Public Assessment Report
Decentralised Procedure

LOPRAZOLAM 1MG TABLETS
(loprazolam mesilate)

Procedure No: UK/H/5197/001/DC
UK Licence No: PL 41830/0039

NRIM LIMITED
This is a summary of the public assessment report (PAR) for Loprazolam 1mg Tablets (PL 41830/0039). It explains how Loprazolam 1mg Tablets 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 Loprazolam 1mg Tablets.

For practical information about Loprazolam 1mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What is Loprazolam 1mg Tablets and what is it used for?

Loprazolam 1mg Tablets is a ‘generic medicine’. This means that Loprazolam 1mg Tablets is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Loprazolam 1mg Tablets.

Loprazolam 1mg Tablets is prescribed to treat short term sleep problems in adults such as:

- difficulty falling asleep
- waking frequently during the night

How is Loprazolam 1mg Tablets used?

This medicine can only be obtained with a prescription. Loprazolam 1mg Tablets is used for short term sleep problems and is not meant to be used every day for long periods of time. It is recommended that this medicine should be taken, whole with a drink of water, just before bedtime. Loprazolam 1mg Tablets should not be taken for more than 4 weeks.

How Loprazolam 1 mg does Tablets work?

Loprazolam 1mg Tablets belong to a group of medicines called hypnotics. This medicine works by acting on your brain, to help you sleep.

How has Loprazolam 1mg Tablets been studied?

Loprazolam 1mg Tablets is a generic medicine; studies in patients have been limited to tests to determine that this medicine 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 benefits and risks of Loprazolam 1mg Tablets?

Loprazolam 1mg Tablets is a generic medicine and is bioequivalent to the reference medicine. Therefore, the benefits and risks are taken as being the same as those of the reference medicine.

Why is Loprazolam 1mg Tablets approved?

It was concluded that, in accordance with EU requirements, Loprazolam 1mg Tablets has been shown to have comparable quality and to be bioequivalent to the reference medicine. Therefore, the view was that, as for the reference medicine, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Loprazolam 1mg Tablets?

A risk management plan has been developed to ensure that Loprazolam 1mg Tablets 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 Loprazolam 1mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Loprazolam 1mg Tablets**

France, Portugal, Spain and the UK agreed to grant a Marketing Authorisation for Loprazolam 1mg Tablets on 27 February 2014. A Marketing Authorisation was granted in the UK on 28 March 2014.

The full PAR for Loprazolam 1mg Tablets follows this summary. For more information about treatment with Loprazolam 1mg Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in 05-2014.
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## Module 1
### Information about initial procedure

<table>
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<tr>
<th>Product Name</th>
<th>Loprazolam 1mg Tablets</th>
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<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td>Active Substances</td>
<td>Loprazolam mesilate</td>
</tr>
<tr>
<td>Form</td>
<td>Tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>1 mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>NRIM Limited&lt;br&gt;Unit 15 Moorcroft&lt;br&gt;Harlington Road&lt;br&gt;Hillingdon&lt;br&gt;UB8 3HD&lt;br&gt;United Kingdom</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>France, Portugal, Spain</td>
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<tr>
<td>Procedure Number</td>
<td>UK/H/5197/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 27 February 2014</td>
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</table>
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflet for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Loprazolam 1mg 28’s Carton
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Loprazolam 1mg Tablets (PL 41830/0039; UK/H/5197/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and France, Portugal, Spain as Concerned Member States (CMS).

This product can only be obtained with a prescription (legal classification POM).

This application was made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference product, Loprazolam 1mg Tablets (PL 17780/0306). Dormonoct 1mg Tablets (as Loprazolam 1mg Tablets was known at that time) was granted a Marketing Authorisation to Roussel Laboratories Limited (PL 00109/0080) on 29 March 1983. Following a series of change of ownership procedures the Marketing Authorisation was transferred to the current Marketing Authorisation Holder, Winthrop Pharmaceuticals UK Limited on 17 March 2009.

Loprazolam 1mg Tablets contains the active substance loprazolam mesilate. Loprazolam mesilate is a benzodiazepine, indicated for the short-term treatment of insomnia, including difficulty in falling asleep and/or frequent nocturnal awakenings. Benzodiazepines should be used to treat insomnia only when it is severe, disabling or subjecting the individual to extreme distress. An underlying cause of insomnia should be sought before deciding upon the use of benzodiazepines for symptomatic relief. Loprazolam mesilate stimulates gamma-amino butyric acid (GABA) receptors in the brain which causes the release of a neurotransmitter called GABA in the brain. GABA is a neurotransmitter that acts as a natural 'nerve-calming' agent. It helps keep the nerve activity in the brain in balance, and is involved in inducing sleepiness, reducing anxiety and relaxing muscle.

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

With the exception of the bioequivalence study comparing the pharmacokinetics of this product with that of the reference product, Loprazolam 1mg Tablets (Winthrop Pharmaceuticals UK Limited), no new clinical studies were conducted. This 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. The bioequivalence study was carried out in accordance with Good Clinical Practise (GCP).

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

The RMS and CMS considered that the application could be approved at the end of procedure on 27 February 2014. After a subsequent national phase, a licence was granted in the UK on 28 March 2014.
## ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Loprazolam 1mg Tablets</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Loprazolam mesilate</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Benzodiazepines (N05CD11)</td>
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<td>Tablets 1 mg</td>
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<td>Reference Member State</td>
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<td>PL 41830/0039</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>NRIM Limited</td>
</tr>
<tr>
<td></td>
<td>Unit 15 Moorcroft</td>
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<td></td>
<td>Harlington Road</td>
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<td>Hillingdon</td>
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<td>UB8 3HD</td>
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<td></td>
<td>United Kingdom</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – loprazolam mesilate

rINN: loprazolam mesilate

Chemical name: $(Z)$-6-(2-chlorophenyl)-2,4-dihydro-2-(4-methylpiperazin-1-ylmethylene)-8-nitroimidazo[1,2-a][1,4]benzodiazepin-1-one methanesulphonate monohydrate,

Structure:

Molecular formula: $C_{23}H_{21}ClN_6O_3\cdot CH_3SO_3H, H_2O$

Molecular weight: 579.1 g/mol

Appearance: Yellow crystalline powder

Solubility: Slightly soluble in water and ethanol (96%), very slightly soluble in ether.

