SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Levomepromazine hydrochloride 25mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of the solution contains Levomepromazine hydrochloride 25mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Solution for injection.

Clear, colourless solution contained in a clear glass ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Management of the terminally ill patient. 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.

Levomepromazine 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 Injection is indicated in the management of pain and accompanying restlessness or distress in the terminally ill patient.
4.2 Posology and method of administration

Intramuscular and intravenous injection
Dosage varies with the condition and individual response of the patient. Levomepromazine Injection may be administered by intramuscular injection or intravenous injection after dilution with an equal volume of normal saline. The usual dose for adults and the elderly is 12.5mg to 25mg (0.5ml to 1ml) by intramuscular injection, or by the intravenous route after dilution with an equal volume of normal saline immediately before use. In cases of severe agitation, up to 50mg (2ml) may be used, repeated every 6 to 8 hours.

Continuous subcutaneous infusion
Levomepromazine Injection may be administered over a 24 hour period via a syringe driver. The required dose of Levomepromazine Injection (25mg to 200mg per day) should be diluted with the calculated volume of normal saline. Diamorphine hydrochloride is compatible with this solution and may be added if greater analgesia is required. Levomepromazine tablets 25mg may be substituted for the injection if oral therapy is more convenient.

Children
Clinical experience with parenteral levomepromazine in children is limited. Where indicated, doses of 0.35mg/kg/day to 3.0mg/kg/day are recommended.

4.3 Contraindications
Safety in pregnancy has not been established. There are no absolute contraindications to the use of Levomepromazine Injection 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 2nd or 3rd 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 any 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 may be monitored and corrected if necessary, especially during long-term 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 randomised 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 Injection 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 Injection and preventive measures undertaken.

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

Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on Levomepromazine Injection, 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 in caution with epileptic patients.

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 anti-arrhythmics (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 hypokalaemia, 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 Injection, 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 hydrochloride) 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 injection is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

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 injection 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 Injection 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).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common ((\geq 1/10))</th>
<th>Common ((\geq 1/100) to (&lt;1/10))</th>
<th>Uncommon ((\geq 1/1,000) to (&lt;1/100))</th>
<th>Rare ((\geq 1/10,000) to (&lt;1/1,000))</th>
<th>Not known (cannot be estimated from available data)</th>
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<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Agranulocytosis</td>
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<td>Raised ESR</td>
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<tr>
<td>Cardiac disorders</td>
<td>QT Prolongation</td>
<td>Ventricular arrhythmias such as ventricular tachycardia or fibrillationCardiac arrestCardiac rhythm disturbances</td>
<td></td>
<td>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)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Dry mouth</td>
<td>Constipation</td>
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<td>Ileus paralyticNecrotizing enterocolitis (which can be fatal)</td>
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<td>General disorders and administration site conditions</td>
<td>Asthenia</td>
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<tr>
<td>Medical Condition</td>
<td>Reported Adverse Event</td>
<td>Adverse Reaction Description</td>
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<td>Hepatobiliary disorders</td>
<td>Jaundice</td>
<td>Hepatocellular, cholestatic and mixed liver injury</td>
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<td>Metabolism and nutrition disorders</td>
<td>Glucose tolerance impaired</td>
<td>Hyperglycaemia (see Section 4.4)</td>
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<td>Hyponatraemia</td>
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<td>Syndrome of inappropriate antidiuretic hormone secretion (SIADH)</td>
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<td>Nervous system disorders</td>
<td>Somnolence</td>
<td>Parkinsonism (with prolonged high dosage)</td>
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<td>Convulsions</td>
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<td>Neuroleptic malignant syndrome</td>
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<td>Confusional states</td>
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<td>Delirium</td>
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<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
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<td>Drug withdrawal syndrome neonatal (see Section 4.6)</td>
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<td>Reproductive system and breast disorders</td>
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<td>Priapism</td>
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<td>Vascular disorders</td>
<td>Hypotension (especially in elderly patients)</td>
<td>Venous thromboembolism</td>
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<td>Deep vein thrombosis</td>
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<td>Pulmonary embolism</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>Photosensitivity reaction</td>
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<td>Dermatitis allergic</td>
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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 the Yellow Card Scheme www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

General 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 anti-arrhythmic 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

Ascorbic acid
Sodium sulfite
Sodium chloride
Water for Injections.

6.2 Incompatibilities

Incompatible with alkaline solutions.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25ºC. 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.
6.5 Nature and contents of container
1ml neutral glass (Type 1) ampoule. Each pack contains 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Levomepromazine Injection may be administered by intramuscular injection or intravenous injection after dilution with an equal volume of normal saline, or by continuous subcutaneous infusion with an appropriate volume of normal saline. Diamorphine hydrochloride is compatible with this solution.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0462

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
12/10/2012

10 DATE OF REVISION OF THE TEXT
26/04/2017