Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Levomepromazine Maleate 25mg Tablets
Levomepromazine Maleate 50mg Tablets
Levomepromazine Maleate 100mg Tablets

(levomepromazine maleate)

PL 20117/0337-0339

Morningside Healthcare Limited

LAY SUMMARY

Levomepromazine Maleate 25mg Tablets
Levomepromazine Maleate 50mg Tablets
Levomepromazine Maleate 100mg Tablets

(levomepromazine maleate)

This is a summary of the Public Assessment Report (PAR) for Levomepromazine Maleate 25mg, 50mg and 100mg Tablets. It explains how these products 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 these products.

These products will be referred to as Levomepromazine Maleate Tablets in this lay summary for ease of reading.

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

What are Levomepromazine Maleate Tablets and what are they used for?
The application for Levomepromazine Maleate 25mg Tablets is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Nozinan 25mg Tablets.

The applications for Levomepromazine Maleate 50mg and 100mg Tablets are for hybrid medicines. This means that the medicines are similar to the reference medicine Nozinan 25mg Tablets, albeit with certain differences. In this case, Levomepromazine Maleate 50mg and 100mg Tablets, are higher strengths (of the active substance), than the reference product.

Levomepromazine Maleate Tablets are used:
- in the treatment of schizophrenia
- for the relief of pain and accompanying distress in terminally ill patients.

How do Levomepromazine Maleate Tablets work?
Levomepromazine maleate, the active substance, belongs to a group of medicines called phenothiazines.

How are Levomepromazine Maleate Tablets used?
The pharmaceutical form of these medicines are tablets and the route of administration is oral (taken by mouth).

The tablets should be swallowed whole with a glass of water. The tablets can be divided into equal halves.

The recommended dose is as follows:

Schizophrenia
Adults - the initial dose is usually 25mg to 50mg a day, divided into three doses. If the patient is confined to bed, the initial dose may be 100mg to 200mg a day, divided into three doses. These doses may be increased in small steps until a suitable dose is found for the patient.

Elderly – the patient's doctor will decide whether these tablets are appropriate for their patient and will tell them how many to take.

Children - will normally be given no more than 37.5mg a day.

Pain management
Adults and Elderly – 12.5mg to 50mg every four to eight hours; the dose may be varied until a suitable dose is found for the patient.

Children - these tablets are NOT recommended for children for treating pain.

For further information on how Levomepromazine Maleate Tablets are used, refer to the package leaflet and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take these medicines 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 Levomepromazine Maleate have been shown in studies?
Because Levomepromazine Maleate Tablets are generic and hybrid medicines for additional strengths, studies in healthy volunteers have been limited to tests to determine that they are 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 possible side effects of Levomepromazine Maleate Tablets?
Because Levomepromazine Maleate Tablets are generic/hybrid medicines, the benefits and possible side effects are considered to be the same as for the reference medicine.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflet or the SmPCs available on the MHRA website.

Why were Levomepromazine Maleate Tablets approved?
It was concluded that, in accordance with EU requirements, Levomepromazine Maleate Tablets have been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Levomepromazine Maleate Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Levomepromazine Maleate Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet, 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 and reviewed continuously.

Other information about Levomepromazine Maleate Tablets
Marketing Authorisations for Levomepromazine Maleate Tablets were granted in the UK on 17 July 2020.

The full PAR for Levomepromazine Maleate Tablets follows this summary.

This summary was last updated in September 2020.

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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 applications for Levomepromazine Maleate 25mg, 50mg and 100mg Tablets (PL 20117/0337-0339) could be approved.

Levomepromazine Maleate 25mg, 50mg and 100mg Tablets are neuroleptics with indications in psychiatry and general medicine, particularly in terminal illness. Clinically they are more sedative and more potent than chlorpromazine in the management of psychotic conditions and in the relief of severe chronic pain.

The products are approved for the following indications:

- Psychiatry
  As an alternative to chlorpromazine in schizophrenia especially when it is desirable to reduce psychomotor activity.

- General medicine – Terminal illness
  Adjunct therapy in the relief of pain and the accompanying distress.

The active substance, levomepromazine maleate, is a phenothiazine drug with pharmacological activity similar to that of both chlorpromazine and promethazine, and is also known as methotrimeprazine. It is a neuroleptanalgesic - possessing both neuroleptic and analgesic properties. The mechanisms of action of levomepromazine involve blocking of D2, α_1- and α_2-adrenergic, and M_1 cholinergic receptors thereby exerting multiple therapeutic effects.

The application for Levomepromazine Maleate 25mg Tablets was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine of a suitable originator medicinal product, Nozinan 25mg Tablets, that has been licensed within the EU for a suitable time, in line with the legal requirements.

The applications for Levomepromazine Maleate 50mg and 100mg Tablets were submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be hybrid medicinal products of the suitable originator medicinal product, Nozinan 25mg Tablets.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being generic/hybrid medicinal products of a reference product that has been licensed for over 10 years.

With the exception of one bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are based on being generic/hybrid medicinal products of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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

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

Marketing Authorisations were granted for these products on 17 July 2020.

II QUALITY ASPECTS

II.1 Introduction

These products contain 25 mg, 50 mg or 100 mg of levomepromazine maleate in each tablet.

In addition to levomepromazine maleate, these products also contain the excipients lactose monohydrate, pregelatinised maize starch, povidone K-29/32, silica colloidal anhydrous and magnesium stearate.

The finished products are packaged in polyvinylchloride/polyvinylidene chloride-aluminium blisters. All strengths of the product are available in pack sizes of 7, 10, 14, 20, 24, 28, 30, 56, 60, 84, 90,100 and 112 tablets.

Not all pack sizes may be marketed.

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.

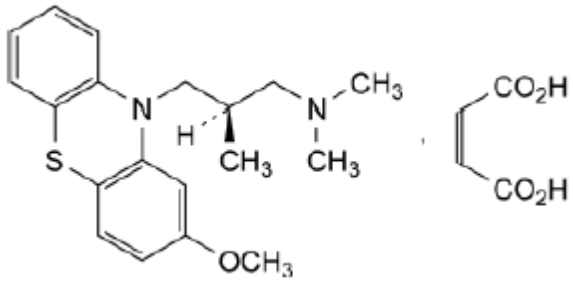
II.2 ACTIVE SUBSTANCE

rINN: Levomepromazine maleate

Chemical Name: (2*R*)-3-(2-methoxy-10*H*-phenothiazin-10-yl)-*N*,*N*,2-trimethylpropan-1-amine-(*Z*)-butenedioate

Molecular Formula: $C_{23}H_{28}N_2O_5S$

Chemical Structure:



Molecular Weight: 444.6 g/mol

Appearance: White or slightly yellowish, crystalline powder

Solubility: Slightly soluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol.

Levomepromazine maleate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance 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 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

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

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 and has shown satisfactory results.

Finished Product Specifications
The finished product specifications 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 2 years, with the storage conditions 'This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.', are 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 Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of levomepromazine maleate 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 these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic/hybrid versions of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of levomepromazine maleate are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for applications of this type. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the applications, the applicant submitted the following bioequivalence study.

Study 18-039

This study was an open-label, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing the test product Levomepromazine maleate 100mg tablets and the reference product Nozinan (levomepromazine maleate) 25mg Tablets (4 x 25 mg tablets; total dose 100mg) in healthy, adult, male subjects under fasting conditions.

Subjects were administered a single dose (100 mg) of the test (1 tablet) or reference (4 tablets) product with 240 ml of water, following an overnight fast of at least 10 hours. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 16 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1 Geometric least square means, ratios and 90% confidence intervals for pharmacokinetic parameters (C_{max} and AUC_{0-t}) of levomepromazine

Pharmacokinetic Parameters (Units)	Ln-transformed Geometric Least Squares Means and it's ratio			90% CI (Parametric)	
	Test Product	Reference Product	(T/R)%	Lower	Upper
C_{max} (ng/mL)	57.5316	52.6131	109.35	100.22	119.31
AUC_{0-72} (ng.hr/mL)	587.2993	573.8818	102.34	94.48	110.84

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between one tablet (100 mg strength) of the test product and four (25 mg strength) tablets of the reference product.

As the 25 mg and 50 mg strengths of the test product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 100 mg strength tablet can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, 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 Marketing Authorisations is recommended for these applications.

V USER CONSULTATION

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. 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

