CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84902

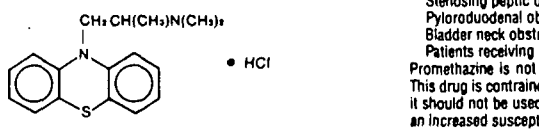
DRAFT FINAL PRINTED LABELING

PROMETHACON™ SUPPRETTES™

(PROMETHAZINE HYDROCHLORIDE SUPPOSITORIES)

DESCRIPTION: Each PROMETHACON™ Supprette™ (suppository) contains either 25 mg (opaque, white) or 50 mg (opaque, blue) promethazine hydrochloride in Neocera® Base — a blend of polyethylene glycol 1000 and 4000 with ascorbyl palmitate, ascorbic acid, purified water and, for the 50 mg strength, FD&C Blue No. 1. Each suppository is grooved for ½ dosage and is intended for rectal administration.

The structural formula of promethazine hydrochloride is as follows:



Chemical Name:
N,N,αtrimethyl-,10H-phenothiazine-10-ethanamine,monohydrochloride

CLINICAL PHARMACOLOGY: Promethazine hydrochloride, a phenothiazine derivative, possesses antihistaminic, sedative, antimotion, antiemetic and anticholinergic effects. The duration of action is generally from 4 to 6 hours. The major side reaction of this agent is sedation. As an antihistamine, it acts by competitive antagonism, but does not block the release of histamine. It antagonizes in varying degrees most, but not all, of the pharmacological effects of histamine. **Bioavailability studies in human volunteers have demonstrated that the rectal administration of PROMETHACON™ Supprettes™ produces blood levels of promethazine hydrochloride which are equivalent to those produced by equivalent doses of oral solutions of the drug.**

INDICATIONS AND USAGE: PROMETHACON (promethazine hydrochloride) is indicated for the following conditions:

- Perennial and seasonal allergic rhinitis;
- Vasomotor rhinitis;
- Allergic conjunctivitis due to inhalant allergens and foods;
- Mild, uncomplicated allergic skin manifestations of urticaria and angioedema;
- Amelioration and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions;
- Dermographism;
- As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled;
- Preoperative, postoperative or obstetric sedation;
- Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery;
- Therapy adjunctive to meperidine or other analgesics for control of postoperative pain;
- Sedation in both children and adults as well as relief of apprehension and production of light sleep from which the patient can be easily aroused;
- Active and prophylactic treatment of motion sickness;
- Antiemetic effect in postoperative patients.

Since rectal administration of Promethacon™ Supprettes™ may be expected to provide a therapeutic response equivalent to that produced by equivalent doses of the drug in oral solution (see Clinical Pharmacology), these dosage forms will be particularly useful in instances where the oral route of administration is not feasible (e.g. severe nausea).

CONTRAINDICATIONS: Promethazine is contraindicated in comatose states, and in patients who have received large amounts of central nervous system depressants (alcohol, barbiturates, narcotics, etc.). It is contraindicated in patients who have bone marrow depression or in those who have demonstrated an idiosyncrasy or hypersensitivity to promethazine or other phenothiazines. Do not use this drug in patients with:

- Asthmatic attack
- Narrow-angle glaucoma
- Prostatic hypertrophy
- Stenosing peptic ulcer
- Pyloroduodenal obstruction
- Bladder neck obstruction
- Patients receiving monoamine oxidase inhibitors

Promethazine is not to be used to treat lower respiratory symptoms. This drug is contraindicated in newborn or premature children. Further, it should not be used in children acutely ill and dehydrated, as there is an increased susceptibility to dystonias.

WARNINGS: Promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as *driving a vehicle or operating machinery. Similarly, it may* impair mental alertness in children. The concomitant use of alcohol or other central nervous system depressants may have an additive effect. Patients should be warned accordingly.

PRECAUTIONS:

General: Promethazine should be used cautiously in persons with acute or chronic respiratory impairment, particularly children. The cough reflex can be suppressed.

This drug should be used cautiously in persons with cardiovascular disease, impairment of liver function or those with a history of ulcer disease.

Because of its antiemetic effect, promethazine may mask signs of overdosage of toxic drugs or may obscure conditions such as brain tumor or intestinal obstruction.

Rectal administration of Promethacon™ Supprettes™ can be expected to produce a pharmacological response equivalent to that produced by oral administration of an equivalent dose of the drug in solution (see Clinical Pharmacology).

Information for Patients: Do not drive or operate machinery while taking this drug. The concomitant use of alcohol or other central nervous system depressants may increase, prolong or intensify the sedative action of this drug.

