Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Baclofen 10mg Tablets
Baclofen 25mg Tablets

(baclofen)

PL 44041/0126-0127

Noumed Life Sciences Limited.

LAY SUMMARY

Baclofen 10 and 25 mg Tablets
(baclofen)

This is a summary of the Public Assessment Report (PAR) for Baclofen 10 and 25 mg Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Baclofen Tablets in this lay summary for ease of reading.

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

What are Baclofen Tablets and what are they used for?
Baclofen 10 mg Tablets
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 Tablets 10 mg.

Baclofen 25 mg Tablets
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU) called Lioresal Tablets 10 mg, albeit with certain differences. In this case, Baclofen 25 mg Tablets is for a change in strength to the reference product.

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

How do Baclofen Tablets work?
Baclofen Tablets contain the active ingredient baclofen which is a muscle-relaxant drug.

How are Baclofen Tablets used?
The pharmaceutical form of these medicines is a tablet and the route of administration is oral (via the mouth).

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 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 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 they are elderly, have kidney problems or have had a stroke.

If the patient feels sick after taking Baclofen Tablets, they may find it helps to take them with food or a milk drink.

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

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

For further information on how Baclofen Tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

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

What benefits of Baclofen Tablets have been shown in studies?
Studies in healthy volunteers have been limited to tests to determine that the medicines are 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 Tablets?
Because Baclofen 10 mg Tablets 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.

Because Baclofen 25 mg Tablets is a hybrid medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being 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 Summaries of Product Characteristics (SmPC) available on the MHRA website.

Why were Baclofen Tablets approved?
It was concluded that, in accordance with EU requirements, Baclofen 10 mg and 25mg Tablets have been shown to be comparable to and to be 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 they can be approved for use.

What measures are being taken to ensure the safe and effective use of Baclofen Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Baclofen Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs 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 Tablets
Marketing Authorisations for Baclofen Tablets were granted in the UK on 28 August 2020.

The full PAR for Baclofen Tablets follows this summary.

This summary was last updated in September 2020.

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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 applications for Baclofen 10 mg and 25 mg Tablets (PL 44041/0126-27) could be approved.

The products are approved for the following indications:

Baclofen 10 mg Tablets:

Baclofen 10 mg Tablets 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.

Baclofen 10 mg Tablets is also indicated 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 10 mg Tablets 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 10 mg Tablets 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 25 mg Tablets:

Baclofen 25mg tablets is indicated in adults 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.

Baclofen 25mg Tablets is also indicated in adults 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.

Baclofen 25mg Tablets is also indicated in adults 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.

Baclofen stimulates gastric acid secretion.

These applications were submitted under Article 10(1) and 10(3) of Directive 2001/83/EC, as amended, as a generic / hybrid medicine of a suitable originator medicinal product, Lioresal Tablets 10 mg that has been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being a generic / hybrid 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 applications are based on being a generic / hybrid 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 these products at all sites responsible for the manufacture, assembly and batch release of these products.

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

Marketing authorisations were granted for these products on 28 August 2020.

II QUALITY ASPECTS

II.1 Introduction

Each tablet contains baclofen 10 mg or 25 mg.

In addition to baclofen, these products also contain the excipients microcrystalline cellulose, maize starch, povidone, colloidal anhydrous silica and magnesium stearate.

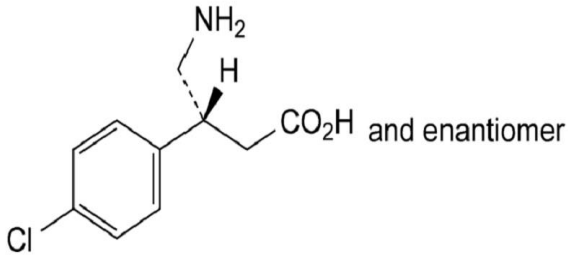
The finished products are packaged in clear transparent PVC 250 microns/ 20 microns aluminium foil blister packs of 28, 56 and 84 tablets. Baclofen 10 mg tablets is additionally available in pack sizes of 100 and 112 tablets.
Not all pack sizes may be marketed.

