

Attachment C

Proposed labeling for

Promethazine HCl and Hydrocodone
Bitartrate Syrup, 6.25 mg / 2.5 mg per 5mL
and

Promethazine HCl and Hydrocodone
Bitartrate Syrup, 6.25 mg / 1.67 mg per 5mL

**Promethazine HCl and
Hydrocodone Bitartrate Syrup,
6.25 mg and 1.67 mg / 5mL
and
6.25 mg and 2.5 mg / 5mL**



Rx Only

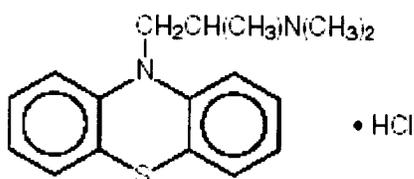
DESCRIPTION

Each 5 mL (one teaspoonful), for oral administration, of Promethazine HCl and Hydrocodone Bitartrate Syrup, 6.25 mg and 1.67 mg / 5mL contains: promethazine hydrochloride USP, 6.25 mg and hydrocodone bitartrate USP, 1.67 mg.

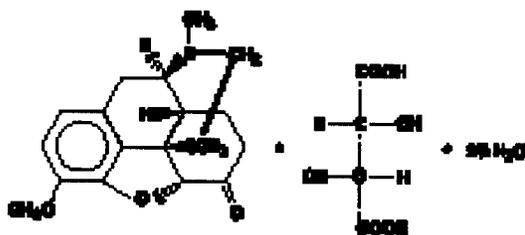
Each 5 mL (one teaspoonful), for oral administration, of Promethazine HCl and Hydrocodone Bitartrate Syrup, 6.25 mg and 2.5 mg / 5mL contains: promethazine hydrochloride USP, 6.25 mg and hydrocodone bitartrate USP, 2.5 mg.

Inactive Ingredients: Ascorbic acid USP, FD&C red # 40, edetate disodium USP, glycerin USP, purified water, saccharin sodium USP, sodium benzoate, strawberry flavor and sugar.

Promethazine hydrochloride, a phenothiazine derivative, is chemically designated as (±)-10-[2- Dimethylamino) propyl] phenothiazine monohydrochloride. Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is soluble in water and freely soluble in alcohol. It has a molecular weight of 320.88, a molecular formula of $C_{17}H_{20}N_2S \cdot HCl$, and the following structural formula:



Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17- methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has a molecular weight of 494.490, a molecular formula of $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2 \frac{1}{2} H_2O$, and the following structural formula:



CLINICAL PHARMACOLOGY

Promethazine: Promethazine is a phenothiazine derivative which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopamine antagonist properties. Promethazine is an H_1 receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects. Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last four to six hours, although they may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites appearing in the urine.

Hydrocodone bitartrate: Hydrocodone bitartrate is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

INDICATIONS AND USAGE

Promethazine HCL and Hydrocodone Bitartrate Syrup is indicated for the temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold.

CONTRAINDICATIONS

Promethazine is contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines. Hydrocodone bitartrate is contraindicated in patients with a known hypersensitivity to the drug. The combination of promethazine hydrochloride and hydrocodone bitartrate is contraindicated in pediatric patients less than 16 years of age, because the combination may cause fatal respiratory depression in this age population. Antihistamines and hydrocodone are both contraindicated for use in the treatment of lower respiratory tract symptoms, including asthma.

WARNINGS

WARNING:
THE COMBINATION OF PROMETHAZINE HYDROCHLORIDE AND HYDROCODONE BITARTRATE IS CONTRAINDICATED IN PEDIATRIC PATIENTS LESS THAN 16 YEARS OF AGE. CONCOMITANT ADMINISTRATION OF PROMETHAZINE PRODUCTS WITH OTHER RESPIRATORY DEPRESSANTS HAS AN ASSOCIATION WITH RESPIRATORY DEPRESSION, AND SOMETIMES DEATH, IN PEDIATRIC PATIENTS. POSTMARKETING CASES OF RESPIRATORY DEPRESSION, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH USE OF PROMETHAZINE HYDROCHLORIDE IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE. A WIDE RANGE OF WEIGHT-BASED DOSES OF PROMETHAZINE HYDROCHLORIDE HAVE RESULTED IN RESPIRATORY DEPRESSION IN THESE PATIENTS.

