CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 11-265/S-027

Trade Name: Phenergran w/dextromethorphan Syrup

Generic Name: promethazine HCl and dextromethorpan HBr

Sponsor: Wyeth-Ayerst Research

Approval Date: February 23, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 11-265/S-027

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 11-265/S-027

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 11-265/S-027

Wyeth-Ayerst Research
P.O. Box 8299
Philadelphia, PA 19101-8299

Attention: Nanette E. Holston
Associate Director
Global Brand Management, Regulatory Affairs

Dear Ms. Holston:

Please refer to your supplemental new drug application dated August 25, 2000, received August 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan with dextromethorphan (promethazine HCl and dextromethorphan HBr) Syrup.

This supplemental new drug application provides for a revision to the package insert in compliance with the Final Rule entitled "*Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use Subsection in Labeling*", published on August 27, 1998, in the Federal Register (62 FR 45313-45326), which amended 21 CFR 201.57. Additionally, this supplement provides for some formatting changes and the addition of the "Rx only" statement to the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling text submitted August 25, 2000, and with the editorial revisions listed below as agreed upon in a telephone conversation between you and Sandy Barnes of this Division on February 23, 2001. Accordingly, the supplemental application is approved, effective on the date of this letter.

1. Revise the "**Geriatric Use**" subsection to read as follows:

> **Geriatric Use**
> Clinical studies of Phenergan formulations did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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 Phenergan with Dextromethorphan Syrup and observed closely.

The final printed labeling (FPL) must be identical to the package insert submitted August 25, 2000, and include the editorial revisions indicated. These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 11-265/S-027." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. David Hilfiker, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Robert Meyer
2/23/01 05:25:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 11-265/S-027

APPROVED LABELING

APPROVED

FEB 23 200

Phenergan®
with dextromethorphan
(Promethazine Hydrochloride and Dextromethorphan Hydrobromide)
Syrup

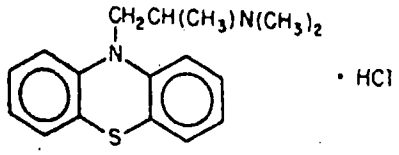
R_x only

~~**Description**~~ **DESCRIPTION**

Each teaspoon (5 mL) of Phenergan with dextromethorphan contains 6.25 mg promethazine hydrochloride and 15 mg dextromethorphan hydrobromide in a flavored syrup base with a pH between 4.7 and 5.2. Alcohol 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C Yellow 10, FD&C Yellow 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

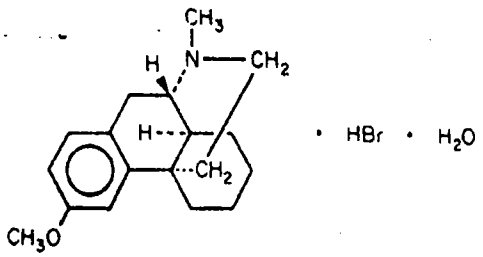
Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S{\cdot}HCl$ and its molecular weight is 320.88.

Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as 10*H*-Phenothiazine-10-ethanamine, *N*,*N*,α-trimethyl-, monohydrochloride, (±)- with the following structural formula:



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.

Dextromethorphan hydrobromide is a salt of the methyl ether of the dextrorotatory isomer of levorphanol, a narcotic analgesic. It is chemically named as 3-methoxy-17-methyl-9α, 13α, 14α-morphinan hydrobromide monohydrate with the following structural formula:



Dextromethorphan hydrobromide monohydrate occurs as white crystals, is sparingly soluble in water, and is freely soluble in alcohol. The empirical formula is $C_{18}H_{25}NO \cdot HBr \cdot H_2O$, and the molecular weight of the monohydrate is 370.33.

Dextromethorphan HBr monohydrate is dextrorotatory with a specific rotation of +27.6 degrees in water (20 degrees C, sodium D-line).

~~**Clinical Pharmacology**~~ **CLINICAL PHARMACOLOGY**

~~**PROMETHAZINE**~~ **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 dopaminergic (CNS) action.