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

rINN: Baclofen

Chemical Name: (3*RS*)-4-Amino-3-(4-chlorophenyl)butanoic acid
Molecular Formula: $C_{10}H_{12}ClNO_2$
Chemical Structure:



Molecular Weight: 213.66 amu
Appearance: White of almost white powder.
Solubility: Slightly soluble in water, very slightly soluble in ethanol (96%); 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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and 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 products.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

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

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. 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 30 months, with the storage conditions ‘Do not store above 25°C’, 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 marketing authorisations 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 these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic / hybrid versions of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations 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 these types of applications. An overview based on a literature review and a review of this study is, thus, satisfactory.

The 25 mg is a new dosage strength to the UK market; however this has been authorised within other Member States of the EU. While this dosage strength does not cater to the typical posology (up to 60 mg daily in three divided doses); some individuals may require up to 100 mg also in divided doses for which this dosage strength may be helpful.

A clinical demonstration of bioequivalence for the 25 mg dosage strength was performed against Lioresal 25 mg Tabletten, authorised in Germany. This is accepted, given that Lioresal 25 mg Tabletten belongs to the same global marketing authorisation as the primary reference product, Lioresal 10 mg Tablets, authorised in the UK.

IV. 2 Pharmacokinetics

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

STUDY

This study was an open-label, balanced, randomised, two sequence, two period, two treatment, crossover study comparing the test product comparing the test product Baclofen 25 mg Tablets versus the reference product Lioresal 25 mg Tabletten in subjects under fed conditions.

After an overnight fast of at least 10 hours, the subjects were served a standardised high fat high calorie vegetarian breakfast, which they consumed within 30 minutes. A single dose of either the test or reference product was administered to each subject 30 minutes after breakfast according to the randomisation schedule, with 240 mL of drinking water in a sitting posture. Subjects were instructed not to chew the tablets; a mouth check was performed. Subjects remained fasting for a further 4 hours and were instructed not to drink further water for a period of 1 hour prior to dosing and 1 hour after dosing.
Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 4 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Tables:
Geometric mean ratios & 90% confidence intervals for C_{max} and AUC_{0-t}:
Test vs. Reference (log-transformed values; least square means, geometric least square means, ratio, 90 % confidence intervals and intrasubject CV%)

Relative Bioavailability Results for R-Baclofen

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
lnC_{max}	194.704	202.952	95.9	91.25 - 100.86	10.1	100.0
$lnAUC_{0-t}$	1200.069	1210.819	99.1	96.86 - 101.42	4.6	100.0
$lnAUC_{0-\infty}$	1262.637	1274.533	99.1	96.88 - 101.31	4.5	100.0

Relative Bioavailability Results for S-Baclofen

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
lnC_{max}	131.737	130.581	100.9	95.66 - 106.40	10.8	100.0
$lnAUC_{0-t}$	1082.619	1067.405	101.4	98.33 - 104.62	6.3	100.0
$lnAUC_{0-\infty}$	1135.686	1120.234	101.4	98.38 - 104.47	6.1	100.0

Tables: ANOVA p-values for formulation, sequence, period and sampling

ANOVA p-values for R-Baclofen

Parameters	ANOVA (p-value)			
	Formulation	Sequence	Period	Subject (Seq)
lnC_{max}	0.1689	0.6199	0.1546	0.0022
$lnAUC_{0-t}$	0.5128	<0.0001	0.1788	<0.0001
$lnAUC_{0-\infty}$	0.4792	<0.0001	0.1270	<0.0001

Note: p-value is statistically significant if it is < 0.05.

ANOVA p-values for S-Baclofen

Parameters	ANOVA (p-value)			
	Formulation	Sequence	Period	Subject (Seq)
lnC_{max}	0.7788	0.1860	0.7133	0.0003
$lnAUC_{0-t}$	0.4417	0.0017	0.9276	<0.0001
$lnAUC_{0-\infty}$	0.4417	0.0005	0.9865	<0.0001

Note: p-value is statistically significant if it is < 0.05.

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.

As the additional strength of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 25 mg product strength can be extrapolated to the 10 mg strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications 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 these applications.

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 marketing authorisations is recommended for these applications.

V USER CONSULTATION

The Patient Information Leaflet (PIL) 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 results show that the PIL 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.

