Public Assessment Report

Decentralised Procedure

LORAZEPAM 1MG TABLETS
LORAZEPAM 2.5MG TABLETS

Procedure No:
UK/H/3130/001 & 002/DC
UK/H/4683/001 & 002/DC
UK/H/4684/001 & 002/DC
UK/H/4685/001 & 002/DC

UK Licence No:
PL 20117/0161 & 0162
PL 20117/0191 & 0192
PL 20117/0193 & 0194
PL 20117/0195 & 0196

Morningside Healthcare Limited
LAY SUMMARY

On 23 September 2012, Germany, Estonia, Spain, Ireland, Lithuania, the Netherlands and the UK agreed to grant Marketing Authorisations to Morningside Healthcare Limited for the medicinal products Lorazepam 1 and 2.5mg Tablets (PL 20117/0161-2 & 0191-6; UK/H/3130 & 4683-5/001 & 002/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, Marketing Authorisations were granted in the UK on 3 December 2012.

These products contain the active ingredient lorazepam, which is a type of medicine called a benzodiazepine. It relieves anxiety and it is used for short periods to relieve anxiety that is severe, disabling or causing extreme distress, and to treat difficulties with sleep that are caused by anxiety. It may also be used as a sedative shortly before a dental or surgical operation.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking these products outweigh the risks; hence, Marketing Authorisations were granted.

Some of the above licences for Lorazepam 1 and 2.5mg Tablets were cancelled in the UK on 4 January 2013 (PL 20117/0191-6).
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**Module 1**

| **Product Name**     | Lorazepam 1mg Tablets  
|                     | Lorazepam 2.5mg Tablets |
| **Type of Application** | Generic, Article 10(1) |
| **Active Substances**   | Lorazepam               |
| **Form**                | Tablets                 |
| **Strength**            | 1mg and 2.5mg           |
| **MA Holder**           | Morningside Healthcare Limited, 115 Narborough Road, Leicester, LE3 0PA, UK |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | UK/H/3130/001-2/DC: Ireland  
|                            | UK/H/4683/001-2/DC: Estonia, Spain, Lithuania & Netherlands  
|                            | UK/H/4684/001-2/DC: Germany  
|                            | UK/H/4685/001-2/DC: Germany |
| **Procedure Number** | UK/H/3130, 4683-5/001-2/DC |
| **Timetable**           | Day 210 – 23 September 2012 |
Module 2

Summary of Product Characteristics

The current approved UK version of the Summaries of Product Characteristics (SmPCs) for these products is available on the MHRA website.
Module 3

Patient Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for these products is available on the MHRA website.
Module 4
Labelling

Each tablet contains lorazepam 1 mg.
Also contains Lactose Monohydrate.
For further information see package leaflet.
For oral use. Read the package leaflet before use.
Keep out of the reach and sight of children.
Store below 25°C.
Store in original packaging to protect from light.
Each tablet contains lorazepam 2.5mg.
Also contains Lactose Monohydrate.
For further information see package leaflet.
For oral use. Read the package leaflet before use.
Keep out of the reach and sight of children.
Store below 25°C.
Store in original packaging to protect from light.

PAR Lorazepam 1 & 2.5mg Tablets UK/H/3130, 4683-5/001-2/DC
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 applications for Lorazepam 1 and 2.5mg Tablets (PL 20117/0161-2 & 0191-6; UK/H/3130 & 4683-5/001 & 002/DC) could be approved. These applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Germany, Estonia, Spain, Ireland Lithuania and the Netherlands as Concerned Member States (CMS).

These are prescription-only medicines for
- Short-term symptomatic treatment of anxiety and insomnia caused by anxiety, where the anxiety is severe, disabling or subjecting the individual to extreme distress
- Premedication before general anaesthesia or before minor surgical procedures, investigations or operative dentistry

Lorazepam is a benzodiazepine drug with a short to medium duration of action. It has all the well-known intrinsic benzodiazepine effects, such as anxiolytic, sedative/hypnotic, anticonvulsant, and muscle relaxing properties. It is a powerful anxiolytic. It is a unique benzodiazepine insofar as it has also found use as an adjunct antiemetic in chemotherapy.

These were applications submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal products of the UK reference products Lorazepam 1 and 2.5mg Tablets, which were first granted licences to John Wyeth and Brother Limited in 1985 (PL 00011/0108 & 0109). Following a change of ownership in September 1999, the current marketing authorisation holder is Genus Pharmaceutical Holdings Limited (PL 17225/0010 & 0011). The EU originator product is Temesta 2.5mg Tablets (Laboratoires Biodim, France), which was initially granted in June 1973.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

In support of these applications, the applicant has submitted a two-period, two-sequence, two-way, open-label, crossover, randomised study, comparing the pharmacokinetics of the proposed 2.5mg strength tablets versus Temesta 2.5mg tablets (Laboratoire Biodim, France). The bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

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

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 23 September 2012. After a subsequent national phase, the licences were granted in the UK on 3 December 2012.
Some of the above licences for Lorazepam 1 and 2.5mg Tablets were cancelled in the UK on 4 January 2013 (PL 20117/0191-6).

II. ABOUT THE PRODUCTS

| Name of the products in the Reference Member State | Lorazepam 1mg Tablets  
Lorazepam 2.5mg Tablets |
<table>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Benzodiazepine derivatives (N05 BA)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>1mg and 2.5mg Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/3130, 4683-5/001-2/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Germany, Estonia, Spain, Ireland, Lithuania and the Netherlands</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20117/0161-3, 0191-6</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Morningside Healthcare Limited, 115 Narborough Road, Leicester, LE3 0PA, UK</td>
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</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance – Lorazepam

rINN:  Lorazepam

Chemical name:  

\[
(3RS)-7\text{-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one}
\]

\[
2H-1,4\text{-benzodiazepine-2-one,7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-(±)}
\]

\[
(±)-7\text{-Chloro-5(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepine-2-one}
\]

Structure:

![Structure of Lorazepam](image)

Molecular formula:  \(\text{C}_{15}\text{H}_{10}\text{Cl}_{2}\text{N}_{2}\text{O}_{2}\)

Molecular weight:  321.2

Appearance:  White or almost white crystalline powder

Solubility:  Practically insoluble in water, sparingly soluble in ethanol (96%), sparingly soluble or slightly soluble in methylene chloride.

