IPAR

IRISH MEDICINES BOARD
PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Losartan Hydrochlorothiazide Krka
Losartan Potassium
PA1347/40/1-3

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) 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 IMB 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 IMB 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 IMB has granted a marketing authorisation for Losartan / Hydrochlorothiazide Krka 50mg / 12.5mg, 100mg /12.5mg and 100mg / 25mg Film-coated tablets from Krka Pharma on the 8th of November 2013 for the following indications:

Losartan potassium/Hydrochlorothiazide Krka is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at http://www.imb.ie/

Name of the product	Losartan Hydrochlorothiazide Krka
Name(s) of the active substance(s) (INN)	Losartan Potassium
Pharmacotherapeutic classification (ATC code)	C09DA01
Pharmaceutical form and strength(s)	50/12.5mg, 100/12.5mg & 100/25mg
Marketing Authorisation Number(s) in Ireland (PA)	PA1347/040/001-003

II QUALITY ASPECTS

II.1. Introduction

This application is for Losartan / Hydrochlorothiazide Krka 50mg / 12.5mg, 100mg / 12.5mg and 100mg / 25mg Film-coated tablets.

II.2 Drug substance

The active substances are Losartan Potassium, an established active substance described in the European Pharmacopoeia, and Hydrochlorothioazide an established active substance described in the European Pharmacopoeia and both are 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

The drug product is film-coated tablets.

Each 50mg / 12.5mg, film-coated tablet contains 50mg of losartan potassium and 12.5mg of hydrochlorothiazide, each 100mg / 12.5mg film-coated tablet contains 100mg of losartan potassium and 12.5mg of hydrochlorothiazide and each 100mg / 25mg film-coated tablet contains 100mg of losartan potassium and 25mg of hydrochlorothiazide.

The other ingredients are: pregelatinised starch, microcrystalline cellulose, lactose monohydrate and magnesium stearate. The coating contains hypromellose, Macrogol, quinoline yellow (50mg/12.5mg and 100mg/25mg tablets only), titanium dioxide and talc.

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/*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 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 product is presented as Al/PVC/PVDC transparent blisters.

Evidence has been provided that the Al/PVC/PVDC transparent blisters comply with 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 demonstrating the stability of the product for the following:

- Losartan / hydrochlorothiazide 50mg / 12.5mg and 100mg / 25mg: 5 years when tablets are stored at temperature below 30°C in the original package in order to protect from moisture.

- for Losartan / Hydrochlorothiazide 100mg / 12.5mg: 2 years when tablets are stored at a temperature below 30°C in the original package in order to protect from moisture.

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 Losartan / Hydrochlorothiazide Krka 50mg / 12.5mg, 100mg / 12.5mg and 100mg / 25mg Film-coated tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Cozaar Comp (Merck Sharp & Dohme Ireland (Human Health) Limited) on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

IV CLINICAL ASPECTS

IV.1 Introduction

Losartan potassium/hydrochlorothiazide is a well known active substance with established efficacy and tolerability.

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product.

For this generic application, the applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products (Losartan potassium/Hydrochlorothiazide 100 mg/12.5 mg film-coated tablets (KRKA) and Losartan potassium/Hydrochlorothiazide 100 mg/25 mg film-coated tablets (KRKA)) is compared with the pharmacokinetic profile of the reference products (Lorzaar Plus forte 100mg/12.5 mg film-coated tablets (Merck Sharp & Dohme) and Fortzaar 100 mg/25 mg film-coated tablets (Merck Sharp & Dohme), respectively).

1. In a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study - Losartan potassium/ Hydrochlorothiazide 100 mg/12.5 mg film-coated tablets (KRKA) were compared to the reference product Lorzaar Plus forte 100mg/12.5 mg film-coated tablets (Merck Sharp & Dohme). Based on the pharmacokinetic parameters of active substance, the reference tablets - Lorzaar Plus forte 100mg/12.5 mg film-coated tablets marketed by Merck Sharp & Dohme and test tablets -Losartan potassium/Hydrochlorothiazide 100 mg/12.5 mg film-coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

2. In a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study - Losartan potassium/ Hydrochlorothiazide 100 mg/25 mg film-coated tablets (KRKA) were compared to the reference tablets- Fortzaar 100 mg/25 mg film-coated tablets (Merck Sharp & Dohme). Based on the pharmacokinetic parameters of active substance, the reference tablets -Fortzaar 100 mg/25 mg film-coated tablets marketed by Merck Sharp & Dohme and test tablets - Losartan potassium/ Hydrochlorothiazide 100 mg/25 mg film-coated tablets 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 choice of reference tablets used in the bioequivalence studies was justified.

Biowaiver
The bioequivalence studies were performed on Losartan potassium/ Hydrochlorothiazide 100 mg/25 mg film-coated tablets and on Losartan potassium/ Hydrochlorothiazide 100 mg/12.5 mg film-coated tablets.

A justification for the biowaiver for the 50/12.5mg strength has been provided.
The biowaiver conditions are considered to be satisfactorily fulfilled.
The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

Pharmacovigilance System

The Marketing Authorisation Holder submitted a set of documents 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.

The PSUR cycle will follow the PSUR synchronisation scheme agreed for losartan and hydrochlorothiazide and PSURs will be submitted every 3 years.

IV.2 Pharmacokinetics

Absorption

Losartan
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Distribution

Losartan
Both losartan and its active metabolite are ≥ 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Losartan
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite.

Following oral and intravenous administration of 14C-labeled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Losartan
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of 14C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

IV.3 Pharmacodynamics

Losartan is a synthetically produced oral angiotensin-II receptor (type AT1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension.

Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle cell proliferation.

Losartan selectively blocks the AT1 receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

Losartan / Hydrochlorothiazide Krka 50mg / 12.5mg, 100mg / 12.5mg and 100mg / 25mg Film-coated tablets are indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

Losartan and hydrochlorothiazide in combination have been shown to have additive effect on blood pressuer reduction, reducing blood pressure to a greater degree than either component alone.

IV.4 Clinical Efficacy

Clinical efficacy of the active substance was not assessed as part of the bioequivalence trial.

IV.5 Clinical Safety

Adverse events were similar between the two test groups in the bioequivalence trials.

The PSUR cycle will follow the PSUR synchronisation scheme agreed for losartan and hydrochlorothiazide and PSURs will be submitted every 3 years.

IV.6 Discussion on the clinical aspects

As this is a generic application, the need for repetitive tests is avoided. The applicant has submitted suitable bioequivalence trials, which have demonstrated the similarity of the test products against the reference products, in accordance with the relevant guidance. No additional tests are required for this application.

The applicant has submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V OVERALL CONCLUSIONS

Losartan potassium/Hydrochlorothiazide 50mg/12.5, 100mg/12.5mg and 100mg/25mg film-coated tablets are generic forms of Cozaar Comp 50mg/12.5, 100mg/12.5mg and 100mg/25mg film-coated tablets (Merck Sharp & Dohme). Losartan potassium/hydrochlorothiazide is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile. Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SPCs are consistent with that of the reference product.

The IMB, on the basis of the data submitted considered that Losartan/ Hydrochlorothiazide Krka 50mg / 12.5mg, 100mg /12.5mg and 100mg / 25mg Film-coated tablets from Krka Pharma demonstrated bioequivalence with the reference products as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VII UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

Scope	Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/ non approval