# CENTER FOR DRUG EVALUATION AND RESEARCH

# Approval Package for:

***APPLICATION NUMBER:***

## ANDA 40-454

***Name:*** Promethazine Hydrochloride Injection USP

***Sponsor:*** Gensia Sicor Pharmaceuticals, Inc.

***Approval Date:*** August 22, 2002

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 40-454

## CONTENTS

| Reviews / Information Included in this Review | |
|---|---|
| Approval Letter | X |
| Approvable Letter(s) | |
| Approved Labeling | X |
| Labeling Review(s) | X |
| Medical Review(s) | |
| Chemistry Review(s) | X |
| Bioequivalence Review(s) | X |
| Statistical Review(s) | |
| Microbiology Review(s) | X |
| Administrative Document(s) | X |
| Correspondence | X |
| | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 40-454**

# APPROVAL LETTER

ANDA 40-454

AUG 22 2002

Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Lowe
19 Hughes
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application dated October 26, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL, packaged in single-dose vials.

Reference is also made to your amendments dated May 30, June 14, and August 13, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Phenergan® Injection, 25 mg/mL and 50 mg/mL, respectively, of Wyeth Ayerst Laboratories).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 8/22/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-454
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-629/L.Huang/ L. Huang 8/20/02
HFD-623/J.Fan/ 8/20/02
HFD-617/S.Ho/8/19/02 8/20/02
HFD-600/N.Nath/
HFD-600/N.Sweeney L. Enson (for N. Sweeney) 8/20/02
HFD-613/J.Barlow/
HFD-613/J.Grace/ a/sign for Grace 8/22/02

Robert Lyn West 8/22/2002

V:\FIRMSAM\GENSIA\LTRS&REV\40454.AP.doc
F/T by: gp/8/20/02

APPROVAL

Printed 8/20/02

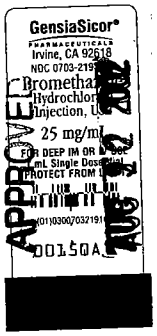
# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

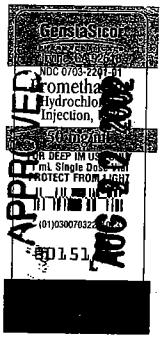
# ANDA 40-454

# APPROVED LABELING

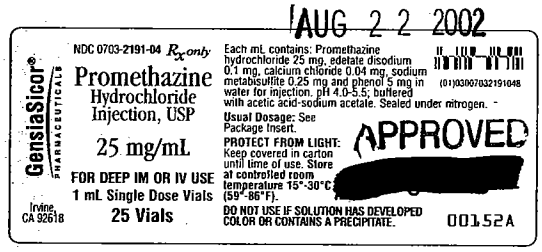
## VIAL LABEL
## 25 mg/mL
## Part #Y29-001-50A



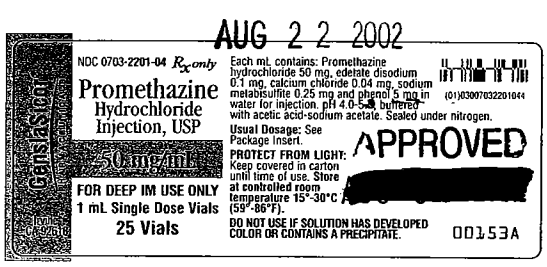

## VIAL LABEL
## 50 mg/mL
## Part #Y29-001-51A




## SHELF PACK A LABEL
## 25 mg/mL
## Part #Y29-001-52A




## SHELF PACK A LABEL
## 50 mg/mL
## Part #Y29-001-53A



Package Insert

$R_x$ only

GensiaSicor® PHARMACEUTICALS

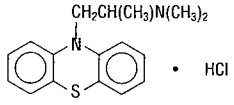
# Promethazine Hydrochloride Injection, USP

AUG 2 0 2002

APPROVED

## DESCRIPTION

Promethazine hydrochloride injection, is a sterile, pyrogen-free solution for deep intramuscular or intravenous administration. Promethazine hydrochloride (10*H*-phenothiazine-10-ethanamine, *N, N,* α-trimethyl-, monohydrochloride, (±)-) is a racemic compound and has the following structural formula:




$C_{17}H_{21}ClN_2S$ MW=320.89

Each mL contains either 25 mg or 50 mg promethazine hydrochloride with 0.1 mg edetate disodium, 0.04 mg calcium chloride, 0.25 mg sodium metabisulfite, and 5 mg phenol in water for injection. The pH range is 4.0 to 5.5, buffered with acetic acid-sodium acetate, and it is sealed under nitrogen.

