COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Leodizcol 1 mg/ml, oral solution (baclofen)

NL/H/5789/001/DC

Date: 23 October 2025

This module reflects the scientific discussion for the approval of Leodizcol 1 mg/ml, oral solution. The procedure was finalised on 13 August 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
IMP	Investigational Medicinal Product
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 Leodizcol 1 mg/ml, oral solution, from Essential Pharma Limited.

The product is indicated in:

Adults
for the symptomatic treatment of muscular spasms of spinal or cerebral origin, including treatment of spasticity in multiple sclerosis, spinal lesions and other brain diseases of vascular, neoplastic, degenerative or unknown etiology, as well as muscle spasms occurring due to traumatic brain or spinal cord injuries.

Paediatric population
for patients 0 to < 18 years for the symptomatic treatment of muscular spasms of spinal or cerebral origin, including treatment of spasticity in cerebral palsy, multiple sclerosis, spinal lesions and other brain diseases of vascular, neoplastic, degenerative or unknown etiology, as well as muscle spasms occurring due to traumatic brain or spinal cord injuries.

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 a European Reference Product (ERP), Lioresal 5mg/5ml Oral solution, which has been registered in Denmark by Novartis Healthcare A/S via a decentralised procedure (MA-number 13151) since 27 May 1988. The ERP information was circulated during validation period.

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

II. QUALITY ASPECTS

II.1 Introduction

Leodizcol 1 mg/ml, oral solution is a clear yellowish solution with an odour and flavour of raspberry. Each mL oral solution contains 1 mg baclofen as active substance.

The excipients are: sorbitol, liquid (non-crystallising) (E420), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), raspberry flavour (contains propylene glycol (E1520)), carmellose sodium (E466) and purified water.

The oral solution is packaged in a 300 mL amber glass bottle (type III) with child resistant and tamper evident high-density polyethylene/ polypropylene (HDPE/PP) cap with an low density

polyethylene (LDPE) liner and a high-density polyethylene (HDPE) ring. The bottle is packed in a cardboard carton containing a 1 mL and a 10 mL oral syringe (polypropylene (PP)) and a syringe adaptor. The 1 mL syringe is graduated every 0.05 mL and is to be used in the dosing range of up to 3 mL. The 10 mL syringe is graduated every 0.5 mL and is to be used in the dosing range of 3 mL and above.

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 crystalline powder and is slightly soluble in water, very slightly soluble in ethanol 96% and practically insoluble in acetone. The active substance also dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Baclofen shows polymorphism according to the Ph.Eur. monograph of the drug substance. However, tests for particle size and polymorphism are not deemed necessary as the drug product is an oral solution.

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 any other detectable impurity and residual solvents in accordance with the requirements from the CEP's. Batch analytical data demonstrating compliance with this specification have been provided for four commercial scaled batches.

Stability of drug substance

The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM). Based on stability data submitted by the manufacturing product, a re-test period of 5 years could be granted.

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 choices of the packaging and manufacturing process are justified in relation to the innovator. The antimicrobial preservatives methyl parahydroxybenzoate and propyl parahydroxybenzoate are both covered by Ph.Eur. monographs. A preservative efficacy test at development has been performed to determine the lowest concentration for which adequate preservative efficacy can be observed. Moreover, the applicant has demonstrated that the lower shelf life limit for the assay of preservatives is suitable to still comply with the preservative efficacy test. Discussion on the selection of the excipients and their quantities for the target (paediatric) population has been provided, as per EMA Guideline on pharmaceutical development of medicines for paediatric use. Following the recommendations of this guideline, two multi-dose measuring devices (a 1 mL and a 10 mL graduated syringe with a syringe adaptor) are included in the marketing package of the medicinal product. It has been demonstrated that the devices are suitable to measure all recommended doses as per the aforementioned EMA Guideline. Clear instructions for using the devices have been included in the package leaflet.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques and consists of mixing the drug substance with the excipients in an aqueous solution, filling and labelling. Process validation data on the product have been presented for three commercial batches.

Control of excipients

The excipients comply with Ph.Eur. requirements, except for the in-house excipient raspberry flavour that is used as flavouring agent. 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, pH, identification of baclofen and preservatives, assay of baclofen, assay of preservatives, related substances, viscosity, uniformity of mass of delivered doses from multidose container and microbial quality. The analytical methods have been adequately described. Limits in the specification at release and shelf life have been justified and are considered appropriate for adequate quality control of the product. Adequate elemental impurities and nitrosamines risk evaluation reports have been provided. Elemental impurities are lower than 30% of PDE and meet therefore the ICH Q3D requirements for oral drug products. No risk for presence of nitrosamines in the drug product was identified. The results are acceptable and no additional controls for impurities are necessary.

Adequate validation data for the analytical methods have been provided. However, for stability indication methods, additional validation data on forced degradation of the product are required. A commitment has been made to provide the results post authorisation, see section II.4 of this PAR.

