

**SUMMARY OF PRODUCT CHARACTERISTICS**  
**LEVOMEPRMAZINE**  
**25 MG COATED TABLETS**

**1. Name of the medicinal product** – Levomepromazine 25mg coated tablets

**2. Qualitative and quantitative composition**

Each coated tablet contains 25 mg levomepromazine maleate

For excipients, see 6.1.

**3. Pharmaceutical form**

White, oval, biconvex coated tablets with scored on one side, odorless.

**4. Clinical particulars**

**4.1 Therapeutic indications**

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.

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.

**4.2 Posology and method of administration**

Dosage varies with the condition under treatment and the individual response of the patient.

1. Terminal illness

Levomepromazine coated tablets 25mg may be substituted for the injection if oral therapy is more convenient, the dosage being 12.5mg to 50mg every 4 to 8 hours.

Elderly

No specific dosage recommendations.

2. Psychiatric conditions

Adults

Ambulant patients: initially the total daily oral dose should not exceed 25mg to 50mg usually divided into 3 doses; a larger portion of the dosage may be taken at bedtime to minimise diurnal sedation. The dosage is then gradually increased to the most effective level compatible with sedation and other side effects.

Bed patients: initially the total daily oral dosage may be 100mg to 200mg, usually divided into 3 doses, gradually increased to 1g daily if necessary. When the patient is stable attempts should be made to reduce the dosage to an adequate maintenance level.

Children

Children are very susceptible to the hypotensive and soporific effects of levomepromazine. It is advised that a total daily oral dosage of 1½ tablets should not be exceeded. The average effective daily intake for a ten year old is ½ to 1 tablet.

Elderly patients

It is not advised to give levomepromazine to ambulant patients over 50 years of age unless the risk of a hypotensive reaction has been assessed.

**4.3 Contraindications**

Safety in pregnancy has not been established.

There are no absolute contraindications to the use of Levomepromazine in terminal care.

**4.4 Special warnings and precautions for use**

The drug should be avoided, or used with caution, in patients with liver dysfunction or cardiac disease.

The hypotensive effects of Levomepromazine should be taken into account when it is administered to patients with cardiac disease and the elderly or debilitated. Patients receiving large initial doses should be kept in bed.

As with other neuroleptics, cases of QT interval prolongation have been reported with levomepromazine very rarely. Consequently, and if the clinical situation permits, absence of the following risk factors for onset of this type of arrhythmia should be verified prior to administration:

- Bradycardia or 2<sup>nd</sup> or 3<sup>rd</sup> degree heart block.
- Metabolic abnormalities such as hypokalaemia, hypocalcaemia or hypomagnesaemia.
- Starvation or alcohol abuse.
- A history of QT interval prolongation, ventricular arrhythmias or Torsades de Pointes.
- A family history of QT interval prolongation.
- Concomitant neuroleptics
- Ongoing treatment with another drug(s) liable to induce marked bradycardia, electrolyte imbalance, slowed intracardiac conduction or prolonged QT interval.

Prior to initiation of treatment with levomepromazine, it may be appropriate to consider an ECG with measurement of serum calcium, magnesium and potassium levels. Periodic serum electrolyte levels should be monitored and corrected if necessary, especially during long-term chronic usage. An ECG may be appropriate to assess the QT interval whenever dose escalation is proposed and when the maximum therapeutic dose is reached.

Stroke:

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism for this increased risk is not known.

An increased risk cannot be excluded for other antipsychotics or other patient populations.

Levomepromazine should be used with caution in patients with risk factors for stroke.

Increased Mortality in Elderly people with Dementia:

Data from two large observational studies showed that elderly people with dementia who are treated with conventional (Typical) antipsychotics are at a small increased risk of death compared with those who are not treated.

There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Levomepromazine is not licensed for the treatment of dementia-related behavioural disturbances.

Venous thromboembolism:

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Levomepromazine and preventive measures undertaken.

Hyperglycaemia:

Hyperglycaemia or intolerance to glucose has been reported in patients treated with Levomepromazine.

Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on Levomepromazine, should get appropriate glycaemic monitoring during treatment (see Section 4.8).

Convulsions:

Levomepromazine may lower epileptic threshold (see section 4.8) and should be used with caution in epileptic patients.

## Excipients

Levomepromazine coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Combinations requiring precaution:

**Cytochrome P450 2D6 Metabolism:** Levomepromazine and its non-hydroxylated metabolites are reported to be potent inhibitors of cytochrome P450 2D6 (CYP2D6). Co-administration of levomepromazine and drugs primarily metabolised by the CYP2D6 enzyme system may result in increased plasma concentrations of these drugs. Monitor patients for dose-dependent adverse reactions associated with CYP2D6 substrates such as amitriptyline/amitriptylinoxide.

There is an increased risk of arrhythmias when neuroleptics are used with drugs that prolong the QT interval such as certain class 1A and III antiarrhythmics (such as quinidine, disopyramide, procainamide, amiodarone, sotalol and dofetilide), certain antimicrobials (such as sparfloxacin, moxifloxacin and erythromycin IV), tricyclic antidepressants (e.g. amitriptyline), tetracyclic antidepressants (e.g. maprotiline), other neuroleptics (e.g. phenothiazines, pimozide and sertindole), antihistamines (e.g. terfenadine), cisapride, bretylium and antimalarials (e.g. quinine and mefloquine).

The anticholinergic effect of neuroleptics may be enhanced by other anticholinergic drugs. Avoid concomitant neuroleptics and any other drugs that may cause electrolyte imbalance. Diuretics, in particular those causing hypokalemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

Simultaneous administration of desferrioxamine and prochlorperazine has been observed to induce a transient metabolic encephalopathy, characterised by loss of consciousness for 48 to 72 hours. It is possible that this may occur with Levomepromazine since it shares many of the pharmacological activities of prochlorperazine. Adrenaline (epinephrine) must not be used in patients overdosed with neuroleptics. Alcohol should be avoided.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

Safety in pregnancy has not been established.

Neonates exposed to antipsychotics (including Levomepromazine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.

Consequently, newborns should be monitored carefully.

Animal studies are insufficient with respect to reproductive toxicity. In humans, the teratogenic risk of levomepromazine has not been evaluated. Different prospective epidemiological studies conducted with other phenothiazines have yielded contradictory results regarding teratogenic risk. Levomepromazine is not recommended during pregnancy and in women of childbearing potential not using contraception.

### Lactation

Levomepromazine is excreted in breast milk in low amounts in human milk. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Levomepromazine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

### Fertility

There are no fertility data in animals.

In humans, because of the interaction with dopamine receptors, levomepromazine may cause hyperprolactinaemia which can be associated with impaired fertility in women. Some data suggest that levomepromazine treatment is associated with impaired fertility in men.

#### 4.7 Effects on ability to drive and use machines

Levomepromazine can cause drowsiness, disorientation, confusion or excessive hypotension, which may affect the patient's ability to drive or operate machinery.

#### 4.8 Undesirable effects

Adverse effects have been ranked under headings of frequency using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ;  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ;  $< 1/100$ ); rare ( $\geq 1/10,000$ ;  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); frequency not known (cannot be estimated from the available data).

System organ class	Very common ( $\geq 1/10$ )	Common ( $\geq 1/100$ to $< 1/10$ )	Uncommon ( $\geq 1/1,000$ to $< 1/100$ )	Rare ( $\geq 1/10,000$ to $< 1/1,000$ )	Not known (cannot be estimated from available data)
Blood and lymphatic system disorders			Agranulocytosis		Raised ESR
Cardiac disorders		QT prolongation		Ventricular arrhythmias such as ventricular tachycardia or fibrillation Cardiac arrest Cardiac rhythm disturbances	Sudden death/sudden cardiac death (see Section 4.4) Torsades de Pointes (treatment of which should include discontinuation of levomepromazine and correction of hypoxia, electrolyte abnormalities and acid base disturbances)
Gastrointestinal disorders	Dry mouth		Constipation		Ileus paralytic Necrotizing enterocolitis (which can be fatal)
General disorders and administration site conditions		Asthenia Heat stroke (in hot and humid conditions)			
Hepatobiliary disorders				Jaundice	Hepatocellular, cholestatic and mixed liver injury
Metabolism and nutrition disorders					Glucose tolerance impaired Hyperglycaemia (see Section 4.4). Hyponatraemia Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Nervous system	Somnolence		Parkinsonism		Neuroleptic