Promethazine hydrochloride injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

## CLINICAL PHARMACOLOGY

Promethazine hydrochloride is a phenothiazine derivative which possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. Promethazine is a competitive $H_1$ receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines results in its relative lack (⅒) of dopamine antagonist properties. In therapeutic doses, promethazine hydrochloride produces no significant effects on the cardiovascular system. Clinical effects are generally apparent within 5 minutes of an intravenous injection and within 20 minutes of an intramuscular injection. Duration of action is four to six hours, although effects may persist up to 12 hours. Promethazine hydrochloride is metabolized in the liver, with the sulfoxides of promethazine and N-desmethylpromethazine being the predominant metabolites appearing in the urine. Following intravenous administration in healthy volunteers, the plasma half-life for promethazine has been reported to range from 9 to 16 hours. The mean plasma half-life for promethazine after intramuscular administration in healthy volunteers has been reported to be 9.8±3.4 hours.

## INDICATIONS AND USAGE

Promethazine hydrochloride is indicated for the following conditions:

1. Amelioration of allergic reactions to blood or plasma.
2. In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
5. Active treatment of motion sickness.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. Preoperative, postoperative, and obstetric (during labor) sedation.
9. Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and poor-risk patients, with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

## CONTRAINDICATIONS

Promethazine hydrochloride is contraindicated in comatose states and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine or other phenothiazines.

Under no circumstances should promethazine hydrochloride be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see **WARNINGS, Inadvertent Intra-arterial Injection**).

Promethazine hydrochloride should not be given by the subcutaneous route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

## WARNINGS

### Sulfite Sensitivity

**Promethazine hydrochloride contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthma episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.**

### CNS Depression

Promethazine hydrochloride may impair the mental and 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, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. (see **PRECAUTIONS, Information for Patients**).

### Lower Seizure Threshold

Promethazine hydrochloride may lower seizure threshold and 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 hydrochloride should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when promethazine has been used in association with other known marrow-toxic agents.

### Use in Pediatric Patients

**PROMETHAZINE HYDROCHLORIDE IS NOT RECOMMENDED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.**

**CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HYDROCHLORIDE TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PROMETHAZINE HYDROCHLORIDE ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PROMETHAZINE HYDROCHLORIDE SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.**

Excessively large dosages of antihistamines, including promethazine hydrochloride, in pediatric patients may cause hallucinations, convulsions, and sudden death. In pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine hydrochloride.

### Inadvertent Intra-arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of promethazine hydrochloride, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arteriolar irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with promethazine hydrochloride. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of promethazine hydrochloride, the injection should be stopped immediately to provide for evaluation of possible arterial placement or perivascular extravasation.

### Visual Inspection

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

### Other Considerations

Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

Administration of promethazine has been associated with reported cholestatic jaundice.

## PRECAUTIONS

### General

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

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

### Information for Patients

Promethazine hydrochloride may cause marked drowsiness or impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc, with promethazine hydrochloride may enhance impairment. Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities.

Patients should be advised to report any involuntary muscle movements.

Persistent or worsening pain or burning at the injection site should be reported immediately.

Avoid prolonged exposure to the sun.

### Drug Interactions

*CNS Depressants*

Promethazine hydrochloride may increase, prolong, or intensify the sedative action of central-nervous-system depressants, such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitanty with promethazine hydrochloride, 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 hydrochloride 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*

Although reversal of the vasopressor effect of epinephrine has not been reported with promethazine hydrochloride, it is recommended that epinephrine NOT be used in the case of promethazine hydrochloride overdose.

