Public Assessment Report

Decentralised Procedure

Baclofen 5mg/5ml Oral Solution

(Baclofen)

Procedure No: UK/H/6037/001/DC

UK Licence No: PL 39307/0055

Syri Limited (trading as Thame Laboratories).
LAY SUMMARY

Baclofen 5mg/5ml Oral Solution
(baclofen, oral solution, 5mg/5ml)

This is a summary of the Public Assessment Report (PAR) for Baclofen 5mg/5ml Oral Solution (PL 39307/0055; UK/H/6037/001/DC). It explains how Baclofen 5mg/5ml Oral Solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Baclofen 5mg/5ml Oral Solution.

The product will be referred to as Baclofen throughout the remainder of this PAR.

For practical information about using Baclofen, patients should read the package leaflet or contact their doctor or pharmacist.

What is Baclofen and what is it used for?
Baclofen is a ‘generic medicine’. This means that Baclofen is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Lioresal 5mg/5ml Oral Solution (Novartis Pharmaceuticals UK Limited).

Baclofen is used to reduce and relieve the excessive tension in the patient’s muscles (spasms) occurring in various illnesses such as cerebral palsy, multiple sclerosis, cerebrovascular accidents, spinal cord diseases and other nervous system disorders.

How does Baclofen work?
Baclofen (the active ingredient in this medicine) belongs to a group of medicines called muscle-relaxant drugs. This medicine relaxes skeletal muscles; the muscles that move the skeleton (and also called striated muscle).

How is Baclofen used?
The pharmaceutical form of Baclofen is an oral solution and the route of administration is via the mouth (oral).

The patient must take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

The patient’s doctor will tell the patient the best time to take the medicine. Some people take it only at night or before doing a task such as washing, dressing, shaving, etc.

The final dose of Baclofen depends on how each person responds to the drug. The patient will be started on a low dose, and this will be increased gradually over a few days, under the supervision of the doctor, until the patient is having the dose which is right for them. If the starting dose is too high, or if the dose is increased too quickly, the patient may experience side effects, particularly if the patient is elderly, has kidney problems or has had a stroke.

The patient should not stop taking Baclofen suddenly. If the doctor decides to stop their treatment with Baclofen, the dose will be reduced gradually to prevent withdrawal symptoms such as muscle spasms and increased muscle rigidity, fast heart rate, fever, confusion, hallucinations, changes in mood and emotion, mental disorders, feeling persecuted or convulsions (fits).
Baclofen should be taken during meals with a little liquid. If the patient feels sick after taking Baclofen, they may find it helps to take it with food or a milk drink.

**Adults**
- The usual dose is 20ml (20mg) three times a day
- The maximum daily dose is 100ml (100mg) except if the patient is in hospital when a higher dose may be used.

**Children (0 < 18 years)**
Children’s treatment is adjusted to their body weight. Children’s treatment usually starts with a very low dose (approximately 0.3 mg/kg/day), in 2-4 divided doses (preferably in 4 doses). The dosage is then gradually increased until it becomes sufficient for the child’s individual requirements, this may be between 0.75 and 2 mg/kg body weight.
The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Baclofen can only be obtained with a prescription.

**What benefits of Baclofen have been shown in studies?**
No additional studies were needed as Baclofen is a generic medicine that is taken orally, as a solution, and contains the same active substance, in the same concentration, as the reference medicine, Lioresal 5mg/5ml Oral Solution (Novartis Pharmaceuticals UK Limited).

**What are the possible side effects of Baclofen?**
Because Baclofen is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Baclofen, see section 4 of the package leaflet available on the MHRA website.

**Why was Baclofen approved?**
It was concluded that, in accordance with EU requirements, Baclofen has been shown to have comparable quality and to be comparable to Lioresal 5mg/5ml Oral Solution (Novartis Pharmaceuticals UK Limited). Therefore, the MHRA decided that, as for Lioresal 5mg/5ml Oral Solution (Novartis Pharmaceuticals UK Limited), the benefits are greater than their risk and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Baclofen?**
A risk management plan (RMP) has been developed to ensure that Baclofen is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Baclofen including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.
Other information about Baclofen
Ireland and the UK agreed to grant a Marketing Authorisation for Baclofen on 12 January 2016. A Marketing Authorisation was granted in the UK on 09 February 2016.

The full PAR for Baclofen follows this summary.

For more information about treatment with Baclofen read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2016.
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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.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:

![Structural formula of Baclofen](image)

Molecular formula: \( \text{C}_{10}\text{H}_{12}\text{ClNO}_{2} \)
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.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.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:

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<th>Summary table of safety concerns</th>
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<td>Use in patients with renal impairment</td>
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<td>Withdrawal syndrome with abrupt withdrawal of baclofen, especially after long term medication</td>
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<td>Neonatal convulsions after intrauterine exposure</td>
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<td>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)</td>
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<td>Hypotension on concomitant use of antihypertensives and concomitant use of morphine with intrathecal baclofen</td>
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<td>Aggravated hyperkinetic symptoms on concomitant use with lithium</td>
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<td>Use in patients with rare hereditary problems of fructose intolerance</td>
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<td>Signs of central nervous depression with overdose</td>
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<tr>
<th>Important potential risks</th>
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<td>Use in elderly</td>
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<td>Exacerbation of psychotic disorders, schizophrenia, depressive or manic disorders, confusional states, Parkinson’s disease and epileptic manifestations</td>
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<tr>
<td>Use in patients suffering from cerebrovascular accidents and respiratory or hepatic impairment</td>
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### Summary of safety concerns

<table>
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<th>Important missing information</th>
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<tr>
<td>• Use in children under the age of one year</td>
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| • 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 |

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.

### 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.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Baclofen is presented below: