



Public Assessment Report

National Procedure

Baclofen 10mg/5ml Oral Solution

(baclofen)

PRODUCT LICENCE NUMBER:

PL 39307/0090

Syri Limited trading as Thame Laboratories.

LAY SUMMARY

Baclofen 10mg/5ml Oral Solution (baclofen)

This is a summary of the Public Assessment Report (PAR) for Baclofen 10mg/5ml Oral Solution. It explains how this product 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 this product.

For practical information about using Baclofen 10mg/5ml Oral Solution patients should read the package leaflet or contact their doctor or pharmacist.

What is Baclofen 10mg/5ml Oral Solution and what is it used for?

This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Lioresal 10 mg Tablets.

Baclofen 10mg/5ml Oral Solution 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 10mg/5ml Oral Solution work?

Baclofen 10mg/5ml Oral Solution contains the active ingredient baclofen which is a muscle-relaxant drug. Baclofen works by relaxing the muscles, which reduces pain and discomfort.

How is Baclofen 10mg/5ml Oral Solution used?

The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (via the mouth).

The patient should always take Baclofen 10mg/5ml Oral Solution 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 them how much Baclofen 10mg/5ml Oral Solution to take and when to take it. The patient should always follow his/her instructions carefully. The dose will be on the pharmacist's label. Check the label carefully. If the patient is not sure, they should ask their doctor or pharmacist.

The 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 10mg/5ml Oral Solution 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 they are 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 they are elderly, have kidney problems or have had a stroke.

If the patient feels sick after taking Baclofen 10mg/5ml Oral Solution, they may find it helps to take it with food or a milk drink.

The recommended dose is:**Adults**

The usual dose is 20mg (10ml) three times a day.

The maximum daily dose is 100mg (50ml) except if the patient is in hospital when a higher dose may be used.

Children (0 to < 18 years)

Children's treatment is adjusted to their body weight. Children's treatment usually starts with a very low dose [approximately 0.3mg/kg/day (0.15ml/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 0.75mg/kg (0.375ml/kg) and 2mg/kg (1ml/kg) body weight. The total daily dose should not exceed a maximum of 40mg/day (20ml/day) in children below 8 years of age.

In children over 8 years of age a maximum daily dose of 60mg/day (30ml/day) may be given.

In children under 8 years of age, or for individual doses less than 10mg, the patient's doctor is likely to prescribe Baclofen 5mg/5ml Oral Solution.

Patients with kidney problems

Patients with kidney problems will probably be given a much lower dose. The doctor will decide what the dose should be.

For further information on how Baclofen 10mg/5ml Oral Solution is used, including the route and method of administration, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Baclofen 10mg/5ml Oral Solution have been shown in studies?

Because Baclofen 10mg/5ml Oral Solution is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Baclofen 10mg/5ml Oral Solution?

Because Baclofen 10mg/5ml Oral Solution is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Baclofen 10mg/5ml Oral Solution approved?

It was concluded that, in accordance with EU requirements, Baclofen 10mg/5ml Oral Solution has been shown to be comparable to and bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Baclofen 10mg/5ml Oral Solution

A Risk Management Plan (RMP) has been developed to ensure that Baclofen 10mg/5ml Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, 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 and reviewed continuously.

Other information about Baclofen 10mg/5ml Oral Solution

A Marketing Authorisation for Baclofen 10mg/5ml Oral Solution was granted in the UK on 06 June 2019.

The full PAR for Baclofen 10mg/5ml Oral Solution follows this summary.

This summary was last updated in July 2019.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Baclofen 10mg/5ml Oral Solution (PL 39307/0090) could be approved.

The product is approved for the following indications:

- 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.
- in adults and children for the relief of spasticity of voluntary muscle arising from e.g. cerebrovascular accidents, cerebral palsy, meningitis, traumatic head injury.

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

Baclofen is indicated 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.

Baclofen 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, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

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 GABA_B 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 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.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine. The reference medicinal product is Lioresal 10 mg Tablets (PL 00101/0504), which was granted a marketing authorisation in the UK to Novartis Pharmaceuticals UK Limited on 21 September 1997.