*Anticholinergics*

Concomitant use of other agents with anticholinergic 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. Although such a reaction has not been reported with promethazine hydrochloride, the possibility should be considered.

### Laboratory Test Interactions

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 glucose tolerance has been reported in patients receiving promethazine hydrochloride.

$R_x$ only $R_x$ only

**Carcinogenesis, Mutagenesis and Impairment of Fertility**

Long term animal studies have not been performed to assess the carcinogenic potential of promethazine hydrochloride, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility. Promethazine hydrochloride was nonmutagenic in the Ames *Salmonella* test system.

**Pregnancy**

*Teratogenic Effects—Pregnancy Category C*

Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of promethazine hydrochloride. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of promethazine hydrochloride in pregnant women. Because animal reproduction studies are not always predictive of human response, promethazine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the action of the drug on parturition, lactation and development of the animal neonate have not been conducted.

*Nonteratogenic Effects*

Promethazine hydrochloride received within two weeks of delivery may inhibit platelet aggregation in the newborn.

**Labor and Delivery**

Promethazine hydrochloride may be used alone or as an adjunct to narcotic analgesics during labor (see **DOSAGE AND ADMINISTRATION**). 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 on later growth and development of the newborn is unknown. (See also *Nonteratogenic Effects*.)

**Nursing Mothers**

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

**Pediatric Use**

Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Promethazine hydrochloride should be used with caution in pediatric patients 2 years of age and older (see **WARNINGS, Use in Pediatric Patients**).

**Use in Geriatric Patients (approximately 60 years or older)**

Since therapeutic requirements for sedative drugs tend to be less in geriatric patients, the dosage should be reduced for these patients.

## ADVERSE REACTIONS

**CNS Effects**

Drowsiness is the most prominent CNS effect of the drug. Extrapyramidal reactions may occur with high doses; this is almost always responsive to a reduction in dosage. Other reported reactions include dizziness, lassitude, tinnitus, incoordination, fatigue, blurred vision, euphoria, diplopia, nervousness, insomnia, tremors, convulsive seizures, oculogyric crises, excitation, catatonic-like states, hysteria, and hallucinations.

**Cardiovascular Effects**

Tachycardia, bradycardia, faintness, dizziness, and increases and decreases in blood pressure have been reported following the use of promethazine hydrochloride. Venous thrombosis at the injection site has been reported. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see **WARNINGS, Inadvertent Intra-arterial Injection**).

**Gastrointestinal Effects**

Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy.

**Allergic Reactions**

These include urticaria, dermatitis, asthma, and photosensitivity. Angioneurotic edema has been reported.

**Other Reported Reactions**

Leukopenia and agranulocytosis, usually when promethazine have been used in association with other known marrow-toxic agents, have been reported. Thrombocytopenic purpura and jaundice of the obstructive type have been associated with the use of promethazine. The jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Nasal stuffiness may occur. Dry mouth has been reported.

**Paradoxical Reactions (Overdosage)**

Hyperexcitability and abnormal movements, which have been reported in pediatric patients following a single administration of promethazine hydrochloride, may be manifestations of relative overdosage, in which case, consideration should be given to the discontinuation of promethazine hydrochloride and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

## OVERDOSAGE

Signs and symptoms of overdosage range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness.

Stimulation may be evident, especially in pediatric patients and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in pediatric patients receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

Atropine-like and symptoms—dry mouth, fixed, dilated pupils, flushing, etc., as well as gastrointestinal symptoms, may occur.

**Treatment**

Treatment of overdosage is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs, including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of promethazine hydrochloride are not reversed by naloxone.

Avoid analeptics, which may cause convulsions. The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of levarterenol or phenylephrine should be considered. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic blockade may further lower the blood pressure. Extrapyramidal reactions may be treated with anticholinergic antiparkinson agents, diphenhydramine, or barbiturates. Oxygen may also be administered. Limited experience with dialysis indicates that it is not helpful.

