

CORE SEDATING ANTIHISTAMINE PRODUCT INFORMATION

List of substances:

- Chlorpheniramine maleate
- Dexchlorpheniramine maleate
- Diphenhydramine hydrochloride
- Doxylamine succinate
- Promethazine hydrochloride
- Triprolidine hydrochloride

Product description

This section should include:

- a description of the dosage form;
- a list of the active ingredients expressed quantitatively; and
- a list of the excipients expressed qualitatively

Pharmacology

Pharmacokinetics:

Chlorpheniramine maleate is absorbed relatively slowly from the gastrointestinal tract, with peak plasma concentrations occurring about 2.5 to 6 hours after oral administration. Chlorpheniramine appears to undergo considerable first-pass metabolism. Bioavailability is low, values of 25 to 50% having been reported. About 70% of chlorpheniramine in the circulation is bound to plasma proteins. There is wide inter-individual variation in the pharmacokinetics of chlorpheniramine; half-life values ranging from 2 to 43 hours have been reported. Chlorpheniramine is widely distributed in the body and enters the CNS.

Chlorpheniramine maleate is metabolised extensively. Metabolites include desmethyl- and didesmethylchlorpheniramine. Unchanged drug and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces.

A duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters.

More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children compared to adults.

Dexchlorpheniramine maleate is the dextrorotatory isomer of chlorpheniramine maleate. is absorbed relatively slowly from the gastrointestinal tract, with peak plasma concentrations occurring about 2.5 to 6 hours after oral administration. Dexchlorpheniramine appears to undergo considerable first-pass metabolism. Bioavailability is low, values of 25 to 50% having been reported. About 70% of dexchlorpheniramine in the circulation is bound to plasma proteins. There is wide inter-individual variation in the pharmacokinetics of dexchlorpheniramine; half-life values ranging from 2 to 43 hours have been reported. Dexchlorpheniramine is widely distributed in the body, and enters the CNS.

Dexchlorpheniramine maleate is metabolised extensively. Metabolites include desmethyl- and didesmethylchlorpheniramine. Unchanged drug and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces.

A duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters.

More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children compared to adults.

Dexchlorpheniramine has approximately twice the activity of chlorpheniramine by weight.

Diphenhydramine hydrochloride is well absorbed from the gastro-intestinal tract, although high first-pass metabolism appears to affect systemic availability. Peak plasma concentrations are achieved about 1 to 4 hours after oral administration. Diphenhydramine is widely distributed throughout the body, including the CNS. It crosses the placenta and has been detected in breast milk. Diphenhydramine is highly bound to plasma proteins. Metabolism is extensive. Diphenhydramine is excreted mainly in the urine as metabolites; little is excreted as unchanged substance. The elimination half-life has been reported to range from 2.4 to 9.3 hours.

Doxylamine succinate is readily absorbed from the gastrointestinal tract. Following oral administration, the mean peak plasma concentration occurs after 2-3 hours. It has an elimination half-life of about 10 hours in healthy adults. It is excreted in the urine as unchanged doxylamine (60%) and metabolites (nordoxylamine and dinordoxylamine).

The major metabolic site is the liver and major metabolic pathways are N-demethylation, N-oxidation, hydroxylation, N-acetylation, N-desalkylation and ether cleavage.

Promethazine hydrochloride is well absorbed after oral administration. Peak plasma concentrations have been observed 2 to 3 hours after administration. There is low systemic bioavailability after oral administration due to first-pass metabolism in the liver. Promethazine crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Values ranging from 76 to 93% have been reported for plasma-protein binding. Promethazine undergoes extensive metabolism, predominantly to promethazine sulfoxide, and also to N-desmethylpromethazine. It is excreted slowly via the urine and bile, chiefly as metabolites. Elimination half-lives of 5 to 14 hours have been reported.

Tripolidine hydrochloride: After absorption from the gastro-intestinal tract, tripolidine is metabolised; a carboxylated derivative accounts for about half the dose excreted in the urine. Reported half-lives vary from 3 to 5 hours or more. Tripolidine is distributed into breast milk.

