Public Assessment Report

UKPAR

Isosorbide Mononitrate/Angitate 10 mg Tablets
Isosorbide Mononitrate/Angitate 20 mg Tablets
Isosorbide Mononitrate/Angitate 40 mg Tablets

(Isosorbide mononitrate)

UK Licence No: PL 17907/0522-0524

Bristol Laboratories Limited.
LAY SUMMARY

Isosorbide Mononitrate/Angitate 10 mg Tablets
Isosorbide Mononitrate/Angitate 20 mg Tablets
Isosorbide Mononitrate/Angitate 40 mg Tablets

(Isosorbide mononitrate, tablet, 10 mg, 20 mg or 40 mg).

This is a summary of the Public Assessment Report (PAR) for Isosorbide Mononitrate/Angitate 10 mg Tablets (PL 17907/0522), Isosorbide Mononitrate/Angitate 20 mg Tablets (PL 17907/0523) and Isosorbide Mononitrate/Angitate 40 mg Tablets (PL 17907/0524). It explains how Isosorbide Mononitrate/Angitate 10 mg, 20 mg and 40 mg Tablets 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 Isosorbide Mononitrate/Angitate 10 mg, 20 mg and 40 mg Tablets.

The products will be collectively referred to as Isosorbide Mononitrate Tablets throughout the remainder of this public assessment report (PAR).

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

What are Isosorbide Mononitrate Tablets and what are they used for?
Isosorbide Mononitrate Tablets are similar to ‘reference medicines’ containing the same active substance, already authorised in the European Union (EU), called Uniket 20 mg and 40mg Comprimidos (LACER S.A.C/ Sardenya 35008025 Barcelona, Spain).

Isosorbide Mononitrate 10 mg, 20 mg and 40 mg Tablets are used to prevent angina pectoris. Angina usually feels like a tight pain in the chest, neck or arm area. The pain comes from the heart muscle and is a sign that part of it is not getting enough oxygen for the amount of work it is doing.

Isosorbide Mononitrate 20 mg and 40 mg Tablets can also be used to treat congestive heart failure. Heart failure can happen when the heart muscle is not strong enough to pump the blood around the body. It may cause problems with breathing and swelling of the legs.

How do Isosorbide Mononitrate Tablets work?
This medicine contains an active ingredient called isosorbide mononitrate, which belongs to a group of medicines called organic nitrates. Organic nitrates work by widening the blood vessels in the heart to allow an increased amount of blood to flow to areas which need it.

How are Isosorbide Mononitrate Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

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

Important:
The patient’s doctor will choose the dose that is right for them. The patient’s dose will be shown clearly on the label that their pharmacist puts on their medicine. If it does not, or the patient is not sure, they should ask their doctor or pharmacist.

Adults
- The usual adult dose is one tablet two or three times a day.
The patient’s doctor will tell them when they should take their tablets. The patient will need to have a period of time (usually when they are sleeping) when no tablets are taken. This is called a “nitrate low” period and is needed to make sure the patient’s medicine remains effective.

- Swallow the tablets whole with a drink of water.
- The patient’s doctor may increase their dose, up to a maximum of 120 mg per day.

**Do not use Isosorbide Mononitrate Tablets to treat an actual angina attack. The patient’s doctor will give them a different medicine such as a GTN (glyceryl trinitrate) spray or tablet for this.**

**The elderly**

No dose adjustment is necessary.

**Children**

This medicine is not suitable for children.

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

This medicine can be obtained without a prescription.

**What benefits of Isosorbide Mononitrate Tablets have been shown in studies?**

As Isosorbide Mononitrate Tablets are hybrid medicines, studies in patients have been limited to tests to determine that the medicines are bioequivalent/therapeutically equivalent to the reference medicines, Uniket 20 mg and 40mg Comprimidos (LACER S.A.C/ Sardenya 35008025 Barcelona, Spain). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Isosorbide Mononitrate Tablets?**

Like all medicines, Isosorbide Mononitrate Tablets can cause side effects, although not everybody gets them.

**Very common (may affect more than 1 in 10 people)**

- Headaches

**Common (may affect up to 1 in 10 people)**

- Dizziness
- Sleepiness
- Feeling weak
- Fast heartbeat
- Lowering of blood pressure when standing up

They may occur for the first few days of treatment or after the patient’s dosage has been increased.

