IPAR

Public Assessment Report for a Medicinal Product for Human Use

Scientific discussion

Eprosartan Teva 300 mg, 400 mg, 600 mg Film-coated Tablets

IE/H/452/001-003/DC

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.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Eprosartan Teva 300 mg, 400 mg, 600 mg Film-coated Tablets, from Teva B.V. on 29th May 2015 for the treatment of essential hypertension.

The application was made under reference to Article 10 (1) of the Directive 2001/83/EC. The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory framework.

The HPRA acted as Reference Member State (RMS) in a European decentralised procedure involving the following Concerned Member States (CMS); the United Kingdom (UK), the Netherlands (NL) and Germany (DE).

This medicinal product is subject to prescription supply.

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	Eprosartan Teva
Name(s) of the active substance(s) (INN)	Eprosartan Mesilate
Pharmacotherapeutic classification (ATC code)	C09C A02, Angiotensin II antagonists, plain
Pharmaceutical form and strength(s)	Film-coated Tablets; 300 mg, 400 mg, 600 mg

Marketing Authorisation Number(s) in Ireland (PA)	PA1986/018/001-003
Marketing Authorisation Holder	Teva B.V.
MRP/DCP No.	IE/H/452/001-003/DC
Reference Member State	Ireland (IE)
Concerned Member State	300 mg: UK. 400 mg: UK, NL. 600 mg: UK, NL, DE.

II QUALITY ASPECTS

II.1. Introduction

This application is for Eprosartan Teva 300 mg, 400 mg, 600 mg Film-coated Tablets.

II.2 Drug substance

The active substance is eprosartan mesilate, an established active substance, 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 regulatory requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each film-coated tablet contains eprosartan mesilate equivalent to 300 mg, 400 mg, or 600 mg eprosartan.
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 guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

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 Tablets, 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 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. and relevant 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.

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 Eprosartan Teva 300 mg, 400 mg, 600 mg Film-coated Tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacokinetic, pharmacodynamic and toxicological properties of eprosartan mesilate are well known. Thus the applicant has not provided additional studies and further studies are not required.

A non clinical overview has been provided and written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non submission of an environmental risk assessment.

There are no objections to the approval of this medicinal product from a non clinical perspective.

IV CLINICAL ASPECTS

IV.1 Introduction

Eprosartan mesilate is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Teveten marketed reference.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product.

The bioequivalence study was an open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, replicate bioequivalence study of Eprosartan Teva 600 mg Film-coated Tablets of Unichem Laboratories Limited, India and Teveten® tablets containing Eprosartan Teva 600 mg of Abbott Healthcare Ltd in healthy, adult, male, human subjects under fasting conditions.

Based on the pharmacokinetic parameters of active substance, the reference tablet Teveten® tablets and test tablet Eprosartan Teva 600 mg are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 90% confidence intervals for AUC 0-t and CMax were within the prespecified 80-125 limits, clarification was also provided by the applicant on $AUC_{0-\infty.}$ Values and these were also within the 80-125 confidence intervals and therefore bioequivalence to the reference product has been demonstrated.

A justification with regard to biowaiver for the lower strengths 300 mg and 400 mg has been provided and meet the criteria as specified in the guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr)

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

IV.2 Pharmacokinetics

Absorption

Absolute bioavailability following a single 300 mg oral dose of eprosartan is about 13%, due to limited oral absorption. Eprosartan plasma concentrations peak at 1 to 2 hours after an oral dose in the fasted state. Plasma concentrations are dose proportional from 100 to 200 mg, but less than proportional for 400 and 800 mg doses.

Elimination

The terminal elimination half-life of eprosartan following oral administration is typically 5 to 9 hours. Eprosartan does not significantly accumulate with chronic use. Administration of eprosartan with food delays absorption with minor changes (<25%) observed in C_{max} and AUC which are not of clinical consequence.

Distribution

Plasma protein binding of eprosartan is high (approximately 98%) and constant over the concentration range achieved with therapeutic doses. The extent of plasma protein binding is not influenced by gender, age, hepatic dysfunction or mild-moderate renal impairment but has shown to be decreased in a small number of patients with severe renal impairment.

Following intravenous [^{14}C]eprosartan, about 61% of radioactivity is recovered in the faeces and about 37% in the urine. Following an oral dose of [^{14}C]eprosartan, about 90% of radioactivity is recovered in the faeces and about 7% in the urine.

Following oral and intravenous dosing with [^{14}C]eprosartan in human subjects, eprosartan was the only drug-related compound found in the plasma and faeces. In the urine, approximately 20% of the radioactivity excreted was an acyl glucuronide of eprosartan with the remaining 80% being unchanged eprosartan.

The volume of distribution of eprosartan is about 13 litres. Total plasma clearance is about 130 mL/min. Biliary and renal excretion contribute to the elimination of eprosartan.