Promethazine is an H_1 receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects. In therapeutic dosages, promethazine produces no significant effects on the cardiovascular system.

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.

~~**DEXTROMETHORPHAN**~~ **Dextromethorphan**

Dextromethorphan is an antitussive agent and, unlike the isomeric levorphanol, it has no analgesic or addictive properties.

The drug acts centrally and elevates the threshold for coughing. It is about equal to codeine in depressing the cough reflex. In therapeutic dosage dextromethorphan does not inhibit ciliary activity.

Dextromethorphan is rapidly absorbed from the gastrointestinal tract and exerts its effect in 15 to 30 minutes. The duration of action after oral administration is approximately

three to six hours. Dextromethorphan is metabolized primarily by liver enzymes undergoing O-demethylation, N-demethylation, and partial conjugation with glucuronic acid and sulfate. In humans, (+)-3-hydroxy-N-methylmorphinan, (+)-3-hydroxymorphinan, and traces of unmetabolized drug were found in urine after oral administration.

~~Indications and Usage~~ **INDICATIONS AND USAGE**
Phenergan with dextromethorphan is indicated for the temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold.

~~Contraindications~~ **CONTRAINDICATIONS**
Promethazine is contraindicated in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.

Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms, including asthma.

Dextromethorphan should not be used in patients receiving a monoamine oxidase inhibitor (MAOI) (see "~~Precautions – DRUG INTERACTIONS~~ **PRECAUTIONS – Drug Interactions**").

~~Warnings~~ **WARNINGS**
~~PROMETHAZINE~~ **Promethazine**
Promethazine may cause marked drowsiness. Ambulatory patients should be cautioned against such activities as driving or operating dangerous machinery until it is known that they do not become drowsy or dizzy from promethazine therapy.

The sedative action of promethazine hydrochloride is additive to the sedative effects of central nervous system depressants; therefore, agents such as alcohol, narcotic analgesics, sedatives, hypnotics, and tranquilizers should either be eliminated or given in reduced dosage in the presence of promethazine hydrochloride. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of analgesic depressants, such as morphine or meperidine, should be reduced by one-quarter to one-half.

Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or when giving in combination with narcotics or local anesthetics which may also affect seizure threshold.

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

Antihistamines should be used with caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder obstruction due to symptomatic prostatic hypertrophy and narrowing of the bladder neck.

Administration of promethazine has been associated with reported cholestatic jaundice.

~~DEXTROMETHORPHAN~~ **Dextromethorphan**

Administration of dextromethorphan may be accompanied by histamine release and should be used with caution in atopic children.

~~**Precautions**~~ **PRECAUTIONS**

Animal reproduction studies have not been conducted with the drug combination—promethazine and dextromethorphan. It is not known whether this drug combination can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phenergan with dextromethorphan should be given to a pregnant woman only if clearly needed.

~~GENERAL~~ **General**

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

Dextromethorphan should be used with caution in sedated patients, in the debilitated, and in patients confined to the supine position.

~~INFORMATION FOR PATIENTS~~ **Information for Patients**

Phenergan with dextromethorphan may cause marked drowsiness or 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 Phenergan with dextromethorphan therapy. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.

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.

Patients should be advised to report any involuntary muscle movements or unusual sensitivity to sunlight.

~~DRUG INTERACTIONS~~ **Drug Interactions**

Hyperpyrexia, hypotension, and death have been reported coincident with the co-administration of monoamine oxidase (MAO) inhibitors and products containing dextromethorphan. Thus, concomitant administration of Phenergan with dextro-methorphan and MAO inhibitors should be avoided (see "~~Contraindications~~ **CONTRAINDICATIONS**").

The sedative action of promethazine is additive to the sedative effects of other central nervous system depressants, including alcohol, narcotic analgesics, sedatives, hypnotics, tricyclic antidepressants, and tranquilizers; therefore, these agents should be avoided or administered in reduced dosage to patients receiving promethazine.

