SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prochlorperazine Mesilate 12.5mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 12.5mg (1.25% w/v) of prochlorperazine mesilate.

Excipient(s) with known effect:

Each 1 ml contains 1mg Sodium Sulphite (E221) and 0.75mg Sodium Metabisulphite (E223).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Colourless or almost colourless sterile solution for injection intended for parenteral administration to human beings

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

It is used in the symptomatic treatment of vertigo due to Meniere's syndrome or labyrinthitis and for nausea and vomiting from whatever cause including that associated with migraine, schizophrenia (especially in the chronic stage), acute mania and as an adjunct to the short term management of anxiety.

4.2 Posology and method of administration

Posology

Treatment of nausea and vomiting: 12.5mg by deep I.M. injection followed by oral medication six hours later, if necessary. Schizophrenia and other psychotic disorders: 12.5 to 25mg two or three times a day by deep I.M. injection until oral treatment becomes possible.

Elderly: Prochlorperazine should be used with caution in the elderly with psychotic disorders. Because elderly patients are susceptible to centrally acting drugs, lower initial dosage is recommended. Correct initial diagnosis of the disorder is important. Care should also be taken not to confuse adverse effects of prochlorperazine e.g. orthostatic hypotension with effects due to the primary disorder.

Paediatric population

Intramuscular prochlorperazine should not be used in children under 18 years.

Method of administration

Prochlorperazine injection is for administration by intramuscular injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Paediatric population

The use of Prochlorperazine injection is contraindicated in children as it has been associated with dystonic reactions after the cumulative dose of 0.5mg/kg.

4.4 Special warnings and precautions for use

Prochlorperazine should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis or prostate hypertrophy. It should also be avoided in patients hypersensitive to phenothiazines or with a history of narrow angle glaucoma or agranulocytosis.

Close monitoring is required in patients with epilepsy or a history of seizures, as phenothiazines may lower the seizure threshold.

As agranulocytosis has been reported, regular monitoring of the complete blood count is recommended. The occurrence of unexplained infections or fever may be evidence of blood dyscrasia (see section 4.8), and requires immediate haematological investigation.

It is imperative that treatment be discontinued in the event of unexplained fever, as this may be a sign of neuroleptic malignant syndrome (pallor, hyperthermia, autonomic dysfunction, altered consciousness, muscle rigidity). Signs of autonomic dysfunction, such as sweating and arterial instability, may precede the onset of

hyperthermia and serve as early warning signs. Although neuroleptic malignant syndrome may be idiosyncratic in origin, dehydration and organic brain disease are predisposing factors.

Acute withdrawal symptoms, including nausea, vomiting and insomnia, have very rarely been reported following the abrupt cessation of high doses of neuroleptics. Relapse may also occur, and the emergence of extrapyramidal reactions has been reported. Therefore, gradual withdrawal is advisable.

In schizophrenia, the response to neuroleptic treatment may be delayed. If treatment is withdrawn, the recurrence of symptoms may not become apparent for some time.

Neuroleptic phenothiazines may potentiate QT interval prolongation which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalaemia, and congenital or acquired (i.e. drug induced) QT prolongation. The risk-benefit should be fully assessed before prochlorperazine treatment is commenced. If the clinical situation permits, medical and laboratory evaluations (e.g. biochemical status and ECG) should be performed to rule out possible risk factors (e.g. cardiac disease; family history of QT prolongation; metabolic abnormalities such as hypokalaemia, hypocalcaemia or hypomagnesaemia; starvation; alcohol abuse; concomitant therapy with other drugs known to prolong the QT interval) before initiating treatment with Prochlorperazine Injection and during the initial phase of treatment, or as deemed necessary during the treatment (see also sections 4.5 and 4.8).

Avoid concomitant treatment with other neuroleptics (see section 4.5).

In randomised clinical trials versus placebo performed in a population with 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 of such risk increase is not known. An increase in the risk with other antipsychotic drugs or other populations of patients cannot be excluded. Prochlorperazine Injection should be used with caution with stroke risk factors.

