[sanofi logo]

STEMETIL

INJECTION

Prochlorperazine Mesylate

PROTECT FROM LIGHT

INDICATIONS

STEMETIL is a potent phenothiazine neuroleptic. It is used in vertigo due to Meniere's syndrome, labyrinthitis 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.

KINETICS

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

DOSAGE AND ADMINISTRATION

ADULTS

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. 12·5mg to 25mg two or three times a day by deep i.m. injection until oral treatment becomes possible.

CHILDREN

Intramuscular STEMETIL should not be given to children. When treating children, it is recommended that the syrup or 5mg tablets are used.

STEMETIL is not recommended for children weighing less than 10kg.

ELDERLY

A lower initial dosage is recommended. Please see Precautions section.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Contraindications:

Known hypersensitivity to prochlorperazine or to any of the other ingredients.

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

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.

Neonates exposed to antipsychotics (including Stemetil) during the third trimester of pregnancy are at risk of various degrees of respiratory disorders ranging from tachypnea", "bradycardia", "signs related to the atropinic properties of phenothiazines such as meconium ileus, delayed

meconium passage, abdominal bloating, tachycardia; neurological disorders such as extrapyramidal symptoms"

Neuroleptics may occasionally prolong labour and at such a 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.

Lactation: Phenothiazines may be excreted in milk therefore breastfeeding should be suspended during treatment.

Warnings:

Close monitoring is required in patients with epilepsy or a history of seizures, as phenothiazines may lower the seizure threshold. The occurrence of convulsive seizures necessitates the discontinuation of the treatment. 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 and requires immediate haematological investigation. It is imperative that treatment be discontinued in the event of unexplained fever, as this may be asign 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.

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.

If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a neuroleptic agent and as deemed necessary during treatment.

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.

Stroke:

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. It should be used with caution with stroke risk factors.

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, sedation and extrapyramidal side effects.

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.

Elderly Patients with Dementia:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients.
Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Prolonged administration of any phenothiazine may result in persistent or tardive dyskinesias, particularly in the elderly and the children. Stemetil is not licensed for the treatment of dementia-related behavioural disturbances.

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore, STEMETIL should be used with caution in patients with risk factors for thromboembolism (see also Adverse side effects).

Postural hypotension with tachycardia as well as local pain or nodule formation may occur after intramuscular administration.

Precautions:

STEMETIL should be avoided in patients with liver or renal dysfunction, epilepsy, Parkinson's disease, hypothyroidism, 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. It should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyper-, hypothermia).
Patients should be warned about drowsiness during the early days of treatment, and advised not to drive or operate machinery.
Postural hypotension with tachycardia as well as local pain or nodule formation may occur after i.m. administration.
The elderly are particularly susceptible to postural hypotension. 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. Care should also be taken not to confuse the adverse effects of STEMETIL e.g. orthostatic hypotension with effects due to the underlying disorder.
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 also Adverse side effects).

Interactions:
The CNS depressant actions of neuroleptic agents may be intensified (additively) by alcohol, barbiturates and other sedatives. Respiratory depression may occur.
The hypotensive effect of most antihypertensive drugs especially alpha adrenoceptor blocking agents may be exaggerated by neuroleptics.
The mild anticholinergic effect of neuroleptics may be enhanced by other anticholinergic drugs possibly leading to constipation, heat stroke, etc.
The action of some drugs may be opposed by phenothiazine neuroleptics; these include amphetamine, levodopa, clonidine, guanethidine, adrenaline.
Phenothiazines are potent inhibitors of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. Co-administration with amitriptyline, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline.
Anticholinergic agents may reduce the antipsychotic effect of neuroleptics.
Some drugs interfere with absorption of neuroleptic agents: antacids, anti-Parkinson, lithium. 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.
High doses of neuroleptics reduce the response to hypoglycaemic agents, the dosage of which might have to be raised.
Adrenaline must **not** be used in patients overdosed with STEMETIL.
Most of the above interactions are of a theoretical nature and not dangerous.
Simultaneous administration of desferrioxamine and prochlorperazine has been observed to introduce 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

Adverse side effects:

Immune system disorders:
Type 1 hypersensitivity reactions such as angioedema and urticaria.

Blood and lymphatic system disorder:
A mild leukopaenia occurs in up to 30% of patients on prolonged high dosage.
Agranulocytosis may occur rarely; it is not dose related.

Reproductive system and breast disorders:
Priapism has been very rarely reported in patients treated with Stemetil
Ejaculation disorder

Gastrointestinal disorders:
dry mouth, constipation.

Hepato-biliary disorders:
: Jaundice, usually transient, occurs in a very small percentage of patients taking neuroleptics. A premonitory sign may be a 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 obstructions 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.

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

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 arrhythmia, A-V block, ventricular tachycardia which may results in ventricular fibrillation or cardiac arrest have been reported during neuroleptic therapy, possibly related to dosage. Pre-existing cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose.
Respiratory, thoracic and mediastinal disorders:
Respiratory depression is possible in susceptible patients. Nasal stuffiness may occur.

Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotics drugs (see also Warnings).
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Nervous system disorders:
: Acute dystonias or dyskinesias, including oculogyric crisis usually transitory are more common 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.
Convulsion
Dizziness

Skin and eyes:
Contact skin sensitisation is a serious but rare complication in those frequently handling preparations of certain phenothiazines; the greatest care must be taken to avoid contact of the drug with the skin. 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.
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 possibly happen with STEMETIL.

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

Metabolism and nutrition disorder:
Hyperglycaemia or intolerance to glucose has been reported with antipsychotic phenothiazines (see also Precautions).
Hyponatremia, inappropriate antidiuretic hormone secretion.

General disorder:
Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction and altered consciousness) may occur with any neuroleptic.

TOXICITY AND TREATMENT OF OVERDOSAGE

Symptoms of phenothiazine overdosage include drowsiness or loss of consciousness, hypotension, tachycardia, E.C.G. 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 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.

PHARMACEUTICAL PRECAUTIONS

Protect from light. Store below 25°C. STEMETIL Injection solution rapidly discolours on exposure to light; any such solution should be discarded.

PRESENTATION

STEMETIL 1·25% Injection - colourless solution containing 12·5 mg prochlorperazine mesylate per ml in boxes of 10 x 1 ml ampoules.

The aqueous solution also contains sodium sulphite 0·1% w/v, sodium metabisulphite 0·075% w/v, sodium chloride and ethanolamine.

Manufactured by:

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