Promethazine:

CNS Depression – 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. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore such agents should either be eliminated or given in reduced dosage in the presence of promethazine HCl (see **PRECAUTIONS- Information for Patients and Drug Interactions**).

Respiratory Depression – Promethazine may lead to potentially fatal respiratory depression.

Use of Promethazine in patients with compromised respiratory function (e.g., COPD, sleep apnea) should be avoided.

Lower Seizure Threshold – Promethazine may lower seizure threshold. It should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

Bone-Marrow Depression – Promethazine should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when promethazine HCl has been used in association with other known marrow-toxic agents.

Neuroleptic Malignant Syndrome – A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with promethazine HCl alone or in combination with

antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias). The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of promethazine HCl, antipsychotic drugs, if any, and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. Since recurrences of NMS have been reported with phenothiazines, the reintroduction of promethazine HCl should be carefully considered.

Hydrocodone bitartrate:

Dosage of hydrocodone SHOULD NOT BE INCREASED if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease. Hydrocodone may cause or aggravate constipation. Respiratory depression leading to arrest, coma, and death may occur with the use of hydrocodone antitussives in young children, particularly in the under-one year infants whose ability to deactivate the drug is not fully developed. Administration of hydrocodone may be accompanied by histamine release and should be used with caution in atopic children.

Head Injury and Increased Intracranial Pressure: The respiratory-depressant effects of narcotic analgesics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure. Narcotics may produce adverse reactions which may obscure the clinical course of patients with head injuries.

Asthma and Other Respiratory Conditions: Narcotic analgesics or cough suppressants, including hydrocodone, should not be used in asthmatic patients (see **CONTRAINDICATIONS**). Nor should they be used in acute febrile illness associated with productive cough or in chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on the patient's respiratory function.

Hypotensive Effect: Hydrocodone may produce orthostatic hypotension in ambulatory patients.

Use in Pediatric Patients

THE COMBINATION OF PROMETHAZINE HYDROCHLORIDE AND HYDROCODONE BITARTRATE IS CONTRAINDICATED IN PEDIATRIC PATIENTS LESS THAN 16 YEARS OF AGE. CONCOMITANT ADMINISTRATION OF PROMETHAZINE PRODUCTS WITH OTHER RESPIRATORY DEPRESSANTS HAS AN ASSOCIATION WITH RESPIRATORY DEPRESSION, AND SOMETIMES DEATH, IN PEDIATRIC PATIENTS. THE ASSOCIATION DOES NOT DIRECTLY RELATE TO INDIVIDUALIZED WEIGHT-BASED DOSING, WHICH MIGHT OTHERWISE PERMIT SAFE ADMINISTRATION.

Excessively large dosages of antihistamines, including promethazine hydrochloride, in pediatric patients may cause sudden death (see **OVERDOSAGE**).

Hallucinations and convulsions have occurred with therapeutic doses and overdoses of promethazine hydrochloride in pediatric patients. In pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine HCl.

Other Considerations

Administration of promethazine has been associated with reported cholestatic jaundice.

PRECAUTIONS

Animal reproduction studies have not been conducted with the drug combination- promethazine and hydrocodone. It is not known whether this drug combination can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Promethazine HCl and Hydrocodone Bitartrate Syrup should be given to a pregnant woman only if clearly needed.

General: Promethazine should be used cautiously in persons with cardiovascular disease or with impairment of liver function.

Narcotic analgesics, including hydrocodone, should be administered with caution and the initial dose reduced in patients with acute abdominal conditions, convulsive disorders, significant hepatic or renal impairment, fever, hypothyroidism, Addison's disease, ulcerative colitis, prostatic hypertrophy, in patients with recent gastrointestinal or urinary tract surgery, and in the very young or elderly or debilitated patients.

Drugs having anticholinergic properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder neck obstruction.

Information for Patients: Promethazine and hydrocodone may cause marked drowsiness or may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from promethazine and hydrocodone therapy.

The concomitant use of alcohol or other central nervous system depressants, including narcotic analgesics, sedatives, hypnotics and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.

WARNING:

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Patients should be advised to report any involuntary muscle movements. Avoid prolonged exposure to the sun. Hydrocodone, like other narcotic analgesics, may produce orthostatic hypotension in some ambulatory patients. Patients should be cautioned accordingly.

