IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0073/129/002
Case No: 2076970

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Antigen Pharmaceuticals Ltd

Chandler House, **Castle Street**, **Roscrea**, **Co Tipperary**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Prochlorperazine Injection BP 25mg in 2ml

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **07/04/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prochlorperazine Injection BP 25mg in 2ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2ml of solution contains 25mg (1.25% w/v) of Prochlorperazine Mesilate BP.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Colourless or almost colourless sterile solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the symptomatic treatment of acute vertigo such as is associated with Meniere's syndrome, and for nausea and vomiting from whatever cause including that associated with migraine. It is also used in the management of schizophrenia, acute mania, phobias and similar psychotic reactions, and as an adjunct to the short term management of anxiety.

4.2 Posology and method of administration

Prochlorperazine Injection is for administration by deep intramuscular injection.

Adults:

Meniere's syndrome, nausea and vomiting: 12.5mg by deep IM 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 IM injection until oral treatment becomes possible.

Intramuscular prochlorperazine should not be administered to children.

Elderly:

Prochlorperazine should be used with caution in the elderly. 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 Contraindications

Prochlorperazine should not be administered to patients who are known to be hypersensitive to the active ingredient.

4.4 Special warnings and precautions for use

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

Postural hypotension with tachycardia as well as local pain may occur after IM administrations. The elderly are especially sensitive to postural hypotension.

Phenothiazines should only be used with great caution in patients with a history of jaundice or with a history of liver of renal dysfunction, blood dyscrasias, coronary insufficiency or cardiac disease.

During prolonged use of phenothiazines, regular and careful surveillance is required, with particular attention to potential for inducing eye changes, effects on haemopoiesis, liver dysfunction, myocardial conduction defects, especially if other concurrently administered drugs also have potential effects on these systems.
The anti-emetic action of prochlorperazine may render the assessment of such conditions as cerebral irritation or intestinal obstruction uncertain; therefore, an exact diagnosis should be made before giving the drug.

Prochlorperazine may lower body temperature, and special care should be taken in this regard in the elderly.
The neuroleptic malignant syndrome has been reported in patients of neuroleptic therapy. As the condition is potentially fatal, neuroleptic therapy should be discontinued immediately (see Section 4.8).

This medicinal product contains less than 1mmol sodium (0.273mg sodium per ml), i.e. essentially sodium free.

The excipients, sodium sulphite & sodium metabisulphite, may rarely cause severe hypersensitivity reactions and bronchospasm.

Caution in patients with cardiovascular disease or family history of QT prolongation. Avoid concomitant antipsychotics.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of this product with other drugs such as CNS depressants (including alcohol and anaesthetics), antihypertensives or anticholinergics will result in accentuation of their effects, while potentiation of action will also occur with monoamine oxidase inhibitors, anti-depressants and analgesics. Simultaneous administration of desferrioxamine and prochlorperazine has been observed to induce a transient metabolic encephalopathy characterised by loss of consciousness for 48 - 72 hours.

Avoid concomitant QT prolonging drugs, drugs causing electrolyte imbalance & metabolic inhibitor (CYP_) where known.

4.6 Pregnancy and lactation

Phenothiazines should only be used during pregnancy if it is considered essential by the physician. Because phenothiazines are excreted in breast milk, breastfeeding 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.

4.8 Undesirable effects

Dizziness, dry mouth, nasal stuffiness, agitation and mild skin reactions may occur. Slight transient drowsiness may occur in some patients during the early stages of treatment, but it is rarely of an order to warrant reduction of dosage or withdrawal of the drug. However, patients should not drive or operate machinery until the effect has been ascertained.

Use of phenothiazines at high (relative or absolute) doses may induce extrapyramidal side-effects, dyskinesia, akathisia and dystonia. These are likely to be particularly severe in children.