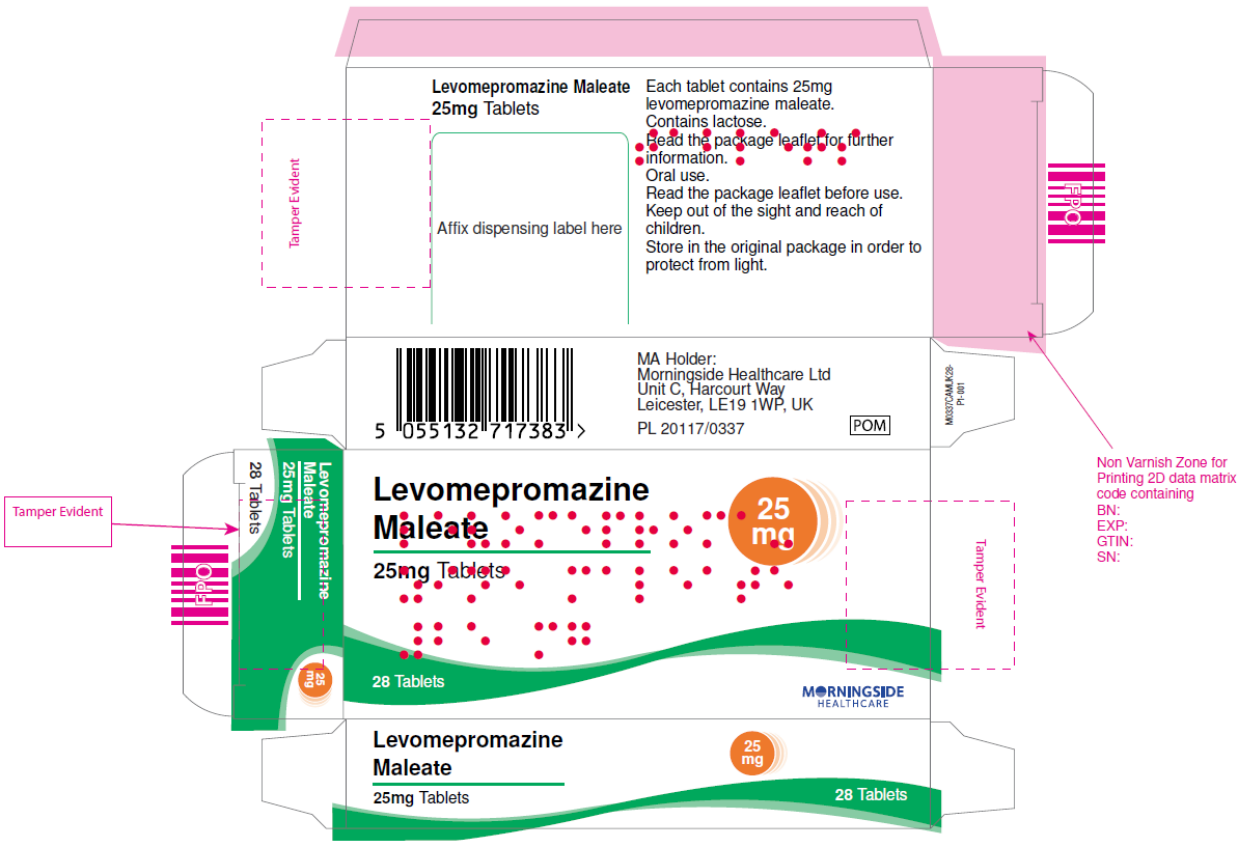
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levomepromazine maleate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

