

Public Assessment Report

Scientific discussion

**Losartankalium/Hydrochloorthiazide Xiromed
100 mg/12.5 mg film-coated tablets
(losartan potassium and hydrochlorothiazide)**

NL/H/5817/001/DC

Date: 20 March 2026

This module reflects the scientific discussion for the approval of Losartankalium/Hydrochloorthiazide Xiromed 100 mg/12.5 mg film-coated tablets. The procedure was finalised on 8 May 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
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 Losartankalium/Hydrochloorthiazide Xiromed 100 mg/12.5 mg film-coated tablets, from Medical Valley Invest AB.

The product is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

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 Fortzaar 100 mg/12.5 mg film-coated tablets (NL/H/1458/003/DC) which has been registered by Merck Sharp & Dohme de España, S.A. since 21 June 1999. The originator product is Cozaar Comp. 100 mg/12,5 mg, filmovertrukne tabletter (NL/H/1458/002/DC), registered in the European Union by Organon N.V. since 19 April 2007.

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

II. QUALITY ASPECTS

II.1 Introduction

Losartankalium/Hydrochloorthiazide Xiromed is a round, white colour film-coated tablets embossed with a "L" on one of the faces.

The tablets contain as active substances 100 mg of losartan potassium, equivalent to 91.7 mg of losartan, and 12.5 mg of hydrochlorothiazide.

The excipients are:

Tablet core - microcrystalline cellulose (E460), pregelatinised maize starch, lactose monohydrate and magnesium stearate (E470b).

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

The film-coated tablets are packed in transparent aluminium-polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVDC) blisters.

II.2 Drug Substance

The active substances are losartan potassium and hydrochlorothiazide, both are established active substances described in the European Pharmacopoeia (Ph.Eur.).

Losartan potassium is a white or almost white, crystalline powder and is freely soluble in water. The active substance contains no chiral centres and can exist in six polymorphic forms. For this product, polymorphic form I is consistently produced.

Hydrochlorothiazide is a white or almost white, crystalline powder and is very slightly soluble in water. The active substance contains no chiral centres. Several polymorphic forms of hydrochlorothiazide were reported in literature. For this product, polymorphic form I consistently produced.

Losartan potassium

The CEP procedure is used for the active substance, and two drug substance suppliers are proposed. 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 for both drug substance suppliers; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for nitrosamine impurities, azido impurities, residual solvents and particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three batches from each active substance supplier.

Stability of drug substance

The active substance is stable for 36 or 60 months (depending on the active substance supplier) when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

Hydrochlorothiazide

The CEP procedure is used for the active substance, and three drug substance suppliers are proposed. 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 for all three drug substance suppliers; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional requirements for formaldehyde and particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for eight batches (two from site II and three batches each for site II and site III).

Stability of drug substance

The active substance is stable for 60 months, 4 years or 5 years (depending on the active substance supplier) 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 choice of excipients is justified and their functions explained. The aim was to develop a generic version of Losartan/Hydrochlorothiazide film-coated tablets product which is bioequivalent to the Fortzaar film-coated tablets reference. Development of the dissolution method and development of the formulation has been described in sufficient detail. Information on the blending, compression, coating process development and scale up of the manufacturing process was provided.

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 batches in accordance with the relevant European guidelines.

Control of excipients

All core excipients comply with Ph.Eur. requirements. In house specifications for the coating mixtures are provided. These specifications are acceptable. Excipients used in the drug products are common for this dosage form.

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, water content, identity tests for both drug substances, assay and dissolution for both drug substances, uniformity of dosage units, related substances for each drug substance and microbial contamination. Limits in the

specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scale batches 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 for three commercial scale batches stored at 25°C/ 60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The stability was tested 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 2 years. The labelled storage condition is "Do not store above 30°C".

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 Losartankalium/Hydrochloorthiazide Xiromed 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 Losartankalium/Hydrochloorthiazide Xiromed 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 Fortzaar 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 and hydrochlorothiazide are well-known active substances 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. In addition, a biowaiver for the 100 mg/12.5 mg strength is performed.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Losartankalium/Hydrochloorthiazide 100 mg/25 mg film-coated tablets (Laboratorios Liconsa, S.A., Spain) was compared with the pharmacokinetic profile of the reference product Fortzaar 100 mg/25 mg film-coated tablets (Merck Sharp & Dohme de España, S.A., Spain).

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. A biowaiver of strength for the 100 mg/12.5 mg Losartan/Hydrochlorothiazide film-coated tablets was supported by dissolution data at pH 1.2, 4.5 and 6.8. Since the dissolution profiles were similar to the reference strength, waiving *in vivo* testing for the 100/12.5 mg strength is considered acceptable.