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

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A Marketing authorisation was granted for this product on 06 June 2019.

II QUALITY ASPECTS

II.1 Introduction

Each 5ml of oral solution contains 10mg of the active ingredient baclofen.

In addition to baclofen, this product also contains the excipients methyl parahydroxybenzoate, carmellose sodium, liquid sorbitol (non-crystallising), raspberry flavour [containing propylene glycol (E1520)] and purified water.

The finished product is packaged in Type III amber glass bottles with a tamper evident, child resistant white plastic cap consisting of polypropylene inner, polyethylene outer, expanded polyethylene (EPE) liner. The finished product is supplied with dosing devices (1ml oral syringe with 0.01ml graduation and 10ml syringe with 0.2ml graduation and a syringe adaptor) and is available in a pack size of 150 ml.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

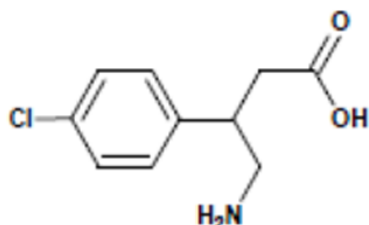
II.2 ACTIVE SUBSTANCE(S)

rINN: Baclofen

Chemical Name: (3RS)-4-amino-3-(4-chlorophenyl)butanoic acid

Molecular Formula: C₁₀H₁₂ClNO₂

Chemical Structure:



Molecular Weight: 213.66 a.m.u.

Appearance: White or almost white powder

Solubility: Slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in acetone.

Baclofen is the subject of a European Pharmacopoeia monograph.

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

II.3 DRUG PRODUCT(S)

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product(s)

A description and flow-chart of the manufacturing method has been provided.

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 and has shown satisfactory results.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that complies with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months with the storage conditions 'Store below 25°C. Store in the original packaging in order to protect from light. Discard 90 days after first opening', is acceptable.

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

The grant of a marketing authorisation is recommended.

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.

III.2 Pharmacology

No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology

No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of baclofen are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV.2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study:

STUDY

This study was a randomised, open label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study comparing the test product Baclofen 10mg/5ml Oral Solution versus the reference product Lioresal 10mg Tablets in subjects under fasted conditions.

Following an overnight fast of at least 10.5 hours, subjects were administered a single 5 ml dose (oral solution) of the test product or a single 10 mg tablet of the reference product, with 240 mL water. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 10 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Table: Geometric means, ratios and 90% Confidence Interval for baclofen

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC _{0-t}	1085.8175	1178.5476	92.1318	89.0823	95.2857
C _{max}	169.0565	190.0541	88.9518	84.2768	93.8861

**Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.*

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

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

V USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to Baclofen 5mg /5ml Oral Solution (Syri Limited t/a Thame Laboratories). The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

