For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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Prochlorperazine Mesylate Injection IP

AMERICAN
Procitil For I.M. Injection
Injection

COMPOSITION:
Each ml contains:
Prochlorperazine Mesylate IP.....12.5mg
Water for injections IP.....q.s.

DOSAGE FORM(S) AND STRENGTH(S):
Injection & 12.5mg/ 1ml

CLINICAL PARTICULARS
THERAPEUTIC INDICATION:
For treatment of nausea and vomiting due to various causes including migraine; vertigo due to Meniere's syndrome and other labyrinthine disorders.

DOSAGE AND ADMINISTRATION:
In Adults:
Treatment of nausea and vomiting:
If oral administration is not practical, a deep IM injection of 1ml (12.5 mg) should be used, followed by oral medication 6 hours later if necessary.
or
As directed by the physician.

Method of administration: For Intramuscular (IM) injection

CONTRA-INDICATION:
- Drug should not be used in patients who are known to be hypersensitive to the prochlorperazine, other phenothiazines, or to any of the other ingredients.
- The use of prochlorperazine injection is contraindicated in children as it has been associated with dystonic reactions after the cumulative dose of 0.5 mg/kg. Prochlorperazine is not recommended for children under 2 years of age or weighing less than 10 kg and should not be given to children by the intramuscular route.
- Do not use in paediatric surgery.

WARNINGS AND PRECAUTIONS:
Hypersensitivity:
Hypersensitivity reactions including anaphylactic reaction, urticaria and angioedema have been reported with prochlorperazine use. In case of allergic reaction, treatment with prochlorperazine must be discontinued and appropriate symptomatic treatment initiated.
Special Risk Patients:
Prochlorperazine should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, seizure disorders, phaeochromocytoma, myasthenia gravis and prostate hypertrophy. It should be avoided in patients with a history of narrow angle glaucoma or agranulocytosis.
Sulfite Sensitivity:
Some parenteral products may contain sulfites.
Withdrawal symptoms:
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.
Agranulocytosis:
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 hematological investigation.
Neuroleptic malignant syndrome (NMS):
NMS has occurred with agents in this class; is potentially fatal. Signs and symptoms are as follows-
- Hyperthermia
- Muscle rigidity
- Altered mental status
- Irregular pulse
- Fluctuating BP
- Tachycardia
- Diaphoresis

QT interval prolongation has been observed with prochlorperazine. Avoid using with other drugs that can cause QT prolongation or in patients at risk of QT prolongation.
Tardive dyskinesia:
Syndrome of potentially irreversible involuntary body and facial movements may develop.
Hypotension:
Postural hypotension with tachycardia with local pain and nodule formation may occur after IM administration.
Sedative effect:
Prochlorperazine may impair mental and physical activity especially during the first few days of therapy. Patients should be warned about activities requiring alertness.
Cerebrovascular Events:
An increased risk of cerebrovascular events has been reported in elderly patients with dementia treated with atypical antipsychotic drugs. An increase in the risk of cerebrovascular events with other antipsychotic drugs or other populations of patients cannot be excluded. Prochlorperazine should therefore be used with caution in patients with stroke risk factors.
Thromboembolism:
Cases of venous thromboembolism (VTE), sometimes fatal, 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 preventative measures undertaken.
Use in the elderly:
It should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyperthermia or hypothermia). There is an increased risk of drug-induced Parkinsonism in the elderly particularly after prolonged use. Careful monitoring of treatment with prochlorperazine is required when administered in elderly patients exhibiting greater susceptibility to orthostatic hypotension, sedation, and extrapyramidal effects; chronic constipation (risk of ileus paralytic); possible prostatic hypertrophy. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. 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 tardive dyskinesias, particularly in the elderly.

USE IN SPECIAL POPULATION:
Pregnancy
There is inadequate evidence of the safety of prochlorperazine in human 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 labor and at such a time should be withheld until the cervix is dilated 3-4cm. Possible adverse effects on the neonate include lethargy or paradoxical hyperexcitability, tremor and a low Apgar score.
Neonates exposed to antipsychotics (including prochlorperazine) 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.

Breast-feeding
Phenothiazines may be excreted in breast milk, breast-feeding should be suspended during treatment.

Pediatric Use
Safety and efficacy not established in children under 2 years of age or those weighing less than 10 kg. Prochlorperazine should not be given to children by the intramuscular route. Avoid use in children and adolescents with suspected Reye's syndrome, since the antiemetic and potential extrapyramidal effects produced by the drug may obscure the diagnosis of or be confused with CNS manifestations of this condition. Not recommended for use in children during surgery or in conditions for which pediatric dosage has not been established. Incidence of extrapyramidal reactions appears to be relatively high in children.
Children with acute illnesses (e.g., varicella-zoster [chickenpox] infections, CNS infections, measles, gastroenteritis) or dehydration appear to be at increased risk of such reactions (particularly dystonic reactions and akathisia); use only under close supervision and at low doses in these patients.

Geriatric Use
It should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyper-, hypothermia). Geriatric patients appear to be particularly sensitive to adverse CNS (e.g., tardive dyskinesia, parkinsonian manifestations, akathisia, sedation) and cardiovascular (e.g., orthostatic hypotension) effects of antipsychotic agents. Possible increased incidence of agranulocytosis in geriatric patients receiving prochlorperazine. Geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of death.
Impaired liver function Since prochlorperazine is extensively metabolized by the liver, dosage reduction and caution may be necessary. A past history of jaundice resulting from phenothiazine therapy indicates a hypersensitivity reaction and there is a likelihood of cross sensitivity to other phenothiazines.

