Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Levorol 5 mg/ml Oral Solution

levomepromazine (as levomepromazine hydrochloride)

PLGB 56809/0001

Galvany Pharma Limited

LAY SUMMARY

Levorol 5 mg/ml Oral Solution
levomepromazine (as levomepromazine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Levorol 5 mg/ml Oral Solution. It explains how this product 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 this product.

This product will be referred to as Levorol in this lay summary for ease of reading.

For practical information about using Levorol, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Levorol and what is it used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised, called Neurocil Tropfen, 40 mg/ml, Tropfen zum Einnehmen, Lösung (Neurocil drops, 40 mg/ml, oral drops, solution), albeit with certain differences. In this case, the difference between Levorol compared to the reference product is a change in strength/concentration of the active substance.

Levorol is used:
- for reducing psychomotor restlessness and agitation in psychotic disorders
- for acute agitation during manic episodes
- as an additional therapy for the treatment of severe and/or chronic pain.

How does Levorol work?
Levorol contains the active substance, levomepromazine (as levomepromazine hydrochloride), which is a phenothiazine neuroleptic medicine used in psychiatry with pain relieving and antiemetic properties.

How is Levorol used?
The pharmaceutical form of this medicine is an oral solution, and the route of administration is oral (taken by mouth).

The daily dose is usually split into three to four individual doses.

Ambulant patients (patients not confined to bed)
The recommended dose is 15-30 mg levomepromazine/day (3-6 ml of Levorol) up to 75-150 mg levomepromazine/day (15-30 ml of Levorol).

Bed patients with psychosis
The total daily oral dosage is 75-100 mg (5 ml, 3 to 4 times), increased to 150 mg/day (10 ml 3 times) up to 300 mg/day (20 ml, 3 times) and for severe psychoses up to 600 mg levomepromazine/day.

For doses higher than 300 mg levomepromazine should be taken in the form of tablets.

Bed patients with severe pain
The total daily recommended dose for bed patients with severe pain is 25-50-75 mg/day (5-10-15 ml), gradually increased, if necessary, up to 300 mg/day (60 ml).

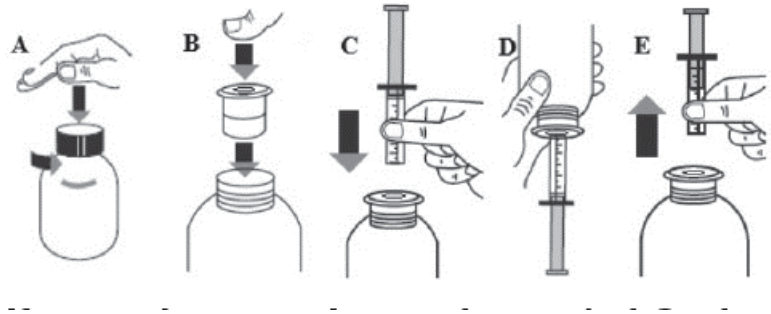
Use in elderly patients and patients with liver and kidney disease
In elderly patients and patients with liver and kidney disease the dose must be adjusted with special caution, as there is an increased risk of side effects.

Use in children and adolescents
This medication is not recommended for children and adolescents under the age of 16.

Method of administration
Levorol is for oral use only.

A 10 ml graduated oral syringe with intermediate graduations of 0.5 ml and a "Press-In" Bottle Adapter (PIBA) are provided with the product.

1. Open the bottle and at first use insert the "Press-In" Bottle Adapter (PIBA) (see pictures A-B).
2. Insert the syringe into the PIBA making sure the plunger is fully down.
   Turn the bottle with syringe in place, upside down and draw out the required volume from the inverted bottle (see pictures C-D).
3. Remove the filled syringe from the bottle in the upright position (see picture E).
4. Discharge the syringe contents into the mouth. Repeat steps 2 to 4 as needed to achieve the required dose.
5. Rinse the syringe and replace the cap on the bottle (PIBA remains in place).



For further information on how Levorol is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine 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 Levorol have been shown in studies?
No additional studies were needed as Levorol contain the same active substance as the reference medicine, and satisfactory data to justify the differences have been provided.

What are the possible side effects of Levorol?
As Levorol is a hybrid medicine and is equivalent to the reference medicine, its 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 PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Levorol approved?
It was concluded that Levorol has been shown to be equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Levorol?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Levorol. The RMP details the important risks of Levorol, how these risks can be minimised, any uncertainties about Levorol (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Levorol:

Summary of safety concerns	
Important identified risks	• Bone marrow function disorders including agranulocytosis • QT interval prolongation, Torsade de Pointes & sudden death • Neuroleptic Malignant Syndrome • Venous thromboembolism
Important potential risks	• None
Missing information	• None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Levorol are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Levorol
A marketing authorisation for Levorol 5 mg/ml Oral Solution (PL 39280/0016) was granted on 15 June 2022 in the UK to the Marketing Holder (MAH) Synchrony Pharma Limited, following the outcome of a national procedure. Subsequent to a change of ownership procedure on 01 December 2022, the marketing authorisation was converted to a GB

Marketing Authorisation and transferred to the current MAH Holder Galvany Pharma Limited (PLGB 56809/0001).

The full PAR for Levorol follows this summary.

