SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Promazine 50mg/5ml Oral Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 50mg Promazine Hydrochloride

Excipient(s) with known effect:
Propylene Glycol (E1520) 78.2 mg/5ml
Methyl Hydroxybenzoate (E218) 2.6 mg/5ml
Ethyl Hydroxybenzoate (E214) 0.6 mg/5ml
Propyl Hydroxybenzoate (E216) 0.4 mg/5ml
Sucrose 1.8 g/5ml
Liquid Glucose 1.3 g/5ml

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Syrup

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an adjunct to non-pharmacological interventions in the short-term management of moderate to severe agitation and restlessness where there is a risk of harm to the individual or to others.

4.2 Posology and method of administration

Posology

For oral administration only.

Dosage varies with the individual and the purpose for which the drug is used, so the following dosages are only for general guidance with regard to possible effectiveness and good tolerance.

Initial dosages should be low, with increments at frequent, regular intervals until the desired response is obtained.

Dosage intervals are usually six to eight hours, but in some patients a single bedtime dose may be sufficient. The lowest effective dose should be used.

The commencement and increase of dosage should be performed under close supervision.

Agitation and restlessness

Adults: 100mg to 200mg, up to four times daily.

Elderly: 25 mg initially, up to 50 mg four times daily

The lowest effective dose for the shortest period possible should be used.

Paediatric population

Children: Promazine is not recommended for children

4.3 Contraindications

Use in patients hypersensitive to the active ingredient or other phenothiazines.

Use in patients in coma or CNS depression

Use in patients with bone marrow depression

Use in patients with phaeochromocytoma

Use during lactation

Do not use during pregnancy, especially during the first three months, unless there are compelling reasons.

4.4 Special warnings and precautions for use

1. Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

2. Phenothiazine should only be used with great caution in patients with a history of jaundice or with existent liver dysfunction, or blood dyscrasias, (perform blood counts if unexplained infection or fever occurs) coronary insufficiency or cardiac disease.

3. Respiratory depression may occur in patients with severe respiratory disease.

4. Promazine should be used with caution in patients with renal failure.

5. Patients receiving phenothiazines over a prolonged period require regular and careful surveillance with particular attention to potential for inducing eye changes (corneal and lens opacities and purplish pigmentation of the skin, cornea, conjunctiva and retina), effects on haemopoiesis, liver dysfunction, myocardial conduction effects, particularly if other concurrently administered drugs also have potential effects on these systems.

6. Use of phenothiazines at high (relative or absolute) doses may induce extrapyramidal side effects, dyskinesia, akathisia, dystonia. These are likely to be particularly severe in children. Caution should be exercised in patients with Parkinson's disease. Anti-parkinson agents should not be prescribed routinely because of the risk of aggravating anticholinergic side effects of Promazine, of precipitating toxic-confusional states or of impairing its therapeutic efficacy. They should be given only as required.

7. Prolonged administration of phenothiazines may result in persistent or tardive dyskinesias particularly in the elderly. The risk of tardive dyskinesia and the likelihood of irreversibility are believed to increase as the duration of therapy and total cumulative dose increase. Neuroleptic therapy should be withdrawn if dyskinesia develops.

8. Care should be exercised if Promazine is used for the treatment of patients with cerebral arteriosclerosis, coronary heart disease or other conditions in which a fall in blood pressure might be undesirable.

9. Caution should be observed with patients suffering from epilepsy or conditions predisposing to epilepsy.

10. Personal or family history of narrow angle glaucoma.

11. Phenothiazines may impair body temperature regulation. Caution should be observed in very hot or very cold weather.

12. Hypothyroidism.

13. Myasthenia gravis.

14. Phaeochromocytoma.

15. Prostatic hypertrophy.

16. Antipsychotic drugs may increase prolactin secretion.

17. An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. Promazine should be used with caution in patients with risk factors for stroke.

18. As with other drugs belonging to the therapeutic class of antipsychotics, promazine may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, promazine should be used with caution in susceptible individuals (with hypoklaemia, hypomagnesia or genetic predisposition) and in patients with a history of cardiovascular disorders, e.g. QT prolongation, significant bradycardia (<50 beats per minute), a recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Concomitant treatment with other antipsychotics should be avoided (See section 4.5).

19. Concomitant use of promazine with other neuroleptics should be avoided.

20. Photosensitisation may occur, particularly at higher doses. Patients should be advised to avoid direct sunlight.

21. The elderly are particularly susceptible to the side effects of promazine, particularly hypotension, sedation and temperature regulation effects.