Batch analytical data of five commercial batches from the proposed production site(s) have been provided demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for numerous commercial and pilot scaled batches stored for long term at 25±2°C/60±5% RH (48 months), intermediate at 30±2°C/65±5% RH (36 months) and accelerated conditions at 40±2°C/75±5% RH (6 months). Results out of specification (OOS) have been found for viscosity and a significant decrease for assay of baclofen have been found under accelerated conditions. Stability data at intermediate conditions show no OOS results. The stability was tested in accordance with the applicable European Guidelines. A photostability study according to ICH Q1B has been submitted. However this should be repeated due to inconsistencies. A commitment has been made to repeat the study and provide the results post authorisation, see section II.4 of this PAR.

On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are:

- Do not store above 30°C. Keep the bottle in the outer carton in order to protect from light. Do not refrigerate or freeze.

Furthermore, two batches of the drug product has been analysed for in-use stability under ambient conditions, following the first opening of the bottle and dilution of the drug product with purified water. Based on the results, the following in-use conditions and shelf life are acceptable:

- Use within 8 weeks after first opening.
- The medicinal product may be diluted with equal amounts of purified water. The shelf life of the diluted solution is 14 days when stored not above 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 Leodizcol 1 mg/ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- to submit additional photostability data on the drug product in line with ICH Q1B.
- to submit additional validation data of the stability indication methods (forced degradation of the drug product).

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Leodizcol 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 Lioresal 5mg/5ml 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

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 member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Leodizcol 1 mg/ml, oral solution (Essential Pharma Limited, The Netherlands) was compared with the pharmacokinetic profile of the reference product Lioresal 5mg/5ml Oral solution (Novartis Healthcare A/S, Denmark) under fed conditions.

The choice of the reference product in the bioequivalence study has been justified. A comparison study between the test and reference products has been conducted. Appearance, weight per mL, volume of fill, assay of baclofen, assay of preservatives, water content, pH, viscosity and related substances have been compared. Overall, the products can be considered comparable from a physical-chemical point of view. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence study

Design

A monocentric, open, randomised, single-dose, two-period, crossover bioequivalence study was carried out under fed conditions in 24 (14 male and 10 female) healthy subjects,

aged 26 - 55 years. Each subject received a high-fat breakfast containing 922 kcal. The subjects received 4 hours post dose a lunch of 978 kcal and 10 hours post dose a dinner of 974 kcal.

Each subject received a single dose (10 mL oral solution equivalent to 10 mg baclofen) of one of the two baclofen formulations. The oral solution was orally administered with 200 mL water, 30 minutes after the start of the breakfast. There were two dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0:10, 0:20, 0:40, 1:00, 1:20, 1:40, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, and 24:00 (hh:min) after administration of the products.

The design of the study is acceptable. As indicated in the SmPC and package leaflet, the drug product should be taken orally during meals with some liquid.

Analytical/statistical methods
The R-enantiomer (R(+)-baclofen) was chosen as the primary target parameter for the bioequivalence decision as this was considered to be the pharmacologically active agent. 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
For this study 24 subjects were enrolled. All 24 subjects received the treatment and were eligible for pharmacokinetic analysis. During the trial were five non-serious adverse events (AEs) registered for 4 subjects. Three AEs (1x palpitations, 1x dizziness, 1x headache) were observed in 3 subjects after administration of the test product. The investigator judged the dizziness as related to the product administration and the palpitations and headache as not related. Two AEs (1x diarrhoea, 1x headache) were observed in two subjects after administration of the reference product. The investigator judged the headache as related to the product administration and the diarrhoea as not related. The pattern of the AEs headache, diarrhoea and dizziness is as expected after the administration of baclofen (data from the investigators brochure).

An overview of the study results is given in Table 1.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of R(+)- baclofen , 10 mg (equivalent to 10 mL oral solution) under fed conditions.

Treatment N=24	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	422.41 (±67.87)	440.39 (±74.42)	71.03 (±15.16)	2.00 (1.00 - 3.50)
Reference	433.06 (±75.73)	450.81 (±80.72)	75.01 (±17.79)	2.00 (1.00 - 3.00)
***Ratio (90% CI)**	0.9779 0.9437 – 1.013	---	0.9517 0.9125 – 0.9926	---

$AUC_{0-\infty}$	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 the last measurable plasma concentration (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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Leodizcol 1 mg/ml, oral solution is considered bioequivalent with Lioresal 5mg/5ml Oral solution.

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 Leodizcol. At the time of approval, the most recent version of the RMP was version 0.5, sign off date 13 March 2024.

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 Lioresal 5mg/5ml. 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 language used for the purpose of user testing the PL was English.

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 Baclofen Xiromed 10 mg and 25 mg, tablets, (NL/H/4687/001-002/DC) for content and to Lyflex 5 mg/5 ml Oral Solution (PL 00427/0285) for lay out. 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

Leodizcol 1 mg/ml, oral solution has a proven chemical-pharmaceutical quality and is a generic form of Lioresal 5mg/5ml Oral solution. 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 Leodizcol 1 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 August 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/5789/ 001/IB/001	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC: - Implementation of wording agreed by the competent authority.	Yes	15-4-2025	Approved	N.A.