Drug Interactions:

Promethazine:

CNS Depressants – Promethazine may increase, prolong, or intensify the sedative action of other central-nervous system depressants, such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore, such agents should be avoided or administered in reduced dosage to patients receiving promethazine HCl. When given concomitantly with promethazine, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine HCl relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine – Because of the potential for promethazine to reverse epinephrine's vasopressor effect, epinephrine should NOT be used to treat hypotension associated with promethazine overdose.

Anticholinergics – Concomitant use of other agents with anticholinergics properties should be undertaken with caution.

Monoamine Oxidase Inhibitors (MAOI) – Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly.

Hydrocodone:

In patients receiving MAO inhibitors, an initial small test dose is advisable to allow observation of any excessive narcotic effects or MAOI interaction.

Drug/Laboratory Test Interactions:

Because narcotic analgesics may increase biliary tract pressure with resultant increases in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after a narcotic analgesic has been given. The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride.

Pregnancy Tests: Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test: An increase in blood glucose has been reported in patients receiving promethazine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to assess the carcinogenic potential of hydrocodone or of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with these agents.

Hydrocodone has been reported to show no evidence of carcinogenicity or mutagenicity in a variety of test systems, including the micronucleus and sperm abnormality assays and the *Salmonella* assay. Promethazine was non-mutagenic in the *Salmonella* test system of Ames.

Pregnancy: Teratogenic Effects –
Pregnancy Category C.

Promethazine: Teratogenic effects have not been demonstrated in rat feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine HCl. These doses are from approximately 2.1 to 4.2 times the maximum recommended total daily dose of promethazine for a 50-kg subject, depending upon the indication for which the drug is prescribed. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats. Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women.

Hydrocodone: There are no adequate and well-controlled studies in pregnant women to assess the teratogenic effects of hydrocodone.

Promethazine and hydrocodone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. Signs usually appear during the first few days of life.

Promethazine administered to a pregnant woman within two weeks of delivery may inhibit platelet aggregation in the newborn.

Labor and Delivery: Limited data suggest that use of promethazine hydrochloride during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect of promethazine and/or hydrocodone on later growth and development of the newborn is unknown.

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see **OVERDOSAGE**).

Nursing Mothers: It is not known whether promethazine is excreted in human milk.

The possibility of clinically important amounts of hydrocodone being excreted in breast milk in individuals abusing hydrocodone should be considered.

Caution should be exercised when Promethazine HCl and Hydrocodone Bitartrate Syrup is administered to a nursing woman.

Pediatric Use: THE COMBINATION OF PROMETHAZINE HYDROCHLORIDE AND HYDROCODONE BITARTRATE IS CONTRAINDICATED IN PEDIATRIC PATIENTS LESS THAN 16 YEARS OF AGE, BECAUSE THE COMBINATION MAY CAUSE FATAL RESPIRATORY DEPRESSION IN THIS AGE POPULATION (see WARNINGS – Black Box Warning and Use in Pediatric Patients).

Geriatric Use: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of Promethazine HCl and Hydrocodone Bitartrate Syrup and observed closely.

ADVERSE REACTIONS

Promethazine:

Central Nervous System - Drowsiness is the most prominent CNS effect of this drug. Sedation, somnolence, blurred vision, dizziness; confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion; lassitude, tinnitus, incoordination, fatigue, euphoria, nervousness, diplopia, insomnia, tremors, convulsive seizures, excitation, catatonic-like states, hysteria. Hallucinations have also been reported.

Cardiovascular - Increased or decreased blood pressure, tachycardia, bradycardia, faintness.

Dermatologic - Dermatitis, photosensitivity, urticaria.

Hematologic - Leukopenia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis.

Gastrointestinal - Dry mouth, nausea, vomiting, jaundice.

Respiratory - Asthma, nasal stuffiness, respiratory depression (potentially fatal) and apnea (potentially fatal). (See **WARNINGS – Promethazine; Respiratory Depression**).

Other - Angioneurotic edema. Neuroleptic malignant syndrome (potentially fatal) has also been reported. (See **WARNINGS – Promethazine; Neuroleptic Malignant Syndrome**).

Paradoxical Reactions – Hyperexcitability and abnormal movements have been reported in patients following a single administration of promethazine HCl. Consideration should be given to the discontinuation of promethazine HCl and to the use of other drugs if these reactions occur.

Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

Hydrocodone:

Nervous System - CNS depression, particularly respiratory depression, and to a lesser extent circulatory depression; light-headedness, dizziness, sedation, euphoria, dysphoria, headache, transient hallucination, disorientation, visual disturbances, and convulsions.

Cardiovascular - Tachycardia, bradycardia, palpitation, faintness, syncope, orthostatic hypotension (common to narcotic analgesics).

Gastrointestinal - Nausea, vomiting, constipation, and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility; in patients with acute ulcerative colitis, toxic dilation has been reported.

Genitourinary - Oliguria, urinary retention; antidiuretic effect has been reported (common to narcotic analgesics).

Allergic - Infrequent pruritus, giant urticaria, angioneurotic edema, and laryngeal edema.

Other - Flushing of the face, sweating and pruritus (due to opiate-induced histamine release); weakness.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Promethazine HCl and Hydrocodone Bitartrate Syrup is a Schedule III Controlled Substance.

Abuse: Hydrocodone is known to be subject to abuse; however, the abuse potential of oral hydrocodone appears to be quite low. Even parenteral hydrocodone does not appear to offer the psychic effects sought by addicts to the same degree as heroin or morphine. However, hydrocodone must be administered only under close supervision to patients with a history of drug abuse or dependence.

Dependence: Psychological dependence, physical dependence, and tolerance are known to occur with hydrocodone.

OVERDOSAGE

Promethazine: Signs and symptoms of overdose with promethazine HCl range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, unconsciousness, and sudden death. Other reported reactions include hyperreflexia, hypertonia, ataxia, athetosis, and extensor-plantar reflexes (Babinski reflex).

Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in children receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares. Atropine-like signs and symptoms – dry mouth, fixed dilated pupils, flushing, as well as gastrointestinal symptoms may occur.

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. The triad of coma, pinpoint pupils, and respiratory depression is strongly suggestive of opiate poisoning. In severe overdose, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur. Promethazine is additive to the depressant effects of hydrocodone. It is difficult to determine what constitutes a standard toxic or lethal dose. Infants and children are believed to be relatively more sensitive to opiates on a body-weight basis than are adults. Elderly patients are also comparatively intolerant to opiates.

Treatment: The treatment of overdose with promethazine and hydrocodone is essentially symptomatic and supportive. Only in cases of extreme overdose or individual sensitivity do vital signs including respiration, pulse, blood pressure, temperature, and EKG need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The

narcotic antagonist, naloxone hydrochloride, may be administered when significant respiratory depression occurs with promethazine and hydrocodone; any depressant effects of promethazine are not reversed with naloxone. Diazepam may be used to control convulsions. Avoid analeptics, which may cause convulsions. Acidosis and electrolyte losses should be corrected. A rise in temperature or pulmonary complications may signal the need for institution of antibiotic therapy.

Severe hypotension usually responds to the administration of norepinephrine or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic blockade may further lower the blood pressure. Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

The combination of promethazine hydrochloride and hydrocodone bitartrate is contraindicated in pediatric patients less than 16 years of age, because the combination may cause fatal respiratory depression in this age population.

The average effective dose for adults (16 years of age and over) is: 1 teaspoonful (5 mL) every 4 to 6 hours, not to exceed 30 mL in 24 hours.

HOW SUPPLIED

Promethazine HCl and Hydrocodone Bitartrate Syrup, 6.25 mg and 1.67 mg / 5mL

contains promethazine hydrochloride USP, 6.25 mg/5 mL, hydrocodone bitartrate USP, 1.67 mg/5 mL, and is available in bottles of 4 fluid ounce (118 mL), NDC 66992-XXX-XX and 16 fluid ounce (473 mL), NDC 66992-XXX-XX.

Promethazine HCl and Hydrocodone Bitartrate Syrup, 6.25 mg and 2.5 mg / 5mL

contains promethazine hydrochloride USP, 6.25 mg/5 mL, hydrocodone bitartrate USP, 2.5 mg/5 mL, and is available in bottles of 4 fluid ounce (118 mL), NDC 66992-XXX-XX and 16 fluid ounce (473 mL), NDC 66992-XXX-XX.

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Manufactured for:
WraSer Pharmaceuticals
Madison, MS 39110

500XXX Rev. 01/07