COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Chloortalidon 12.5 mg Focus Care, tablets (chlortalidone)

NL License RVG: 125763

Date: 22 December 2022

This module reflects the scientific discussion for the approval of Chloortalidon 12.5 mg Focus Care. The marketing authorisation was granted on 9 April 2021. 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
EEC	European economic community
ERA	Environmental Risk Assessment
FRC	Functionality Related Characteristics
ICH	International Conference of Harmonisation
KF	Karl Fischer
L/S	Liquid/solid
MAH	Marketing Authorisation Holder
PDE	Permitted Daily Exposure
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Chloortalidon 12.5 mg Focus Care, tablets, from Focus Care Pharmaceuticals B.V.

This medicinal product is indicated for:

- Arterial hypertension, essential or nephrogenic, to the extent that the creatinine clearance exceeds 30 ml min; as monotherapy or in combination with other antihypertensive agents
- Stable, chronic mild to moderate heart failure (functional class II or III), as far as the creatinine clearance exceeds 30 ml/min
- Oedema of a certain origin
- Oedema due to nephrotic syndrome, only in normokalaemic patients without signs of volume depletion or severe hypoalbumin
- Ascites due to cirrhosis of the liver in stable patients under strict supervision
- Prophylaxis of recurring calcium oxalate calculi in patients with idiopathic, normocalcaemic hypercalciuria

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a hybrid application claiming essential similarity with the innovator product Hygroton 50 mg, tablet, (NL RVG 33245) which has been registered in the Netherlands by Trommsdorf GmbH & Co.KG (Germany) since 8 May 1990 (original product). The difference of the proposed product with the reference product is the change in strength (quantitative change to the active substance).

Chlortalidone is approved and available in several European countries. The first marketing authorisation for the original product, Higrotona, 50 mg, tablets, within the European economic community (EEC) was granted in Spain on 1st April 1968 to Amdipharm Limited. Consequently, the data protection period is already expired and reference can be made to the non-clinical and clinical documentation of the reference products.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Chloortalidon Focus Care are white, circular and convex tablets without break line and contain as active substance 12.5 mg of chlortalidone.

The tablets are packed in blisters (PVC/PVdC/aluminium).

The excipients are microcrystalline cellulose (E460), lactose monohydrate, povidone (K-30) (E2101), sodiumstarchglycolate (type A) and magnesiumstearate (E470b).

II.2 Drug Substance

The active substance is chlortalidone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It appears as a white or yellowish-white powder and is very slightly soluble in water.

Chlortalidone shows polymorphism. Both United States Pharmacopeia (USP) and Ph. Eur. do not include in their respective monographs any mentioning of chlortalidone (CTD) polymorphic structures. However four CTD crystalline forms are described in scientific literature, more specifically, form I, form II, form III and form IV. Form I, the clinically preferred solid state polymorph, was used in all stages of development, from earlier lab laboratory runs to commercial scale validation batches.

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 European Pharmacopoeia.

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 on the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three unmilled batches.

Stability of drug substance

The active substance is stable for five years when stored in a double polyethylene lining, placed in paperboard drums. 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. Relevant information has

been provided on the drug substance: data on solubility, particle size and polymorphism. The functions of the excipients have been explained without discussing the need of using specific grades. The description of the formulation/process development is clear. It was mainly based on the 50 mg strength, the worst case scenario (the strengths 25 mg and 50 mg have also been developed by the MAH, but these strengths have not been submitted in this national NL procedure). Initially, direct compression formulation were tested in trials. However, despite in some cases of good dissolution profiles, in all cases failures were observed: e.g., highly cohesive blends (leading to unsuccessful tablet compression) or poor blend flow-ability.

Trials were continued with wet granulation formulations. Initially by the granulation liquid the dissolution profiles were retarded. Wet granulation time and amount of water were identified as critical. During wet granulation the liquid to solids ratio (L/S ratio) appears to be very important. The L/S ratio was further optimized in design of experiments (DoE) studies. Also other parameters have been investigated, such as granulation time, flow-ability, compressibility index, various particle size descriptors (d10, d50, d90), however, except for the particle size requirement no other space design limits were defined. The same 50 mg test batch has been used in a pilot biostudy and in a pivotal bio-equivalence study. The reference product (Hygroton 50 mg) was obtained from the German market. The biostudies have been assessed by the clinical assessor.

With the dissolution method having the same paddle speed in the three pH media, the test and reference bio-batches were similar; f2 values were > 50. According to the composition table the 50 mg and 12.5 mg tablet strengths were fully dose-proportional. The dissolution results between the two strengths in the three pH media were similar, the f2 values were > 50. The MAH was asked to provide additional data regarding different paddle speeds to justify the use of the chosen speed. The provided data was considered adequate to justify this. Furthermore, the MAH submitted specification data for dissolution setting the specification an amount not in line with reflection paper on the dissolution specification for immediate release products. According to the this reflection paper the set specification should be 80% (Q) in 30 min. This issue was solved through an opinion procedure and was amended adequately.

