs are reported. No racemisation was observed on stability.

The CEP procedure is used for both active substances. 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

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substances

The active substance specifications are considered adequate to control the quality and meet the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with these specifications have been provided for three batches for each active substance.

Stability of drug substances

Dutasteride is stable for two years when stored under the stated conditions. Tamsulosin hydrochloride is stable for three 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 shell and the filling of the dutasteride soft gelatin capsules were optimized, as well as the tamsulosin modified release pellets. The development of the final product has been described as well, the choice of excipients is justified and their functions explained.

For this generic application, the MAH has submitted the synopsis of two exploratory pilot bioavailability studies. In these studies tamsulosin capsules were compared. As this application concerns a different formulation, i.e. dutasteride/tamsulosin capsules, these studies will not be further discussed. Furthermore the MAH submitted three pivotal studies (fasting conditions, study ZNV-P0-421; fed conditions, study ZNV-P2-465, and a multiple dose study ZNV-P7-519), which are discussed in the clinical section (IV).

Manufacturing process

The manufacturing process consists of three parts:

- The manufacture of dutasteride soft capsules consists of the following steps: preparation of gelatin mass, preparation of solution (filler solution), encapsulation, drying, and packing.
- The manufacture of the tamsulosin pellets consists of the following steps: Manufacture of matrix pellets and manufacture of enteric film-coated pellets.
- In the final part of the process one dutasteride soft capsule and the required quantity of tamsulosin pellets are filled in a hard capsule and finally packaged.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale

batches. Additionally, process validation for six production and pilot batches of both dutasteride soft capsules and tamsulosin pellets has been completed.

Control of excipients

All excipients comply with Ph.Eur. except propylene glycol monocaprylate and lecithin, which both comply with the National Formulary (NF). 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 capsule appearance, dutasteride identification, tamsulosin identification, uniformity of dosage units for both drug substances, assay for both drug substances, dissolution for both drug substances, BHT identification, BHT assay, disintegration, loss on drying of the soft shell capsule, water content of the tamsulosin pellets, degradation products, and microbial control. The release and shelf life specifications are identical except for loss on drying of the soft shell capsule, and total impurities. 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 four batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three full scale batches and one pilot scale batch stored at 25°C/60% RH (24 months), 30°C/75% RH (12 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are in accordance with the ICH stability guideline. The proposed shelf-life of 24 months and storage condition (store below 30°C) are acceptable. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

In use stability data has been provided demonstrating that the stability of the drug product is not impacted by opening and closing of the container and no separate in-use shelf-life is required.

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

Scientific data and/or 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 satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dutasteride/Tamsulosinehydrochloride Teva 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/Tamsulosinehydrochloride Teva 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 Combodart 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/Tamsulosinehydrochloride Teva 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.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Dutasteride/Tamsulosinehydrochloride Teva 0.5 mg/0.4 mg hard capsules (Teva

B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Duodart 0.5 mg/0.4 mg prolonged release capsules (GlaxoSmithKline, Germany).

As the application concerns a prolonged release capsule with regard to tamsulosin, a single dose study under fasting and fed conditions and a multiple dose study has been submitted, which is in accordance with the guidelines. In the multiple dose study only tamsulosin has been evaluated, as tamsulosin is the prolonged release component in the capsule, which is acceptable.

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.

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.

Bioequivalence studies

Study ZNV-P0-421: Single dose study under fasting conditions

Design

A single-dose, two-period, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 19-68 years. Each subject received a single dose (0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 21 days.

For dutasteride, blood samples were taken pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 48 and 72 hours after administration of the products. For tamsulosin, blood samples were taken pre-dose and at 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Results

All 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=48	AUC _{0-t} (ng.h/ml)	C _{max} (ng/ml)	t _{max} (h)
Test	48.1 \pm 20.7	2.5 \pm 0.7	3.5 (1.67 – 10.0)
Reference	51.0 \pm 23.2	2.7 \pm 0.8	2.5 (1.0 – 5.5)
*Ratio (90% CI)	0.94 (0.91 - 0.98)	0.92 (0.88 - 0.97)	--
CV (%)	11.2	15.7	--
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 CV coefficient of variation			

**In-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{\max} (median, range)) of tamsulosin under fasted conditions.

Treatment N=48	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	C _{max} (ng/ml)	t _{max} (h)	t _{1/2} (h)
Test	202 \pm 74	206 \pm 79	15.3 \pm 3.7	5.0 (2.5 – 7.0)	11.3 \pm 2.5
Reference	197 \pm 63	201 \pm 67	14.1 \pm 3.4	5.0 (2.5 – 7.0)	11.4 \pm 2.7
*Ratio (90% CI)	1.01 (0.96 – 1.06)	1.01 (0.96 – 1.06)	1.08 (1.03 – 1.14)	--	--
CV (%)	14.5	14.6	15.7	--	--
AUC _{0-∞} 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 t hours C _{max} maximum plasma concentration t _{max} time for maximum concentration t _{1/2} half-life CV coefficient of variation					

**In-transformed values*

Study ZNV-P2-465: Single dose study under fed conditions

Design

A single-dose, two-period, crossover bioequivalence study was carried out under fed conditions in 72 healthy male subjects, aged 18-67 years. Each subject received a single dose (0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride) of one of the two active substance formulations. The tablet was orally administered with 240 ml water 30 minutes

after the start of a high fat high calorie breakfast. There were two dosing periods, separated by a washout period of 21 days.