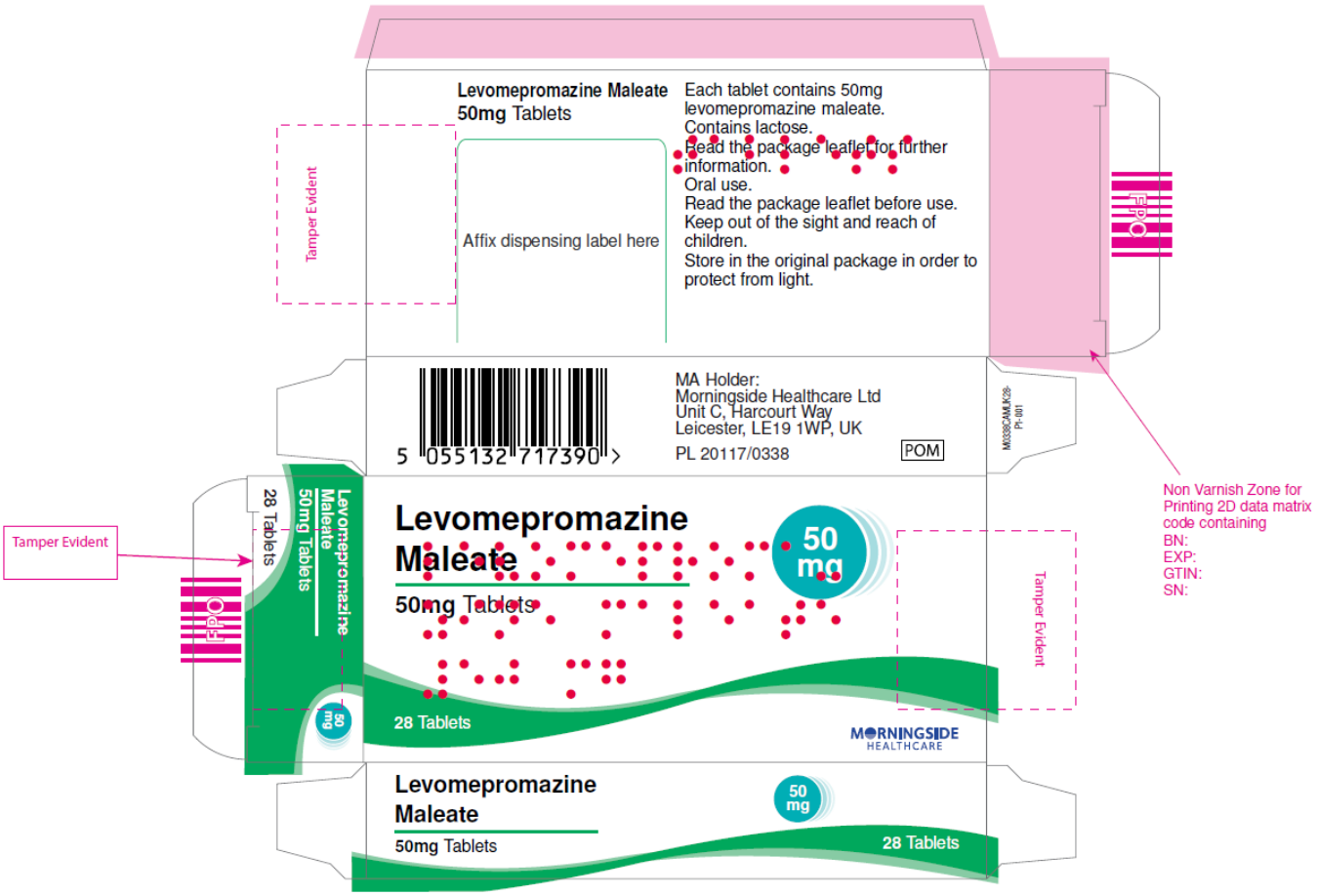
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

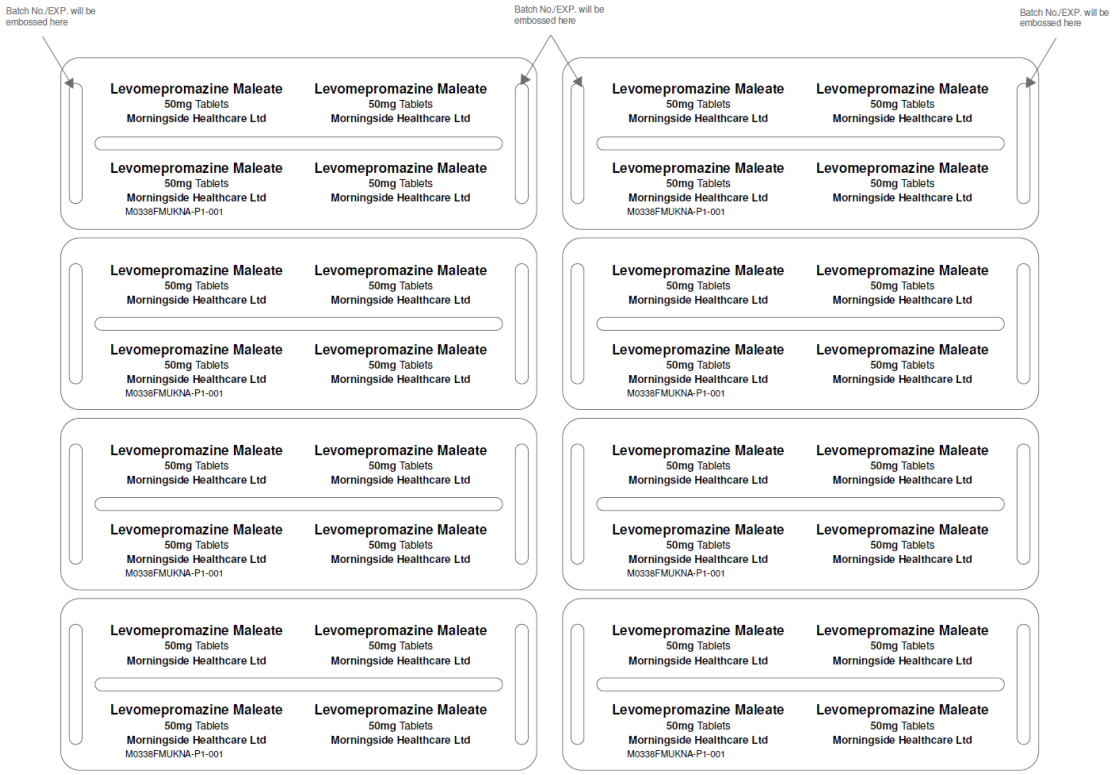
Representative copies of the labels at the time of UK licensing are provided below.