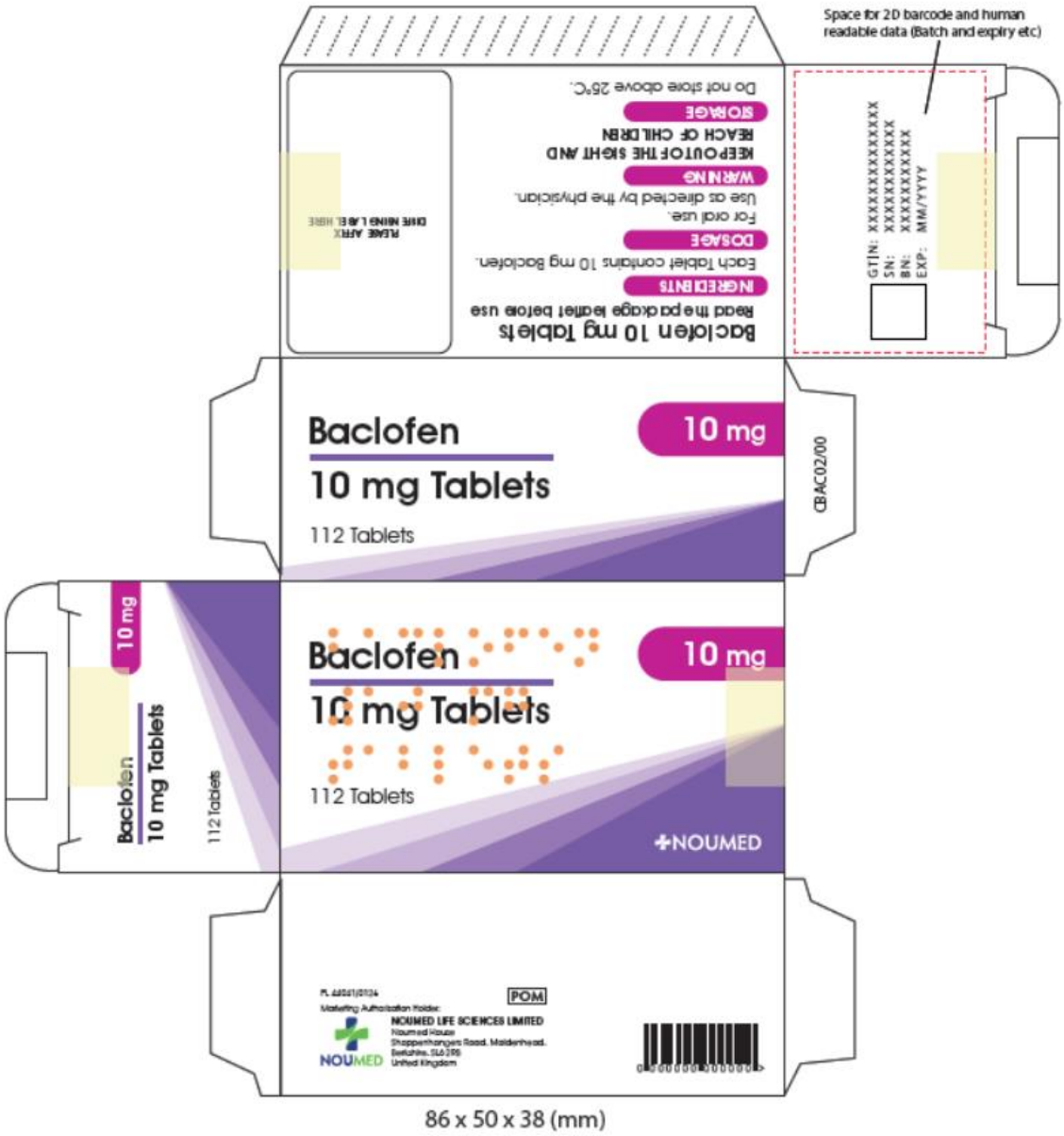
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