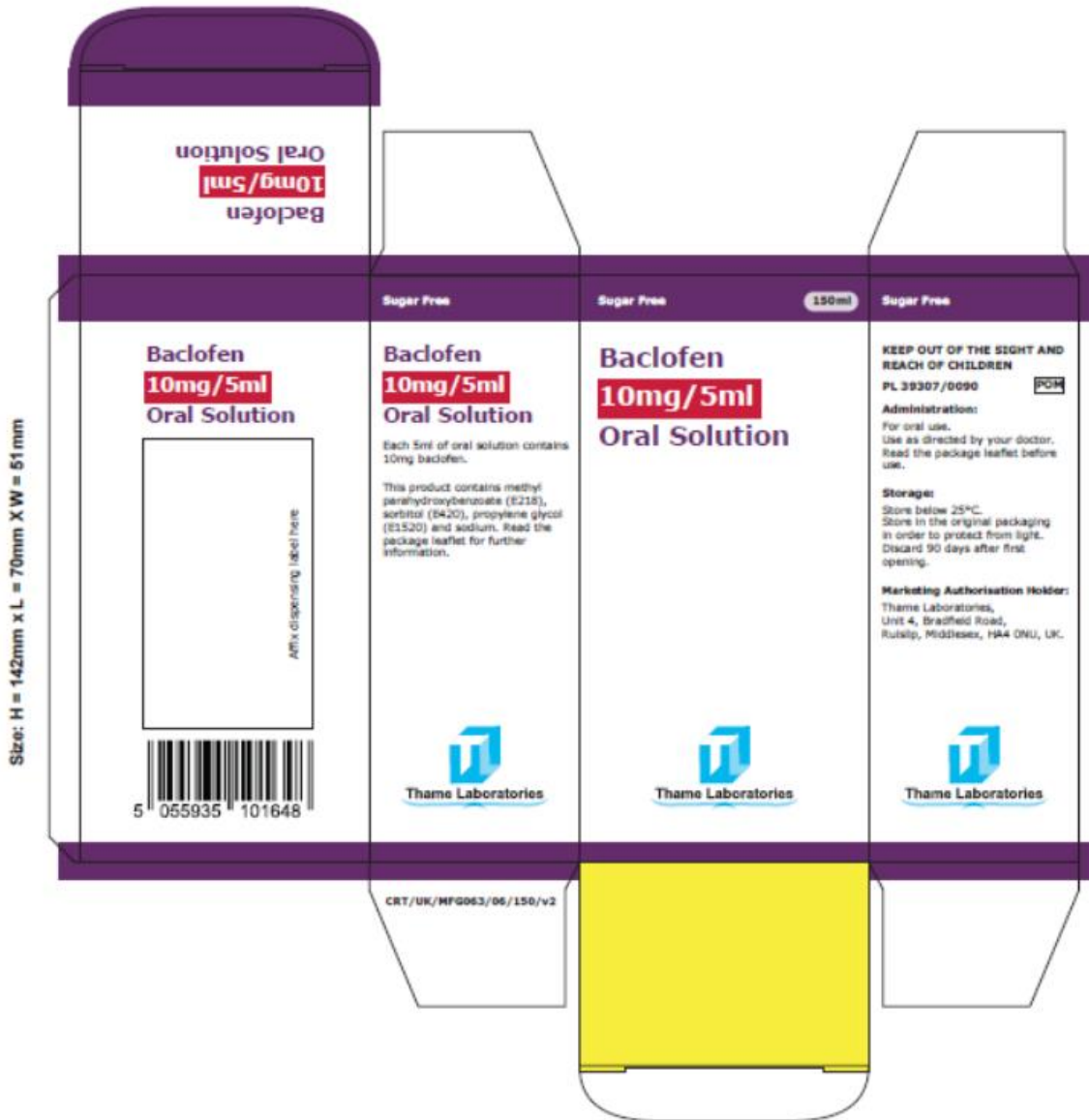
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with baclofen is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product(s).

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.

<p>Each 5ml of oral solution contains 10mg baclofen.</p>	<p>Sugar Free</p>	<p>150ml</p>	<p>Batch:</p>
<p>This product contains methyl parahydroxybenzoate (E218), sorbitol (E420), propylene glycol (E1520) and sodium. Read the package leaflet for further information.</p>	<p>Baclofen 10mg/5ml Oral Solution</p>		<p>Exp:</p>
<p>KEEP OUT OF THE SIGHT AND REACH OF CHILDREN</p>			<p>Marketing Authorisation Holder:</p>
<p>PL 39307/0090</p>	<p>POM</p>	<p>Thame Laboratories, Unit 4, Bradfield Road, Ruislip, Middlesex, HA4 0NU, UK.</p>	
<p>Administration:</p>	<p>For oral use. Use as directed by your doctor. Read the package leaflet before use.</p>	 5 055935 101648	
<p>Storage:</p>	<p>Store below 25°C. Store in the original packaging in order to protect from light. Discard 90 days after first opening.</p>		



Size: H = 142mm x L = 70mm X W = 51 mm

2D barcode will be printed on the carton when introduced by the company, which would not affect the text.