## DOSAGE AND ADMINISTRATION

**Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

Do not use promethazine hydrochloride if solution has developed color or contains precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

**Important Notes on Administration**

The preferred parenteral route of administration for promethazine hydrochloride is by deep intramuscular injection. The proper intravenous administration of this product is well-tolerated, but use of this route is not without some hazard. Not for subcutaneous administration.

**INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see WARNINGS, Inadvertent Intra-arterial Injection). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see CONTRAINDICATIONS).**

Injection into or near a nerve may result in permanent tissue damage.

When used intravenously, promethazine hydrochloride should be given in concentration no greater than 25 mg/mL at a rate not to exceed 25 mg per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

**Allergic Conditions**

The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as existing circumstances permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for amelioration of allergic reactions to blood or plasma is 25 mg.

**Sedation**

In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of promethazine hydrochloride.

**Nausea and Vomiting**

For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

**Preoperative and Postoperative Use**

As an adjunct to preoperative or postoperative medication, 25 to 50 mg promethazine hydrochloride in adults may be combined with appropriately reduced doses of analgesics and atropine-like drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

**Obstetrics**

Promethazine hydrochloride in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg (average dose, 50 mg) promethazine hydrochloride may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. If necessary, promethazine hydrochloride with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg of promethazine hydrochloride may be administered during a 24-hour period to patients in labor.

**Pediatric Patients**

Promethazine hydrochloride is not recommended for use in pediatric patients less than two year of age.

In pediatric patients 2 years of age and older, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in pediatric patients (see **WARNINGS, Use in Pediatric Patients**).

## HOW SUPPLIED

Promethazine Hydrochloride Injection, USP is available as follows:

| NDC Number | Strength | Package |
|---|---|---|
| 0703-**2191-04** | 25 mg/mL | 1 mL fill in a 2 mL vial 25 vial per shelf tray |
| 0703-**2201-04** | 50 mg/mL | 1 mL fill in a 2 mL vial 25 vial per shelf tray |

**Store at controlled room temperature 15°-30°C (59°-86°F).**

**Protect from light. Keep covered in carton until time of use.**

**Do not use if solution has developed color or contains a precipitate.**

---

Issued: May 2002
Gensia Sicor Pharmaceuticals, Inc.
Irvine, CA 92618

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 40-454

# LABELING REVIEW(S)

**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

---

ANDA Number: 40-454
Dates of Submission: October 26, 2001
Applicant's Name: Gensia-Sicor Pharmaceuticals, Inc.
Established Name: Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL (Vials)

---

**Labeling Deficiencies**

1. **CONTAINER Labels**
   a. FRONT PANEL: (25 mg/mL vial) - We encourage you to revise to read as follows -

**PROMETHAZINE HYDROCHLORIDE**
**INJECTION, USP**
**(25 mg/mL)**
**FOR DEEP IM OR IV USE**
**1 mL Single Dose Vial**

   b. FRONT PANEL: (50 mg/mL vial) - We encourage you to revise to read as follows –

**PROMETHAZINE HYDROCHLORIDE**
**INJECTION, USP**
**(50 mg/mL)**
**FOR DEEP IM USE ONLY**
**1 mL Single Dose Vial**

2. **CARTON Labeling**: (Shelf Pack A Label); (25 mg/mL vials & 50 mg/mL vials)
   See comments 1.(a.) and 1.(b.) above.

3. **CARTON Labeling**: (Shelf Pack B Label); (25 mg/mL vials & 50 mg/mL vials)
   Satisfactory in **draft** as of the October 26, 2001 submission.

4. **PROFESSIONAL PACKAGE INSERT LABELING**:
   a. GENERAL COMMENTS
   Please revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug, Phenergan® Injection (NDA 8-857/S-009, approved September 18, 1998). **(See enclosed copy of this most recently approved labeling for Phenergan® Injection. Also, we encourage you to make the following revision listed below.**

   b. WARNINGS - Sulfite Sensitivity
   We encourage you to utilize bold print throughout this subsection.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



**Enclosed: A copy of the most recently approved labeling for Phenergan® Injection (NDA 8-857/S-009, approved September 18, 1998).**