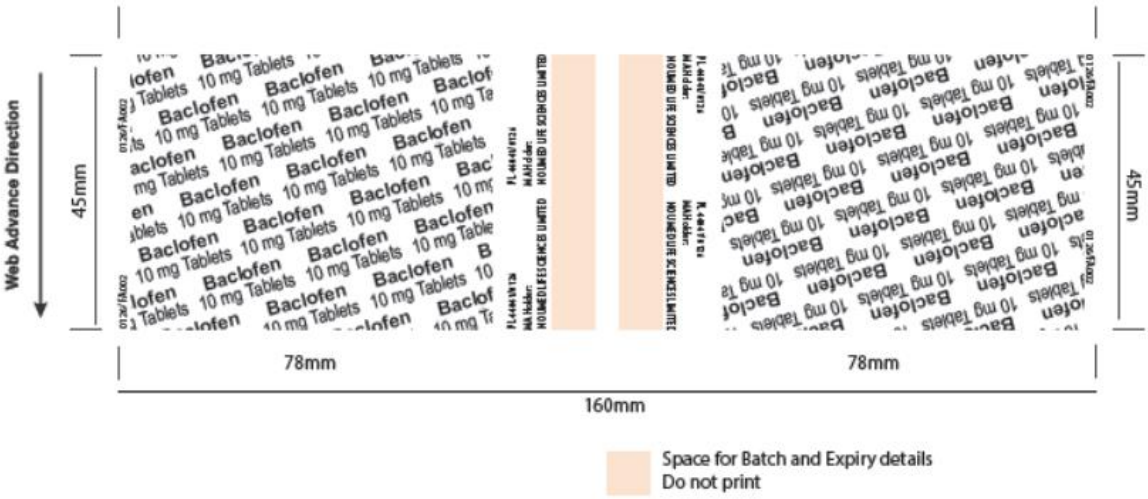
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with baclofen is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

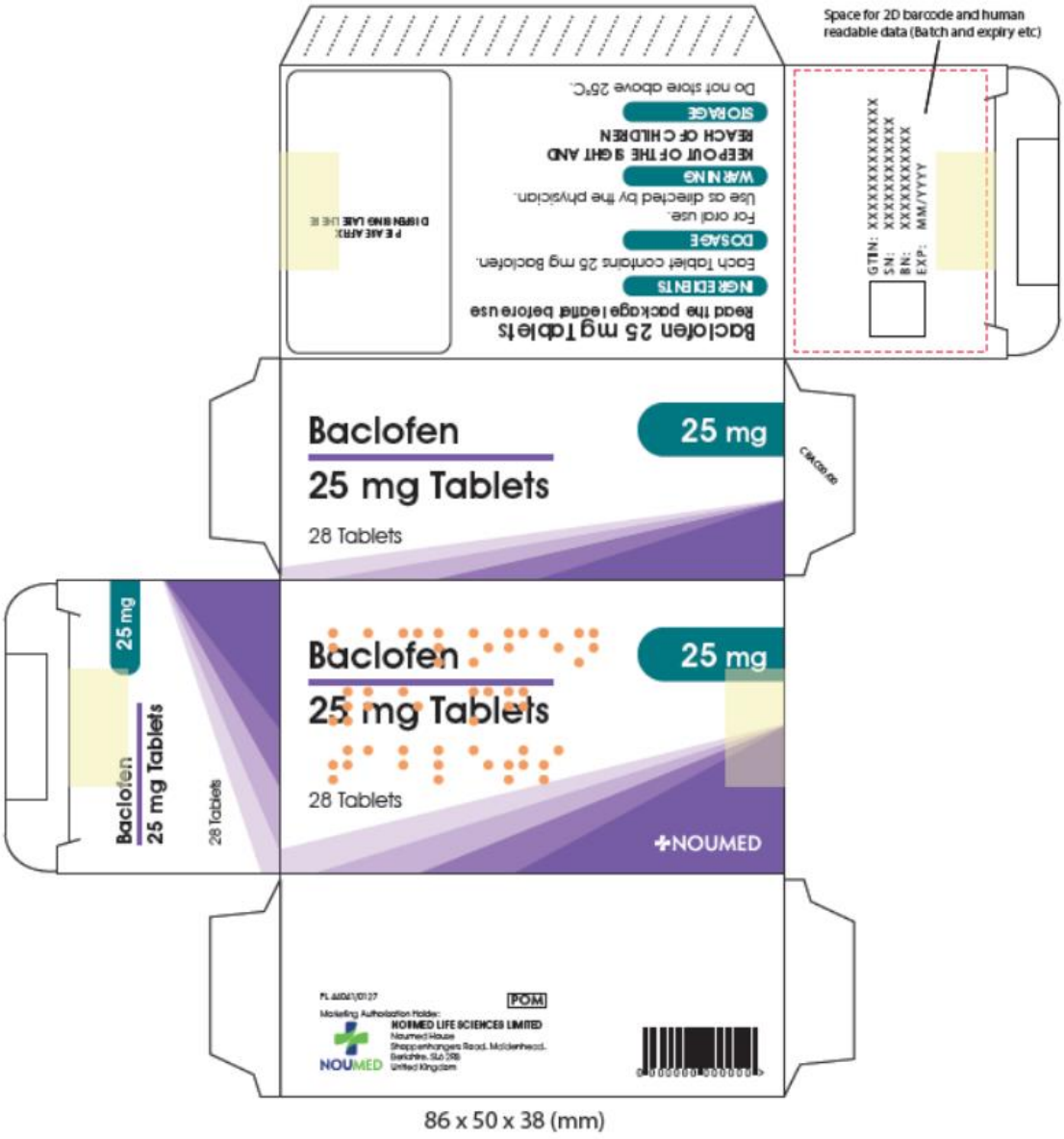
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