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

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

**Why are Isosorbide Mononitrate Tablets approved?**

The MHRA decided that the benefits of Isosorbide Mononitrate Tablets outweigh the identified risks and it was recommended that they be approved for use.
What measures are being taken to ensure the safe and effective use of Isosorbide Mononitrate Tablets?
A risk management plan (RMP) has been developed to ensure that Isosorbide Mononitrate Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPC) and the package leaflets for Isosorbide Mononitrate Tablets 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 Isosorbide Mononitrate Tablets
Marketing Authorisations were granted in the UK on 24 March 2017.

The full PAR for Isosorbide Mononitrate Tablets follows this summary.

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

This summary was last updated in May 2017.
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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) granted Bristol Laboratories Limited, marketing authorisations for the medicinal products Isosorbide Mononitrate Tablets (PL 17907/0522-0524). Isosorbide Mononitrate 10 mg, 20 mg and 40 mg Tablets are pharmacy medicines (P) indicated for the prophylaxis of angina pectoris. Isosorbide Mononitrate 20 mg and 40 mg Tablets are also indicated as adjunctive therapy in congestive heart failure not responding to cardiac glycosides or diuretics.

The applications for Isosorbide Mononitrate Tablets were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The application for Isosorbide Mononitrate 10 mg Tablets (PL 17907/0522) is for a change in strength and the applications for Isosorbide Mononitrate 20 mg and 40 mg Tablets (PL 17907/0523-524) are for a change in therapeutic indications compared to the reference products. The European reference product for Isosorbide Mononitrate 20 mg Tablets (PL 17907/0523) is Uniket 20 mg Comprimidos and the European reference product for Isosorbide Mononitrate 10 mg and 40 mg Tablets is Uniket 40mg Comprimidos. The European reference products were first authorised in Spain to the marketing authorisation holder (MAH) LACER S.A.C/ Sardenya 35008025 Barcelona on 01 January 1986.

Isosorbide mononitrate is an organic nitrate which, in common with other cardioactive nitrates, is a vasodilator. It produces decreased left and right ventricular end-diastolic pressures to a greater extent than the decrease in systemic arterial pressure, thereby reducing afterload and especially the preload of the heart.

Isosorbide mononitrate influences the oxygen supply to ischaemic myocardium by causing the redistribution of blood flow along collateral channels and from epicardial to endocardial regions by selective dilation of large epicardial vessels.

It reduces the requirement of the myocardium for oxygen by increasing venous capacitance, causing a pooling of blood in peripheral veins, thereby reducing ventricular volume and heart wall distension.

One bioequivalence study (conducted under fasting conditions) was submitted to support these applications. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were hybrid applications for products similar to an originator product that has been in clinical use for over 10 years.

The MHRA 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 these products.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Isosorbide Mononitrate Tablets outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 10 mg, 20 mg or 40 mg isosorbide mononitrate. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, anhydrous lactose, colloidal silicon dioxide and magnesium stearate.

All strengths of the finished product are packed into blisters comprised of polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) on hard tempered aluminium foil and are available in pack sizes of 14, 28, 30, 56 and 60 tablets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
Diluted isosorbide mononitrate
INN: Diluted isosorbide mononitrate

Structure:

![Structure Image]

Molecular formula: C₆H₉NO₆
Molecular weight: 191.1 g/mol
Description: Undiluted isosorbide mononitrate is a white or almost white, crystalline powder.
Solubility: Undiluted isosorbide mononitrate is freely soluble in water, in acetone, in ethanol (96 per cent) and in methylene chloride. The solubility of the diluted product depends on the diluent and its concentration.

Diluted isosorbide mononitrate is the subject of a European Pharmacopoeia monograph.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable, tablets containing 10 mg, 20 mg or 40 mg isosorbide mononitrate per tablet that were comparable in performance to the European reference medicinal products Uniket 20 mg and 40mg Comprimidos (LACER S.A.C/ Sardenya 35008025 Barcelona, Spain). Suitable pharmaceutical development data have been provided for these applications.

Comparative in vitro dissolution profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.
With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Manufacture of the products**
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 at commercial-scale batch size and shown satisfactory results.

**Finished Product Specification**
The finished product specifications proposed are 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 24 months with the storage conditions ‘Store below 25ºC. Store in the original package in order to protect from moisture and light.’