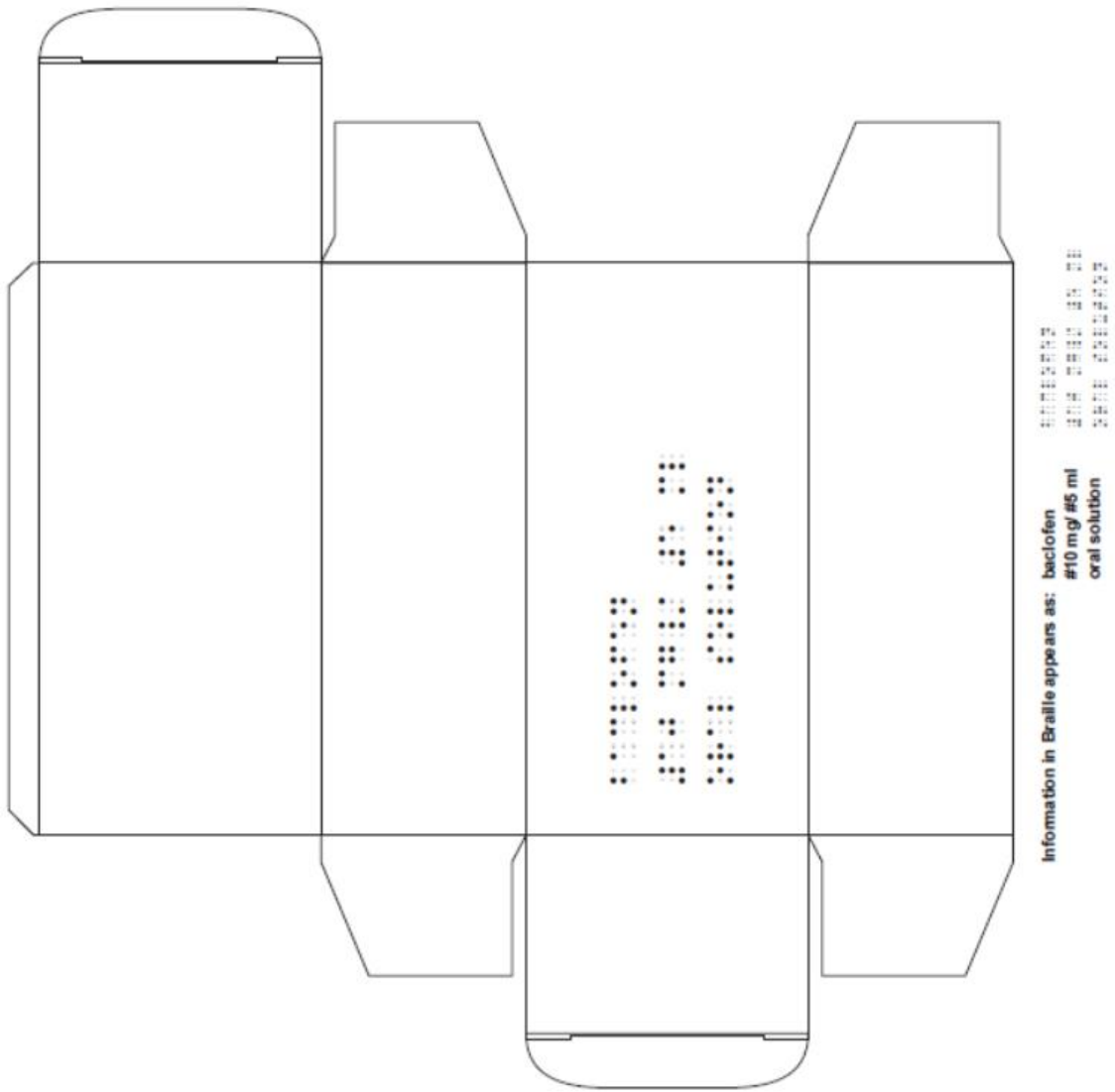


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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N