

**PROCHLORPERAZINE 5MG TABLETS
(PROCHLORPERAZINE MALEATE)**

PL 17907/0072

UKPAR

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**PROCHLORPERAZINE 5MG TABLETS
(PROCHLORPERAZINE MALEATE)**

PL 17907/0072

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Prochlorperazine 5mg Tablets (PL 17907/0072) on 23rd April 2007. This is a prescription-only medicine (POM).

Prochlorperazine 5mg Tablets contain the active ingredient prochlorperazine, as prochlorperazine maleate, which belongs to a group of medicines called phenothiazines. Prochlorperazine 5mg tablets are used for the treatment of vertigo caused by a variety of reasons including diseases of the inner ear such as Meniere's syndrome and labyrinthitis. This product may also be used for the prevention and treatment of nausea and vomiting from a variety of causes, including migraine. The tablets can also be used to treat schizophrenia, mania, and in combination with other treatments for the short term treatment of anxiety.

The test product was considered to be a generic product of the reference product Stemetil 5mg Tablets (PL 16946/0006, Castlemead Healthcare Ltd) based on the bioequivalence study submitted, and no new safety issues arose as a result of this study.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Prochlorperazine 5mg Tablets outweigh the risk, hence a Marketing Authorisation has been granted.

**PROCHLORPERAZINE 5MG TABLETS
(PROCHLORPERAZINE MALEATE)**

PL 17907/0072

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Bristol Laboratories Limited a Marketing Authorisation for the medicinal product Prochlorperazine 5mg Tablets (PL 17907/0072) on 23rd April 2007. The product is a prescription-only medicine (POM).

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Stemetil 5mg Tablets (PL 16946/0006, Castlemead Healthcare Ltd) that was originally granted a UK licence as PL 000012/5263R (May & Baker Limited) on 22/02/1973.

Prochlorperazine 5mg Tablets contain the active ingredient prochlorperazine (as prochlorperazine maleate), which belongs to a group of medicines called phenothiazines. Prochlorperazine is a potent phenothiazine neuroleptic well characterised in the literature. Prochlorperazine tablets are indicated for 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.

The application depends upon the bioequivalence study presented by the applicant comparing the test product Prochlorperazine 5mg Tablets with the reference product Stemetil 5mg Tablets (PL 16946/0006, Castlemead Healthcare Ltd).

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

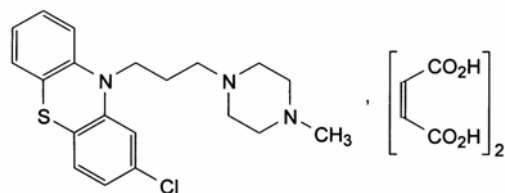
Prochlorperazine maleate

Nomenclature:

INN: Prochlorperazine maleate

Chemical name: 2-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10*H*-phenothiazine bis[hydrogen (*Z*)-butenedioate]

Structure:



Molecular formula: $C_{20}H_{24}ClN_3S, 2C_4H_4O_4$

Molecular weight: 606.2

CAS No: 84-02-6

Physical form: A white or pale-yellow, crystalline powder

Solubility: Very slightly soluble in water and in alcohol, practically insoluble in ether

Stereochemistry: There is no potential isomerism.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the materials used are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided which is in line with that set by the DMF holder, and based upon the European and US Pharmacopeia monograph specifications. Additional, satisfactory, in-house tests are included to control residual solvents. Satisfactory Certificates of Analysis have been provided for any working standards used.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

The active substance, prochlorperazine maleate, is stored in appropriate packaging. It is packed in double polyethylene bags, sealed individually with plastic strips and placed in fibre carton drums. Specifications and Certificates of Analysis have been provided for all packaging materials used. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated for active substance stored in similar packaging to the commercial packaging. This data demonstrates the stability of the drug substance and supports a retest period of 5 years, with the storage conditions “Do not store above 25°C” and “Protect from light”, when stored in the proposed packaging.