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 these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of isosorbide mononitrate 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 applicant’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 Isosorbide Mononitrate Tablets are 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 or necessary for this type of application.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV  CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of isosorbide mononitrate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required to support these applications.

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 isosorbide mononitrate.

Based on the data provided, Isosorbide Mononitrate 40 mg Tablets (Bristol Laboratories Ltd, UK) can be considered bioequivalent to Uniket 40mg Comprimidos (LACER S.A.C/ Sardenya 35008025 Barcelona, Spain).

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted results from the following bioequivalence study:

STUDY
An open label, randomised, two-period, two-treatment, two-sequence, single dose, crossover study to compare the pharmacokinetics of the applicant’s test product Isosorbide Mononitrate 40 mg Tablets (Bristol Laboratories Ltd, UK) versus the reference product, Uniket 40mg Comprimidos (LACER S.A.C/ Sardenya 35008025 Barcelona, Spain), in healthy adult subjects under fasting conditions.

After an overnight fast of at least 10 hours the subjects were administered a single dose (1 x 40 mg tablet) of either the test or the reference product with 240 mL of water. Blood samples were collected for plasma levels before dosing and up to and including 36 hours after each administration. The washout period between the treatment phases was 10 days. The pharmacokinetic results are presented below:

The summary statistics table for the pharmacokinetic parameters for isosorbide 5-mononitrate is presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>2535.2324</td>
<td>2655.8983</td>
</tr>
<tr>
<td>$\text{AUC}_{0,4}$ (ng hr/mL)</td>
<td>18049.9713</td>
<td>16776.0636</td>
</tr>
<tr>
<td>$\text{AUC}_{0,\infty}$ (ng hr/mL)</td>
<td>18359.8494</td>
<td>17037.2125</td>
</tr>
</tbody>
</table>

AUC$_{0,4}$ area under the plasma concentration-time curve from zero to 4 hours
AUC$_{0,\infty}$ area under the plasma concentration-time curve from zero to t hours
$C_{\text{max}}$ maximum plasma concentration
Conclusion
The 90% confidence intervals of the test/reference ratio for AUC, and C$_{\text{max}}$ values for isosorbide 5-mononitrate lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product Isosorbide Mononitrate 40 mg Tablets (Bristol Laboratories Ltd, UK), is bioequivalent to the reference product Uniket 40mg Comprimidos (LACER S.A.C/ Sardenya 35008025 Barcelona, Spain).

As the 10 mg, 20 mg and 40 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 40 mg strength can be extrapolated to the 10 mg and 20 mg strength tablets.

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 these applications.

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 Isosorbide Mononitrate Tablets.

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

Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Use in patients with a known sensitivity to isosorbide mononitrate or any other excipients or other nitrates</th>
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<tr>
<td></td>
<td>Use in patients with acute myocardial infarction with low filling pressures</td>
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<td></td>
<td>Rise in symptoms of circulatory collapse in patients with labile circulation</td>
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<tr>
<td></td>
<td>Risk of postural hypotension and syncope</td>
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<tr>
<td></td>
<td>Use in patients with hypertrophic obstructive cardiomyopathy (HOCM), cardiac pericarditis, cardiac tamponade, low cardiac filling pressures and aortic/mitral valve stenosis</td>
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<td>Risk of venous dilatation in patients with a raised intra-cranial pressure</td>
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<td></td>
<td>Use in patients with marked anaemia</td>
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<td></td>
<td>Use in patients with closed angle glaucoma</td>
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<td></td>
<td>Potentiation of the hypotensive effects of nitrates with concomitant use of phosphodiesterase type-5 inhibitors</td>
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<td>Reduced efficacy with the development of tolerance on chronic use</td>
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</table>
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. This is satisfactory.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

V User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Isosorbide-5-mononitraat Accord 20 mg and 40 mg (NL/H/2157/001-002/MR). The bridging report submitted by the applicant is acceptable.

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 isosorbide mononitrate 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 this medicine is presented below:
Angitate® 20 mg Tablets

20 mg Tablets

PAR Isosorbide Mononitrate/Angitate 10 mg, 20 mg and 40 mg mg Tablets

PL 17907/0522 - 0524

KEEP OUT OF THE REACH AND REACH OF CHILDREN

For professional use only
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**Angiato 20 mg Tablets**

Isosorbide mononitrate
Bristol Laboratories Ltd.

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Annex 1

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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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