Public Assessment Report

Decentralised Procedure

LEVOMEPRAMAZINE HYDROCHLORIDE 25MG/ML SOLUTION FOR INJECTION

Procedure No: UK/H/4410/001/DC

UK Licence No: PL 29831/0462

WOCKHARDT UK LTD
LAY SUMMARY

On 05 September 2012, Malta and the UK agreed to grant a Marketing Authorisation to Wockhardt UK Ltd for the medicinal product Levomepromazine hydrochloride 25mg/ml Solution for Injection (PL 29831/0462; UK/H/4410/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 12 October 2012. This product is a prescription-only medicine (POM).

Levomepromazine hydrochloride 25mg/ml Solution for Injection belongs to a group of medicines called phenothiazines. It is used for the relief of severe pain and as a sedative to relieve anxiety and distress associated with severe pain, particularly in terminally ill patients.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Levomepromazine hydrochloride 25mg/ml Solution for Injection outweigh the risks and Marketing Authorisations have been granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure  Page 4
Module 2: Summary of Product Characteristics  Page 5
Module 3: Patient Information Leaflet  Page 6
Module 4: Labelling  Page 7
Module 5: Scientific Discussion  Page 8
   1 Introduction
   2 Quality aspects
   3 Non-clinical aspects
   4 Clinical aspects
   5 Overall conclusions
Module 6: Steps taken after initial procedure  Page 14
## Module 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Levomepromazine hydrochloride 25mg/ml Solution for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Levomepromazine hydrochloride</td>
</tr>
<tr>
<td>Form</td>
<td>Solution for injection</td>
</tr>
<tr>
<td>Strength</td>
<td>25mg/ml</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member State (CMS)</td>
<td>Malta</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/4410/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 187 – 05 September 2012</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

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.
Module 3
Patient Information Leaflet (PIL)

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.
Module 4
Labelling

Carton:

Ampoule label:
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 Levomepromazine hydrochloride 25mg/ml Solution for Injection (PL 29831/0462; UK/H/4410/001/DC) could be approved. This application was submitted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Malta as Concerned Member State (CMS).

The product is a prescription-only medicine (POM) indicated in the management of pain and accompanying restlessness or distress in terminally ill patients.

Levomepromazine hydrochloride 25mg/ml Solution for Injection potentiates the action of other central nervous system depressants but may be given in conjunction with appropriately modified doses of narcotic analgesics in the management of severe pain. Levomepromazine Injection does not significantly depress respiration and is particularly useful where pulmonary reserve is low.

Levomepromazine belongs to the pharmacotherapeutic group of antipsychotics and resembles chlorpromazine and promethazine in the pattern of its pharmacology. It possesses anti-emetic, antihistamine and anti-adrenaline activity and exhibits a strong sedative effect.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross-referring to the reference product Nozinan 25 mg/ml injection which was authorised in the UK on 14 February 1994 to the marketing authorisation holder (MAH), Archimedes Pharma UK Limited, (which in turn cross refers to Levomepromazine Injection, PL 00012/5007R which was first authorised in 1985) which subsequently underwent a change of ownership to the current MAH, Aventis Pharma Limited on 12 June 2009 (PL 04425/0659).

No new non-clinical studies were conducted, which 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.

No new clinical data have been submitted and none are required for an application of this type. A bioequivalence study was not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) 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 with the end of procedure (Day 187) on 05 September 2012. After a subsequent national phase, the licence was granted in the UK on 12 October 2012.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Levomepromazine hydrochloride 25mg/ml Solution for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Levomepromazine hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antipsychotics (ATC code: NO5AA02)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Solution for injection, 25mg/ml</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised procedure</td>
<td>UK/H/4410/001/DC</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member State (CMS)</td>
<td>Malta</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0462</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Wockhardt UK Ltd</td>
</tr>
<tr>
<td></td>
<td>Ash Road North</td>
</tr>
<tr>
<td></td>
<td>Wrexham</td>
</tr>
<tr>
<td></td>
<td>LL13 9UF</td>
</tr>
<tr>
<td></td>
<td>UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Levomepromazine hydrochloride
Chemical name: (2R)-3-(2-methoxy-10H-phenothiazin-10-yl)-N,N,2-trimethylpropan-1-amine hydrochloride

Structure:

![Structure of Levomepromazine hydrochloride]

Molecular formula: C_{19}H_{25}ClN_{2}OS
Molecular mass: 364.9
Appearance: Levomepromazine hydrochloride is a white or very slightly yellow crystalline powder.
Solubility: Levomepromazine hydrochloride is freely soluble in water and alcohol.

Levomepromazine hydrochloride is the subject of a European Pharmacopoeia monograph.

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 substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

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 ascorbic acid, sodium sulphite, sodium chloride and Water for Injections.
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.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to produce a solution for injection containing levomepromazine hydrochloride 25mg/ml that could be considered as a generic medicinal product of the reference product Nozinan 25 mg/ml injection (Aventis Pharma Limited).

Suitable pharmaceutical development data have been provided for this application.

Satisfactory comparative impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**

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 at pilot scale and has shown satisfactory results. In addition, the Marketing Authorisation Holder has committed to conduct process validation on future production scale batches.

**Finished Product Specification**

The proposed finished product specification is 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 product is packaged in 1 ml neutral (Type I) glass ampoules in pack sizes of 10 ampoules.

Satisfactory specifications and Certificates of Analysis have been provided for the primary packaging. The 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 the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months for the unopened product with the storage conditions ‘Store in the original container and protect from light. The product should be used immediately after opening. The completion of administration may last up to 24 hours in a closed system if necessary.’

**Bioequivalence/bioavailability**

No bioequivalence studies have been submitted and none are required to support an application of this type.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are 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 leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

MAA (Marketing Authorisation Application) forms
The MAA form is satisfactory.

Expert report (Quality Overall Summary)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical view-point.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of levomepromazine hydrochloride are well-known, no new 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.

Since Levomepromazine hydrochloride 25mg/ml Solution for Injection is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

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

III.3 CLINICAL ASPECTS
Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), a bioequivalence study is not required if the test product is administered as an aqueous intravenous solution containing the same active substance as the reference product. No bioequivalence study has been submitted or is required for this application.

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

Safety
No new safety data were submitted and none were required for this application.
Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in line with current guidance. The labelling is in line with current guidance.

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

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 this application.

Conclusion
There are no objections to the approval of this application from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Levomepromazine hydrochloride 25mg/ml Solution for Injection 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 were required for an application of this type. The pharmcodynamic, pharmacokinetic and toxicological properties of levomepromazine hydrochloride are well known.

EFFICACY
No new efficacy data were submitted and none were required for an application of this type. As the safety profile of levomepromazine hydrochloride is well-known, no additional data were required. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate, and are in line with current guidance.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levomepromazine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>