disorders			(with prolonged high dosage) Convulsions		malignant syndrome Confusional states, delirium
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders					Priapism
Vascular disorders		Hypotension (especially in elderly patients)	Venous thromboembolism		Deep vein thrombosis Pulmonary embolism
Skin and subcutaneous tissue disorders					Photosensitivity reaction Dermatitis allergic

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Arpimed "LLC" by going to [www.arpimed.com](http://www.arpimed.com) and fill out the appropriate form "Report an adverse reaction or inefficiency of drug". Hotline number: (+374 55) 05 79 86. And by using Scientific Centre of Drug and Medical Technology Expertise after academician E. Gabrielyan "CJSC", going to the site: [www.pharm.am](http://www.pharm.am) in "Report about adverse effect of medicine" section and fill out the "Report of adverse reaction or manufacturing problem of medicinal product". Hotline numbers: +37410200505; +37496220505.

### 4.9 Overdose

Symptoms of levomepromazine overdose include drowsiness or loss of consciousness, hypotension, tachycardia, ECG changes, ventricular arrhythmias hypothermia and convulsions. Severe extrapyramidal dyskinesias may occur.

If the patient is seen sufficiently soon (up to 6 hours) after ingestion of a toxic dose, gastric lavage may be attempted. Pharmacological induction of emesis is unlikely to be of any use. Activated charcoal should be given. There is no specific antidote. Treatment is supportive. Generalised vasodilatation may result in circulatory collapse; raising the patient's legs may suffice but, in severe cases, volume expansion by intravenous fluids may be needed; infusion fluids should be warmed before administration in order not to aggravate hypothermia.

Positive inotropic agents such as dopamine may be tried if fluid replacement is insufficient to correct the circulatory collapse. Peripheral vasoconstrictor agents are not generally recommended; avoid use of adrenaline (epinephrine).

Ventricular or supraventricular tachy-arrhythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If persistent or life-threatening, appropriate antiarrhythmic therapy may be considered. Avoid lidocaine (lignocaine) and, as far as possible, long acting anti-arrhythmic drugs.

Pronounced central nervous system depression requires airway maintenance or, in extreme circumstances, assisted respiration. Severe dystonic reactions usually respond to procyclidine (5mg to 10mg) or orphenadrine (20mg to 40mg) administered intramuscularly or intravenously. Convulsions should be treated with intravenous diazepam.

Neuroleptic malignant syndrome should be treated with cooling. Dantrolene sodium may be tried.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

ATC Code: NO5AA02

Pharmacotherapeutic group: Antipsychotics

Levomepromazine 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.

### **5.2 Pharmacokinetic properties**

Maximum serum concentrations are achieved in 2 to 3 hours depending on the route of administration. Excretion is slow, with a half-life of about 30 hours. It is eliminated via urine and faeces.

### **5.3 Preclinical safety data**

There are no pre-clinical safety data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Tablet core: Microcrystalline cellulose

Lactose monohydrate

Povidone K30

Maize starch

Magnesium stearate

Sodium starch glycolate

Coating: Titanium dioxide

Hypromellose

Talc purified

Propylene glycol

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Store at a temperature below 25°C, protect from light and moisture and out of the reach of children.

### **6.5 Nature and contents of container**

10 tablets in blister PVC-Aluminum .

5 blisters (50 tablets) and leaflet inserted in the cardboard box.

### **6.6 Special precautions for disposal and other handling**

None.

**7. Marketing authorisation holder**

**“ARPIMED” LLC**

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**8. Marketing authorisation number**

**9. Date of first authorisation/renewal of the authorisation**

12.10.2012 / 27.06.2017

**10. Date of revision of the text**