Biowaiver

A biowaiver is requested for the 100 mg/12.5 mg strength, based on the provided bioequivalence data for the 100 mg/25 mg strength.

The following general requirements were met so a waiver for additional strength could be claimed according to the EMA Bioequivalence guideline:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths
- appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Furthermore, the MAH provided EPAR and literature-sourced information on dose linearity of hydrochlorothiazide in support of the requested biowaiver of strengths. As a result, the biowaiver of strength for the 100 mg 12.5 mg strength can now be granted.

Bioequivalence study

Design

A single-dose, balanced, randomised, open label, four-period, two-treatment, two-sequence, full replicate crossover bioequivalence study was carried out under fasted conditions in 38 healthy male/female subjects, aged 18-45 years. Each subject received a single dose (100 mg losartan and 25 mg hydrochlorothiazide) of one of the two losartan/hydrochlorothiazide 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 seven days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

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

Three subjects were withdrawn from the study on medical grounds in study period I: one subject because of cough and wheezing, another subject for pain and redness over left forearm at cannulation site and the third subject experienced a single episode of syncope.

In period II, one subject discontinued on her own accord and another subject was withdrawn from the study on medical grounds (itching and redness over groin region).

One subject was withdrawn from the study on medical grounds (boil over philtrum) in period III. In this period, the subject that discontinued on her own accord in the previous period was reintroduced to the study population.

In period IV, the subject that was withdrawn from the study on medical grounds in the previous period was reintroduced to the study population. Another subject discontinued on his own accord in period IV. Thirty-four subjects were eligible for pharmacokinetic analysis.

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

Treatment N=34	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	C _{max} (ng/ml)	t _{max} (h)
Test	1729 $\pm$ 705	1749 $\pm$ 713	1042 $\pm$ 518	1.00 (0.50-2.68)
Reference	1659 $\pm$ 717	1678 $\pm$ 725	999 $\pm$ 648	1.33 (0.50-4.00)
*Ratio (90% CI)	1.06 (1.00-1.13)	1.06 (1.00-1.12)	1.11 (0.99-1.248)	-
AUC_{0-∞} 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 = 72 hours C_{max} Maximum plasma concentration t_{max} Time after administration when maximum plasma concentration occurs CI Confidence interval				

**In-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ (median, range)) of hydrochlorothiazide, 25 mg under fasted conditions.

Treatment N=34	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	C _{max} (ng/ml)	t _{max} (h)
Test	1296 $\pm$ 317	1327 $\pm$ 325	178 $\pm$ 44	2.33 (0.75-5.00)
Reference	1234 $\pm$ 363	1265 $\pm$ 370	172 $\pm$ 51	2.67 (1.00-5.00)
*Ratio (90% CI)	1.06 (1.01-1.12)	1.06 (1.01-1.11)	1.06 (1.00-1.13)	-
AUC_{0-∞} 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 = 72 hours C_{max} Maximum plasma concentration t_{max} Time after administration when maximum plasma concentration occurs CI Confidence interval				

**In-transformed values*

Conclusion on bioequivalence study:

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Losartankalium/Hydrochloorthiazide 100 mg/25 mg film-coated tablets are considered bioequivalent with Fortzaar 100/25 mg.

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 Losartankalium/Hydrochloorthiazide Xiromed. At the time of approval, the most recent version of the RMP was version 0.1 dated 29 May 2023.

Table 3. 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 Fortzaar. 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 Comp. 50 mg/12.5 mg, 100 mg/12.5 mg, 100 mg/25 mg film-coated tablets, NL/H/1458/002, for key safety messages. Design/layout is bridged with another product of Laboratorios Liconsas S.A.: Losartan potassium/Hydrochlorothiazide 50 mg/12.5 mg, 100 mg/25 mg filmcoated tablets. The applicant demonstrated that the 'parent' and 'daughter' leaflet(s) are sufficiently similar for bridging. 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

Losartankalium/Hydrochloorthiazide Xiromed 100 mg/12.5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Fortzaar 100 mg/12,5 mg film-coated tablets. Fortzaar 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 Losartankalium/Hydrochloorthiazide Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 May 2024.

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
NL/H/5817/IB/001/G	Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier. - Re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data. Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	No	10-2-2025	Refused	The proposed grouped variation is not acceptable since the proposed re-test period of 60 days is not justified. It has not been demonstrated that all parameters included in the active substance specification comply with the acceptance criteria during the proposed re-test period.
NL/H/5817/001/IA/003	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products	Yes	18-2-2025	Approved	N.A.

	- Other variation.				
NL/H/5817/001 /IB/002	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH.	Yes	20-2-2025	Approved	N.A.
NL/H/5817/001 /IA/004	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process.	No	14-4-2025	Approved	N.A.
NL/H/5817/001 /IA/005/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	No	23-01-2026	Approved	N.A.