For dutasteride, blood samples were taken pre-dose and at 0.5, 1, 1.5, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 14, 16, 24, 48 and 72 after administration of the products.

For tamsulosin, blood samples were taken pre-dose and at 1.5, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Results

Two subjects withdrew consent before period-II for personal reasons. Two subjects were withdrawn as the subjects did not consume the complete breakfast. One subject was withdrawn due to non-compliance. And one subject was withdrawn due to a positive opiate result. Therefore 66 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of dutasteride under fasted conditions.

Treatment N=48	AUC _{0-t} (ng.h/ml)	C _{max} (ng/ml)	t _{max} (h)
Test	46.1 \pm 23.2	2.1 \pm 0.8	5.5 (2.0 – 24.0)
Reference	45.5 \pm 23.3	2.1 \pm 0.9	5.3 (2.0 – 24.0)
*Ratio (90% CI)	1.02 (1.00 - 1.04)	1.04 (0.98 – 1.11)	--
CV (%)	7.8	22.4	--
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 CV coefficient of variation			

**In-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of tamsulosin under fasted conditions.

Treatment N=48	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	C _{max} (ng/ml)	t _{max} (h)	t _{1/2} (h)
Test	198 \pm 89	198 \pm 83	10.8 \pm 3.6	7.5 (4.5 – 24.0)	11.8 \pm 2.8
Reference	203 \pm 94	204 \pm 91	10.4 \pm 3.6	8.0 (4.5 – 24.0)	11.8 \pm 2.9
*Ratio (90% CI)	0.98 (0.93 – 1.03)	0.98 (0.36 – 1.03)	1.05 (0.99 – 1.11)	--	--

CV (%)	16.4	16.0	20.6	--	--
AUC_{0-∞}	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 t hours				
C_{max}	maximum plasma concentration				
t_{max}	time for maximum concentration				
t_{1/2}	half-life				
CV	coefficient of variation				

**In-transformed values*

Study ZNV-P7-519: Multiple dose study under fed conditions

Design

A multi-dose, two-period, crossover bioequivalence study was carried out under fed conditions in 72 healthy male subjects, aged 18-62 years. Each subject received for seven days a single dose (0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride) of both two active substance formulations. The tablet was orally administered with 240 ml water 30 minutes after the start of a high fat high calorie breakfast. There were two dosing periods, separated by a washout period of 21 days.

For tamsulosin, blood samples were taken pre-dose at day 5, 6 and 7 and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 18 and 24 hours after administration of the products.

The design of the study is acceptable. As the capsule should be taken with food, the fed state in the multiple dose study is adequate.

Results

Six subjects withdrew consent for personal reasons. One subject was withdrawn as the subject did not consume the complete breakfast at day 7. One subject was withdrawn due to dosing at day 6 with the wrong product. One subject was withdrawn for safety reasons. Furthermore one subject was excluded due to significant gastro-intestinal events within ten hours of dosing. Therefore 62 subjects were eligible for pharmacokinetic analysis.

Table 5. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=62	AUC_τ (ng.h/ml)	C_{max} (ng/ml)	C_{tau,ss} (ng/ml)	T_{max} (h)	PTF% (%)
Test	170 ± 74	13.2 ± 4.6	4.6 ± 3.0	6.0 (3.0 – 12.0)	143 ± 52
Reference	162 ± 66	12.3 ± 4.4	4.6 ± 2.7	6.0 (3.0 – 24.0)	133 ± 42
*Ratio (90% CI)	1.05 (1.01 - 1.09)	1.08 (1.03 – 1.114)	0.98 (0.91 – 1.04)	--	--
CV (%)	13.0	16.5	22.4	--	--

AUC_τ	area under the plasma concentration-time curve over the dosing interval
C_{max}	maximum plasma concentration
C_{max,ss}	concentration at the end of the dosing interval at steady state
PTF%	fluctuation index
CV	coefficient of variation

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞}, AUC_τ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Dutasteride/Tamsulosinehydrochloride Teva is considered bioequivalent with Duodart.

The MEB has been assured that the bioequivalence studies have 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/Tamsulosinehydrochloride Teva.

Table 6. 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 disorder) that may persist after discontinuation of drug • Breast disorders (enlargement and tenderness) • Cardiac failure • Depressed mood <p><u>Associated with tamsulosin</u></p> <ul style="list-style-type: none"> • SJS, dermatitis exfoliative and erythema multiforme • Priapism
Important potential risks	<ul style="list-style-type: none"> • Cardiovascular events (other than cardiac failure) including atrial fibrillation, tachycardia, arrhythmias associated with tamsulosin. • Male breast cancer • High-grade prostate cancer • Interference with formation of external

	male genitalia in foetus
Missing information	<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 Combodart. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies 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 Duodart (content; DE/H/2251-2252/001/DC) and Youzain 600 mg and 800 mg film-coated tablets (design, layout, and style of writing; DE/H/4454-4456/001-002/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dutasteride/Tamsulosinehydrochloride Teva 0.5 mg/0.4 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Combodart 0.5 mg/0.4 mg prolonged release capsule. Combodart 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/Tamsulosinehydrochloride Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 31 July 2019.

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