~~DRUG/LABORATORY TEST INTERACTIONS~~ **Drug/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 blood glucose has been reported in patients receiving promethazine.

~~CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY~~

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine or of dextromethorphan. There are no animal or human data concerning the carcinogenicity, mutagenicity, or impairment of fertility with these drugs. Promethazine was nonmutagenic in the Salmonella test system of Ames.

~~PREGNANCY~~ **Pregnancy Category C**

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 of promethazine. These doses are 8.3 and 16.7 times the maximum recommended total daily dose for a 50-kg subject. 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, including promethazine, 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.

Phenergan with dextromethorphan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

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

~~LABOR AND DELIVERY~~ **Labor and Delivery**

See "*Nonteratogenic Effects*."

~~NURSING MOTHERS~~ **Nursing Mothers**

It is not known whether promethazine or dextromethorphan is excreted in human milk. Caution should be exercised when Phenergan with dextromethorphan is administered to a nursing woman.

~~PEDIATRIC USE~~ **Pediatric Use** This product should not be used in children under 2 years of age because safety for that use has not been established.

Geriatric Use

Clinical studies of Phenergan did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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.

~~**Adverse Reactions**~~ **ADVERSE REACTIONS**

~~PROMETHAZINE~~ **Promethazine**

Nervous System—Sedation, sleepiness, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).

Cardiovascular—Increased or decreased blood pressure.

Dermatologic—Rash, rarely photosensitivity.

Hematologic—Rarely leukopenia, thrombocytopenia; agranulocytosis (1 case).

Gastrointestinal—Nausea and vomiting.

~~DEXTROMETHORPHAN~~ **Dextromethorphan**

Dextromethorphan hydrobromide occasionally causes slight drowsiness, dizziness, and gastrointestinal disturbances.

~~**Drug Abuse and Dependence**~~ **DRUG ABUSE AND DEPENDENCE**

According to the WHO Expert Committee on Drug Dependence, dextromethorphan could produce very slight psychic dependence but no physical dependence.

~~**Overdosage**~~ **OVERDOSAGE**

~~PROMETHAZINE~~ **Promethazine**

Signs and symptoms of overdosage with promethazine 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 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.

~~DEXTROMETHORPHAN~~ **Dextromethorphan**

Dextromethorphan may produce central excitement and mental confusion. Very high doses may produce respiratory depression. One case of toxic psychosis (hyperactivity, marked visual and auditory hallucinations) after ingestion of a single dose of 20 tablets (300 mg) of dextromethorphan has been reported.

~~TREATMENT~~ **Treatment**

Treatment of overdosage with Phenergan with dextromethorphan 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. 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. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. The antidotal efficacy of narcotic antagonists to dextromethorphan has not been established; note that any of the depressant effects of promethazine are not reversed by naloxone. Avoid analeptics, which may cause convulsions.

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~~ **DOSAGE AND ADMINISTRATION**

The average effective dose for adults is one teaspoon (5 mL) every 4 to 6 hours, not to exceed 30.0 mL in 24 hours. For children 6 years to under 12 years of age, the dose is one-half to one teaspoon (2.5 to 5.0 mL) every 4 to 6 hours, not to exceed 20.0 mL in 24 hours. For children 2 years to under 6 years of age, the dose is one-quarter to one-half teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 10.0 mL in 24 hours.

Phenergan with dextromethorphan is not recommended for children under 2 years of age.

~~How Supplied~~ **HOW SUPPLIED**

Phenergan® with dextromethorphan (Promethazine Hydrochloride and Dextromethorphan Hydrobromide) Syrup is a clear, yellow solution supplied as follows:

NDC 0008-0548-02, case of 24 bottles of 4 fl. oz. (118 mL).
NDC 0008-0548-03, bottle of 1 pint (473 mL).

Keep bottles tightly closed and store at room temperature between 15° and 25° C (59° and 77° F).

Protect from light.

Dispense in light-resistant, glass, tight containers.

