COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Chloortalidon Glenmark 12.5 mg, 25 mg and 50 mg tablets (chlortalidone)

NL/H/5822/001-003/DC

Date: 8 December 2025

This module reflects the scientific discussion for the approval of Chloortalidon Glenmark 12.5 mg, 25 mg and 50 mg tablets. The procedure was finalised on 10 April 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 Chloortalidon Glenmark 12.5 mg, 25 mg and 50 mg tablets, from Glenmark Arzneimittel GmbH.

The product is indicated in adults for the treatment of:

- Hypertension
- Stable, chronic heart failure (*New York Heart Association, NYHA functional class II or III*)
- Hepatic and nephrogenic oedema
- Renal diabetes insipidus if other medicinal measures are unsuitable

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

For the 25 mg and 50 mg strengths, the marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

For the 12.5mg strength, the marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application.

In this decentralised procedure, essential similarity is proven between the new product and a European Reference Product (ERP), Hygroton 25 mg and 50 mg tablets (NL RVG 33245), which have been registered in the Netherlands by Trommsdorf GmbH & Co.KG since 8 May 1990.

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

II. QUALITY ASPECTS

II.1 Introduction

Chloortalidon Glenmark are white to off-white, round shaped flat uncoated tablets.

The 12.5 mg tablets are engraved with “Y” on one side and “37” on other side. Each tablet contains as active substance 12.5 mg of chlortalidone.

The 25 mg tablets are plain on one side and on the other side engraved with “Y” and “53” on either side of the break line. Each tablet contains as active substance 25 mg of chlortalidone.

The 50 mg tablets are plain on one side and on the other side engraved with “Y” and “55” on either side of the break line. Each tablet contains as active substance 50 mg of chlortalidone.

The excipients are: cellulose microcrystalline (E460), lactose monohydrate, sodium starch glycolate (Type A), povidone K30 (E1201), colloidal anhydrous silica (E551), magnesium stearate (E470b) and purified water.

The three tablet strengths are dose proportional.

The tablets are packed in aluminium/aluminium (Alu/Alu) blisters or white opaque polyvinyl chloride/polyvinylidene chloride (PVC/PVDC) blisters. The blisters are packed in cardboard cartons.

II.2 Drug Substance

The active substance is chlortalidone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or yellowish-white powder which is very slightly soluble in water, soluble in acetone and in methanol and practically insoluble in methylene chloride. Chlortalidone shows polymorphism (crystalline form I).

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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and additional requirements of the CEP, with additional in-house tests and acceptance limits for residual solvents, polymorphic identity, particle size distribution and microbiological quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 60 months 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 main development studies performed were the characterisation of the reference product, dissolution method development, comparative dissolution studies (complementary to the bioequivalence study and in support of the biowaiver of strength), formulation optimisation studies and the subdivision of tablets study. The dissolution development has been adequately described and discriminatory power is demonstrated.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. 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 the Ph.Eur. requirements and additional in-house tests for microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, silica colloidal anhydrous, magnesium stearate and purified water are performed. 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 description, identification, average weight, dissolution, uniformity of dosage units, related substances, assay, water content and microbial examination of non-sterile products. 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 pilot scale batches of each 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 for three production scale batches of each strength stored at 25°C/ 60% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for six months at accelerated and twelve months at long term conditions. No significant changes or trends are observed in the conducted stability studies. 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.

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 Chloortalidon Glenmark 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 Chloortalidon Glenmark 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

The 25 mg and 50 mg strengths of this product are generic formulations of Hygroton and the 12.5 mg strength is a hybrid formulation of Hygroton 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

Chlortalidone 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 in which the pharmacokinetic profile of the test product Chloortalidon Glenmark 12.5 mg, 25 mg and 50 mg tablets (Glenmark Arzneimittel GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Hygroton 25 mg and 50 mg tablets (Trommsdorf GmbH & Co.KG, Germany).

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

A biowaiver of strength for the 12.5 mg and 25 mg tablets, based on the bioequivalence study with the 50 mg, can be granted as:

a. the strengths have been manufactured by the same process and manufacturer
b. the qualitative composition of the different strengths are the same
c. the composition of the strengths are quantitatively proportional
d. the pharmacokinetics of chlorthalidone can be considered dose-linear over the 12.5 mg – 50 mg dose range

The dissolution is comparable for the strengths at pH 1.2, 4.5 and 6.8. 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.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 21-44 years. Each subject received a single dose (50 mg) of one of the two chlortalidone formulations. The subjects fasted overnight for at least 10 hours. The tablet was orally administered with 240 ml water 30 minutes after consumption of a standardised high fat, high caloric breakfast (937 kcal). There were two dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120 144 and 168 hours after administration of the products.

The design of the study is acceptable.

During treatment with Chloortalidon Glenmark, patients should ensure adequate fluid intake and eat potassium-rich foods (bananas, vegetables, nuts) because of increased depletion of potassium.

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
Out of the dosed 36 subjects, 33 subjects completed the clinical phase of the study successfully. One subject discontinued from the study as he was found positive in urine alcohol test during check in of period II. Another subject discontinued from the study due to adverse event (nausea and vomiting) after dosing in period I. A third subject discontinued from the study due to adverse event (vomiting) after dosing in period II of the study. A total of 33 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of chlortalidone, 50 mg under fed conditions.

Treatment N=33	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	11173 ± 1966	12257 ± 2381	360 ± 68	3.00 (1.33 - 6.00)
Reference	11360 ± 1933	12404 ± 2329	332 ± 61	4.50 (1.33 - 10.00)
***Ratio (90% CI)**	0.98 (0.96 - 1.01)	-	1.08 (1.04 - 1.13)	-

$AUC_{0-\infty}$	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 = 168 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 Chloortalidon Glenmark is considered bioequivalent with Hygroton 50 mg tablets.

The results of the BE study with the 50 mg formulation can be extrapolated to other strengths, 12.5 mg and 25 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 Chloortalidon Glenmark. At the time of approval, the most recent version of the RMP was version 0.1 dated 28 March 2023.

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 Hygroton. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Additionally, a biowaiver is granted for the 12.5 mg strength. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test with 5 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Chloortalidon Glenmark 25 mg and 50 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Hygroton 25 mg and 50 mg tablets. The 12.5 mg tablets are a

hybrid form of Hygroton. Hygroton 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 Chloortalidon Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 April 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/5822/001 -003/E/001	Repeat-use application: CMS Portugal added	No	6-1-2025	Approved	N.A.
NL/H/5822/001 -003/IA/001	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance - Minor changes to an approved test procedure	No	12-3-2025	Approved	N.A.
NL/H/5822/001 -003/IA/002	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Yes	7-4-2025	Approved	N.A.
NL/H/5822/001 -003/IB/003	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation: To add a new ERA report	Yes	12-9-2025	Refused	Assessment report was found unacceptable