**REVIEW OF PROFESSIONAL LABELING CHECK LIST**

| Established Name | Yes | No | N/A |
|---|---|---|---|
| Different name than on acceptance to file letter? | | x | |
| Is this product a USP item? If so, USP supplement in which verification was assured. USP 24 | X | | |
| Is this name different than that used in the Orange Book? | | x | |
| If not USP, has the product name been proposed in the PF? | | | x |
| **Error Prevention Analysis** | | | |
| Has the firm proposed a proprietary name? If yes, complete this subsection. | | X | |
| Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? | | | X |
| Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? | | | X |
| **Packaging** | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | | X | |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | X | |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | | X |
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | X | | |
| Are there any other safety concerns? | | X | |
| **Labeling** | | | |
| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | X | |
| Has applicant failed to clearly differentiate multiple product strengths? | | | X |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | | X | |
| **Labeling(continued)** | **Yes** | **No** | **N/A** |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | X | |
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | | X |
| | | | |

| | | | |
|---|---|---|---|
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | | |
| Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR | | | |
| Is the scoring configuration different than the RLD? | | | X |
| Has the firm failed to describe the scoring in the HOW SUPPLIED section? | | | X |
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |
| Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? | | X | |
| Do any of the inactives differ in concentration for this route of administration? | | X | |
| Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? | | X | |
| Is there a discrepancy in inactives between DESCRIPTION and the composition statement? | | X | |
| Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported? | | X | |
| Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray? | | | X |
| Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION? | | | X |
| Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) | | | X |
| USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) | | | |
| Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | X | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | X | | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | | | |

**FOR THE RECORD:**

1. **Model Labeling: Insert – Used the most recently approved labeling for NDA 08-857/supplement 9 for Phenergan Injection; approved September 18, 1998. (AR 4/4/2000) Note that the firm did NOT utilize this labeling. Therefore, we forwarded them a copy.**

2. The firm states that there are no existing patents or exclusivities for Wyeth-Ayerst's Phenergan Injection. This statement is correct.

3. **PACKAGING:**

   **RLD -**

   FOR IV/IM USE:

   10 x 1 mL **Tubex** 25 mg/mL with a BLUNT POINTE

   10 X 1 mL **Tubex** 25 mg/mL with a 22 gauge 1 ¼" needle

FOR **IM** USE **ONLY:**
10 x 1 mL Tubex 50 mg/mL with a 22 gauge 1 ¼" needle

**ANDA -**
FOR IV/IM USE:
25 x 1 mL vials 25 mg/mL

FOR IM USE ONLY:
25 x 1 mL vials 50 mg/mL

4. **INACTIVE INGREDIENTS:**
   **The inactive ingredients listed in the DESCRIPTION section appear to be consistent with the firm's composition statement [vol. A. 1.1, section pg. 1042]**

5. **STORAGE recommendations:**
   **RLD - Store at room temperature between 15 to 25°C (59 to 77°F). Protect from light. Use this carton to protect contents from light.**

   **ANDA- Store at controlled room temperature 15-30°C (59-86°F). Protect from light. Keep covered in carton until time of use.**

6. CONTAINER:
   **2 mL Type I Amber vial; gray 13mm stopper and Al Seal)**
   **[Vol. A. 1.1 pg. 1407 ]**

---

Date of Review: May 6, 2002
Dates of Submission: October 26, 2001

Primary Reviewer: Jim Barlow Date: 5/7/02

Team Leader: John Grace Date: 5/7/2002

---

cc:

ANDA: 40-454
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\GENSIA\LTRS&REV\40454na1.l
Review

# APPROVAL SUMMARY

## REVIEW OF PROFESSIONAL LABELING
## DIVISION OF LABELING AND PROGRAM SUPPORT
## LABELING REVIEW BRANCH

---

ANDA Number: 40-454
Dates of Submission: ~~June 14, 2002~~ May 30, 2002
Applicant's Name: Gensia-Sicor Pharmaceuticals, Inc.
Established Name: Promethazine Hydrochloride Injection USP, 25 mg/mL and 50 mg/mL (Vials)

