IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dutasteride/Tamsulosin Rowa
Dutasteride
Tamsulosin Hydrochloride
PA0074/076/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Dutasteride/Tamsulosin Rowa 0.5mg/0.4mg hard capsules, from Rowa Pharmaceuticals Limited on 11th September 2020 for the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH) and reduction in the risk of acute urinary retention (AUR).

The application is a national procedure in Ireland under Article 10(1) generic application.

This product will be available by prescription only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie .

Name of the product	Dutasteride/Tamsulosin Rowa
Name(s) of the active substance(s) (INN)	Dutasteride, Tamsulosin Hydrochloride
Pharmacotherapeutic classification (ATC code)	G04CA52-tamsulosin and dutasteride
Pharmaceutical form and strength(s)	Capsule, hard-0.5/0.4 milligram(s)
Marketing Authorisation Number(s) in Ireland (PA)	PA0074/076/001
Marketing Authorisation Holder	Rowa Pharmaceuticals Limited, (0074), Newtown, Bantry, Co. Cork, Ireland
MRP/DCP No.	CRN009189

II. QUALITY ASPECTS

II.1. Introduction

This application is for Dutasteride/Tamsulosin Rowa 0.5mg/0.4mg hard capsules.

II.2 Drug substance

The active substance is Dutasteride and Tamsulosin Hydrochloride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each hard capsule contains 0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride (equivalent to 0.367 mg tamsulosin).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Adventitious Agent Safety

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

Scientific data and/or certificates of suitability issued by EDQM have been provided for gelatin and compliance with the Note For Guidance on Minimising the Risk if Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Dutasteride/Tamsulosin Rowa 0.5mg/0.4mg hard capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Dutasteride/Tamsulosin Rowa is a generic formulation of Combodart with the same active substances, dutasteride and tamsulosin hydrochloride. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of dutasteride and tamsulosin hydrochloride are well known. As dutasteride and tamsulosin hydrochloride are widely used, well-known active substances, the applicant has not provided additional studies. An overview based on literature review is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since Dutasteride/Tamsulosin Rowa 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

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As dutasteride and tamsulosin hydrochloride are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dutasteride/Tamsulosin 0.5/0.4mg is a well known active combination with established efficacy and tolerability.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Dutasteride/Tamsulosin Rowa 0.5/0.4mg is compared with the pharmacokinetic profile of the reference product Duodart 0.5/0.4mg.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Duodart 0.5/0.4mg marketed by GlaxoSmithKline BmbH&Co. Germany

A bioequivalence study (Study ZNV-P0-421) has been submitted to support the application. It was a single centre, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design in healthy male subjects.

This marketing authorisation addressed pharmacokinetic data in respect of this bioequivalence study.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Dutasteride:
Following oral administration of a single 0.5 mg dutasteride dose, the time to peak serum concentrations of approximately 40 ng/mL is 1 to 3 hours. The bioavailability of dutasteride is not affected by food.

The main pharmacokinetic parameters of interest for Dustasteride are Cmax and AUC(0-72). Cmax was found to be 92.35% and AUC(0-72) was 94.42%.

Tamsulosin:
After a single dose of tamsulosin in the fed state, plasma concentrations of tamsulosin peak at around 6 hours and, in the steady state, which is reached by day 5 of multiple dosing, the mean steady state Cmax in patients is about two thirds higher than that reached after a single dose.

The pharmacokinetic results demonstrate that the ratios of Cmax,ss, AUC(0-τ), and Cτ,ss of tamsulosin were 108.42%, 104.72%, and 97.60%, respectively. For all parameters, the corresponding 90% confidence intervals were included within the range of 80.00% to 125.00%. The results of this study indicate that average bioequivalence criteria were met following the administration of 7 consecutive doses of the Test formulation and the reference product under fed conditions.

Dutasteride is mainly eliminated via metabolism. In vitro studies indicate that this metabolism is catalyzed by CYP3A4 and CYP3A5.

IV.3 Pharmacodynamics

Dutasteride, is a dual 5 α-reductase inhibitor (5 ARI) and tamsulosin hydrochloride, an antagonist of α1a and α1d adrenoreceptors. These drugs have complementary mechanisms of action that rapidly improve symptoms, urinary flow and reduce the risk of acute urinary retention and the need for benign prostatic hyperplasia related surgery.