Levomepromazine maleate 25mg Tablets

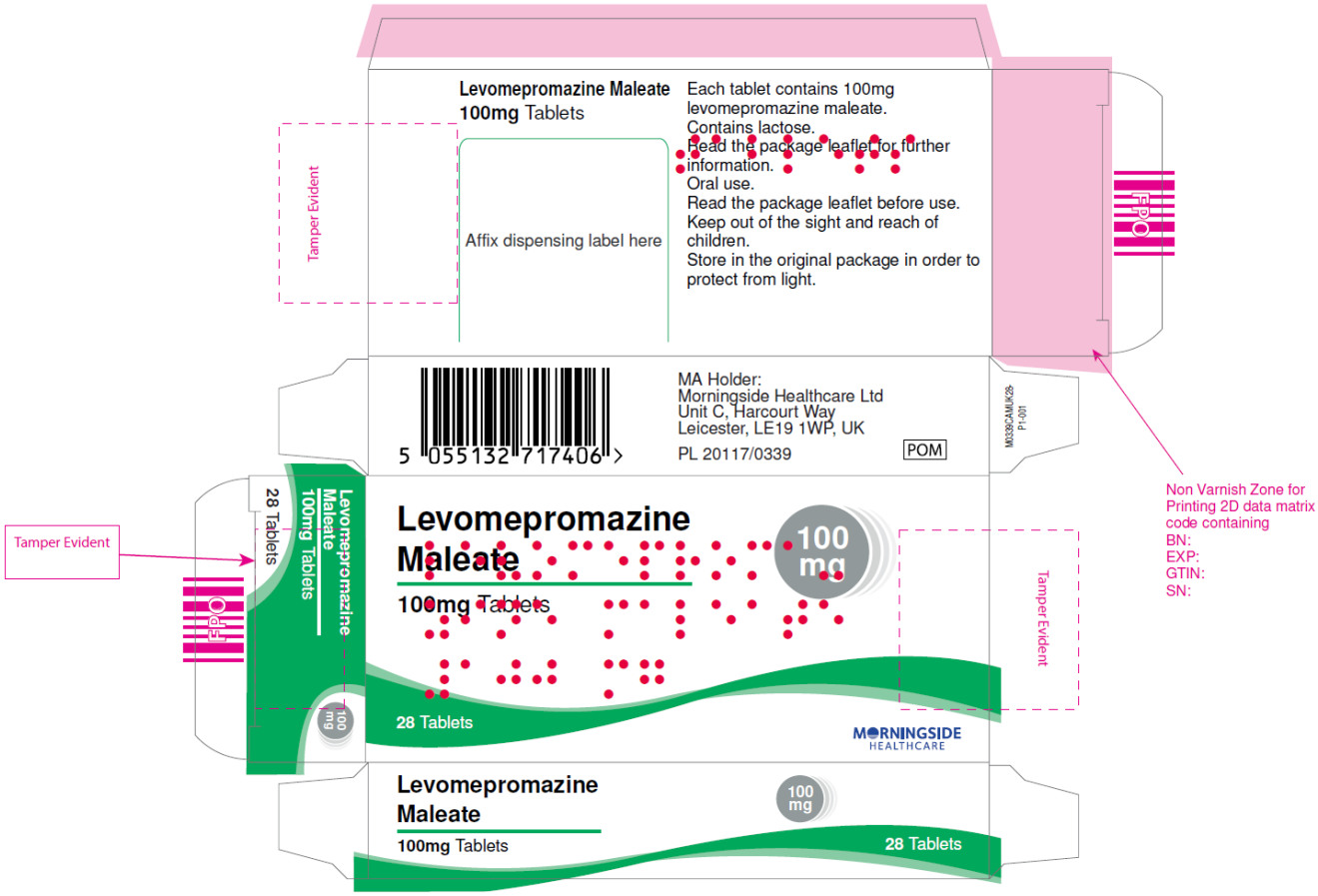


Levomepromazine Maleate 50mg Tablets





Levomepromazine Maleate 100mg Tablets



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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 are 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**