---

**APPROVAL SUMMARY**

1. **Do you have 12 Final Printed Labels and Labeling?** Yes

2. **CONTAINER Labels**

a. FRONT PANEL: (25 mg/mL vial) - We encourage you to revise to read as follows - Satisfactory in **final print** as of the ~~June 14~~, 2002 submission (see red jacket volume 2.1) May 30, jr

b. FRONT PANEL: (50 mg/mL vial) - We encourage you to revise to read as follows – Satisfactory in **final print** as of the ~~June 14~~, 2002 submission (See red jacket volume 2.1) May 30, jr

2. **CARTON Labeling**: (Shelf Pack A Label); (25 mg/mL vials & 50 mg/mL vials) Satisfactory in **final print** as of the ~~June 14~~, 2002 submission (See red jacket volume 2.1) May 30, jr

3. **CARTON Labeling**: (Shelf Pack B Label); (25 mg/mL vials & 50 mg/mL vials) Satisfactory in **final print** as of the October 26, 2001 submission.

4. **PROFESSIONAL PACKAGE INSERT LABELING**: Satisfactory in **final print** as of the ~~June 14~~, 2002 submission (See red jacket volume 2.1) May 30, jr

5. **Patent Data**

**NDA – 08-857**

| Patent No. | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| None | *None* | None | There are no unexpired patents for this product in the Orange Book Database. | N/A | None |

**Exclusivity Data– NDA 08-857**

| Code | Reference | Expiration | Labeling Impact |
|---|---|---|---|
| None | There is no unexpired exclusivity for this product in the Orange Book Database. | *N/A* | *None* |

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Phenergan® Injection
NDA Number: N 08-857/SL-009 for Phenergan Injection
NDA Drug Name: Phenergan® Injection
NDA Firm: Wyeth Laboratories, Inc.
Date of Approval of NDA Insert and supplement: N 08-857/supplement 9 for Phenergan Injection; approved September 18, 1998. (AR 4/3/2000)
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug.
Basis of Approval for the Carton Labeling: Most recently approved labeling of the reference listed drug.

## REVIEW OF PROFESSIONAL LABELING CHECK LIST

| Established Name | Yes | No | N/A |
|---|---|---|---|
| Different name than on acceptance to file letter? | | x | |
| Is this product a USP item? If so, USP supplement in which verification was assured. USP 24 | X | | |
| Is this name different than that used in the Orange Book? | | x | |
| If not USP, has the product name been proposed in the PF? | | | x |
| **Error Prevention Analysis** | | | |
| Has the firm proposed a proprietary name? If yes, complete this subsection. | | X | |
| Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? | | | X |
| Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? | | | X |
| **Packaging** | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | | X | |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | X | |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | | X |
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | X | | |
| Are there any other safety concerns? | | X | |
| **Labeling** | | | |
| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | X | |
| Has applicant failed to clearly differentiate multiple product strengths? | | | X |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | | X | |
| **Labeling(continued)** | **Yes** | **No** | **N/A** |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | X | |

| | | | |
|---|---|---|---|
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | | X |
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | | |
| Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR | | | |
| Is the scoring configuration different than the RLD? | | | X |
| Has the firm failed to describe the scoring in the HOW SUPPLIED section? | | | X |
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |
| Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? | | X | |
| Do any of the inactives differ in concentration for this route of administration? | | X | |
| Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? | | X | |
| Is there a discrepancy in inactives between DESCRIPTION and the composition statement? | | X | |
| Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported? | | X | |
| Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray? | | | X |
| Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION? | | | X |
| Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) | | | X |
| USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) | | | |
| Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | X | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | X | | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | | | |

**FOR THE RECORD:**

1. **Model Labeling: Insert – Used the most recently approved labeling for NDA 08-857/supplement 9 for Phenergan Injection; approved September 18, 1998. (AR 4/4/2000)**

2. **NDA – 08-857**

| Patent No. | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| None | ***None*** | None | There are no unexpired patents for this product in the Orange Book Database. | N/A | None |

**Exclusivity Data– NDA 08-857**

| Code | Reference | Expiration | Labeling Impact |
|---|---|---|---|
| None | There is no unexpired exclusivity for this product in the Orange Book Database. | *N/A* | *None* |

