Public Assessment Report
Scientific discussion

Dutasteride/Tamsulosin Teva 0.5 mg/0.4 mg Hard Capsules

Dutasteride
Tamsulosin Hydrochloride

ES/H/0465/001/DC

Applicant: Laboratorios Liconsa S.A.

This module reflects the scientific discussion for the approval of **Dutasteride/Tamsulosin Teva 0.5 mg/0.4 mg Hard Capsules**. The procedure was finalised on July 2018. For information on changes after this date please refer to the module 'Update'.

INTRODUCTION

This decentralised procedure application concerns a fixed dose combination of Dutasteride/Tamsulosin hydrochloride under Dutasteride/Tamsulosin Teva 0.5 mg/0.4 mg Hard Capsules trade name.

The Marketing Authorisation Aplication has been submitted according to the Article 10b of Directive 2001/83/EC, as amended, i.e. fixed dose combination-FDC.

Safety and efficacy of the applied fixed dose combination product is based on the information of both individual components, the experience of its concomitant use, which is recognised in the SmPC of Avidart® (dutasteride reference product), and the accepted clinical use of both active substances. In addition, the Applicant submits bioequivalence studies for demonstration of bioequivalence of the applied product to the existing individual components (Avidart® + Omnic®). All this information is considered adequate to support the requested application.

The Concerned Member States involved in this procedure are AT, BG, EE, LV, PL.

The approved indications are:

- Treatment is indicated in patients already controlled with tamsulosin and dutasteride given concurrently at the same level to appropriately control the 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.

The recommended dose of Dutasteride/Tamsulosin is one capsule (0.5 mg/ 0.4 mg) taken orally approximately 30 minutes after the same meal each day.

A comprehensive description of the product information is given in the SmPC.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Reference Member State has granted a marketing authorisation for Dutasteride/Tamsulosin Teva 0.5 mg/0.4 mg Hard Capsules.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Active substances

The drug product contains dutasteride and tamsulosin hydrochloride as drug substances.

A Ph. Eur. Certificate of Suitability has been submitted to support the quality of each active substance.

Control of the drug substances by the drug product manufacturer is acceptable.

Finished product

Description of the product

Dutasteride/Tamsulosin 0.5 mg/0.4 mg hard capsules are oblong hard capsules number 0 with brown body and orange cap printed with C001 in black ink.

Each hard capsule contains:

- one oblong soft gelatine capsule of dutasteride of light yellow colour.
- tamsulosin modified release pellets of white to off white colour.

The composition of the product is clearly stated.

The product is packed in HDPE bottles with silica gel desiccant contained in the polypropylene cap.

Pharmaceutical development

The development of the product has been described for each of the individual components (dutasteride soft capsules and tamsulosin modified release pellets) and for the final drug product (dutasteride/tamsulosin 0.5 mg/0.4 mg hard capsules).

The function of the key excipients has been extensively discussed. The pharmaceutical development has been adequately described.

Manufacture of the product and process controls

The manufacturing process is sufficiently described and the in-process controls are appropriate, considering the nature of the product and the manufacturing method.

The dossier includes sufficient validation data to guarantee that the manufacturing process is controlled and to ensure batch to batch reproducibility and compliance with product specifications.

Excipients

The excipients used in the product are described in the Ph. Eur. and/or NF. The information provided is sufficient.

Product specifications

The product specifications are adequate. The limits proposed for the different parameters have been properly justified.

Analytical procedures are adequately described and validated in accordance with ICH guidelines.

Container closure system

The product is packaged in HDPE bottles with silica gel desiccant contained in the polypropylene cap. The packaging materials comply with the current legislation on plastic materials and articles intended to come into contact with food.

Stability

The stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life, in-use shelf-life and storage conditions.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substances has been provided, which is based on up-to-date and adequate scientific literature.

Since the toxicological profiles of tamsulosin and dutasteride are well established, no new nonclinical studies have been conducted for this proposed fixed combination product.

Environmental Risk Assessment (ERA)

Since Dutasteride/Tamsulosin Teva is intended to be a medicinal product therapeutically equivalent to co-administration of the two independent products included in the formulation, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

II.3 Clinical aspects

Introduction

The proposed dutasteride/tamsulosin fixed dose combination is compared with the reference immediate release soft gelatin capsule of dutasteride and the prolonged release hard gelatine capsule of tamsulosin administered simultaneously.