300

Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

305 CI 4872~~-1-~~ ~~Issued September 6, 1996~~ Revised Printed in USA

Best Available Copy

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 11-265/S-027

MEDICAL REVIEW(s)

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS (HFD-570)

APPLICATION #:	11-265	**APPLICATION TYPE:**	NDA Labeling Supplement
SPONSOR:	Wyeth-Ayerst	**TRADE NAME:**	Phenergan® with Dextromethorphan Syrup
CATEGORY:	H1 blocker & antitussive	**GENERIC NAME:**	promethazine/ dextromethorphan
		ROUTE:	oral
MEDICAL OFFICER:	Raymond F. Anthracite	**REVIEW DATE:**	02/23/2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

DOCUMENT DATE	CDER DATE	SUBMISSION TYPE	COMMENTS
08/25/2000 (#27)	08/28/2000	NDA supplement	geriatric labeling

RELATED APPLICATIONS

DOCUMENT DATE	APPLICATION TYPE	COMMENTS

REVIEW SUMMARY:

There appears to by a paucity of published information of controlled evaluations of various Phenergan formulations and their components involving adequate numbers of geriatric patients upon which to base specific safety and/or efficacy information beyond what is currently included in the product labeling. The appropriate boilerplate language from 21 CFR 201.57(f)(10)(ii)(A) and 21 CFR 201.57(f)(10)(v) is suggested for inclusion in the label under the "Geriatric Use" subsection to comport with this lack of information and with the sedative effect of promethazine.

OUTSTANDING ISSUES:

None.

RECOMMENDED REGULATORY ACTION

NEW CLINICAL STUDIES:		PROCEED		HOLD		(HOLD TYPE)
NDA/SUPPLEMENTS:		APPROVAL	XX	APPROVABLE		NOT APPROVABLE
OTHER ACTION:						

SIGNATURES

Reviewer: _____ **Date:** 02/23/2001

Team Leader: _____ **Date:** _____

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY

This is a fairly routine geriatric labeling supplement of Phenergan® With Dextromethorphan Syrup, an orally administered decongestant and antitussive for the upper respiratory symptoms of colds and allergy that contains promethazine and dextromethorphan as active components [1:1:2-4]. Referencing of the original submission in this review is difficult because the sponsor has not provided a unique identifier for each page of the submission. The best that can be done is to include the volume number, attachment tab number and page references (e.g. [Volume:Attachment:Pages]), which is the approach adopted by this reviewer.

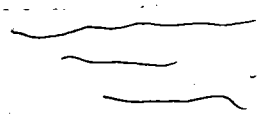
The sum of evidence from published literature, proprietary trial results and spontaneous adverse event reports is, as stated by the sponsor [1:2:12-3]:

> "There appears to by a paucity of published information of controlled evaluations of Phenergan involving adequate numbers of geriatric patients upon which to base specific safety and/or efficacy information beyond what is currently included in the product labeling."

The appropriate boilerplate language from 21 CFR 201.57(f)(10)(ii)(A) is suggested for inclusion in the label under the "Geriatric Use" subsection to comport with this lack of information and with the sedative effect of promethazine.

II. LITERATURE REVIEW

The search and analytic procedures followed by the sponsor were quite reasonable and fairly complete. Information specific to the use of the Phenergan product line in the geriatric population was sought in the following databases for the following years:



The search strategies used keywords alone and in the combinations for active ingredients in the Phenergan product line. The keywords and combinations for these are as follows:

DATA BASE SEARCH STRATEGIES FOR GERIATRIC SUPPLEMENTS TO NDA'S 08-306, 08-604 AND 11-265				
	Phenergan	**Phenergan with Codeine**	**Phenergan with Dextromethorphan**	**Phenergan VC**
1	Phenergan or promethazine	Phenergan or promethazine	Phenergan or promethazine	Phenergan VC or phenylephrine
2	clinical trials	codeine	dextromethorphan	clinical trials