DRUG PRODUCT

Description & Composition

The drug product is a direct-release uncoated tablet containing 5mg of the active substance. The tablets are white to off white, round, with “5” embossed on one side.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, maize starch, colloidal anhydrous silica, and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as milk collected for human consumption.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution profiles of Prochlorperazine 5mg Tablets were shown to be comparable with Stemetil 5mg tablets.

Comparative impurity data were presented for Prochlorperazine 5mg tablets and Stemetil 5mg tablets. Impurity profiles for the test product were found to be similar to those for the reference product, and all the impurities are within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on validation batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The tablets are packed in opaque PVC (polyvinyl chloride) / PVDC (polyvinylidene chloride) / aluminium foil blisters, which are placed with the PIL into cardboard outer cartons. The product is packaged in pack sizes of 14, 28, 56 or 84 tablets, although the MA holder has stated that not all pack sizes will be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. The storage instructions are 'Do not store above 25°C' and 'Store in the original package'.

Bioequivalence Study

A bioequivalence study was submitted comparing the test product, Prochlorperazine 5mg Tablets, to the innovator product, Stemetil 5mg Tablets (PL 16946/0006, Castlemead Healthcare Ltd).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

Product Information

The approved SPC, leaflet, and labelling are satisfactory.

Conclusion

The test product is pharmaceutically equivalent to the reference product which has been licensed in the UK for over 10 years. On this basis, and considering the bioequivalence data provided, the applicant's claim that Prochlorperazine 5mg Tablets is a generic medicinal product of Stemetil 5mg Tablets appears justified.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A marketing authorisation may be granted.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Prochlorperazine 5mg Tablets are indicated for the treatment of vertigo due to Meniere's Syndrome, labyrinthitis and other causes, and for nausea and vomiting from whatever cause including that associated with migraine. The tablets may also be used for schizophrenia (particularly in the chronic stage), acute mania and as an adjunct to the short-term management of anxiety.

The indications are consistent with those for the innovator product and are satisfactory.

POSODOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the innovator product.

TOXICOLOGY

No new data has been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

Bioequivalence Study

The bioequivalence study compared the test product, Prochlorperazine 5mg Tablets (PL 17907/0072, Bristol Laboratories Limited), to the reference product Stemetil 5mg Tablets (PL 16946/0006, Castlemead Healthcare Ltd). The study was of an appropriate design and was conducted in compliance with principles of Good Clinical Practice.

The bioequivalence study compared the test and reference products in healthy adult male volunteers, under fasting conditions. The design was a conventional comparative open label, randomised, two-treatment, two period, two sequence, single dose, crossover study. Thirty volunteers were enrolled for the study, 26 completed the study and were analysed.

After an overnight fast (of at least 10 hours), patients received 1 x 5mg of either the applicant's test product or the reference product, according to the randomisation schedule, with a washout period of 14 days between treatments. Blood samples were taken pre-dose, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 48 and 72 hours. Plasma prochlorperazine levels were determined by a validated HPLC with MS/MS method. Log-transformed data for AUC_t, AUC_{inf} and C_{max} were analysed by ANOVA. T_{max} was analysed non-parametrically.

Two subjects vomited during the first study period and were withdrawn. Two others were withdrawn prior to commencing period 2 for personal reasons. As per the protocol and guidelines the data of these four subjects were not analysed. There were no other major protocol violations and 26 subjects completed the study.

Bioequivalence results for log-transformed data with 90% Confidence Intervals:

AUC_t	103.2 (93.2 – 114.3)
AUC_{inf}	102.5 (92.9 – 113.1)
C_{max}	101.9 (89.9 – 115.7)
T_{max}	3.1 hrs test, 3.2 hrs reference

The individual patient data are generally reassuring, showing mostly good superimposability of the plots and an appropriate degree of inter-individual and intra-individual variation. There were no significant period or sequence effects

Bioequivalence has been satisfactorily demonstrated and it can be concluded that Prochlorperazine 5 mg tablets are bioequivalent to Stemetil 5 mg tablets.

EFFICACY

No new data are submitted and none are required for this type of application.

Efficacy is reviewed in the clinical expert report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

SAFETY

No new data are submitted and none are required for this type of application.

There were no important adverse events in the bioequivalence study and the literature review in the expert report identifies no new safety issues.

