

## **1. NAME OF THE MEDICINAL PRODUCT**

Prochlorperazine Injection B.P. 12.5mg/ml, 1ml & 2ml

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

## **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**

Prochlorperazine injection is for administration by intramuscular injection.

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.

Intramuscular prochlorperazine should not be administered to children.

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.

### **4.3. Contra-indications**

Should not be used in patients who are known to be hypersensitive to the active ingredient.

### **4.4 Special warnings and precautions for use**

Intramuscular prochlorperazine should not be administered to children.

Prochlorperazine should be avoided in patients with liver or renal dysfunction, epilepsy,

Parkinson's disease, hypothyroidism, pheochromocytoma, myasthenia gravis or prostate hypertrophy. It should also be avoided in patients hypersensitive to phenothiazines or with a history of narrow angle glaucoma.

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

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

Postural hypotension with tachycardia as well as local pain or nodule formation may occur after I.M. administration. The elderly or volume depleted patients are especially susceptible to postural hypotension. This is more likely to occur after intramuscular administration. (See section 4.8)

Patients with cardiac disease, hypokalaemia, and those on antidepressants may be at risk of developing cardiac arrhythmias.

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.

#### 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.

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

#### **4.5. Interactions with other Medicaments and other forms of Interaction**

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.

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

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

Anticholinergic drugs may decrease the antipsychotic effects of neuroleptics.

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

Antidepressants, including tricyclic drugs may predispose cardiac arrhythmias. (See section 4.4 and 4.8)

Adrenaline must not be used in patients overdosed with prochlorperazine.

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

#### **4.6. Pregnancy and Lactation**

Prochlorperazine is contra-indicated in pregnancy. There is inadequate evidence of the safety of prochlorperazine in human pregnancy but it has been used extensively for many years without apparent deleterious effects in pregnancy. There is, however, evidence of harmful effects in animals. Like other drugs, it 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. Possible adverse effects on the neonate include lethargy or paradoxical hyperexcitability, tremor and low Apgar score. Phenothiazines may be excreted in milk and breast feeding should be stopped 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 if affected.

#### **4.8 Undesirable effects**

Minor side effects of neuroleptics are nasal stuffiness, dry mouth, insomnia, agitation.

Adverse effects of neuroleptics: Liver function: 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. Neuroleptic-induced jaundice has the bio-chemical 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 discontinued if jaundice develops.

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

Cardiac arrhythmias, including atrial arrhythmia, A-V block, ventricular tachycardia and fibrillation have been reported during neuroleptic therapy, possibly related to dosage. Preexisting cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose. ECG changes, usually benign, include widened QT intervals, ST depression, Uwaves and T-wave changes. Respiratory depression is possible in susceptible patients.

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

Blood picture: A mild leukopenia occurs in up to 30% of patients on prolonged high dosage. Agranulocytosis may occur rarely; it is not dose related. The occurrence of unexplained infections or fever requires immediate haematological investigation.

Extrapyramidal: Acute dystonias 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.

Akathisia 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).

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.

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 happen with prochlorperazine.

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

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

#### **4.9. Overdose**

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. Treatment is symptomatic and supportive.

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 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 - 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.

## **Pharmacological Properties**

### **5.1. Pharmacodynamic Properties**

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.

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 interindividual 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.

## **PHARMACEUTICAL PARTICULARS**

### **6.1. List of Excipients**

Sodium Sulphite B.P.

Sodium Metabisulphite B.P.

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 ampoules in the outer carton.

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.

## **6.6. Instruction for Use/Handling**

For deep intramuscular injection.

Use as directed by the physician.

Keep out of reach of children.

If only part used, discard the remaining solution.

## **7. MARKETING AUTHORISATION HOLDER**

Antigen International Ltd.,  
Roscrea,  
Co. Tipperary,  
Ireland.

**8. MARKETING AUTHORISATION NUMBER**

PL 2848/0165.

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

27/02/2009

**10 DATE OF REVISION OF THE TEXT**

January 2010