As with all antipsychotic drugs, Prochlorperazine Injection should not be used alone where depression is predominant. However, it may be combined with antidepressant therapy to treat those conditions in which depression and psychosis coexist.

Because of the risk of photosensitisation, patients should be advised to avoid exposure to direct sunlight.

To prevent skin sensitisation in those frequently handling preparations of phenothiazines, the greatest care must be taken to avoid contact of the drug with the skin (see section 4.8).

Postural hypotension with tachycardia as well as local pain or nodule formulation may occur after I.M. administration.

It should be used with caution in the elderly, particularly during very hot or very cold weather because of the risk of hyper-, hypothermia.

The elderly are particularly susceptible to postural hypotension.

Prochlorperazine Injection should be used cautiously in the elderly owing to their susceptibility to drugs acting on the central nervous system and a lower initial dosage is recommended. There is an increased risk of drug-induced Parkinsonism in the elderly particularly after prolonged use. Care should also be taken not to confuse the adverse effects of Prochlorperazine Injection, e.g. orthostatic hypotension, with the effects due to the underlying disorder.

<u>Increased Mortality in Elderly people with Dementia:</u>

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.

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

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 prochlorperazine and preventive measures undertaken.

Hyperglycaemia or intolerance to glucose had been reported in patients treated with antipsychotic phenothiazines. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes, who are started on Prochlorperazine Injection, should get appropriate glycaemic monitoring during treatment (see section 4.8).

Excipients:

This medicine contains less than 1mmol sodium (23mg) per ml, that is to say essentially 'sodium-free'.

This medicine also contains the preservatives sodium sulphite (E221) and sodium metabisulphite (E223) which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Adrenaline must not be used in patients overdosed with prochlorperazine.

The CNS depressant actions of these agents may be potentiated by alcohol, barbiturates and other sedatives. Respiratory depression may occur. The hypotensive effect of most antihypertensive drugs especially alpha adrenoreceptor blocking agents may be exaggerated by neuroleptics.

Anticholinergic drugs may decrease the antipsychotic effects of neuroleptics.

The mild anticholinergic effect of neuroleptics may be enhanced by other anticholinergic drugs possibly leading to constipation, heat stroke, etc.

Some drugs interfere with absorption of neuroleptic agents: antacids, antiparkinson drugs and lithium.

Where treatment for neuroleptic-induced extrapyramidal symptoms is required, anticholinergic antiparkinsonian agents should be used in preference to levodopa, since neuroleptics antagonise the antiparkinsonian action of dopaminergics.

High doses of neuroleptics reduce the response to hypoglycaemic agents, the dosage of which might have to be increased.

Phenothiazine neuroleptics may oppose the action of some drugs, including amfetamine, levodopa, clonidine, guanethidine and adrenaline.

Increases or decreases in the plasma concentrations of a number of drugs, e.g. propranolol, phenobarbital have been observed but were not of clinical significance.

Simultaneous administration of desferrioxamine and prochlorperazine has been observed to induce a transient metabolic encephalopathy characterised by loss of consciousness for 48 - 72 hours.

There is an increased risk of arrhythmias when antipsychotics are used with concomitant QT prolonging drugs (including certain antiarrhythmics, antidepressants and other antipsychotics) and drugs causing electrolyte imbalance.

There is an increased risk of agranulocytosis when neuroleptics are used concurrently with drugs with myelosuppressive potential, such as carbamazepine or certain antibiotics and cytotoxics.

In patients treated concurrently with neuroleptics and lithium, there have been rare reports of neurotoxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is inadequate evidence of safety in pregnancy. There is evidence of harmful effects in animals. Prochlorperazine should be avoided in pregnancy unless the physician considers it essential. Neuroleptics may occasionally prolong labour and at such a time it should be withheld until the cervix is dilated 3 - 4cm.

Neonates exposed to antipsychotics (including prochlorperazine) 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.

Breast-feeding

Phenothiazines may be excreted in milk and breast feeding should be stopped during treatment.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Prochlorperazine has minor influence on the ability to drive and use machines.