The proposed Clinical Plan including the comparison of the fixed dose combination of dutasteride/tamsulosin versus the co-administration therapy of dutasteride (GSK) and tamsulosin (Astellas Pharma) in a single dose study in fasting state, a single dose study in fed state (high fat meal) and a multiple dose study in fed state (high fat meal) is considered appropriate in addition to the existing bibliography to support the demonstration of efficacy and safety of the product.

Biowaiver

Not applicable. The Applicant only applies for the Dutasteride/Tamsulosin 0.5 mg/0.4 mg strength.

Bioequivalence

The Application concerns a product that should be taken approximately 30 minutes after the same meal each day.

Tamsulosin is formulated in a prolonged release hard capsule and according to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms at least a single dose in fasting and fed conditions as well as a multiple dose study in fed conditions is required.

Three bioequivalence studies were conducted to support this application.

Two measured dutasteride/tamsulosin:

- A Single-Dose, Comparative Bioavailability Study of Dutasteride/Tamsulosin HCl 0.5 mg/0.4 mg Capsules under Fasting Conditions (Study No. 2015-3931)
- A Single-Dose, Comparative Bioavailability Study of Dutasteride/Tamsulosin HCl 0.5 mg/0.4 mg Capsules under Fed Conditions (Study No. 2015-3932)

One measured only tamsulosin:

- A Multiple-Dose, Comparative Bioavailability Study of Dutasteride/Tamsulosin HCl 0.5 mg/0.4 mg Capsules under Fed Conditions (Study No. 2015-3933).

This approach is considered acceptable since dutasteride does not need to be investigated at steady state since it is formulated as an IR product.

In addition, according to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms in vitro studies to investigate the release in alcohol solutions was performed to confirm that there is no higher risk of dose-dumping in case of concomitant intake with alcohol.

Study Protocol number: Study No: LIE1-CH-DUTT-0255-CTB-02-15

This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioavailability study in healthy, adult, male human subjects under fasting conditions with a washout period of 21 days.

The clinical part of the study was carried out from November 28th, 2015 to December 23rd, 2015 at Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6.

The analytical part was conducted at Pharma Medica Research Inc. 6100 Belgrave Road Mississauga, Ontario, Canada, L5R 0B7 from:

- Dutasteride: December 30th, 2015 to January 18th, 2016
- Tamsulosin: December 30th, 2015 to January 17th, 2016

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP were issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms three bioequivalence studies (single dose in fasting and fed conditions and multiple-dose in fed conditions) are required. This is the first study in the fasting condition.

The wash-out period and the sampling schedule are considered acceptable for an adequate characterisation of the systemic exposure of drugs with such a half-life and t_{max}.

Test Product: Dutasteride/Tamsulosin HCI 0.5 mg/0.4 mg hard capsules, manufactured by Laboratories León Farma S.A. Batch number: LF00392A. Batch size: 120,000 hard capsules. Shelf life: February 2016. Assay (content): 95.9 % and 100.3% of label claim for dutasteride and tamsulosin, respectively.

Reference Product: Avidart® (Dutasteride 0.5 mg soft capsules) manufactured by GlaxoSmithKline, S. A. (from the Spanish market). Batch number: ZD0956. Expiry date: March 2019. Assay (content): 100.8 % of label claim.

Reference Product: Omnic® (Tamsulosin 0.4 mg modified release hard capsules) manufactured by Astellas Pharma S.A. (from the Spanish market). Batch number: 14L02/31. Expiry date: December 2018. Assay (content): 96.4 % of label claim.

The reference products are adequate with regards to expiry date, content and they were obtained from the Spanish market.

All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

A total of 56 male subjects were selected according to the inclusion and exclusion criteria and 51 subjects completed the study. Subject No. 03 withdrew from the study due to AEs, subjects No. 15, 17, and 30 were drop outs due to consent withdrawal and subject No. 32 was dismissed due to positive urine drug test.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

The selected primary pharmacokinetics C_{max} and AUC_{0-t} or AUC_{0-72} variables for dutasteride are appropriate for a single dose bioequivalence study of an IR product. However, in addition to C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ have been used for tamsulosin because it is formulated in a modified release product.

Statistical analysis

The methods used in this study for the statistical evaluation are considered acceptable. ANOVA was performed on ln-transformed AUC_{0-72} and C_{max} for dutasteride and AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for tamsulosin.