Because of the osmotic effects incurred by the water-soluble nature of the Promethacon™ suppository base and the acid environment induced by dissolution of promethazine, a warm sensation and an urge to defecate may be experienced after insertion. These sensations will generally subside within a short time. The patient should be alerted to the possible occurrence of these sensations and be urged to retain the suppository.

Drug Interactions: Promethazine may significantly affect the actions of other drugs. It may increase, prolong or intensify the sedative action of central nervous system depressants such as anesthetics, barbiturates or alcohol. The dose of a narcotic or barbiturate may be reduced ¼ or ½ the usual amount when promethazine is administered concomitantly. Excessive amounts of promethazine, relative to a narcotic, may lead to restlessness and motor hyperactivity in the patient with pain.

Promethazine can block and even reverse some of the actions of epinephrine.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies in animals to evaluate the carcinogenic potential of promethazine have not been performed.

PREGNANCY:

Teratogenic Effects:

Pregnancy Category C. Animal reproduction studies have not been conducted with promethazine. It is also not known whether promethazine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Promethazine should be given to a pregnant woman only if clearly needed. There are reports of jaundice and prolonged extra-pyramidal symptoms in infants whose mothers received phenothiazines during pregnancy.

Nursing Mothers: It is not known whether promethazine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when promethazine is administered to a nursing woman.

ADVERSE REACTIONS:

Note: Not all of the following adverse reactions have been reported with this specific drug; however, pharmacological similarities among the phenothiazine derivatives require that each be considered when promethazine is administered. There have been occasional reports of sudden death in patients receiving phenothiazine derivatives chronically.

CNS Effects: Drowsiness is the most prominant CNS effect of this drug. Extrapyramidal reactions may occur, particularly with high doses. Hyperreflexia has been reported in the newborn when a phenothiazine was used during pregnancy. Other reported reactions include dizziness, lassitude, tinnitus, incoordination, fatigue, blurred vision, euphoria, diplopia, nervousness, insomnia, tremors and grand mal seizures.

Cardiovascular Effects: Postural hypotension is the most common cardiovascular effect of promethazine. Reflex tachycardia may be seen. Bradycardia, faintness, dizziness and cardiac arrest have been reported. ECG changes, including blunting of T waves and prolongation of the Q-T interval, may be seen.

Gastrointestinal Effects: Anorexia, nausea, vomiting, epigastric distress, constipation and dry mouth may occur. Mild, local discomfort and a transient urge to defecate may be experienced following suppository administration. In the presence of abraded or denuded rectal lesions the patient may experience initial local discomfort.

Genitourinary Effects: Urinary frequency and dysuria may occur.

Allergic Reaction: These include urticaria, dermatitis, asthma, laryngeal edema, angioedema and anaphylactoid reactions.

Jaundice, leukopenia, agranulocytosis and extrapyramidal effects have been reported with all phenothiazines, but are less common with promethazine.

DRUG ABUSE AND DEPENDENCE: No specific dependence reports have been recorded for promethazine hydrochloride. Attempted suicides with promethazine have resulted in deep sedation, coma, rarely convulsions and cardiorespiratory symptoms compatible with the depth of sedation present. A paradoxical reaction, characterized by hyperexcitability and nightmares, has been reported in children receiving single doses of 75 mg to 125 mg orally.

OVERDOSAGE: Signs of overdosage include excitation, ataxia, incoordination, athetosis, convulsions and coma. Common signs in children are fixed dilated pupils, fever and a flushed face. The treatment is symptomatic and supportive.

DOSAGE AND ADMINISTRATION:

Note: Both the Supprette™ (suppository) and the inserting finger should be moistened with tap water to facilitate insertion. Suppositories are scored for ½ dosage.

Nausea and Vomiting: The average effective dose of promethazine hydrochloride for the active therapy of nausea and vomiting in children or adults is 25 mg. One-half to one 25 mg suppository (12.5 mg to 25 mg) may be given rectally as necessary at four to six hour intervals.

For nausea and vomiting in children, the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.

For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is one 25 mg suppository rectally repeated at four to six hour intervals as necessary.

Sedation: Promethazine relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Rectal administration of one-half to one 25 mg suppository (12.5 mg to 25 mg) at bedtime will provide sedation in children. Adults usually require one 25 mg or 50 mg suppository for nighttime, presurgical or obstetrical sedation.