Drug Interactions

No.	Drug	Drug interaction
1.	Alcohol or other CNS depressants	May result in increased CNS depression and may precipitate dystonic reactions.
2.	QT prolonging drugs	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.
3.	Anticholinergics	May reduce therapeutic effects of prochlorperazine
4.	Cytochrome P450 2D6 Metabolism	Some 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/amitriptyline oxide, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline. Monitor patients for dose-dependent adverse reactions associated with amitriptyline/amitriptyline oxide.
5.	Beta-blockers	May result in increased plasma levels of beta-blocker and prochlorperazine. Careful patient monitoring is recommended.
6.	Cisapride, Sparfloxacin	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
7.	Guanethidine	Hypotensive action of guanethidine may be inhibited.

UNDESIRABLE EFFECT:
Nervous system: Insomnia, agitation, extrapyramidal reactions, acute dystonias, dyskinesias, akathisia, Parkinsonism, tardive dyskinesia, tremors, drowsiness, dizziness
Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction, altered consciousness)
Gastrointestinal: Dry mouth, constipation
Renal and urinary disorders: Urinary retention
Cardiovascular: Postural hypotension especially in elderly or volume depleted patients, cardiac arrhythmias, atrial arrhythmias, ventricular tachycardia, ventricular fibrillation, AV block, ECG changes such as prolonged QT interval, ST depression, U-waves and T-wave changes.
Respiratory: Respiratory depression, nasal congestion.
Blood: Agranulocytosis, mild leukopenia
Skin: Dermatitis allergic, maculopapular eruptions, erythema multiforme, urticaria, photosensitivity reaction, pigmentation disorder
Endocrine: Hyperprolactinemia, hyperglycemia, galactorrhea, gynecomastia, amenorrhea, impotence
Eye disorders: Blurred vision

PHARMACOLOGICAL PROPERTIES:
PHARMACODYNAMICS:
Prochlorperazine is a phenothiazine with a piperazine moiety in the side chain. It possesses strong antiemetic and antipsychotic activity with less sedative action

MECHANISM OF ACTION:
As with other phenothiazines, prochlorperazine has actions on several neurotransmitter systems:
1. Anti-dopamine action, which probably contributes to both the therapeutic effect and unwanted effects including extrapyramidal disorders and endocrine disturbances.
2. α-Adrenoreceptor antagonism, which contributes to cardiovascular side effects such as orthostatic hypotension and reflex tachycardia.
3. Potentiation of noradrenaline by blocking its reuptake into nerve terminals.
4. Weak anticholinergic action.
5. Weak antihistamine action.
6. Weak serotonin antagonism.

PHARMACOKINETICS:

	Prochlorperazine
Absorption	Prochlorperazine is quickly absorbed following deep intramuscular injection.
Distribution	Large volume of distribution; crosses the placenta and is distributed into breast milk. Protein binding is at least 90%.
Metabolism	Hepatic to active and inactive metabolites.
Excretion	Renal and biliary, with some enterohepatic recycling.
Onset of action	10 to 20 min (IM).

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

PRECLINICAL SAFETY DATA
Genotoxicity
No data available.
Carcinogenicity
No data available.

OVERDOSE:
There is no known antidote for prochlorperazine thus overdose treatment should be supportive and symptomatic. Symptoms of central nervous system depression, such as somnolence or coma, may also be observed. Overdose of prochlorperazine may produce dystonic reactions that involve extrapyramidal mechanism. To reduce these symptoms, anti-parkinsonism drugs may be used. In the event of overdose of prochlorperazine, take all appropriate measures immediately.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Transient drowsiness may occur in some patients during the initial stages of therapy and patients should be advised against the performance of potentially hazardous tasks such as driving a car or operating machinery until the effect has been ascertained.

INCOMPATIBILITIES:
No incompatibility study has been found.

PATIENT COUNSELLING INFOMRATION:
Importance of advising patients and caregivers that elderly patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of death. Patients and caregivers also should be informed that prochlorperazine is not approved for treating elderly patients with dementia-related psychosis.
Potential for drug to impair mental alertness or physical coordination; use caution when driving or operating machinery until effects on individual are known.
Importance of clinicians informing patients of risk of extrapyramidal reactions and providing reassurance that these reactions usually can be controlled by administration of antiparkinsonian drugs (e.g., benztropine) and by subsequent dosage reduction. Importance of informing patients and caregivers about the risk of NMS, which can cause high fever, stiff muscles, sweating, fast or irregular heart beat, change in BP, confusion, and kidney damage.
Importance of clinicians informing patients in whom chronic use is contemplated of risk of tardive dyskinesia, taking into account clinical circumstances and competency of patient to understand information provided.
Importance of avoiding exposure to temperature extremes.
Risk of leukopenia, neutropenia, and agranulocytosis. Importance of advising patients with a preexisting low WBC count or history of drug-induced leukopenia/neutropenia that their CBC count should be monitored during prochlorperazine therapy. Importance of informing clinician if sore throat or other signs of infection occur.
Importance of informing clinician of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., cardiovascular disease, seizures).
Importance of women informing clinicians If they are or plan to become pregnant or plan to breast-feed. Importance of clinicians informing patients about the benefits and risks of taking antipsychotics during pregnancy. Importance of advising patients not to stop taking prochlorperazine if they become pregnant without consulting their clinician; abruptly stopping antipsychotic agents may cause complications.

PACKAGING INFORMATION:
Available as 1 ml ampoules: 5 per blister pack, 20 blister packs per carton with leaflet.

SHELF LIFE:
Refer to Pack

STORAGE AND HANDLING INSTRUCTIONS:
Store at a temperature not exceeding 30ºC.
Protect from light.

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