22. 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 Promazine and preventive measures undertaken.

Increased Mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are treated with 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.

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

Excipient Warnings

This medicine contains:

- Propylene Glycol (E1520). This medicine contains 78.2mg propylene glycol in each 5ml.
- Methyl Hydroxybenzoate (E218), Ethyl Hydroxybenzoate (E214) and Propyl Hydroxybenzoate (E216). May cause allergic reactions (possibly delayed).
- Liquid Glucose. This medicine contains 1.3g liquid glucose in each 5ml. This should be taken into account in patients with diabetes mellitus. Patients with rare glucose-galactose malabsorption should not take this medicine. May be harmful to the teeth.
- Sucrose. This medicine contains 1.8g sucrose in each 5ml. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to the teeth.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant administration of this product with other medication such as central nervous system depressants (including alcohol and anaesthetics) or antihypertensives, opioids, anticholinergic or dopaminergic drugs may result in accentuation of their effects, while potentiation of action may also occur with monoamine oxidase inhibitors, antidepressants and analgesics. Promazine may impair the effects of anticonvulsants. Promazine may affect the control of diabetes and possibly antagonises the hypoglycaemic effect of sulfonylureas. Undesirable anticholinergic effects can be enhanced by anti-parkinson or other anticholinergic drugs.

The concomitant administration of this product with myelosuppressive drugs (carbamazepine, co-trimoxazole, chloramphenicol, sulphonamides, pyralizone analgesics (e.g. azapropazone), penicillamine and cytotoxics) increases the risk of toxicity.

Lithium administration will result in an increased risk of extrapyramidal effects and the possibility of neurotoxicity.

Coadministration of phenothiazines with metoclopramide or tetrabenazine increases the risk of extrapyramidal effects.

An increase in plasma concentration of antipsychotic drugs may occur if taken with ritonavir.

There is an increased risk of convulsions when promazine is coadministered with tramadol

Antipsychotic drugs antagonize the pressor effects of sympathomimetics.

The effects of antipsychotic drugs may be enhanced by cimetidene and reduced by memantine.

Antacids and kaolin may reduce absorption of phenothiazines.

Caution should be used when using antipsychotics with reboxetine.

Sotalol administration will result in an increased risk of ventricular arrhythmia.

Concomitant use of promazine with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Therefore concomitant use of these products is not recommended. Examples include certain antiarrhythmics, such as those of Class 1A (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone, sotalol and dofetilide), certain antimicrobials (sparfloxacin, moxifloxacin, erythromycin IV), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), other neuroleptics (e.g. phenothiazines, pimozide, sertindole and haloperidol), certain antihistamines (such as terfenadine), cisapride, bretylium and certain antimalarials such as quinine and mefloquine. This list is not comprehensive.

Concurrent use of drugs causing electrolyte imbalance is not recommended. Diuretics, in particular those causing hypokalemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

4.6 Fertility, pregnancy and lactation

Do not use during pregnancy, especially during the first three months, unless there are compelling reasons. There is insufficient evidence of the safety of Promazine in human pregnancy nor is there evidence from animal studies that it is free from hazard.

Promazine should not be used during lactation.

Neonates exposed to antipsychotics (including Promazine) 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.

4.7 Effects on ability to drive and use machines

Phenothiazines may impair alertness and induce drowsiness especially at the start of treatment. Alcohol and many other drugs (see section 4.5) may enhance these effects and impair the ability to drive.

Persons taking these drugs should not drive or operate machinery unless the drug has been shown not to interfere with physical or mental ability.

4.8 Undesirable effects

Promazine is a member of the phenothiazine group of drugs and the size effects associated with that group have been noted.

System Organ Class	
Blood and lymphatic system disorders	Sensitivity reactions including agranulocytosis, leucopenia, haemolytic anaemia.
Psychiatric disorders	Apathy, confusional state. Some individuals may be susceptible to the drug in low dosage and show paradoxical effects of excitement, agitation or insomnia and other minor side effects. Withdrawal symptoms, including nausea, vomiting, sweating, insomnia, recurrence of psychotic symptoms and involuntary movement disorders have been noted (see Section 4.4).
Nervous system disorders	Drowsiness, dizziness, headache, sedation, epileptic fits, extrapyramidal symptoms (dystonia, tremor, tardive dyskinesia and akathisia), neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction altered consciousness) may occur with any neuroleptic.
Eye disorders	Blurred vision, precipitation of glaucoma, corneal and lens opacities and purplish pigmentation of the skin, cornea,