Motion Sickness: The average adult dose is one 25 mg suppository, rectally twice daily. The initial dose should be administered one to two hours before anticipated travel and be repeated eight to twelve hours later if necessary. On succeeding days of travel, it is recommended that one 25 mg suppository be given on arising and repeated in the evening. For children, one-half to one 25 mg suppository (12.5 to 25 mg) twice daily may be administered rectally.

Perisurgical Care: Rectal administration of one-half to one 25 mg suppository (12.5 to 25 mg) in children and one 50 mg suppository in adults the night before surgery relieves apprehension and produces a quiet sleep.

For preoperative medication, children require doses of 0.5 mg per pound of body weight in combination with an equal dose of meperidine and the appropriate dose of an atropine-like drug. Depending on body weight, one-half 25 mg suppository (12.5 mg) in children up to three years of age, one 25 mg suppository in children three to ten years of age, or one 50 mg suppository in older children may be used in lieu of oral or parenteral medication. The usual adult dosage is one 50 mg suppository with an appropriate amount of meperidine and the required amount of a belladonna alkaloid.

Postoperative sedation and adjunctive use with analgesics may be obtained by the rectal administration of one-half to one 25 mg suppository in children (12.5 mg to 25 mg) and one 25 mg or 50 mg suppository in adults.

Allergy: While the oral administration of promethazine hydrochloride is preferred in this condition, PROMETHACON 25 mg Supprettes may be used when the oral route is not feasible. The usual dose for adults and children is one 25 mg suppository rectally. Oral therapy should be resumed after an appropriate period if indicated and existing circumstances permit. The rectal administration of one 25 mg suppository prior to or during blood transfusion will prevent or control minor transfusion reaction of an allergic nature.

HOW SUPPLIED: PROMETHACON 25 mg (opaque, white) scored for ½ dose in dispensing cartons of 12 unit dose Supprettes (NDC 0991-1010-12); PROMETHACON 50 mg (opaque, blue) scored for ½ dosage in dispensing cartons of 12 unit dose Supprettes (NDC 0991-1020-12). The products require no refrigeration and should be stored at controlled room temperature (59°F-86°F).

WEBCON™
WEBCON PHARMACEUTICALS DIVISION
ALCON LABORATORIES (PUERTO RICO), INC.
HUMACAO, PUERTO RICO 00661

Rev. 7/81 23813 Printed in USA

ABBREVIATED NEW DRUG APPLICATION

Labeling: Orig 84-902 12-5-75

Reviewed by:

APPLICANT:
Alcon Laboratories (Puerto Rico), Inc.
Post Office Box 3000
Humacao, Puerto Rico 00661

NAME OF DRUG:
Promethazine HCl Suppettes™ 50 mg

PART 4 PAGE 8
[December 5, 1975]

LOT: EXP:

WEBCON™

NDC 0991-1020-12

PROMETHACON™
SUPPRETTES™ 50 MG
PROMETHAZINE HYDROCHLORIDE
SUPPOSITORIES

CAUTION: Federal law prohibits dispensing without prescription.

Each suppository contains: Active: Promethazine Hydrochloride, 50 mg; Vehicle (Neocera® Base): Polyethylene Glycol 1000, Polyethylene Glycol 4000, Ascorbyl Palmitate, Ascorbic Acid, Purified Water, Coloring.

USUAL DOSAGE: One SUPPRETTE™, rectally, as directed by physician. Moisten before inserting.

Read package insert.

Grooved for 1/2 dosage.

Store at room temperature (59° to 86° F)

12 SUPPRETTES™

ALCON LABORATORIES (Puerto Rico), Inc.
Humacao, P.R. 00661

PROMETHACON™
SUPPRETTES™ 50 MG
PROMETHAZINE HYDROCHLORIDE SUPPOSITORIES
Made in USA

WEBCON™

NDC 0991-1020-12

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Humacao, P.R. 00661

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SUPPRETTES™ 50 MG
PROMETHAZINE HYDROCHLORIDE SUPPOSITORIES

12 SUPPRETTES™

NDC 0991-1020-12
PROMETHACON™
SUPPRETTES™ 50 MG
PROMETHAZINE HYDROCHLORIDE
SUPPOSITORIES

WEBCON™

00000 9/75

Consecutive Page No. 0091

APPLICANT:
Alcon Laboratories (Puerto Rico), Inc.
Post Office Box 3000
Humacao, Puerto Rico 00661

NAME OF DRUG:
Promethazine HCl Supprettes™
50 mg

LOT: EXP:

WEBCON™

NDC 0991-1020-12

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Made In USA

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12 SUPPRETTES™

PROMETHAZINE HYDROCHLORIDE
SUPPOSITORIES
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