Results

The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} and AUC_{0-t} / $AUC_{0-\infty}$ (tamsulosin) or AUC $_{0-72}$ (dutasteride) were all within the 80.00 to 125.00% bioequivalence range.
The 90% confidence intervals of the T/R ratios are shown in the following table:

Bioequivalence evaluation of dutasteride

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-72})	91.69	88.78-94.70
Ln (C_{max})	94.33	89.16-99.79

Bioequivalence evaluation of tamsulosin

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	94.86	88.74-101.41
Ln (C_{max})	94.21	86.97-102.07
Ln ($AUC_{0-\infty}$)	94.89	88.70-101.51

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as for both analytes the 90% confidence intervals for the ln-transformed C_{max} and AUC_{0-t} or AUC_{0-72} (for dutasteride) and $AUC_{0-\infty}$ (for tamsulosin) are within the acceptance range of 80-125% for both analytes.

No clinically significant differences were observed between the median t_{max} of test and reference products

Study Protocol number: Study No: LIE1-CH-DUTT-0255-CTB-01-15

This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioavailability study in healthy, adult, male human subjects under fed conditions with a washout period of 28 days.

The clinical part of study was carried out from September 26th, 2015 to October 28th, 2015 at Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6.

The analytical part was conducted at Pharma Medica Research Inc. 6100 Belgrave Road Mississauga, Ontario, Canada, L5R 0B7 from:

- Dutasteride: November 02nd, 2015 to November 12th, 2015
- Tamsulosin: October 30th, 2015 to November 13th, 2015

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms three bioequivalence studies (single dose in fasting and fed conditions and multiple-dose in fed conditions) are required. This is the second study: single dose study in the fed condition.

The wash-out period and the sampling schedule are considered acceptable for an adequate characterisation of the systemic exposure of a drug with such a half-life and t_{max}.

Test and reference products

The same test and reference batches were used in this study as in the previous one. Please refer to test and reference product in the previous fasting bioequivalence study.

The meal provided approximately 340 kcal from carbohydrate, 144 kcal from protein, and 504 kcal from fat with a total of 997 kcal. The composition of the meal is in accordance with the Guideline on the investigation of bioequivalence and it is considered adequate.

In the present study, sixty-seven (67) male subjects were selected according to the inclusion and exclusion criteria and 67 subjects completed the study.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Analytical methods

The same LC-MS/MS analytical methods as in the previous study (Study No: LIE1-CH-DUTT-0255-CTB-02-15) were used for the determination of dutasteride and tamsulosin in plasma samples.

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable

The selected primary pharmacokinetics C_{max} and AUC_{0-t} or AUC_{0-72} variables for dutasteride are appropriate for a single dose bioequivalence study of an IR product. However AUC_{0-t} and $AUC_{0-\infty}$ have been used for tamsulosin because it is formulated in a modified release product.

Statistical analysis

The methods used in this study for the statistical evaluation are considered acceptable. ANOVA was performed on ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} or AUC_{0-72} (dutasteride) and $AUC_{0-\infty}$ (tamsulosin) as the primary pharmacokinetic parameters.

Results

The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} and AUC_{0-t} / $AUC_{0-\infty}$ (tamsulosin) or AUC_{0-72} (dutasteride) were all to be within the 80.00 to 125.00% bioequivalence range.

The 90% confidence intervals of the T/R ratios are shown in the following table:

Bioequivalence evaluation of dutasteride

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-72})	94.71	92.95-96.49
Ln (C_{max})	89.30	83.12-95.94

Bioequivalence evaluation of tamsulosin

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	96.97	93.27-100.82

Ln (C_{max})	94.15	88.74-99.89
Ln ($AUC_{0-\infty}$)	97.63	93.69-101.73

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as for both analytes the 90% confidence intervals for the ln-transformed C_{max} and AUC_{0-t} or AUC_{0-72} (for dutasteride) and $AUC_{0-\infty}$ (for tamsulosin) are within the acceptance range of 80-125% for both analytes.

Study Protocol number: Study No: LIE1-CH-DUTT-0255-CTB-03-15

This was an open-label, multiple-dose, randomized, two-period, two-treatment, two-sequence, crossover comparative bioavailability study in healthy, adult, male human subjects under fed conditions.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms three bioequivalence studies (single dose fasting and fed conditions and multiple-dose in fed conditions) are required. This is the third study, a multiple-dose study in the fed condition. The steady-state study was performed under fed conditions as recommended in the SmPC for tamsolusin.

