SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Stemetil 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active component of the Stemetil tablets is prochlorperazine maleate BP 5 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Off-white to pale cream coloured circular tablets for oral use. The tablets are marked on one face 'STEMETIL' around a centrally impressed '5', reverse face plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vertigo due to Meniere's Syndrome, labyrinthis and other causes, and for nausea and vomiting from whatever cause including that associated with migraine. It may also be used for schizophrenia (particularly 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

Adults

Indication	**Dosage**
Prevention of nausea and vomiting	5 – 10 mg b.d. or t.d.s.
Treatment of nausea and vomiting	20 mg stat, followed if necessary by 10 mg two hours later.
Vertigo and Meniere's syndrome	5 mg t.d.s. increasing if necessary to a total of 30 mg daily. After several weeks dosage may be reduced gradually to 5 – 10 mg daily.
Adjunct in the short term management of anxiety	15 – 20 mg daily in divided doses initially but this may be increased if necessary to a maximum of 40 mg daily in divided doses.

Schizophrenia and other psychotic disorders	Usual effective daily oral dosage is in the order of 75 – 100 mg daily. Patients vary widely in response. The following schedule is suggested: Initially 12.5 mg twice daily for 7 days, the daily amount being subsequently increased 12.5 mg at 4 – 7 days interval until a satisfactory response is obtained. After some weeks at the effective dosage, an attempt should be made reduce this dosage. Total daily amounts as small as 50 mg or even 25 mg have sometimes been found to be effective.

Paediatric population

Indication	**Dosage**
Prevention and treatment of nausea and vomiting	If it is considered unavoidable to use Stemetil for a child, the dosage is 0.25 mg/kg bodyweight two or three a day. Stemetil is not recommended for children weighing less than 10 kg or below 1 year of age.

Elderly
A lower dose is recommended (see section 4.4).

Method of administration
Oral administration.

4.3 Contraindications

Known hypersensitivity to prochlorperazine, to other phenothiazines or to any of the other ingredients listed in section 6.1.

4.4 Special warnings and precautions for use

Stemetil should be avoided in patients with:

- liver or renal dysfunction
- Parkinson's disease
- hypothyroidism
- cardiac failure
- phaeochromocytoma
- myasthenia gravis
- prostate hypertrophy
- a history of narrow angle glaucoma or agranulocytosis

Monitoring advice
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.

Blood disorders

The occurrence of unexplained infections or fever may be evidence of blood dyscrasia (see section 4.8) and requires immediate haematological investigation.

Neuroleptic Malignant Syndrome
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.

Withdrawal
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.

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

QT prolongation
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 Stemetil 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 Stemetil and during the initial phase of treatment, or as deemed necessary during the treatment (see also sections 4.5 and 4.8).

Psychiatric disorders
As with all antipsychotic drugs, Stemetil 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.

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.

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

Skin reactions
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).

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

The elderly are particularly susceptible to postural hypotension.

Stemetil 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 Stemetil, e.g. orthostatic hypotension, with the effects due to the underlying disorder.

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.

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

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 of such risk increase is not known. An increase in the risk with other antipsychotic drugs or other populations of patients cannot be excluded. Stemetil should be used with caution in patients with stroke risk factors.

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 Stemetil and preventative measures undertaken.

Paediatric population
Stemetil has been associated with dystonic reactions particularly after a cumulative dosage of 0.5 mg/kg. It should therefore be used cautiously in children

Hyperglycaemia
Hyperglycaemia or intolerance to glucose has 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 Stemetil, should get appropriate glycaemic monitoring during treatment (see section 4.8).

Hypersensitivity

Hypersensitivity reactions including anaphylaxis, urticaria and angioedema have been reported with Stemetil use. In case of allergic reactions, treatment with Stemetil must be discontinued and appropriate symptomatic treatment initiated (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Adrenaline must not be used in patients overdosed with Stemetil (see section 4.9).

The CNS depressant actions of neuroleptic agents may be intensified (additively) by alcohol, barbiturates and other sedatives. Respiratory depression may occur.