3. **PACKAGING**:

**RLD -**

FOR IV/IM USE:

10 x 1 mL **Tubex** 25 mg/mL with a BLUNT POINTE

10 X 1 mL **Tubex** 25 mg/mL with a 22 gauge 1 ¼" needle

FOR **IM** USE **ONLY:**

10 x 1 mL Tubex 50 mg/mL with a 22 gauge 1 ¼" needle

**ANDA -**

FOR IV/IM USE:

25 x 1 mL vials 25 mg/mL

FOR IM USE ONLY:

25 x 1 mL vials 50 mg/mL

4. **INACTIVE INGREDIENTS:**

**The inactive ingredients listed in the DESCRIPTION section appear to be consistent with the firm's composition statement [vol. A. 1.1, section pg. 1042]**

5. **STORAGE recommendations:**

**RLD - Store at room temperature between 15 to 25°C (59 to 77°F). Protect from light. Use this carton to protect contents from light.**

**ANDA- Store at controlled room temperature 15-30°C (59-86°F). Protect from light. Keep covered in carton until time of use.**

6. CONTAINER:

**2 mL Type I Amber vial; gray 13mm stopper and Al Seal)**
**[Vol. A. 1.1 pg. 1407 ]**

7. Note that the firm did NOT submit 12 copies of final printed shelf CARTOn labels (Shelf Pack B) but after discussig this with Team Leader John Grace it was deemed not necessary becaust these are the lkabels that are utilized by the shelf to which the product will be stored.

---

Date of Review:
June 26, 2002

Dates of Submission:
~~June 14, 2002~~ May 30, 2002

Primary Reviewer: Jim Barlow Date: 6/28/02

Team Leader: John Grace Date: John Grace 6/28/2002

cc:

ANDA: 40-454
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\GENSIA\LTRS&REV\40454ap.s
Review

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 40-454

# CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1 (one)

2. ANDA # 40-454

3. NAME AND ADDRESS OF APPLICANT
Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Love
19 Hughs
Irvine, CA 92618-1902

4. LEGAL BASIS FOR SUBMISSION
Satisfactory
Promethazine Hydrochloride Injection USP, 25 mg/mL, and 50 mg/mL in vials
RLD: NDA 08-857 Phenergan® Injection 25 mg/mL and 50 mg/mL ampoules
Manufactured by Wyeth Laboratory Inc., a Wyeth Ayerst Company
Gensia Scior Pharmaceuticals, Inc., certifies that there are no patents that claim the listed drug referred to this application or that claim the use of the listed drug.
Exclusivity
No marketing exclusivity is currently in effect for Wyeth Ayerst's Phenergan® Injection.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Promethazine Hydrochloride Injection USP, 25 mg/mL, and 50 mg/mL

8. SUPPLEMENT(s) PROVIDE(s) FOR:
None

9. AMENDMENTS AND OTHER DATES:
Date of submission: October 26, 2001
Amendment: November 29, 2001

10. PHARMACOLOGICAL CATEGORY
antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

RLD: NDA 08-857 Phenergan® Injection 25 mg/mL and 50 mg/mL ampoules
Manufactured by Wyeth Laboratory Inc., a Wyeth Ayerst Company

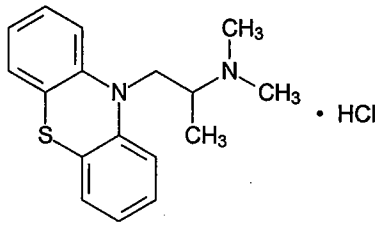
DMF _____

13. DOSAGE FORM
Injection

14. POTENCY
25 mg/mL and 50 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Promethazine Hydrochloride. 10*H*-Phenothiazine-10-ethanamine, *N*,*N*,α-trimethyl-, monohydrochloride, (±)-.$C_{17}H_{20}N_2S \cdot HCl$. 320.89. 58-33-3. Anti-emetic, antihistaminic.