The clinical part of the study was carried out from November 30th, 2015 to December 22nd, 2015 at Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6.

The analytical part was conducted at Pharma Medica Research Inc. 6100 Belgrave Road Mississauga, Ontario, Canada, L5R 0B7 from January 13th, 2016 and January 22nd, 2016.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

The washout between drug administrations for each subject was 14 days (±3 hours).

The wash-out period and the sampling schedule are considered acceptable for an adequate characterisation of the systemic exposure of a drug with such a half-life and t_{max}.

Test and reference products

The same test and reference batches were used in this study as in the previous one. Please refer to test and reference product in the previous fasting bioequivalence study.

The meal provided approximately 340 kcal from carbohydrate, 144 kcal from protein, and 504 kcal from fat with a total of 997 kcal. The composition of the meal is in accordance with the Guideline on the investigation of bioequivalence and it is considered adequate.

Sixty male subjects were selected according to the inclusion and exclusion criteria and 55 subjects completed the study. Subject No. 10 was dismissed due to AE, subject No. 22 was dismissed due to positive urine drug test, subject No. 39 was dismissed due to vitals out of range and subjects No. 46 and 57 were drop outs due to consent withdrawal.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Analytical methods

The same LC-MS/MS analytical method as in the previous studies (Study No: LIE1-CH-DUTT-0255-CTB-02-15and Study No: LIE1-CH-DUTT-0255-CTB-01-15) was used for the determination of tamsulosin in plasma samples.

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

The selected primary pharmacokinetics variables ($AUC_{0-\tau,ss}$, $C_{max,ss}$, and $C_{\tau,ss}$) for tamsulosin are appropriate for a multiple dose bioequivalence study according to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms.

In order to assess the attainment of steady state tamsulosin concentrations by Day 7, pre-dose levels were collected on day 5, 6, and 7 of the study. The Days 5, 6 and 7 pre-dose tamsulosin levels were analysed and it was observed that the steady state was attained [Mean pre-dose Tamsulosin Plasma Concentrations on Days 5 (5.3242 ng/mL), 6 (4.172 ng/mL), 7 (5.1942 ng/mL)]. In addition, according to the innovator SmPC the steady state is reached by day 5 of multiple dosing.

Statistical analysis

Analysis of variance (ANOVA) was applied to log-transformed $AUC_{0-\tau,ss}$, $C_{max,ss}$, and $C_{\tau,ss}$.

Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means, and the corresponding standard errors of these differences were estimated for log-transformed $AUC_{0-\tau,ss}$, $C_{max,ss}$, and $C_{\tau,ss}$ parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated.

Results

The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters $AUC_{0-\tau,ss}$, $C_{max,ss}$, and $C_{\tau,ss}$ were all within the 80.00 to 125.00% bioequivalence range.

The 90% confidence intervals of the T/R ratios are shown in the following table:

Bioequivalence evaluation of tamsulosin

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln $AUC_{0-\tau,ss)}$	97.99	94.14-102.00
Ln ($C_{max,\ ss}$)	94.86	89.91-100.08
Ln ($C_{\tau,ss}$)	114.58	108.22-121.31

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as for tamsulosin the 90% confidence intervals for the ln-transformed $AUC_{0-\tau,ss}$, $C_{max,ss}$, and $C_{\tau,ss}$ are within the acceptance range of 80-125%.

In vitro studies to investigate the release in alcohol solutions

Some modified-release oral dosage forms contain active substances and/or excipients that exhibit higher solubility in ethanolic solutions compared to water. Concomitant consumption of alcoholic beverages with such products may induce dose dumping.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, for oral formulation, *in vitro* studies to investigate the release in alcohol solutions

should be performed to confirm that there is no higher risk of dose-dumping is case of concomitant intake with alcohol.

Dutasteride/Tamsulosin 0.5/0.4 mg hard capsules is composed by a soft gelatine capsule containing 0.5 mg of Dutasteride + modified release pellets of Tamsulosin (0.4 mg).

Therefore, the following dissolution profiles were performed at pH 1.2 with increasing ethanol concentrations of 0, 10, 20 and 40% on Tamsulosin modified release pellets (Batch 5ZR4563) and on Omnic® capsules (Batch 14L02/31) in order to confirm the dose dumpling effect on the test product and to compare it with the effect on the reference product.

Comparing the behaviour of test product vs. the reference product of tamsulosin, it can be observed that the effect of ethanol on tamsulosin hydrochloride release is higher on the reference product Omnic®.

