COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Losartan kalium Pharmaclan 50 mg and 100 mg film-coated tablets (losartan potassium)

NL/H/5449/001-002/DC

Date: 20 November 2023

This module reflects the scientific discussion for the approval of Losartan kalium Pharmaclan 50 mg and 100 mg film-coated tablets. The procedure was finalised on 23 March 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ACE	Angiotensin-converting enzyme
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
ECG	Electrocardiogram
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Losartan kalium Pharmaclan 50 mg and 100 mg film-coated tablets, from Pharmaclan s.r.o.

The product is indicated for:

- 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.
- Treatment of chronic heart failure in adult patients when treatment with Angiotensin-converting enzyme (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 electrocardiogram (ECG).

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Cozaar 50 mg and 100 mg, film-coated tablets by N.V. Organon which has been registered in the Netherlands via a mutual recognition procedure (NL/H/1457/002-003/E001) since 14 March 1995 and 5 March 2002, respectively.

The concerned member states (CMS) involved in this procedure were Germany, Italy, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Losartan kalium Pharmaclan are white to off white film-coated, oval shaped tablets. Each tablet contains as active substance 50 mg or 100 mg of losartan potassium. The two strengths can be distinguished by their dimensions and debossing and that the 50 mg strength has a score line.

Losartan kalium Pharmaclan 50 mg tablets are debossed with “l” and “17” on either side of a score line on one side and plain on the other side. Approximately, the tablet dimensions are 8.9 mm x 5.1 mm.

Losartan kalium Pharmaclan 100 mg tablets are debossed with “l18” on one side and plain on the other side. Approximately, the tablet dimensions are 11.70 mm x 7.10 mm.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), low substituted hydroxypropyl cellulose (E463), pregelatinised maize starch and magnesium stearate (E572).

Film-coating - hypromellose (E464), macrogol 400 (E1521) and titanium dioxide (E171).

The two strengths are fully dose proportional.

The film-coated tablets are packed in PVC/PE/PVDC/Alu (polyvinyl chloride/polyethylene/polyvinylidene chloride/aluminium) blister or HDPE (high-density polyethylene) bottle.

II.2 Drug Substance

The active substance is losartan potassium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is crystalline hygroscopic powder and is freely soluble in water and methanol and slightly soluble in acetonitrile. Polymorphic forms exist and controls are in place to confirm the required polymorphic forms.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is in line with the CEP, with additional requirements for in-house tests for polymorphic forms, residual solvents and particle size distribution. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified and their functions explained. The pharmaceutical development of the product has been adequately performed. The MAH has submitted one single dose bioequivalence study with the 100 mg film-coated tablet under fasting conditions. For the 50 mg film-coated tablet a biowaiver was requested by the MAH. For the comparison studies of the dissolution profile of the reference and drug product, *in vitro* dissolution tests were developed.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three common blend pilot batches and three tablet pilot batches (per strength) in accordance with the relevant European guidelines. A common blend batch is manufactured which will be used for both tablet strengths. The blend is then granulated and compressed into tablets. The core tablets are film-coated. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, average weight, dimensions, assay, dissolution, uniformity of dosage units, water content, subdivision of tablets, related substances, nitrosamine impurities and microbial quality. The release and shelf-life specifications are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Appropriate tests for nitrosamine presence are performed on the final product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three pilot scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided from three pilot scaled batches stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of

the data submitted, a shelf life was granted of 24 months. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability data have been provided for the HDPE bottles demonstrating that no in-use shelf life needs to be defined in the product information.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Losartan kalium Pharmaclan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Losartan kalium Pharmaclan is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Cozaar which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Losartan potassium is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study under fasting conditions in which the pharmacokinetic profile of the test product Losartan kalium Pharmaclan 100 mg film-coated tablets (Pharmaclan s.r.o., Czechia) was compared with the pharmacokinetic profile of the reference product Cozaar 100 mg, film-coated tablets (N.V. Organon, The Netherlands). A biowaiver was requested for the additional 50 mg strength, based on *in vitro* dissolution data.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The MAH was granted a biowaiver for *in vitro* bioequivalence studies for the 50 mg strength, based on these criteria:

a) the 50 mg and 100 mg strength are manufactured by the same manufacturing process,
b) the qualitative composition of the two strengths is the same,
c) the composition of the strengths are quantitatively proportional,
d) appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution of the 50 and 100 mg test product was investigated according to the EMA Bioequivalence guideline at pH 1.2 (0.1 N HCl), pH 4.5 (acetate buffer and phosphate buffer) and pH 6.8 (phosphate buffer). The calculated f2 similarity factor values were within criteria (>50%). An f2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Design

An open label, balanced, randomised, two-treatment, two-sequence, four-period, full replicate reference scaled, cross-over, single-dose, oral bioequivalence study was carried out under fasted conditions in 34 healthy male subjects, aged 20-40 years. Each subject received a single dose (100 mg) of one of the two losartan potassium formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period of 7 or 8 days. A washout Period of 7 days was maintained between the dosing days of Period I & Period II, 8 days was maintained

between the dosing days of Period II & Period III and 7 days was maintained between the dosing days of Period III & Period IV.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable.

Losartan potassium may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of losartan potassium. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
A total of 36 subjects were enrolled for the study, one subject was withdrawn from the study in period III due to personal reasons and missed to collect last three consecutive blood samples. However, this subject was included for pharmacokinetic and statistical analysis as per protocol. Two subjects were not included in the pharmacokinetic and statistical analysis, as the subjects did not report to the clinical facility for check-in activity and hence considered as dropout. 34 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of losartan potassium, 100 mg under fasted conditions.

Treatment N=34	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1497 ± 389	1542 ± 398	1061 ± 509	0.92 (0.33 – 2.67)
Reference	1477 ± 387	1515 ± 394	1059 ± 498	1.25 (0.50 – 3.00)
***Ratio (90% CI)**	1.01 (0.97 – 1.05)	-	0.99 (0.89 – 1.10)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Losartan kalium Pharmaclan is considered bioequivalent with Cozaar 100 mg.

The results of the study with the 100 mg formulation can be extrapolated to the other strength, 50 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Losartan kalium Pharmaclan.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cozaar. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Cozaar, NL/H/1457/002-003/E001. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Losartan kalium Pharmaclan 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Cozaar 50 mg and 100 mg, film-coated tablets Cozaar is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Losartan kalium Pharmaclan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 March 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-