Patients should be warned about drowsiness during the early days of treatment and advised not to drive or operate machinery if affected.

4.8 Undesirable effects

Generally, adverse reactions occur at a low frequency; the most common reported adverse reactions are nervous system disorders.

Not known (cannot be estimated from available data)

Adverse effects:

System organ class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Not known	A mild leukopenia occurs in up to 30% of patients on prolonged high dosage. Agranulocytosis may occur rarely; it is not dose related (see section 4.4).
Immune system disorders	Not known	Type I hypersensitivity reactions such as angioedema and urticaria
Endocrine disorders	Not known	Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia; amenorrhoea; impotence
Nervous system disorders	Not known	*Acute dystonia or dyskinesias, **Akathisia, ***Tardive dyskinesia, Insomnia and agitation may occur.
Eye disorders	Not known	Ocular changes and the development of a metallic greyish-mauve coloration of exposed skin have been noted in some individuals mainly females, who have received chlorpromazine continuously for long periods (four to eight years). This could happen with prochlorperazine.
Cardiac disorders	Not known	ECG changes include QT prolongation (as with other neuroleptics), ST depression, U-Wave and T-Wave changes. Cardiac arrhythmias, including ventricular arrhythmias and atrial arrhythmias, A-V block, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest have been reported during neuroleptic phenothiazine therapy, possibly related to dosage. Pre-existing

		cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose. There have been isolated reports of sudden death, with possible causes of cardiac origin (see section 4.4, above), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.
Vascular disorders	Not known	Hypotension, usually postural, commonly occurs. Elderly or volume depleted subjects are particularly susceptible; it is more likely to occur after intramuscular injection. Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs.
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression is possible in susceptible patients. Nasal stuffiness may occur.
Gastrointestinal disorders	Not known	Dry mouth
Hepatobiliary disorders	Not known	Jaundice, usually transient, occurs in a very small percentage of patients taking neuroleptics. A premonitory sign may be sudden onset of fever after one to three weeks of treatment followed by the development of jaundice. Neuroleptic jaundice has the biochemical and other characteristics of obstructive jaundice and is associated with obstruction of the canaliculi by bile thrombi; the frequent presence of an accompanying eosinophilia indicates the allergic nature of this phenomenon. Treatment should be discontinued if jaundice develops (see section 4.4).
Skin and subcutaneous tissue disorders	Not known	Contact skin sensitisation is a serious but rare complication in those frequently handling preparations of certain phenothiazines (see section 4.4); Skin rashes of various kinds may also be seen in patients treated with the drug. Patients on high dosage should be warned that they may develop photosensitivity in sunny weather and should avoid exposure to direct sunlight.
Reproductive system and breast disorders	Not known	Pregnancy, puerperium and perinatal conditions: Drug withdrawal syndrome neonatal (see 4.6).
General disorders and administration site conditions	Not known	Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction and altered consciousness) may occur with any neuroleptic (see section 4.4). Intolerance to glucose, hyperglycaemia (see

		section 4.4).

* usually transitory are commoner in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases.

** characteristically occurs after large initial doses. Parkinsonism is commoner in adults and the elderly. It usually develops after weeks or months of treatment. One or more of the following may be seen: tremor, rigidity, akinesia or other features of Parkinsonism. Commonly just tremor.

*** If this occurs, it is usually, but not necessarily, after prolonged or high dosage. It can even occur after treatment has been stopped. Dosage should therefore be kept low whenever possible.

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

4.9 Overdose

Symptoms

Possible symptoms of phenothiazine overdosage include drowsiness or loss of consciousness, hypotension, tachycardia. E.C.G. changes, ventricular arrhythmias and hypothermia. Severe extra-pyramidal dyskinesias may occur. There is no specific antidote.

Management

Treatment is symptomatic and supportive.

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.

Generalised vasodilatation may result in circulatory collapse; raising the patient's legs may suffice and, in severe cases, volume expansion by intravenous fluids may be needed; infusion fluids should be warmed before administration to avoid aggravating hypothermia.