Anticholinergic agents may reduce the antipsychotic effect of neuroleptics and 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, anti-Parkinson drugs and lithium.

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

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

The hypotensive effect of most antihypertensive drugs especially alpha adrenoceptor blocking agents may be exaggerated by neuroleptics.

The action of some drugs may be opposed by phenothiazine neuroleptics; these include amphetamine, levodopa, clonidine, guanethidine, 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 transient metabolic encephalopathy characterised by loss of consciousness for 48 – 72 hours.

There is an increased risk of arrhythmias when neuroleptics are used with concomitant QT prolonging drugs (including certain anti-arrhythmics, 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.

Some phenothiazines are potent inhibitors of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines,

and CYP2D6 substrates. Co-administration of phenothiazines with amitriptyline/amitriptylinoxide, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline/amitriptylinoxide. Monitor patients for dose-dependent adverse reactions associated with amitriptyline/amitriptylinoxide.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies are insufficient with respect to reproductive toxicity. However, potential harmful effect in animals cannot be ruled out. There is inadequate evidence of safety in pregnancy. Data from epidemiological studies do not suggest a risk of congenital malformations in children exposed in utero to Stemetil.

As a precautionary measure, Stemetil should be avoided during pregnancy unless the potential benefits outweigh the potential risks.

Neuroleptics may occasionally prolong labour and at such time should be withheld until the cervix is dilated 3 – 4 cm. Possible adverse effects on the neonate include lethargy or paradoxical hyperexcitability, tremor and low apgar score.

Neonates exposed to antipsychotics (including Stemetil) 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, therefore breast feeding should be suspended during treatment.

4.7 Effects on 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.

4.8 Undesirable effects

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

Immune system disorders:

- Anaphylactic reactions
- Type I hypersensitivity reactions such as angioedema and urticaria.

Blood and lymphatic system disorders:

- 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).

Endocrine disorders:

- Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea and impotence.

Nervous system disorders:
- Acute dystonia or dyskinesias, including oculogyric crisis, usually transitory are commoner in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases.
- Akathisia characteristically occurs after large initial doses.
- Parkinsonism is more common 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.
- Tardive dyskinesia: 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.
- Insomnia and agitation may occur.
- Convulsions.

Eye disorders:
Ocular changes and the development of 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 possibly happen with Stemetil.

Cardiac disorders:
- 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), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Vascular disorders:
- 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 – Frequency unknown

Gastrointestinal disorders:
Dry mouth may occur.

Metabolism and nutrition disorders:
- Hyponatraemia
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Respiratory, thoracic and mediastinal disorders:

- Respiratory depression is possible in susceptible patients.
- Nasal stuffiness may occur.

Hepatobiliary disorders:
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 withheld on the development of jaundice (see section 4.4).

Skin and subcutaneous tissue disorders:

- Contact skin sensitisation may occur rarely 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.

General disorders and administration site conditions:
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)

Pregnancy, puerperium and perinatal conditions:
Drug withdrawal syndrome neonatal (see section 4.6) – Frequency not known.

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

Symptoms of phenothiazine overdose include drowsiness or loss of consciousness, hypotension, tachycardia, ECG changes, ventricular arrhythmias and hypothermia. 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. 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 the use of adrenaline.

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 – 10 mg) or orphenadrine (20 – 40 mg) 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: Psycholeptics; Phenothiazines with piperazine structure, ATC code: N05AB04

Stemetil is a potent phenothiazine neuroleptic.

5.2 Pharmacokinetic properties

There is little information about blood levels, distribution and excretion in humans. The rate of metabolism and excretion of phenothiazines decreases in old age.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Maize starch

Aerosil (E551)

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in original packaging in order to protect from light.

6.5 Nature and contents of container

Stemetil tablets 5mg are available in “securitainers” or HDPE bottles in packs of 25, 250 and 1000 tablets and PVDC coated UPVC/aluminium foil blisters containing 28 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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