All data on the evaluation of the process parameters for manufacturing are adequate. It was already stated by the MAH that this evaluation of process parameters is not an assurance of an industrial scale-up trouble-free process. The MAH argues that at the low scales there no pivotal clinical batches. However, important critical process parameters for the wet granulation stage have been discussed, the stage where these parameters may exert a pivotal influence on the performance (dissolution) of the drug product. In this evaluation the performance of lab scale batches have been compared with commercial scale batches. The results obtained from this comparison are comparable and thus considered acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The MAH discusses the criticality of process parameters like L/S ratio, wet granulation time and compaction force. Regression model fittings are used for evaluating the effect of wet granulation parameters on two dissolution time-point results (Q=75% at 30 min

and Q=80% at 45 min). The parameters L/S ratio and wet granulation process time were the most significant factors on % dissolution at 30 min. It was clear that all studied factors have a negative effect on % dissolution at 30 and 45 min (i.e., the larger the value of the input factor the lower the dissolution at 30 or 45 min). It was also clear that the L/S ratio working range is narrowed with increased tablet strength. In other words, the higher the granulation water amount, the lower the acceptable range for tablet hardness. The in-process controls are considered acceptable. The prospective validation for the common granulate blend, the final lubricated blend, the compression process and the packaging process is considered acceptable.

Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications are acceptable. The MAH discussed the functionality related characteristics (FRCs) for the excipients if relevant for the performance of the drug product. Various FRCs have been defined.

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, Karl Fischer (KF) water content, average mass and mass uniformity, resistance to crushing of tablets, disintegration, dissolution, assay, chlortalidone related substances (single largest unspecified impurity, total impurities), uniformity of dosage units and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

All analytical procedures have been described. Sufficient validation data on the analytical procedures have been provided. Batch analysis results are provided for three batches of the 12.5 mg tablets. Batch analysis results for the requested dissolution specification should be provided.

The elemental risk evaluation as performed above is done in line with ICH Q3D. Concentrations of elemental impurities in three batches drug product are below 30% of the permitted daily exposure (PDE) limits involved. Additional control tests on elemental impurities are not deemed necessary.

Stability of drug product

Stability data on the product have been provided for four commercial scale 12.5 mg tablet batches. The batches were stored for 36 months at 25°C/60% RH, 12 months at 30°C/65% RH, and six months at 40°C/75% RH. This was in accordance with applicable European guidelines demonstrating the stability of the product for three years. All stability results meet the set requirements. It was shown in the forced degradation studies that chlortalidone both as drug substance and in the drug product is not light sensitive. On basis of the data submitted, a shelf life was granted of three years in PVC/PVdC blister packaging without specific storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose monohydrate 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 MEB considers that Chloortalidon Focus Care has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- To perform new stability studies for bulk product, considering the new proposed specification for dissolution, as soon as new batches are manufactured

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Chloortalidon Focus Care is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of chlortalidone are well known. As chlortalidone is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on a non-clinical overview is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

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 overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

For this hybrid application, the MAH has submitted two bioequivalence studies and one dissolution study, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies, one under fasted and one under fed conditions, in which the pharmacokinetic profile of the test product Chloortalidon Focus Care (Focus Care Pharmaceuticals B.V.) is compared with the pharmacokinetic profile of the reference product Hygroton 50 mg (Trommsdorf GmbH & Co.KG, Germany).

The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The analytical methods of the performed studies have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable. The design of the studies are acceptable as well.

Biowaiver

The MAH has submitted dissolution data to allow extrapolation between the Chloortalidon 50 mg Focus Care and Chloortalidon 12.5 mg Focus Care tablets and obtain a biowaiver for the 12.5 mg tablet. Based on the submitted pivotal bioequivalence study the Chloortalidon Focus 50 mg tablet is considered bioequivalent with the Hygroton 50 mg tablet.

Initially, dissolution data were submitted at several pH levels showing comparable dissolution. A higher rotation speed was applied in the paddle apparatus. However, for a biowaiver of additional strengths a lower rotation speed should be applied, as this is more sensitive to detect differences in dissolution between formulations. A higher rotation speed may be applied if justified, i.e. due to coning. An adequate drug substance release is not a considered a justification to increase to rotation speed for a biowaiver of an additional strength. Therefore, the MAH was asked to submit dissolution data with a lower rotation speed, unless it can be justified that a higher dissolution speed is needed to prevent coning. Furthermore, the calculated f2 values were below 50, which means that the comparable dissolution could not be shown.

Therefore, the MAH submitted additional data at the lower rotation speed and recalculations of the f2 values. The obtained results were considered adequate and a biowaiver on strength was granted for the 12.5 mg tablets.

Bioequivalence studies

Pilot study I

Design

A single-dose, open-label, randomized, two-way crossover, single dose bioequivalence study was carried out under fasted conditions in 16 healthy volunteers, aged 18-45 years. Each subject received a single dose (50 mg; 1 x 50 mg tablet) of both the test and the reference

(batch I or II, depending on the group) chlortalidone formulations. The subjects were divided into two groups of eight subjects; one group received the test vs. reference chlortalidone batch I and the other group the test vs. reference chlortalidone batch II. The tablets were administered after an overnight fast with 240 ml water. There were two dosing periods, separated by a washout period of 21 days.

Blood samples were taken at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 18, 24, 36, 48 and 72 hours after administration.

Results

Out of a total of 16 subjects, 15 were used for statistical analysis. One subject was withdrawn after period I due to an adverse event.

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

Treatment N=15	AUC_{0-72} (mcg.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)	Ln $AUC_{0-72\ h}$ C.I 90% (mcg.h/ml)	Ln $AUC_{0-72\ h}$ Inter/Intra (mcg.h/ml)	Ln C_{max} C.I 90% (ng/ml)	Ln C_{max} Inter/Intra (ng/ml)
Test	179 ± 40	3.7 ± 1.0	10.0 (8.0 – 24.0)	46 ± 8	--	--	--	--
Reference I	164 ± 24	3.3 ± 0.5	10.0 (9.0 – 14.0)	45 ± 9	96.4 – 113.5	11.0 – 8.4	93.8 -116.4	4.6 – 11.1
Reference II	173 ± 48	3.5 ± 1.0	11.0 (9.0 – 12.0)	48 ± 9	88.4 – 110.8	24.3 – 10.4	91.1 – 111.4	26.3 – 9.2

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half life
C.I confidence interval
Ln logarithmic

Pivotal study II

Design

A single-dose, randomised, two-treatment, crossover, single dose study under fed conditions. 22 healthy subjects, 11 females and 11 males, aged 18 - 44 years, were included in this study. Each subject received a single dose (50 mg; 1 x 50 mg tablet) of both the test and the reference chlortalidone formulations. The tablets were administered with 240 ml water 30 min after start of intake of a high fat, high caloric breakfast (milk, toast, sugar, sausage, oil and cheese). For each subject there were two dosing periods, separated by a washout period of 28 days.

Blood samples were taken pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 18, 24, 36, 48 and 72 hours after administration of the products.

According to the SmPC, the tablet should be taken preferably before breakfast. As such, the fed condition applied in this study is considered adequate.

Results

Out of a total of 22 subjects, 20 were included for statistical analysis. One subject was withdrawn after period I due to an adverse event and another subject withdrew because of a positive drug test.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of chlortalidone (test vs. reference 50 mg) under fed conditions.

Treatment N=20	**AUC_{0-72}** (mcg.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)	**AUC_{0-t}** (mcg.h/ml)
Test	231 ± 26	4.8 ± 0.7	10.0 (4.0 – 14.0)	49 ± 16	--
Reference I	228 ± 30	4.8 ± 0.7	11.0 (6.0 – 18.0)	47 ± 11	--
Ratio's (test/ref) 90% CI	--	1.00 (0.98 – 1.03)	--	--	1.02 (0.99 – 1.05)
COV (%)	--	4.9	--	--	4.7

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half life
C.I confidence interval
COV coefficient of variation

A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablet should be taken preferably before breakfast. As such, the fed condition applied in the study is considered adequate.

<u>Conclusion on bioequivalence studies</u>

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-72h}, C_{max} and t_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Chloortalidon 12.5 mg Focus Care is considered bioequivalent with Hygroton.

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).

The results obtained for the 50 mg tablet could not be extrapolated to the 12.5 mg tablet, as the conditions for a biowaiver for additional strengths were not fulfilled, i.e. a rotation speed difference between the 50 mg and 12.5 mg tablets. This was solved when the MAH submitted new data with the correct rotation speed, which was then considered to be adequate to extrapolate the results from the 50 mg tablet to the 12.5 mg tablet. This is

according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

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 Focus Care.

Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• None
Missing information	• None

The MEB 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 50 mg. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. The MAH also showed through a dissolution study that the dissolution profile of the product is similar to the dissolution 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 information leaflet (PIL) has been performed on the basis of a bridging report making reference to the package leaflets of Chloortalidon Teva 12,5 mg, tablets (RVG 28635) for key safety messages and language and Megestrolacetaat 160 mg Focus, tablets (RVG 122993) for design and layout. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Chloortalidon Focus Care, tablets has a proven chemical-pharmaceutical quality and is a generic 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. However, an opinion procedure was started to solve during the application procedure. Points of concern were the non-adequacy of the dissolution limit and the use of a higher rotation speed during the dissolution studies that was required for the approval of the biowaiver of strength. The MAH was asked to submit additional data to confirm comparable dissolution between the 50 mg and 12.5 mg tablets. The results submitted by the MAH did confirm comparable dissolution and a biowaiver of strength was granted. All outstanding issues were solved and the opinion procedure was finished with a positive outcome.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Chloortalidon Focus Care with the reference product, and have therefore granted a marketing authorisation. Chloortalidon Focus Care was authorised in the Netherlands on 9 April 2021.

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
n/a	n/a	n/a	n/a	n/a	n/a