	conjunctiva and retina.
Cardiac disorders	Tachycardia, cardiovascular effects include hypotension. Phenothiazines can produce ECG changes with prolongation of QT interval and T-wave changes, ventricular arrhythmias (VF, VT (rare)), sudden unexplained death, cardiac arrest and Torsades de pointes have been reported.
Respiratory, thoracic and mediastinal disorders	Nasal stuffiness
Gastrointestinal disorders	Gastrointestinal disturbances, dry mouth, constipation.
Hepatobiliary disorders	Transient abnormalities of liver function tests may occur without jaundice. Rarely - obstructive jaundice associated with stasis in biliary canaliculi. Treatment should then be withdrawn and not given again.
Skin and subcutaneous tissue disorder	Sensitivity reactions including allergic skin reactions, rashes, photosensitisation and contact sensitization.
Renal and urinary disorders	Urinary hesitancy or retention when due to enlarged prostate.
Reproductive system and breast disorders	Menstrual disturbances, galactorrhoea, gynaecomastia, impotence.
General disorders and administration site conditions	Hypothermia, hyperpyrexia.
Pregnancy, puerperium and perinatal conditions	Not known: Drug withdrawal syndrome neonatal (see 4.6).
Investigations	Weight gain

The elderly are particularly susceptible to side effects of Promazine, especially to the sedative, hypotensive and temperature regulation effects. This may be dose related.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs – Frequency unknown

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Ingestion of large amounts of Promazine is followed by deep sleep, with or without a pronounced fall in blood pressure and without particular change in respiration rate, other than the slowing attendant upon sedation. Occasionally an initial period of excitement may precede coma, followed by grand mal seizures.

In the absence of any specific antidote, treatment should be based on ordinary therapeutic principles with special emphasis on the following measures:

a. Gastric lavage;

b. Treat convulsions if present;

c. Correction of acute hypotension if necessary;

d. Counteraction of the effects of an excess of Promazine on the central nervous system;

e. Control and natural recovery of hypothermia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Promazine is a member of the phenothiazine group with weak extrapyramidal properties, moderate anti-emetic properties and strong antimuscarinic, hypotensive and sedative properties.

It is thought to improve psychotic conditions by blocking postsynaptic mesolimbic dopaminergic receptors in the brain. It also produces an alpha-adrenergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones. However, blockade of dopamine receptors increases prolactin release by the pituitary.

It acts centrally to inhibit or block the dopamine receptors in the medullary chemoreceptor trigger zone and peripherally by blocking the vagus nerve in the gastrointestinal tract. It is thought to act as a sedative by causing indirect reductions

in arousal and increased filtering of internal stimuli to the brainstem reticular system. The alpha-adrenergic blocking effects may also produce sedation.

5.2. Pharmacokinetic Properties

Even with oral liquid administration, absorption can be erratic and unpredictable. It is highly lipophilic about 90% will be protein or membrane bound. It accumulates in the brain, lung and other tissues with a high blood supply.

The pharmacokinetics follow a mutiphasic pattern. Elimination half-life in respect to total plasma concentrations is 20-40 hrs.

Main route of metabolism is by oxidative processes mediated by hepatic microsomal and other drug metabolising enzymes. Conjugation with glucuronic acid is a prominent route. Hydrophilic metabolites are excreted in the urine, and to a lesser extent, in the bile. Most oxidised metabolites are biologically inactive, but a few are not. The foetus, infant and elderly have diminished capacity to metabolise and eliminate; children metabolise more rapidly than adults.

5.3. Preclinical Safety Data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Propylene glycol (E1520), methyl hydroxybenzoate (E218) , ethyl hydroxybenzoate (E214), propyl hydroxybenzoate (E216), sucrose, liquid glucose, ascorbic acid (E300), lime flavour 545523E and purified water.

6.2. Incompatibilities

None known.

6.3. Shelf-Life

36 months.

6.4. Special Precautions for Storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Bottle: Amber (type III) glass bottle

Capacity: 150ml

Closure: HDPE, EPE wadded, tamper evident, child resistant closure.

6.6. Instructions for Use, Handling and Disposal

Dispense in amber glass bottles. If a dose of under 5ml is required, the oral syrup should be administered using an oral dosing device.

7 MARKETING AUTHORISATION HOLDER

Rosemont Pharmaceuticals Ltd

Rosemont House

Yorkdale Industrial Park

Braithwaite Street

Leeds

LS11 9XE

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00427/5014R

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