16. RECORDS AND REPORTS
None

17. COMMENTS

This application is not approvable due to deficiencies in the following areas. (1) component and composition, (2) in-process controls, (3) Stability.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable.

| 19. REVIEWER: | DATE COMPLETED: |
|---|---|
| Liang-Lii Huang, Ph.D. | 1/31/02;2/28/02 |
| Endorsed by James Fan | 1/31/02;2/28/02 |

Redacted 12 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-454 APPLICANT: Gensia Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Promethazine Hydrochloride Injection USP, 25 mg/mL, and 50 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

5.

6.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

2. Please provide all available long-term stability data.

3. Information related to labeling and sterilization assurance are to be reviewed by OGD scientists. After the reviews are completed, any deficiencies found will be communicated to you under separate covers.

4. In the event of a dispute, the USP method will be considered as the regulatory method.

5. Pages 1420 and 1421 of your application are illegible. Please submit legible photocopies for these pages.

Sincerely yours,

Paul - Lum for 3/15/02

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

ANDA 40-454
ANDA DUP 40-454
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/Liang-Lii Huang, Ph.D. /1/31/02;2/28/02 L. Huang 3/7/02
HFD-627/James Fan, Team Leader /1/31/02;2/28/02/3/2/02 3/7/02
HFD-617/Sarah Ho, Project Manager /2/28/02/3/6/02 3/7/02

V:\FIRMSAM\GENSIA\LTRS&REV\40454rev1.doc
F/T by: DJ 3/6/02

February 28, 2002

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

1. CHEMISTRY REVIEW NO. 2 (two)

2. ANDA # 40-454

3. NAME AND ADDRESS OF APPLICANT
Gensia Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Love
19 Hughs
Irvine, CA 92618-1902

4. LEGAL BASIS FOR SUBMISSION
Satisfactory
Promethazine Hydrochloride Injection USP, 25 mg/mL, and 50 mg/mL in vials
RLD: NDA 08-857 Phenergan® Injection 25 mg/mL and 50 mg/mL ampoules
Manufactured by Wyeth Laboratory Inc., a Wyeth Ayerst Company
Gensia Scior Pharmaceuticals, Inc., certifies that there are no patents that claim the listed drug referred to this application or that claim the use of the listed drug.
Exclusivity
No marketing exclusivity is currently in effect for Wyeth Ayerst's Phenergan® Injection.

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Promethazine Hydrochloride Injection USP, 25 mg/mL, and 50 mg/mL

8. SUPPLEMENT(s) PROVIDE(s) FOR:
None

9. AMENDMENTS AND OTHER DATES:
Date of submission: October 26, 2001
Amendment: November 29, 2001
Amendment: June 14, 2002
Telephone amendment: August 13, 2002

10. PHARMACOLOGICAL CATEGORY
antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

RLD: NDA 08-857 Phenergan® Injection 25 mg/mL and 50 mg/mL ampoules
Manufactured by Wyeth Laboratory Inc., a Wyeth Ayerst Company

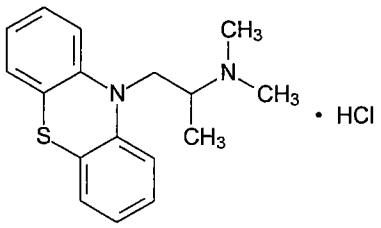
DMF _____

13. DOSAGE FORM
Injection

14. POTENCY
25 mg/mL and 50 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Promethazine Hydrochloride. 10*H*-Phenothiazine-10-ethanamine, *N*,*N*,α-trimethyl-, monohydrochloride, (±)-.$C_{17}H_{20}N_2S \cdot HCl$. 320.89. 58-33-3. Anti-emetic, antihistaminic.




16. RECORDS AND REPORTS
None

17. COMMENTS

This application is approvable.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approvable.

| 19. REVIEWER: | DATE COMPLETED: |
|---|---|
| Liang-Lii Huang, Ph.D. | August 15, 2002 |
| Endorsed by James Fan | August 15, 2002 |

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

34. BIOEQUIVALENCY STATUS
satisfactory
Bio reviewer: P. M. Sathe, Ph.D.
Status: A waiver is granted 12/27/01.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
satisfactory

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes_XX_____
No _____

If no, explain reason(s) below