IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Losartan Rowa 100mg film-coated tablets
Losartan potassium
PA0074/082/003

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Losartan Rowa 50mg and 100mg film-coated tablets from Rowa Pharmaceuticals Limited on 5th June 2020 for the following indication:

-Treatment of essential hypertension in adults and in children and adolescents 6 – 18 years of age.
-Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment (see sections 4.3, 4.4, 4.5, and 5.1).
-Treatment of chronic heart failure in adult patients, when treatment with ACE inhibitors is not considered suitable due to incompatibility*, especially cough,* or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be clinically stable and on an established treatment regimen for chronic heart failure.
-Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG

This is a new national application submitted for a generic of Losartan submitted under Article 10 (1) of 2001/83 EC as amended.

Losartan is an oral, specific angiotensin-II receptor (type AT1) antagonist. Losartan Rowa 50mg and 100mg film-coated tablets will be subject to prescription.

The Reference Product is Cozaar 50mg and 100mg film-coated tablets by Merck Sharp & Dohme, containing losartan 50mg and 100mg

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	Losartan Rowa 50mg Film-coated tablet and Losartan Rowa 100mg Film-coated tablet
Name(s) of the active substance(s) (INN)	Losartan potassium
Pharmacotherapeutic classification (ATC code)	C09CA01
Pharmaceutical form and strength(s)	Film-coated tablet 50mg and 100mg
Marketing Authorisation Number(s) in Ireland (PA)	PA0074/082/002 and PA0074/082/003
Marketing Authorisation Holder	Rowa Pharmaceuticals Limited

II. QUALITY ASPECTS

II.1. Introduction

This application is for Losartan Rowa 50mg Film-coated tablet and Losartan Rowa 100mg Film-coated tablet

II.2 Drug substance

The active substance is Losartan potassium, 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

Losartan Rowa 50 mg film-coated tablet contains 50 mg of the active ingredient losartan potassium
Losartan Rowa 100 mg film-coated tablet contains 100 mg of the active ingredient losartan potassium

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/ICHg uidelines 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(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.

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 Rowa 50mg Film-coated tablet and Losartan Rowa 100mg Film-coated tablet.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Cozaar Tablets on the European market. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of losartan are well known. As losartan potassium is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

III.2 Ecotoxicity/environmental risk assessment

Since Losartan Rowa 50mg & 100mg film-coated tablets are 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 pharmacodynamic, pharmacokinetic and toxicological properties of losartan are well known. As losartan is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Cozaar (Losartan) marketed by Merck Sharp & Dohme.

For this generic application, the applicant has submitted one single dose bioequivalence study. A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Losartan/liconsa 100 mg tablets (test formulation) was compared to the reference product vs. Losartan® 100 mg Tablets (reference formulation) marketed by Merck Sharp & Dohme, Spain. Based on the pharmacokinetic parameters of active substance Losartan and losartan metabolite the reference tablet and test tablet 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 applicant requested a biowaiver for the Losartan 50 mg strength. This approach is justified because the kinetics of losartan is linear over the dose range commonly used, the therapeutic margin is wide and because the other strengths.

Bioequivalence was demonstrated for 100 mg strength. A biowaiver can be considered for the 50 mg respect to the 100 mg bioequivalence study as all the requirements are fulfilled including comparable dissolution profiles as described in this most recent BE guideline and therefore the requested biowaiver for the 50 mg strength is acceptable.

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

IV.2 Pharmacokinetics

Absorption
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 standardised meal.

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

Biotransformation
About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite.

Elimination
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-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

IV.3 Pharmacodynamics

Losartan is an oral, specific angiotensin-II receptor (type AT1) antagonist. 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 proliferation. Based on binding and pharmacological bioassays, it binds selectively to the AT1 receptor. In vitro and in vivo, both 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 synthesis.

Losartan binds selectively to the AT1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin.

In an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) which was persistent in chronic therapy.

IV.4 Clinical Efficacy

This is a generic application therefore no new clinical studies were performed.

IV.5 Clinical Safety

In this generic application, it is noted that the safety profile of the proposed active substance is well-established over many years. No new safety concerns arise from the data presented.
Please see the SmPC and package leaflet for full prescribing safety information.

Risk Management Plan (RMP)

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describingthe pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Losartan Rowa film-coated tablets.

A summary of the safety concerns as approved in the RMP is provided below:

Summary of safety concerns	
Important identified risks	-Renal dysfunction as a consequence of dual RAAS blockade -Foetotoxicity when used during 2nd and 3rd trimester of pregnancy

	-Hyperkalaemia
Important potential risks	-Teratogenicity during the 1st trimester of pregnancy
Missing information	-Exposure during breast feeding -Treatment of proteinuria in children under 1 year of age -Treatment of hypertension in children under 6 months of age

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.

Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

PSURs shall be submitted 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. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

Common renewal date

Common renewal date will be 5 years after the finalisation of the procedure

IV.6 Discussion on the clinical aspects

For this generic application, a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Losartan/liconsa 100 mg tablets (test formulation) was compared to the reference product vs. Losartan® 100 mg Tablets (reference formulation) marketed by Merck Sharp & Dohme, Spain. Based on the pharmacokinetic parameters of active substance Losartan and losartan metabolite the reference tablet and test tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

In conclusion, Losartan/liconsa 100 mg tablets (test formulation) is bioequivalent to the reference product Losartan® 100 mg Tablets (reference formulation) marketed by Merck Sharp & Dohme, Spain.

The Biowaiver applied on 50 mg losartan strengths is justified.

V. OVERALL CONCLUSIONS

Losartan Rowa 50mg and 100mg film coated tablets are a generic form of Cozaar 50mg and 100mg film coated tablets. Cozaar 50mg and 100mg film coated tablets 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 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 Losartan Rowa 50mg and 100mg film coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE