COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Baclofen Xiromed 10 mg and 25 mg, tablets

(baclofen)

NL/H/4687/001-002/DC

Date: 25 May 2020

This module reflects the scientific discussion for the approval of Baclofen Xiromed 10 mg and 25 mg, tablets. The procedure was finalised at 19 March 2020. 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
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
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 Baclofen Xiromed 10 mg and 25 mg, tablets, from Medical Valley Invest AB.

The product is indicated for muscular spasms of spinal or cerebral origin.

Paediatric population
The product is indicated for patients 0 to <18 years for the symptomatic treatment of spasticity of cerebral origin, especially where due to cerebral palsy, as well as cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.

The product is also indicated for the symptomatic treatment of muscle spasms occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic or unknown origin, such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, diffuse or transverse myelitis, traumatic paraplegia or paraparesis and compression of the spinal cord.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lioresal 10 mg and 25 mg, tablets which has been registered in The Netherlands by Novartis Pharma B.V. since 9 February 1972.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Baclofen Xiromed 10 mg tablets are white, biconvex, circular tablets with a break line on one side. Each tablet contains 10 baclofen.
Baclofen Xiromed 25 mg tablets are white, flat-faced, bevel-edge tablets with a quadrisect marking on one side. Each tablet contains 25 baclofen.

The tablets are packed in transparent PVC/Aluminium blisters.

The excipients are microcrystalline cellulose (E 460), starch maize, povidone and magnesium stearate (E 470 b).

II.2 Drug Substance

The active substance is baclofen, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder and odourless or practically odourless. It is slightly soluble in water, very slightly soluble in methanol and in 96% ethanol, practically insoluble in acetone, insoluble in chloroform, dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Polymorphic form B is consistently produced.

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. with additional tests for residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

The active substance is stable for 5 years or 36 months (depending on the manufacturer) 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. A bioequivalence study has been performed using the 25 mg tablet strength. Comparative dissolution data has been provided between the 25 mg test and reference product used in a bioequivalence study in three media. Results show similarity. In support of the biowaiver of strength, dissolution data are provided on the 25

mg and 10 mg. The dissolution results show over 85% dissolved in 15 minutes for both products. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process consists of wet granulation followed by extra-granular mixing and compression of tablets. The process is considered a standard and has been validated according to relevant European guidelines. Process validation data on the product have been presented for a total of nine batches in accordance with the relevant European guidelines.

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, uniformity of dosage content, identification, assay, impurities, dissolution and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The shelf-life and release specifications are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two batches of the 10 mg strength and four batches of the 25 mg 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 two production scale batches of each strength stored at 25°C/60% RH (up to 24 months and 25 months for dissolution aspect) and 40°C/75% RH (6 months). A photostability study showed that the product is sensitive to light. On basis of the data submitted, a shelf life was granted of 24 months when stored below 25°C.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Baclofen 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 Baclofen Xiromed is 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Lioresal which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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

Baclofen 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Baclofen Xiromed 25 mg, tablets (Medical Valley Invest AB, Sweden) is compared with the pharmacokinetic profile of the reference product Lioresal 25 mg, tablets (Novartis Pharma B.V., Netherlands).

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

Biowaiver

A biowaiver has been requested for the lower strength. Both strengths are manufactured by the same process and the composition is qualitatively the same. Additionally, the composition of the different strengths is dose proportional. Dissolution data have been provided at a pH 1.2, 4.5 and 6.8 showing comparable dissolution. Hence, all conditions have been met and a biowaiver has been granted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 24 healthy male subjects, aged 21-43 years. Each subject received a single dose (25 mg) of one of the 2 baclofen formulations. The tablet was orally administered with 240 ml water after the start of intake of a high fat high caloric breakfast (consisting of bread toast, masala eggs, hash brown potatoes, chicken tikka and milk). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.167, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.33, 1.5, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the tablets should be taken with food. As such, the fed condition applied in the study is considered adequate.

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

All 24 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=24	**AUC_{0-t}** (ng.min/ml)	**$AUC_{0-\infty}$** (ng.min/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	1071 ± 122	1142 ± 138	177 ± 25	2.5 (1.0 - 6.0)	6.3 ± 0.6
Reference	1027 ± 121	1090 ± 135	177 ± 35	1.6 (0.5 - 4.0)	6.3 ± 0.7
***Ratio (90% CI)**	1.04 (1.02 – 1.07)	--	1.01 (0.93 – 1.09)	--	--
CV (%)	4.4	--	14.1	--	--

$AUC_{0-\infty}$	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 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of S-baclofen under fed conditions.

Treatment N=24	**AUC_{0-t}** (ng.min/ml)	**$AUC_{0-\infty}$** (ng.min/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	995 ± 113	1062 ± 125	128 ± 17	3.0 (1.5-6.0)	5.9 ± 0.5
Reference	941 ± 132	1001 ± 141	127 ± 25	2.5 (1.0 – 5.0)	6.0 ± 0.6
***Ratio (90% CI)**	1.06 (1.03 – 1.10)	--	1.02 (0.95 – 1.09)	--	--
CV (%)	6.0	--	11.5	--	--

$AUC_{0-\infty}$	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 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Baclofen Xiromed is considered bioequivalent with Lioresal.

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 Baclofen Xiromed.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	- Withdrawal symptoms - Overdose/lack of efficacy
Important potential risks	None
Missing information	- Use in pregnant and breastfeeding women

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 Lioresal. 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

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 test consisted of a pilot test, 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

Baclofen Xiromed 10 mg and 25 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Lioresal 10 mg and 25 mg, tablets. Lioresal 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 Baclofen Xiromed with the

reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 March 2020.

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