Prolonged administration of phenothiazines may result in persistent or tardive dyskinesia, particularly in the elderly. This is a syndrome characterised by involuntary dyskinetic movements. Although most usually associated with cases where there is high total cumulative dosing, a few cases have been reported after only small doses have been given or even after therapy has been stopped. Fine vermicular movements of the tongue are reported to be an early sign and their appearance is an indication that treatment should be discontinued. In most instances, the syndrome will resolve or not progress. Groups particularly at risk include the elderly and females. As with all medication, treatment should be maintained at the lowest effective dose and only for as long as the patient<?xml:namespace prefix = st1 ns = "urn:schemas-microsoft-com:office:smarttags" /><st1:PersonName w:st="on">'</st1:PersonName>s condition requires it. Phenothiazines may induce contact allergic reactions on handling.

Other side effects include QT prolongation, Ventricular arrhythmias - VF, VT (rare), Sudden unexplained death, Cardiac arrest & Torsades de pointes.

The neuroleptic malignant syndrome may occur with use of any neuroleptic agent. The syndrome is characterised by hyperthermia, together with some or all of the following: muscular rigidity, autonomic instability, (labile blood pressure, tachycardia, diaphoresis) akinesia, and altered consciousness sometimes progressing to stupor or coma. Leucocytosis, elevated CPK, liver function test abnormalities, and acute renal failure may also occur. Treatment involves immediate cessation of neuroleptic therapy and symptomatic management as appropriate. The condition is potentially fatal.

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

4.9 Overdose

Symptoms of phenothiazine overdosage include drowsiness, loss of consciousness, convulsions, dystonic reactions, hypotension, tachycardia, ventricular arrhythmias and hypothermia.

There is no specific antidote and treatment is symptomatic and supportive.

Patients should be kept under close observation and an open airway should be maintained, since extrapyramidal involvement may produce respiratory difficulty in severe overdosage and assisted respiration may be required in extreme circumstances. Diazepam may be given intravenously to control convulsions. Severe dystonic reactions usually respond to procyclidine 5 - 10mg or orphenadrine 20 - 40mg administered intramuscularly or intravenously. If hypotension occurs, standard measures for managing circulatory shock should be initiated; elevation of the lower limbs may suffice and, in severe cases, volume expansion with intravenous fluids, pre-warmed to avoid aggravating hypothermia, may be required. A positive inotropic agent such as dopamine may be used if fluid replacement fails to correct circulatory collapse; peripheral vasoconstrictor drugs such as adrenaline should be avoided, since their alpha-mediated vasoconstrictor effects are impaired by phenothiazines and a further reduction in blood pressure could occur. 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, therapy with an anti-arrhythmic agent may be considered; lidocaine should be avoided and, as far as possible, long-acting anti-arrhythmic agents.

Dantrolene is the drug of choice in management of the neuroleptic malignant syndrome.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Prochlorperazine 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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Sodium Sulphite
Sodium Metabisulphite
Ethanolamine
Water for Injections

6.2 Incompatibilities

An immediate precipitate was reported to have occurred when prochlorperazine mesilate 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 etamivan 2g per litre in Sodium Chloride Injection. An immediate precipitate also occurred with phenobarbital sodium 800mg per litre, sulfadiazine sodium 4g per litre, sulfadimidine 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 mesilate was mixed with amphotericin 200mg per litre or methohexital 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, phenobarbital sodium, and thiopental sodium.

6.3 Shelf Life

3 years.

If only part of contents of an ampoule is used, then the remaining solution should be discarded.

6.4 Special precautions for storage

Keep ampoules in the outer carton.
Do not store above 25^{o}C.

6.5 Nature and contents of container

2 ml clear glass ampoules, glass type 1 Ph. Eur. packed in cardboard cartons to contain 5 or 10 ampoules.

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

For deep intramuscular injection.
If only part of contents of an ampoule is used, the remaining solution should be discarded.
Prochlorperazine Injection rapidly discolours on exposure to light: any such solution be discarded.

7 MARKETING AUTHORISATION HOLDER

Antigen Pharmaceuticals Ltd.,
Chandler House
Castle Street
Roscrea,
Co. Tipperary.

8 MARKETING AUTHORISATION NUMBER

PA 0073/129/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 1993

Date of last renewal: 23 February 2008

10 DATE OF REVISION OF THE TEXT

April 2010