Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Stemetil 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg of Prochlorperazine Maleate.
Excipients: Also includes lactose monohydrate, 67 mg per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Off-white to pale cream coloured circular tablets approximately 6.4 mm in diameter and 3.2 mm thick: not mottled or speckled. Smooth almost biconvex surfaces, one face impressed ‘STEMETIL’ around a centrally impressed 5, reverse face plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications
Stemetil tablets are recommended in the management of acute vertigo such as is associated with Meniere’s syndrome, nausea and vomiting, migraine and anxiety states. The course of treatment should not normally exceed 2 weeks duration.

In the management of phobias, schizophrenia, acute mania, and similar psychotic reactions.

4.2 Posology and method of administration
The route of administration is oral

*Recommended Dosage:*

**Adults:**
For the management of Meniere’s syndrome, nausea and vomiting: -
The usual total daily dosage is 10-40mg in divided doses

In schizophrenia and other psychotic disorders:
The usual total daily dosage is 75-100mg in divided doses.

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

**Children:** Not recommended for use in children.
4.3 Contraindications

Use in patients with a known hypersensitivity to the prochlorperazine or to any of the other ingredients.
Use in patients with impaired liver function.

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. It should be avoided in patients known to be 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.

Patients receiving phenothiazines over a prolonged period require regular and careful surveillance with particular attention to potential for inducing eye changes, liver dysfunction, myocardial conduction effects, particularly if other concurrently administered drugs also have potential effects on these systems.

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 Undesirable effects), 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.

Treatment involves the immediate cessation of neuroleptic therapy and symptomatic management as appropriate.

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.

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.

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 Undesirable effects).

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, dyskinesia, akathisia, dystonia, particularly after prolonged use.
These are likely to be particularly severe in children. 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.

Prolonged administration of any phenothiazine may result in persistent or tardive dyskinesias, particularly in the elderly.

Phenothiazines should only be used with great caution in patients with coronary insufficiency, cardiovascular disorders which may predispose to prolongation of the QT interval.

As with other neuroleptics, very rare cases of QT-interval prolongation have been reported with Stemetil.

Cases of QT prolongation, possibly dose related have been reported with neuroleptic drugs. This effect can increase the risk of serious ventricular disorders such as torsades de pointes. As a precaution before administration of Prochlorperazine, it is recommended if possible, to eliminate the risk factors for cardiac rhythm disturbances:

- Brachycardia <55 beats/minute
- Hypokalemia
- Congenital or acquired QT prolongation
- Ongoing treatments with drugs which can result in brachycardia (<55 beats/minute), hypokalemia, slowed intracardiac conduction, QT prolongation (see section 4.5 interactions).

Except in emergencies, it is recommended that an ECG be performed as part of the initial evaluation of patients due to receive treatment with a neuroleptic drug.

There have been isolated reports of sudden death with phenothiazines with possible causes of a cardiac origin.

Avoid concomitant prescription of other antipsychotics.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

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 Undesirable Effects).

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 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.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant drugs which could induce prolongation of the QT interval or torsade de pointes (see 4.4 Warnings):
- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine; digitalis.
- Medications which induce electrolyte imbalance, in particular those causing hypokalaemia (such as hypokalaemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactides). Electrolyte imbalance should be corrected.
- Class Ia antiarrhythmic agents such as quinidine, disopyramide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Other medications such as pimozide, sulthiame, haloperidol, imipramine antidepressants, lithium, cisaipride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

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

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

The CNS depressant actions of neuroleptic agents may be intensified (additively) by alcohol, barbiturates and other sedatives. Respiratory depression may occur. Potentiation of action will also occur with monoamine oxidase inhibitors, antidepressants and analgesics.

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/amitriptylineoxide, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline/amitriptylineoxide. Monitor patients for dose-dependent adverse reactions associated with amitriptyline/amitriptylineoxide.

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.

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

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 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, phenobarbitone have been observed but were not of clinical significance.

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.
4.6 Fertility, pregnancy and lactation

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, bradycardia, tachycardia, feeding disorder, meconium ileus, delayed meconium passage, abdominal bloating. Consequently, newborns should be monitored carefully in order to plan appropriate treatment.

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.

Adverse effects:

**Immune systems disorders**
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 Special Warnings and Special Precautions for Use).

**Pregnancy, puerperium and perinatal conditions:**
Drug withdrawal syndrome neonatal (see section 4.6)/frequency not known.

**Endocrine:** Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea; impotence.

Hyperglycaemia or intolerance to glucose has been reported with antipsychotic phenothiazines (see section 4.4 Special Warnings and Precautions for Use).

**Nervous system disorders:** Acute dystonia or dyskinesias, usually transitory are commoner in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases. Convulsions.

**Metabolism and nutrition disorders:** Hyponatraemia, Inappropriate antidiuretic hormone secretion

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.
Dizziness or drowsiness may occur.
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: 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. ECG changes, usually benign, include widened QT interval, ST depression, U-Wave and T-Wave changes (see section 4.4 Special Warnings and Special Precautions for Use).

There have been isolated reports of sudden death, with possible causes of cardiac origin (see section 4.4 Special Warnings and Special Precautions for Use), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs – Frequency unknown (see section 4.4 Special Warnings and Special Precautions for Use).

Vascular disorders: Hypotension, usually postural, commonly occurs. Elderly or volume depleted subjects are particularly susceptible; it is more likely to occur after intramuscular injection.

Gastrointestinal disorders: dry mouth may occur.

Respiratory, thoracic and mediastinal disorders: Respiratory depression is possible in susceptible patients. Nasal stuffiness may occur.

Hepato-biliary 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 Special Warnings and Special Precautions for Use).

Skin and subcutaneous tissue disorders: Contact skin sensitisation may occur rarely in those frequently handling preparations of certain phenothiazines (see section 4.4 Special Warnings and Special Precautions for Use). 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 Special Warnings and Special Precautions for Use).

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of phenothiazine overdosage 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 tachyarrhythmias 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 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 (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: Phenothiazines with piperazine structure. ATC code: N05AB04

Stemetil is a potent phenothiazine neuroleptic.

5.2 Pharmacokinetic properties

Potent phenothiazine neuroleptic with anti-emetic properties with an elimination t½ of approximately 6-12 hours depending on the route and formulation.

The rate of metabolism and excretion of phenothiazines decreases in old age.

5.3 Preclinical safety data

There are no preclinical datat 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 monohydrate
Maize starch
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Boxes containing 250 tablets in white blister packs: 250 μm opaque white, unplasticated, uPVC film coated with 40gsm PVdC and 20 μm hard temper aluminium foil, PVC-Acrylate heat seal lacquer.

HDPE bottles containing 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Ltd. T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/127/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY

Date of first authorisation: 01 April 1977
Date of last renewal: 01 April 2007

10 DATE OF REVISION OF THE TEXT

March 2018