Both AUC and C_{max} values of eprosartan are increased in the elderly (on average, approximately 2 fold), but this does not necessitate alterations in dosing.

Following administration of a single 100 mg dose of eprosartan, AUC values of eprosartan (but not C_{max}) are increased, on average, approximately 40% in patients with hepatic impairment.

Compared to subjects with normal renal function mean AUC and C_{max} values were approximately 30% higher in patients with moderate renal impairment (creatinine clearance 30-59 mL/min), approximately 50% higher in a small number of patients with severe renal impairment (creatinine clearance 5-29 mL/min) and approximately 60% in patients undergoing dialysis.

There is no difference in the pharmacokinetics of eprosartan between males and females.

IV.3 Pharmacodynamics

Mechanism of action

Eprosartan is a synthetic, orally active non-biphenyl non-tetrazole angiotensin II receptor antagonist.

Angiotensin II is a potent vasoconstrictor and the primary active hormone of the renin-angiotensin-aldosterone system, playing a major part in the pathophysiology of hypertension.

Pharmacodynamic effects

Eprosartan antagonised the effect of angiotensin II on blood pressure, renal blood flow and aldosterone secretion in normal volunteers. Blood pressure control is maintained over a 24 hour period with no first dose postural hypotension or reflex tachycardia. Discontinuation of treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

Eprosartan was evaluated in mild to moderate hypertensive patients (sitting DBP ≥95 mm Hg and <115 mm Hg) and severe hypertensive patients (sitting DBP ≥115 mm Hg and ≤125 mm Hg).

Doses up to 1200 mg per day, for 8 weeks, have been shown in clinical trials to be effective with no apparent dose relationship in the incidence of adverse experiences reported.

In patients with hypertension, blood pressure reduction did not produce a change in heart rate.

Beneficial effects of eprosartan on mortality and cardiovascular morbidity are currently unknown.

Eprosartan does not compromise renal autoregulatory mechanisms. In normal adult males eprosartan has been shown to increase mean effective renal plasma flow. Eprosartan has no deleterious effects on renal function in patients with essential hypertension and patients with renal insufficiency. Eprosartan does not reduce glomerular filtration rate in normal males, in patients with hypertension or in patients with varying degrees of renal insufficiency. Eprosartan has a natriuretic effect in normal subjects on a salt restricted diet. Eprosartan may be safely administered to patients with essential hypertension and to patients with varying degrees of renal insufficiency without causing sodium retention or a deterioration of renal function.

Eprosartan does not significantly affect the excretion of urinary uric acid.

Eprosartan does not potentiate effects relating to bradykinin (ACE mediated) e.g. cough. In a study specifically designed to compare the incidence of cough in patients treated with eprosartan and an angiotensin converting enzyme inhibitor, the incidence of dry persistent cough in patients treated with eprosartan (1.5%) was significantly lower ($p<0.05$) than that observed in patients treated with an angiotensin converting enzyme inhibitor (5.4%). In a further study investigating the incidence of cough in patients who had previously coughed while taking an angiotensin converting enzyme inhibitor, the incidence of dry, persistent cough was 2.6% on eprosartan, 2.7% on placebo, and 25.0% on an angiotensin converting enzyme inhibitor ($p<0.01$, eprosartan versus angiotensin converting enzyme inhibitor).

Clinical efficacy and safety

In three clinical studies (n=791) the blood pressure lowering effect of eprosartan has been shown to be at least as great as the ACE inhibitor enalapril, with one study in severe hypertensives showing a statistically significantly greater decrease in sitting and standing systolic blood pressure for eprosartan over enalapril.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and

angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group

IV.4 Clinical Efficacy

As bioequivalence has been established additional efficacy or safety studies are not required.

IV.5 Clinical Safety

The bioequivalence study conducted did not highlight any additional safety issues.
The marketing authorisation holder (MAH) submitted a summary describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

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 Eprosartan Teva 300 mg, 400 mg, 600 mg.

Based on consideration of the identified risks, the potential risks and the need for additional information on the medicinal product, it is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

With regard to PSUR submission, the MAH should take the following into account:
• For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list. This applies to this medicinal product. Marketing authorisation holders shall continuously check the European medicines web-portal for any changes to this.

IV.6 Discussion on the clinical aspects

There is no objection to the approval of this medicinal product from a clinical perspective.

V OVERALL CONCLUSIONS

Eprosartan Teva 300 mg, 400 mg, 600 mg Film-coated Tablets is a generic form of Teveten® tablets marketed by Solvay Healthcare Limited. Teveten® is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Eprosartan Teva 300 mg, 400 mg, 600 mg Film-coated Tablets.

Bioequivalence has been shown between the test and reference product at 600 mg and biowaivers for the lower strengths 300 mg and 400 mg are in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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

The HPRA, on the basis of the data submitted considered that Eprosartan Teva 300 mg, 400 mg, 600 mg Film-coated Tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.