This summary was last updated in November 2023.

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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 application for Levorol 5 mg/ml Oral Solution (PLGB 56809/0001, previously PL 39280/0016) could be approved.

Levomepromazine is a neuroleptic with indications in psychiatry and general medicine, particularly in terminal illness. Clinically it is more sedative and more potent than chlorpromazine in the management of psychotic conditions and in the relief of severe chronic pain and possesses anti-emetic effects.

Levorol 5 mg/ml Oral Solution is indicated:

- for suppression of psychomotor restlessness and agitation within the context of psychotic disorders
- for acute agitation states in manic episodes
- as an adjunct therapy for the treatment of severe and/or chronic pain.

The active substance, levomepromazine (as levomepromazine hydrochloride) belongs to the group of phenothiazines. Levomepromazine antagonizes dopamine receptors in the Central Nervous System, depressing the cerebral cortex, hypothalamus and limbic system. The clinical effects produced by this action include: a depressant action on conditioned responses and emotional responsiveness; a sedative action useful for the treatment of restlessness and confusion; an anti-emetic effect through blockade of the chemoreceptor trigger zone (CTZ), which is useful to treat vomiting; and
antihistamine activity.

Levorol 5 mg/ml Oral Solution was approved under Regulation 52A (and previously under Regulation 52B) of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Neurocil Tropfen, 40 mg/ml, Tropfen zum Einnehmen, Lösung (Neurocil drops, 40 mg/ml, oral drops, solution), that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a hybrid medicinal product of a suitable reference product.

A biowaiver was submitted with this application which was accepted. No bioequivalence or therapeutic equivalence studies were required, and none were provided with this application.

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

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

A marketing authorisation for Levorol 5 mg/ml Oral Solution (PL 39280/0016) was granted on 15 June 2022 in the UK to the Marketing Holder (MAH) Synchrony Pharma Limited, following the outcome of a national procedure. Subsequent to a change of ownership procedure on 01 December 2022, the marketing authorisation was converted to a GB Marketing Authorisation and transferred to the current MAH Holder Galvany Pharma Limited (PLGB 56809/0001).

II QUALITY ASPECTS

II.1 Introduction

This product contains 5 mg levomepromazine (as levomepromazine hydrochloride) in each ml of oral solution.

In addition to levomepromazine (as levomepromazine hydrochloride), this product also contains the excipients propylene glycol (E1520), glycerol (E422), sodium benzoate (E211), saccharin sodium (E954), orange flavour (including propylene glycol, E1520 and benzyl alcohol, E1519), hydrochloric acid, concentrated (E507) (for pH adjustment) and purified water.

The finished product is packaged in amber, type III glass bottles, each safely closed with a child-resistant high-density polyethylene (HDPE) screw cap with tamper evident closure. Each bottle contains 100 ml of this medicinal product. A 10 ml graduated oral syringe with intermediate graduations of 0.5 ml and a "press-in" syringe/bottle adapter are also provided.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

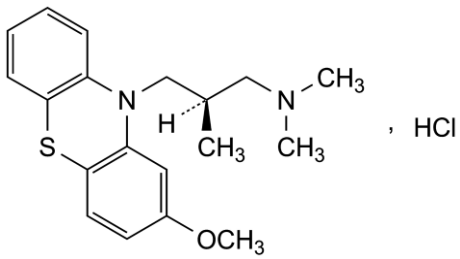
II.2 ACTIVE SUBSTANCE

rINN: Levomepromazine hydrochloride

Chemical Name: (2*R*)-3-(2-Methoxy-10*H*-phenothiazin-10-yl)-*N*,*N*,2-trimethylpropan-1-amine hydrochloride

Molecular Formula: $C_{19}H_{25}ClN_2OS$

Chemical Structure:



Molecular Weight: 364.9 g/mol

Appearance: White or very slightly yellow, crystalline powder, slightly hygroscopic

Solubility: Freely soluble in water and in ethanol (96 per cent), practically insoluble in heptane

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 specifications 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. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European Pharmacopoeia 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 finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

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

Satisfactory batch formulation data have been provided for the manufacture of the product, 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 at release and shelf-life 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 36 months for the unopened product and one month after first opening the product (bottle), with the storage conditions ‘This medicinal product does not require any special temperature storage conditions.’ and ‘Store in the original package in order to protect from light.’, 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 a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of levomepromazine 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 this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology

No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

In accordance with the regulatory requirements, the applicant has provided a suitable biowaiver. No bioequivalence or therapeutic equivalence studies have been submitted with this application.

IV. 2 Pharmacokinetics

No new pharmacokinetic data have been submitted for this application, and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application, and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for this application, and none were required.

IV.5 Clinical safety

No new safety data were submitted with this application, and none were required. The safety profile for this product is considered to be the same as Neurocil Tropfen, 40 mg/ml, Tropfen zum Einnehmen, Lösung (Neurocil drops, 40 mg/ml, oral drops, solution).

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, 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 a marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. 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 product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Extensive clinical experience with levomepromazine is considered to have demonstrated the therapeutic value of the product.

The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory and in line with current guidelines.

In accordance with legal requirements, the current approved versions of the SmPC and PIL for this product is available on the MHRA website.

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, is 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**