EXPERT REPORT

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. It includes a summary of the bioequivalence study and a brief review of the pharmacology, efficacy and safety of prochlorperazine. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics

The final SmPC is consistent with that for the innovator product and is acceptable.

Patient Information Leaflet

The PIL is in line with the approved SPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

DISCUSSION AND CONCLUSION

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test and reference products within general acceptance limits.

Sufficient clinical information has been submitted to support this application. When used as indicated, Prochlorperazine 5mg Tablets has a favourable benefit-to-risk ratio. Therefore, a Marketing Authorisation may be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Prochlorperazine 5mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Prochlorperazine 5mg Tablets and the reference product, Stemetil 5mg Tablets (Castlemead Healthcare Ltd).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory and consistent with that for Stemetil 5mg Tablets.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with prochlorperazine maleate is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**PROCHLORPERAZINE 5MG TABLETS
(PROCHLORPERAZINE MALEATE)**

PL 17907/0072

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the marketing authorisation application on 5th March 2004
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 23rd March 2004
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 7th October 2004
- 4 The applicant responded to the MHRA's request, providing further information for the quality sections on 16th June 2005
- 5 Following assessment of the response the MHRA requested further information relating to the quality sections on 26th September 2006
- 6 The applicant responded to the MHRA's request, providing further information for the quality sections on 14th January 2007
- 7 Following assessment of the response the MHRA requested further information relating to the quality sections on 8th March 2007
- 8 The applicant responded to the MHRA's requests, providing further information for the quality sections on 27th March 2007
- 9 The application was determined on 23rd April 2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Prochlorperazine 5mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Prochlorperazine 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Prochlorperazine Maleate 5 mg

Also contains lactose monohydrate 70.0 mg

For full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off white, circular, uncoated tablets with '5' embossing on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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 as an adjunct to the short-term management of anxiety.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults

Indication	Dosage
Prevention of nausea and vomiting	5 to 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.

Children:

Indication	Dosage
Prevention and treatment of nausea and vomiting	If it is considered unavoidable to use Prochlorperazine for a child, the dosage is 0.25 mg/kg bodyweight two or three times a day. Prochlorperazine is not recommended for children weighing less than 10 kg or below 1 year of age and Prochlorperazine 5 mg Tablets are suitable only for children above 20 kg. Prochlorperazine syrup is available for adjustment of dosage in children.

Elderly: A lower dose is recommended. Please see 'Special warnings and special for precautions for use' section.

4.3 CONTRAINDICATIONS

Known hypersensitivity to Prochlorperazine or to any other ingredients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prochlorperazine 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.

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 below), 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.

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 other neuroleptics, cases of QT interval prolongation have been reported with prochlorperazine very rarely (see section 4.8, below). The risk-benefit should be fully assessed before Prochlorperazine treatment is commenced, and patients with predisposing factors for ventricular arrhythmias, (e.g. cardiac disease; metabolic abnormalities such as hypokalaemia, hypocalcaemia or hypomagnesaemia; starvation; alcohol abuse; concomitant therapy with other drugs known to prolong the QT interval) should be carefully monitored (biochemical status and ECG), particularly during the initial phase of treatment.

As with all antipsychotic drugs, Prochlorperazine 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 co-exist.

Because of the risk of photosensitisation, patients should be advised to avoid exposure to direct sunlight. To prevent skin sensitization 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, below).

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

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.

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

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Adrenaline must not be used in patients overdosed with Prochlorperazine (see section 4.9, below).

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 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.

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 concurrently with drugs which prolong the QT interval, including certain antiarrhythmics, antidepressants, and other antipsychotics (see section 4.8, below).

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.

4.6 PREGNANCY AND LACTATION

There is inadequate evidence of safety in pregnancy. There is evidence of harmful effects in animals. Prochlorperazine should be avoided in pregnancy unless the physician considers it essential. 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.

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:

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, above).

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

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.

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.

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 (up four to eight years). This could possibly happen with Prochlorperazine.