Pharmacodynamics/Mechanism of action:

[Name of antihistamine] competes with histamine at central and peripheral histamine₁-receptor sites, preventing the histamine-receptor interaction and subsequent mediator release.

[Name of antihistamine] is a highly lipophilic molecule that readily crosses the blood-brain barrier.

[Name of antihistamine] is highly selective for histamine₁-receptors but has little effect on histamine₂ or histamine₃ receptors. [Name of antihistamine] also activate 5-hydroxytryptamine (serotonin) and α -adrenergic receptors and blocks cholinergic receptors.

Indications

This section must contain the indications of the product as specified in the ARTG. If the indications are not specified in the ARTG (e.g. for a non-validated grandfathered product), the indications must be as specified on the product label.

Contraindications

[Name of antihistamine] is contraindicated for use in patients with:

- a history of hypersensitivity to the substance or substances of similar chemical structure (or any of the other ingredients in the product)
- narrow-angle glaucoma
- stenosing peptic ulcer
- symptomatic prostatic hypertrophy
- bladder neck obstruction
- pyloroduodenal obstruction

[Name of antihistamine] is contraindicated for use in:

- newborns or premature infants
- [For promethazine] infants less than 12 months of age
- lactating women
- patients taking monoamine oxidase inhibitors (MAOIs)

Refer to 'Interactions with other medicines' for additional information

Precautions

[Name of antihistamine] may cause drowsiness and may increase the effects of alcohol. Drowsiness may continue the following day. Those affected should not drive or operate machinery; alcohol should be avoided.

Use with caution in patients with renal or hepatic impairment and in patients with epilepsy.

Refer to 'Interactions with other medicines' for additional information

Use in children and the elderly

Children and the elderly may experience paradoxical excitation with [name of antihistamine]. The elderly are more likely to have central nervous system (CNS) depressive side effects, including confusion. (See contraindications).

Promethazine hydrochloride should not be used in infants under 12 months.

Use in pregnancy

Chlorpheniramine, Dexchlorpheniramine, Diphenhydramine, Doxylamine and Triprolidine (Category A): [Name of antihistamine] has been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects of on the foetus having been observed.

Promethazine (Category C): Promethazine, owing to its pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

When promethazine has been given in high doses during late pregnancy, promethazine has caused prolonged neurological disturbances in the infant.

Promethazine should be used in pregnancy only if the potential benefits to the patient are weighed against the possible risk to the foetus.

Use in lactation

[Name of antihistamine] is excreted in breast milk. Therefore it is not recommended for breastfeeding mothers unless the potential benefits to the patient are weighed against the possible risk to the infant.

Interaction with other medicines

The following interactions with [Name of antihistamine] have been noted:

- central nervous system (CNS) depressants (alcohol, sedatives, opioid analgesics, hypnotics) – may cause an increase in sedation effects
- monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) – may prolong and intensify the anticholinergic and CNS depressive effects
- **dexchlorpheniramine** when taken with monoamine oxidase inhibitors (MAOIs) may cause a decrease in blood pressure
- **chlorpheniramine** when taken concomitantly with phenytoin may cause a decrease in phenytoin elimination

Adverse reactions

Central Nervous System (CNS) effects

CNS depressive effects of [Name of antihistamine] include sedation and impaired performance (impaired driving performance, poor work performance, incoordination, reduced motor skills, and impaired information processing). Performance may be impaired in the absence of sedation and may persist the morning after a night-time dose.

CNS stimulatory effects of [Name of antihistamine] may include anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.

High doses of [Name of antihistamine] may cause nervousness, tremor, insomnia, agitation, and irritability.

Anticholinergic effects

Side effects of [Name of antihistamine] associated with cholinergic blockage include dryness of the eyes, mouth and nose, blurred vision, urinary hesitancy and retention, constipation and tachycardia.

Dosage

This section must contain the current dosage instructions of the registered product, as specified on the product label.

Overdosage

In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26; in New Zealand call 0800 764 766) for advice.

Presentation

Information should be included on:

- *the presentation, including dosage form and pack sizes;*
- *identifying details (eg. colour, shape, identifying markings);*
- *poisons schedule details; and*
- *name and address of the sponsor*

Include the date of approval as the date on which the notification application is lodged