IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Baclofen 5mg/5ml oral solution
Baclofen
PA22697/005/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6037/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 12/09/2018 under procedure number IE/H/0766/1/DC
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/005/001
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.
12/09/2018
The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Baclofen (PL 39307/0055; UK/H/6037/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated for:

- the relief of spasticity of voluntary muscle resulting from such disorders as: multiple sclerosis, other spinal lesions, e.g. tumours of the spinal cord, syringomyelia, motor neurone disease, transverse myelitis, traumatic partial section of the cord.
- the relief of spasticity of voluntary muscle arising from e.g. cerebrovascular accidents, cerebral palsy, meningitis, traumatic head injury in adults and children.

Patient selection is important when initiating Baclofen therapy; it is likely to be of most benefit in patients whose spasticity constitutes a handicap to activities and/or physiotherapy. Treatment should not be commenced until the spastic state has become stabilised.

Paediatric population

- in patients 0 to <18 years for the symptomatic treatment of spasticity of cerebral origin, especially where due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.
- 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, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS). The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Lioresal 5mg/5ml Oral Solution (PA 0013/058/002), which was originally granted in Ireland to Novartis Pharmaceuticals UK Limited on 18 April 1994. The corresponding reference product in the UK is Lioresal Liquid (PL 00101/0503) which was authorised to the current marketing authorisation holder, Novartis Pharmaceuticals UK Limited on 21 September 1997.

Baclofen is an antispastic agent acting at the spinal level. A gamma-aminobutyric acid (GABA) derivative, Baclofen is chemically unrelated to other antispastic agents.

Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by stimulating the GABAB-receptors, this stimulation in turn inhibiting the release of the excitatory amino acids glutamate and aspartate. Neuromuscular transmission is unaffected by baclofen.

The major benefits of baclofen stem from its ability to reduce painful flexor spasms and spontaneous clonus thereby facilitating the mobility of the patient, increasing his/her independence and helping rehabilitation.

Baclofen also exerts an antinociceptive effect. General well-being is often improved and sedation is less often a problem than with centrally acting drugs.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference products are oral solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 12 January 2016. After a subsequent national phase, a licence was granted in the UK on 09 February 2016.

II. QUALITY ASPECTS

II QUALITY ASPECTS

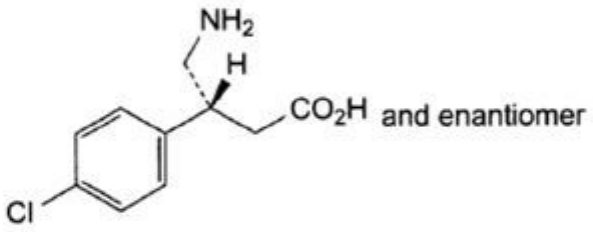
II.1 Introduction

Each 5 ml of oral solution contains 5 mg baclofen. Other ingredients consist of the following pharmaceutical excipients methyl parahydroxybenzoate (E218), sorbitol, liquid (non-crystallising) (E420), carmellose sodium (E466), raspberry flavour [contains propylene glycol (E1520)] and purified water. The finished product is packed into Ph. Eur. amber (Type III) glass bottles with a tamper evident, child resistant white plastic cap closure consisting of polypropylene inner, polyethylene outer and expanded polyethylene (EPE) liner. The product is available in a pack size of 300 ml bottles.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN: Baclofen
Chemical names: (3RS)-4-Amino-3-(4-chlorophenyl)butanoic acid

Structural formula:



Molecular formula: $C_{10}H_{12}ClNO_2$
Molecular mass: 213.7 g/mol
Appearance: A white or almost white powder.
Solubility: Slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in acetone. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

Baclofen is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, baclofen, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, oral solution containing 5 mg baclofen per 5 ml of oral solution that was comparable in performance to the originator product Lioresal 5mg/5ml Oral Solution (Novartis Pharmaceuticals UK Limited). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the raspberry flavour which is controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 12 months for the unopened bottle with the storage conditions 'Do not store above 30°C. Do not refrigerate. Store in the original packaging in order to protect from light.' The in-use shelf life of the product is 60 days after first opening.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of baclofen are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The MAH's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Baclofen 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.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

IV.1 Introduction

In line with the CPMP guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous oral solution containing the same active substance concentration as the approved reference medicinal product. No bioequivalence data have been submitted with this application and none are required.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of baclofen.

Based on the data provided, Baclofen can be considered bioequivalent to the reference product Lioresal 5mg/5ml Oral Solution (Novartis Pharmaceuticals UK Limited).

IV.2 Pharmacokinetics

In line with the CPMP guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous oral solution containing the same active substance concentration as the approved reference medicinal product. No bioequivalence data have been submitted with this application and none are required.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	• Hypersensitivity to baclofen or to any of the excipients • Use in patients with peptic ulceration • Use in patients with renal impairment • Withdrawal syndrome with abrupt withdrawal of baclofen, especially after long term medication • Neonatal convulsions after intrauterine exposure • Mental confusion, hallucinations, nausea and agitation in patients with Parkinson's disease receiving treatment with baclofen and levodopa (alone or in combination with Dopa decarboxylase (DDC) inhibitor, carbidopa) • Hypotension on concomitant use of antihypertensives and concomitant use of morphine with intrathecal baclofen • Aggravated hyperkinetic symptoms on concomitant use with lithium • Use in patients with rare hereditary problems of fructose intolerance • Signs of central nervous depression with overdose
Important potential risks	• Use in elderly • Exacerbation of psychotic disorders, schizophrenia, depressive or manic disorders, confusional states, Parkinson's disease and epileptic manifestations • Use in patients suffering from cerebrovascular accidents and respiratory or hepatic impairment

Summary of safety concerns	
	• Acute retention of urine in patients with pre-existing sphincter hypertonia • Elevation of aspartate aminotransferase, blood alkaline phosphatase and blood glucose levels in serum • Increased sedation on concomitant use with other drugs causing central nervous system (CNS) depression including other muscle relaxants, synthetic opiates and alcohol • Pronounced muscular hypotonia on concomitant use of tricyclic antidepressants • Use during pregnancy • Dizziness, sedation, somnolence and visual impairment leading to impairment of patient's reaction • Use in patients on controlled sodium diet • Serious adverse effects in neonates on co-administration with any substrate of alcohol dehydrogenase
Important missing information	• Use in children under the age of one year

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

No new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

A bioequivalence study was not necessary to support this application as both test and reference products are aqueous oral solutions at the time of administration.

The grant of a marketing authorisation is recommended for this application.

V User consultation

The package leaflet 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 PIL was English.

The results show that the package leaflet 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.*

V. OVERALL CONCLUSIONS

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with baclofen is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

24/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE

		AFFECTED		
RMS transfer	From UK/H/6037/1/DCto IE/H/0766/1/DC			