Dutasteride inhibits both type 1 and type 2, 5 alpha-reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone. Dihydrotestosterone is the androgen primarily responsible for prostate growth and benign prostatic hyperplasia development.
Tamsulosin inhibits α1a and α1d adrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75% of the α1-receptors in the prostate are of the α1a subtype.

IV.4 Clinical Efficacy

Multiple studies have been performed which demonstrate the clinical efficacy of this drug combination.

Listed below are literature reviews in relation to dustasteride and tamsulosin.

Park T, Choi JY: Efficacy and safety of dutasteride for the treatment of symptomatic benign prostatic hyperplasia (BPH): a systematic review and meta-analysis. World J Urol 2014;32:1093-1105.

Wilt TJ, Macdonald R, Hagerty K, Schellhammer P, Tacklind J, Somerfield MR, Kramer BS: 5-alpha-Reductase inhibitors for prostate cancer chemoprevention: an updated Cochrane systematic review. BJU Int 2010;106:1444-1451.

IV.5 Clinical Safety

The submitted bioequivalence study demonstrates a reasonable safety profile with no serious adverse events. There was a similar number of adverse events between test and reference products.
The safety of this drug combination is well established and the SmPC clearly states relevant contraindications and potential adverse reactions.

Risk Management Plan

The Applicant submitted a Risk Management Plan to support this application. The following table outlines the approved summary of safety concerns:

Table 1: Safety specification

Summary of safety concerns	
Important identified risks	• Sexual adverse events (altered [decreased] libido, impotence, ejaculation disorders), that may persist after drug discontinuation • Breast disorders (enlargement and tenderness) • Cardiac failure • Depressed mood Associated with tamsulosin • SJS, dermatitis exfoliative and erythema multiforme • Priapism
Important potential risks	• 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 the foetus

Missing information	• Use in men with severe hepatic impairment • Use in 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 risk minimisation measures and routine pharmacovigilance activities were proposed to address the safety concerns outlined above and this is considered acceptable.

The Applicant should submit Periodic Safety Update Reports (PSUR) Periodic Safety Update Reports (PSUR) in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

Benefits

Dutasteride/Tamsulosin 0.5/0.4mg has an established efficacy and safety profile.
It is indicated for the treatment of men with moderate to severe symptoms of benign prostatic hyperplasia (BPH) and for reduction in the risk of acute urinary retention (AUR) and surgery in men with moderate to severe symptoms of BPH.

Clinical studies reviewing the combined therapy with the 5α-reductase inhibitor dutasteride and the α1-adrenergic antagonist tamsulosin, have shown significant improvements from baseline compared with either drug alone.

The bioequivalence study submitted shows 90% confidence intervals within the range of 80.00% to 125.00% which complies with CPMP/EWP/QWP/1401/98 Rev. 1

Risks

Guidance on PSA monitoring and use in prostate cancer surveillance and diagnosis should be noted.

Caution should be taken when prescribing this medication in men with cardiac failure.

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, this is in line with the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

V. OVERALL CONCLUSIONS

The overall conclusion favours a positive risk benefit profile.

Dutasteride/Tamsulosin 0.5/0.4mg is a generic form of Duodart 0.5/0.4mg marketed by GlaxoSmithKline BmbH&Co. Germany. Duodart 0.5/0.4mg, marketed by GlaxoSmithKline BmbH&Co. Germany, is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The legal basis for the application is Article 10(1) of 2001/83/EC a generic application.

The product will be subject to medical prescription that may be renewed.

Based on the pharmacokinetic parameters of the reference tablet Duodart 0.5/0.4mg marketed by GlaxoSmithKline BmbH&Co. Germany and test tablet Dutasteride/Tamsulosin 0.5/0.4mg are bioequivalent with reference to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in by the EMA in CPMP/EWP/240/95 Rev 1.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Duodart 0.5/0.4mg marketed by GlaxoSmithKline BmbH&Co. Germany.

The HPRA, on the basis of the data submitted considered that Dutasteride/Tamsulosin 0.5/0.4mg product demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Based on the pharmacokinetic parameters of the reference tablet Duodart 0.5/0.4mg marketed by GlaxoSmithKline BmbH&Co. Germany and test tablet Dutasteride/Tamsulosin 0.5/0.4mg are bioequivalent with reference to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in by the EMA in CPMP/EWP/240/95 Rev 1.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Duodart 0.5/0.4mg marketed by GlaxoSmithKline BmbH&Co. Germany.

VI. REVISION DATE

VII. UPDATES