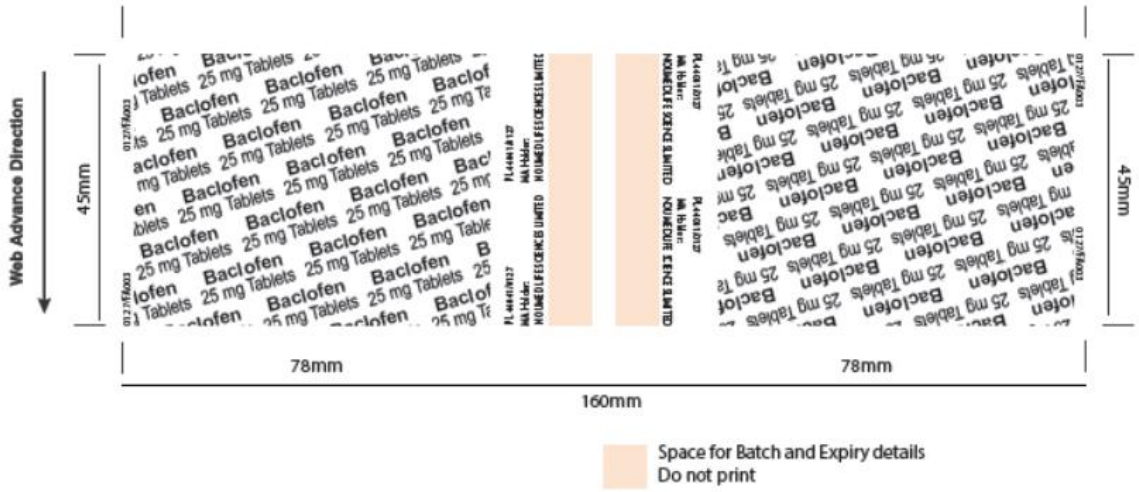
Representative copies of the labels at the time of UK licensing are provided below.




Web Advance Direction
45mm
45mm
78mm
78mm
160mm
Space for Batch and Expiry details
Do not print


Space for 2D barcode and human readable data (Batch and expiry etc)
GTIN: XXXXXXXXXXXXX
SN: XXXXXXXXXXX
BN: XXXXXXXXXX
EXP: MM/YYYY
Baclofen 25 mg Tablets
Read the package leaflet before use
INGREDIENTS
Each Tablet contains 25 mg Baclofen.
DOSAGE
For oral use.
Use as directed by the physician.
WARNING
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
STORAGE
Do not store above 25°C.
Baclofen
25 mg Tablets
28 Tablets
25 mg
Baclofen
25 mg Tablets
28 Tablets
25 mg
Baclofen
25 mg Tablets
28 Tablets
+NOUMED
POM
Marketing Authorisation Holder:
NOUMED LIFE SCIENCES LIMITED
NOUMED

86 x 50 x 38 (mm)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Space for Batch and Expiry details
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TABLE OF CONTENT OF THE PAR UPDATE

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**