Cardiac disorders: Cardiac arrhythmias, including atrial arrhythmia, A-V block, ventricular tachycardia and fibrillation have been reported during neuroleptic therapy, possibly related to dosage. Pre-existing cardiac disease, old age, hypokalemia and concurrent tricyclic antidepressants may predispose. ECG changes, usually benign, include widened QT interval, ST depression, U-waves and T-wave changes (see section 4.4, above).

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, above).

Skin and subcutaneous tissue disorders: Contact skin sensitisation may occur rarely in those frequently handling preparations of certain phenothiazines (see section 4.4, above). 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, above).

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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AB04

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

There is 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 monohydrate
Silica, colloidal anhydrous
Maize starch
Magnesium stearate

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

Al / PVC/PVDC blister of 14 tablets each. Blister strips are packaged into an outer container to give a total of 14, 28, 56 and 84 tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road,
Berkhamsted, Hertfordshire
HP4 1EG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/04/2007

10 DATE OF REVISION OF THE TEXT

23/04/2007

PATIENT INFORMATION LEAFLET

PACKAGE INSERT

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Prochlorperazine Tablets are and what they are used for
2. Before you take Prochlorperazine Tablets
3. How to take Prochlorperazine Tablets
4. Possible side effects
5. Storing Prochlorperazine Tablets

Prochlorperazine 5 mg Tablets (Prochlorperazine maleate)

- Each tablet contains 5 mg Prochlorperazine maleate as the active substance.
- The other ingredients are lactose monohydrate, silica colloidal anhydrous, maize starch and magnesium stearate.

Marketing Authorisation Holder and Manufacturer:

Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Hertfordshire, HP4 1EG, UK

1. WHAT PROCHLORPERAZINE TABLETS ARE AND WHAT THEY ARE USED FOR

Prochlorperazine 5 mg tablets are white to off white circular, uncoated tablets with '5' embossing on one side.

Prochlorperazine Tablets come in packs containing blister strips of 14 tablets (14, 28, 56 or 84 tablets in total). Not all pack sizes may be marketed.

Prochlorperazine belongs to a group of medicines called phenothiazines.

Prochlorperazine tablets are used for the treatment of vertigo from a variety of causes including diseases of the inner ear such as

Meniere's syndrome and labyrinthitis. It may also be used for the prevention and treatment of nausea and vomiting from a variety of causes including migraine, it may be used for in combination with other treatments for the short term treatment of anxiety.

2. BEFORE YOU TAKE PROCHLORPERAZINE TABLETS

Tell your doctor or pharmacist if any of the following apply to you:

- If you are pregnant or breast feeding or think you might be pregnant.
- If you are allergic to any other medicines called phenothiazines.
- If you are allergic to any of the inactive ingredients.
- If the patient is less than 12 years of age
- If you have liver or kidney problems, epilepsy, Parkinson's disease, hypothyroidism (underactive thyroid gland), phaeochromocytoma (high blood pressure caused by a tumour near the kidney), myasthenia gravis (a form of muscle weakness) or prostatic hypertrophy (enlarged prostate gland causing difficulty in passing urine), narrow angle glaucoma (abnormally high pressure in the eye)
- If you have had any heart disorders (heart attack, angina)
- If you have hypokalaemia (low potassium concentration in the blood)
- If you are taking any other medicines. Some medicines may change the way Prochlorperazine works e.g. barbiturates, other sedating drugs, drugs for high blood pressure, amphetamines, levodopa, clonidine, guanethidine, adrenaline, drugs for Parkinson's disease, indigestion remedies, lithium, tablets for diabetes, tricyclic antidepressants (such as amitriptyline, imipramine, dothiepin), other phenothiazines or anticholinergic drugs (such as hyoscine, chlorpromazine, oxybutynin, atropine).
- Particular care should be taken if you are being given desferrioxamine for removal of excess iron in the blood.

If you have to go visit a doctor, dentist or hospital for any reason, tell them that you are taking Prochlorperazine tablets.

Prochlorperazine tablets contain lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

Prochlorperazine is not recommended for use in children under 1 year of age or who weigh less than 10 kg.