Synthesis of the active substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

Appropriate specifications are provided for the active substance loprazolam mesilate, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

Suitable certificates of analysis have been provided for all reference standards used.
Satisfactory specifications have been provided for all packaging used for storing the active substance loprazolam mesilate. The primary packaging has been shown to comply with current legislation concerning materials in contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable. A suitable retest period has been set based on stability data submitted for the active substance stored in the proposed packaging.

**P. Medicinal Product**

**Other Ingredients**

Other ingredients consist of the following pharmaceutical excipients:

Lactose anhydrous, microcrystalline cellulose and magnesium stearate.

All excipients used comply with their respective European Pharmacopoeia monographs.

With the exception of lactose anhydrous, none of the excipients are of animal or human origin. The supplier of lactose anhydrous has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. Magnesium stearate, which can be derived from animals, was sourced from vegetable oil. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the reference product Loprazolam 1mg Tablets (Winthrop Pharmaceuticals UK Limited).

Comparative physico-chemical data, including *in vitro* dissolution and impurity profiles have been provided for the proposed product versus the reference product, and pharmaceutical equivalence has been shown.

A satisfactory account of the pharmaceutical development has been provided.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on two full scale commercial-scale batches of finished product. The results are satisfactory. Confirmation has been provided that a third commercial batch will be validated as per submitted protocol.

**Finished Product Specification**

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

**Container-Closure System**

The finished product is packaged in aluminium/polyvinylchloride blister packs of 7, 10, 14, 15, 20, 28, 30 tablets.

The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.
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 foodstuffs.

**Stability of the product**

Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 2 years with the storage conditions “Do not store above 25°C” and “Store in the original package in order to protect from light and moisture”.

**Bioequivalence/bioavailability**

A bioequivalence study was performed to compare the pharmacokinetics of the test product Loprazolam 1mg Tablets versus the reference product Loprazolam 1mg Tablets (Winthrop Pharmaceuticals UK Limited).

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

The SmPC, PIL and labels are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Marketing Authorisation Application (MAA) form**

The MAA form is satisfactory from a pharmaceutical perspective.

**Quality Overall Summary (Expert report)**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**

The grant of a Marketing Authorisation is recommended.

### III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of loprazolam mesilate are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

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

### III.3 CLINICAL ASPECTS

**Pharmacokinetics and Pharmacodynamics**

With the exception of the below study, no new pharmacodynamic or pharmacokinetic data have been submitted with this application and none are required.

In support of this application, the Marketing Authorisation Holder has submitted the following
bioequivalence study:

An open-label, randomised, balanced, single-dose, two-treatment, two-sequence, two-way, crossover study comparing the pharmacokinetics of the test product Loprazolam 1mg Tablets versus the reference product Loprazolam 1mg Tablets (Winthrop Pharmaceuticals Limited) in healthy male adult subjects under fasting conditions.

The study was of an appropriate design and was conducted to the principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for the test and reference products.

Subjects were dosed orally with either the test or reference product. Blood samples were taken pre-dose and up to 72 hours post dose analysed for the parent drug loprazolam. A washout period of 7 days was maintained between dosing.

Forty-two healthy male volunteers were enrolled in the study. 37 volunteers completed both periods. Five subjects were withdrawn from the study; four subjects were withdrawn due to AEs (Adverse Events) and concomitant medications, one subject was withdrawn due to a positive drug screen. A summary of the main pharmacokinetic results is presented in the table below:

Pharmacokinetic parameters – the test versus reference ratio

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Comparison</th>
<th>Estimated geometric mean ratio [%]</th>
<th>Lower 90% CI [%]</th>
<th>Upper 90% CI [%]</th>
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</thead>
<tbody>
<tr>
<td>Ln-Cₜₐₓ</td>
<td>T vs. R</td>
<td>107.21</td>
<td>97.95</td>
<td>117.34</td>
</tr>
<tr>
<td>Ln-AUC₀₋₇₂</td>
<td>T vs. R</td>
<td>108.68</td>
<td>104.43</td>
<td>113.11</td>
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</tbody>
</table>

AUC₀₋₇₂: area under the plasma concentration-time curve from time zero to t hours
Cₜₐₓ: maximum plasma concentration

The 90% confidence interval of the test/reference ratio for the AUC₀₋₇₂ and Cₜₐₓ was within the pre-defined limits of 80.00-125.00% as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). In conclusion, bioequivalence has been demonstrated between the test and the reference product.

Efficacy
No new data on efficacy have been submitted and none are required for this type of application.

Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues arose during the bioequivalence study.

SmPC, PIL and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A risk management plan has been developed to ensure that Loprazolam 1mg Tablets 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 Loprazolam 1mg Tablets, including the appropriate
precautions to be followed by healthcare professionals and patients.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Loprazolam 1mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

**NON-CLINICAL**
No new non-clinical data were submitted and none are required for an application of this type.

**CLINICAL**
Bioequivalence has been demonstrated between the applicant’s Loprazolam 1mg Tablets product and its respective reference product.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labels are satisfactory and consistent with those for the reference product.

**BENEFIT-RISK ASSESSMENT**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. Extensive clinical experience with loprazolam mesilate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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