Clinical efficacy and safety

Dutasteride/Tamsulosin concerns a fixed dose combination in which the demonstration of efficacy and safety is based on the literature evidence of the concomitant use of dutasteride and tamsulosin. The applicant did not conduct any clinical study to support this application apart from the bioequivalence studies described above. The clinical overview on the clinical pharmacology, efficacy and safety of the active substances has been provided, which is based on up-to-date scientific literature. This clinical overview is considered adequate. The efficacy and safety of the concomitant use of dutasteride and tamsulosin in the proposed indications is well established and documented in the submitted literature. The following published studies have been considered relevant for the assessment of the applied combination:

Andriole G.L et al., 2003 “Safety and Tolerability of the Dual 5a-Reductase Inhibitor Dutasteride in the Treatment of Benign Prostatic Hyperplasia”.

Barkin J. et al., 2003 “Alpha-Blocker Therapy Can Be Withdrawn in the Majority of Men Following Initial Combination Therapy with the Dual 5a-Reductase Inhibitor Dutasteride”.

Barkin J. et al., 2008 “Effect of dutasteride, tamsulosin and the combination on patient-reported quality of life and treatment satisfaction in men with moderate-to-severe benign prostatic hyperplasia: 2-year data from the CombAT trial”.

Becher E et al., 2009 “The effects of dutasteride, tamsulosin, and the combination on storage and voiding in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the Combination of Avodart and Tamsulosin study”.

Brown CT et al., 2003 “Dutasteride: A new 5-alpha reductase inhibitor for men with lower urinary tract symptoms secondary to BPH”.

Choi J. et al., 2016 “Transitional Zone Index as a Predictor of the Efficacy of α-Blocker and 5α-Reductase Inhibitor Combination Therapy in Korean Patients with Benign Prostatic Hyperplasia.

Chung BH et al., 2009 “Efficacy and safety of dutasteride, tamsulosin and their combination in a subpopulation of the CombAT study: 2-year results in Asian men with moderate-to-severe BPH”.

Fenter T.C et al., 2008 “Dutasteride vs Finasteride: Assessment of Differences in Acute Urinary Retention Rates and Surgical Risk Outcomes in an Elderly Population Aged ≥65 Years”.

Greco KA et al., 2008 “The role of combination medical therapy in benign prostatic hyperplasia”.

Issa M.M et al., 2007 “A Large Retrospective Analysis of Acute Urinary Retention and Prostate-related Surgery in BPH Patients Treated with 5- alpha Reductase Inhibitors: Dutasteride Versus Finasteride

Joo, K et al., 2012 “Comparison of α-Blocker Monotherapy and α-Blocker Plus 5α-Reductase Inhibitor Combination Therapy Based on Prostate Volume for Treatment of Benign Prostatic Hyperplasia”

Li, H et at., 2015. “Effect of Tamsulosin on the Pharmacokinetics of Dutasteride in Chinese Male Healthy Volunteers

Narayan P et al., 2005 “Long-Term Efficacy and Safety of Tamsulosin for Benign Prostatic Hyperplasia”.

Roehrborn CG et al., 2002,. Efficacy and safety of a dual inhibitor of 5-α reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia.

Roehrborn CG, et al. 2008 “The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study”.

Tsukamoto T. et al., 2009 “Efficacy and safety of dutasteride in Japanese men with benign prostatic hyperplasia”.

Wu XJ et al., 2013 “Dutasteride for the treatment of benign prostatic hyperplasia”

There is wide clinical experience of the concomitant use used of the mono-components in the proposed indications with an acceptable level of safety and established efficacy. Furthermore, the use of the individual components (dutasteride 0.5 mg, and tamsulosin 0.4 mg) administered concomitantly in the proposed indications has also been established in clinical practice and recognized in clinical guidelines on benign prostatic hyperplasia (BPH).
Therefore, the efficacy and safety of the drug product Dutasteride/Tamsulosin 0.5 mg/0.4 mg hard capsules are sufficiently demonstrated based on literature data, clinical guidelines and the bioequivalence studies conducted by the applicant.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a clinical standpoint, the fixed-dose combination is justified for the applied indications as a substitution therapy in the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH) in patients who are taken both mono-components separately and to reduce the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.

Bioequivalence of the applied product has been shown in compliance with the requirements of European Union guidance documents to the mono-component reference products.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the mono-components. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in July 2018.