Positive inotropic agents such as dopamine may be considered if fluid replacement is insufficient to correct the circulatory collapse. Peripheral vasoconstrictor agents are not generally recommended and the use of adrenaline should be avoided.

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 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 (5 - 10mg) or orphenadrine (20 - 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

Pharmacotherapeutic group: Antipsychotics, Phenothiazines with piperazine structure, ATC code: N05AB04.

Prochlorperazine belongs to the phenothiazine group which have a piperazine group at position 10 of the phenothiazine molecule. This entails a greater risk of inducing extrapyramidal side effects but less tendency to produce sedation or autonomic side effects such as hypotension, unless unusually large doses are employed.

Mechanism of action

At therapeutic doses, prochlorperazine is mainly dopamine antagonist but it also has anticholinergic and anti-adrenoceptor blocking activity. Its actions on dopamine receptors in the medulla chemoreceptor trigger zone probably accounts for its anti emetic effects. Unwanted effects results from the drugs dopamine and adrenoceptor antagonism. Dystonias and dyskinesias and parkinsonism in the elderly can occur with prolonged use or high dosage. Postural hypotension and excessive sedation are risks, especially in the elderly.

5.2 Pharmacokinetic properties

The pharmacokinetics of prochlorperazine in man have been little studied because of its difficulty to assay. The low and variable bioavailability is largely due to extensive metabolism of the drug in the gut wall and liver, to sulphoxide.

Parenteral (intramuscular) administration can increase the availability of the active drug by four to ten times. There is a marked inter individual variation in pharmacokinetics following intravenous administration but no evidence of dose dependent pharmacokinetics; mean terminal half life is of the order of 6.85 hours. A

few generalisations can be made. The phenothiazine group of drugs to which prochlorperazine belongs is highly lipophilic, highly membrane or protein bound and will accumulate in the brain, lung and other tissues with a high blood supply; it also enters the foetal circulation quite easily. This apparent high volume of distribution would confirm that the liver is not the only site of metabolism.

5.3 Preclinical safety data

No further relevant information other than that which is included with other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Sulphite B.P. (E221)

Sodium Metabisulphite B.P. (E223)

Ethanolamine B.P.

Water for Injections B.P.

6.2 Incompatibilities

An immediate precipitate was reported to have occurred when prochlorperazine mesylate 100mg per litre was mixed with aminophylline 1g per litre or with ampicillin sodium 2g per litre in glucose injection and sodium chloride injection, or with ethamivan 2g per litre in sodium chloride injection. An immediate precipitate also occurred with phenobarbitone sodium 800mg per litre, sulphadiazine sodium 4g per litre, or sulphadimide sodium 4g per litre in sodium chloride injection, but when they were mixed in glucose injection, a haze developed over 3 hours. A haze developed over 3 hours when prochlorperazine mesylate was mixed with amphotericin 200mg per litre or methohexitone sodium 2g per litre in glucose injection, or with benzylpenicillin 6g per litre, chloramphenicol 4g per litre, or chlorothiazide 2g per litre in sodium chloride injection.

Loss of clarity was reported to have occurred when solutions of prochlorperazine were mixed with those of calcium gluconate, chlorothiazide

sodium, heparin, hydrocortisone sodium succinate, nitrofurantoin sodium, pentobarbitone sodium, and thiopentone sodium.

6.3 Shelf life

Unopened: 3 years (36 months)*
After reconstitution: Not applicable

* If only part of an ampoule is used, the remainder should be discarded.

6.4 Special precautions for storage

Keep the ampoules in the outer carton in order to protect from light.

Do not store above 25°C.

6.5 Nature and contents of container

1ml and 2ml clear One Point Cut (OPC) glass ampoules, glass type 1 Ph.Eur. packed in cardboard cartons to contain 5x 1ml; 5 x 2ml; 10 x 1ml and 10 x 2ml ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For deep intramuscular injection

Use as directed by the physician

Keep out of the sight and reach of children

If only part used, discard the remaining solution

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd.
Dashwood House,
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London, EC2M 1QS,
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8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0599

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