With the exception of the container-closure system and stability, all aspects of the manufacture and control of the active ingredient are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

P.  Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, povidone (K30), crospovidone (Type A), maize starch, microcrystalline cellulose (E460), sodium starch glycolate, polacriline potassium and magnesium stearate (E572). With the exception of polacriline potassium, all excipients are controlled to their respective European Pharmacopoeia monograph. Polacriline potassium is controlled to a suitable United States Pharmacopoeia/National Formulary specification.

With the exception of lactose monohydrate, no excipients are sourced from animal or human origin. The suppliers of lactose monohydrate have confirmed that the lactose 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.

Pharmaceutical Development

The objective of the development programme was to formulate globally acceptable, stable and bioequivalent products that could be considered generic medicinal products of the
originator products Lorazepam 1 and 2.5mg Tablets, which were first granted licences to John Wyeth and Brother Limited in 1985.

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro assay and impurity profiles have been provided for the proposed products versus the originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the finished products. The manufacturing process has been validated using commercial and pilot-scale batches and has shown satisfactory results.

A commitment has been provided to perform validation studies on the first three commercial-scale batches when they are manufactured.

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

Container-Closure System
The finished products are packaged in opaque polyvinylchloride/polyethylene/polyvinylidene chloride/aluminium blisters in pack sizes of 10, 14, 15, 20, 28, 30, 50, 60, 90, 100 and 500 tablets. Not all pack sizes may be marketed. However, the marketing authorisation holder has committed to submitting mock-ups to the relevant authorities before marketing any pack size.

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.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 15 months, with the storage conditions “Store below 25°C. Store in original package to protect from light.”

Bioequivalence/bioavailability
In support of these applications, the applicant has submitted a two-period, two-sequence, two-way, open-label, crossover, randomised study, comparing the pharmacokinetics of the proposed 2.5mg strength tablets versus Temesta 2.5mg tablets (Laboratoire Biodim, France). The bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PILs and labels are pharmaceutically acceptable.

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) forms**
The MAA forms are pharmaceutically satisfactory.

**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 Marketing Authorisations is recommended.

**III.2 NON-CLINICAL ASPECTS**
As the pharmacodynamic, pharmacokinetic and toxicological properties of lorazepam are well-known, no further non-clinical studies are required and none have been provided.

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

Suitable justification has been provided for the non-submission of an environmental risk assessment. As these products are 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 these products from a non-clinical viewpoint.

**III.3 CLINICAL ASPECTS**

**Clinical Pharmacology**
With the exception of the bioequivalence study, no new clinical pharmacology data have been submitted and none are required for applications of this type.

The below bioequivalence study was submitted to support these applications, in accordance with the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). The bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

A two-period, two-sequence, two-way, open-label, crossover, randomized study, comparing the pharmacokinetics of the proposed test product 2.5mg strength tablets versus the reference product Temesta 2.5mg tablets (Laboratoire Biodim, France) in fasted subjects.

Volunteers were dosed with either treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The two treatment arms were separated by a 6-day washout period.
The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) for serum lorazepam are presented below:

<table>
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<tr>
<th>Parameters (Units)</th>
<th>In-transformed Data</th>
<th>Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
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<tbody>
<tr>
<td></td>
<td>Test Product-B</td>
<td>Reference Product-A</td>
<td>Ratio (B/A)%</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>29.233</td>
<td>29.133</td>
<td>100.087</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/mL)</td>
<td>490.126</td>
<td>478.266</td>
<td>101.663</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-\infty&lt;/sub&gt; (ng.h/mL)</td>
<td>521.872</td>
<td>507.587</td>
<td>101.782</td>
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</tbody>
</table>

AUC<sub>0-\infty</sub> area under the plasma concentration-time curve from time zero to infinity  
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours  
C<sub>max</sub> maximum plasma concentration

The 90% confidence intervals for C<sub>max</sub> and AUC for test versus reference products are within predefined acceptance criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev 1/, Corr**). The data support the claim that the 2.5mg test product is bioequivalent to the 2.5mg reference product.

As the 1 and 2.5mg strengths of the product meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev 1/, Corr**), the extrapolation of results and conclusions from the bioequivalence study on the 2.5mg strength to the 1mg strength is justified.

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

**Safety**
No new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns arose from these applications. Lorazepam as an active ingredient has a well-established and acceptable level of safety for the proposed indications.

**Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PILs), Labels**
The SmPCs, PILs and labels are clinically acceptable. The SmPCs are consistent with those for the innovator products. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

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

**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.

Suitable justification has been provided for not submitting a risk management plan for these products.

**Conclusion**
The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Lorazepam 1 and 2.5mg 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 applications of this type.

CLINICAL
Bioequivalence has been demonstrated between Lorazepam 2.5mg strength tablets and the reference product Temesta 2.5mg tablets (Laboratoire Biodim, France). As the 1 and 2.5mg strengths of the product meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev 1., Corr**), the extrapolation of results and conclusions from the bioequivalence study on the 2.5mg strength to the 1mg strength is justified.

No new or unexpected safety concerns arose from these applications. The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference products.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with lorazepam is considered to have demonstrated the therapeutic value of the compound. The benefit-risk 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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