You are advised not to take alcohol with prochlorperazine

Prochlorperazine may cause drowsiness and affect your ability to drive or operate machinery. This effect is usually only seen during the early days of treatment and commonly wears off with time. You should not therefore drive or operate machinery unless you are sure you are not affected.

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If you are elderly prochlorperazine may affect the control of your body temperature so care should be taken in very hot or cold weather.

3. HOW TO TAKE PROCHLORPERAZINE TABLETS

Always take Prochlorperazine exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The number of tablets you need will depend on your condition. The tablets should be swallowed whole with a small glass of water.

Adults:

- For the prevention of nausea and vomiting the usual dose are one or two tablets twice daily or three times a day.
- For the treatment of nausea and vomiting the usual dose is four tablets to start with, followed if necessary by two tablets two hour later.
- For dizziness or vertigo and Meniere's syndrome the usual dose is one tablet three times a day, increasing up to a total of six tablets daily. After several weeks the dosage may be reduced gradually to one or two tablets daily.
- For the short term management of anxiety the dose may start at one tablet three times a day or one tablet four times a day. This can be increased if necessary to a maximum of two tablets four times a day.
- For the prevention and treatment of nausea and vomiting in children, the dose will be worked out according to the weight of the child.
- For elderly patients a lower dose may be prescribed.

For doses of 25 mg and above, Prochlorperazine 25 mg tablets are available and should be used.

If you miss a dose, you should take it as soon as you remember. Do not take a double dose to make up for forgotten individual doses.

If you take an overdose of Prochlorperazine tablets, contact a doctor immediately or go to your nearest hospital casualty department. Take the pack with you to show to the doctor.

4. POSSIBLE SIDE EFFECTS

Prochlorperazine may cause side effects like all other medicines.

Minor side effects of Prochlorperazine tablets that are well known are nasal stuffiness or dry mouth, difficulty in sleeping, agitation. You do not need to worry about them unless they become troublesome - in which case, you should consult your doctor.

Some side effects may be more serious and you should tell your doctor immediately if you have any of the following

- an urge to move about constantly. This may occur particularly after large starting doses.
- muscle stiffness, shaking or tremors.
- inability to control certain muscles in your body. This may affect your tongue, mouth, arms and legs and is common in young patients. It may occur in the first four days of treatment or after an increase in dose.
- a combination of high temperature, sweating, pale complexion, difficulty passing urine, muscle stiffness, altered levels of alertness (neuroleptic malignant syndrome)
- yellow tinge of the skin or eyes (jaundice)
- heart palpitations (unusually rapid or irregular heart beat)
- unexpected sore throats, infections or fever
- breathing problems.
- fainting or dizziness on standing or sitting up.
- any changes to your eyes
- discoloration or irritation of the skin
- hormonal imbalance- this may cause enlarged breast and impotence in men, milk production in non breast feeding women and loss of menstrual periods.

People taking high doses may develop sensitivity to sunlight. If this occurs you should avoid sun lamps and direct sunlight. Your doctor may advise you to use a sunscreen.

If you are taking Prochlorperazine for a long time period, your doctor may want to do occasional tests. These might include an ECG, which checks that your heart is working normally and a blood test.

If you think you have any other side effects not mentioned here, please tell your doctor or a pharmacist.

5. STORING PROCHLORPERAZINE TABLETS

Keep out of the reach and sight of children.

Store below 25°C. Store in the original package.

Do not use the tablets after the expiry date as shown on the carton or label.

Unless your doctor tells you to, do not keep any tablets that you no longer need.

Give them back to your pharmacist.

Date this leaflet was prepared: March 2007

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LABELLING

Pack size 28

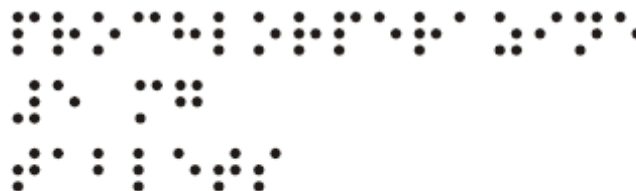


Same size artwork
116 x16 x50 mm

Pack size 84



Braille



Prochlorperazine
5 mg
tablets