DATA BASE SEARCH STRATEGIES FOR GERIATRIC SUPPLEMENTS TO NDA'S 08-306, 08-604 AND 11-265				
	Phenergan	**Phenergan with Codeine**	**Phenergan with Dextromethorphan**	**Phenergan VC**
3	aged	clinical trials	clinical trials	geriatric
4	geriatric	aged	aged	aged
5	elderly	elderly	elderly	elderly
6	1 and 2	geriatric	geriatric	1 and 2
7	1 and 3	1 and 2 and 3	1 and 2 and 3	1 and 3
8	1 and 4	2 and 4	2 and 4	1 and 4
9	1 and 5	2 and 5	2 and 5	1 and 5
10		2 and 6	2 and 6	

Abstracts of the citations found by the searches were reviewed. Those articles reporting on controlled evaluations involving the geriatric population were obtained and summarized. Citations for which abstracts were not available were obtained, reviewed for relevance and summarized, if relevant. Two published articles were from 1959 and 1965, outside time periods covered by the above databases, but were also included in this review by the sponsor. This submission included abstracts retrieved.

Most studies were done in a small number of patients (<100) across a variety of age groups and did not report a geriatric subgroup analysis in the results. One study (Gattera, et. al., Journal of Pain & Symptom Management, 1994, 9(7):454-61) with 71 of 100 patients ≥ 60 years of age was a retrospective case-controlled study of akathisia in the terminally ill to assess medication associations with this adverse event. Akathisia is a condition characterized by an inability to remain in a sitting posture or motor restlessness and a feeling of muscular quivering. Several drugs were associated with increased odds ratios of akathisia compared with retrospective case-matched controls, one of which was promethazine. The sponsor reports that no conclusive link was established between age or gender with promethazine exposure and risk of akathisia.

Another study (Viukari & Miettinen, Neuropsychobiology, 1984, 12(2-3):134-7) involved 40 patients ≥ 62 year old, 20 with mild to moderate dementia, in which three hypnotics were compared against placebo. The active treatment groups evaluated for nocturnal awakenings were diazepam, promethazine and propiomazine. The sponsor reports that adverse events were few and similar in types among groups. Tiredness the next day was reported by four patients who were administered active treatment, one of the four received promethazine [1:2:12-26, 44, 61, 117-8].

III. CLINICAL TRIAL DATABASE REVIEW

The sponsor states that, "Current labeling adequately reflects the database" [2:3:342].

IV. POST-MARKETING ADVERSE EVENTS REVIEW

A search of the [redacted] database by the sponsor identified no information on adverse events in patients older than 65 years of age indicating differences in safety in a geriatric population [2:4:345].

V. SUGGESTED LABELING REVISION

The Geriatric Use section of the label should include the boilerplate language specified in 21 CFR 201.57(f)(10)(ii)(A). The labeling change suggested by the sponsor is not in complete accordance with this language and no explanation was offered to justify the version that was submitted [Cover Letter, 1:1:7]. The following is the complete Geriatric Use subsection, as specified by 21 CFR.

"Clinical studies of Phenergan formulations did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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 Phenergan With Dextromethorphan Syrup and observed closely."

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #11-265
HFD-570/Division Files
HFD-570/Deputy Division Director/Mann
HFD-570/Medical Reviewer/Anthracite
HFD-570/Project Manager/Ostroff

/s/

Raymond Anthracite
2/23/01 09:24:26 AM
MEDICAL OFFICER

Marianne Mann
2/23/01 09:56:49 AM
MEDICAL OFFICER

Robert Meyer
2/23/01 03:47:32 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 11-265/S-027

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Project Manager's Labeling Review

NDA: 11-265/SLR-027 (Geriatric Labeling)

Product: Phenergan with dextromethorphan (promethazine HCl and dextromethorphan HBr) Syrup

Sponsor: Wyeth-Ayerst Research

Submission dated: August 25, 2000

This submission contains draft labeling submitted in compliance with the Final Rule entitled "*Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use Subsection in Labeling*", published on August 27, 1998, in the Federal Register (62 FR 45313-45326), which amended 21 CFR 201.57.

The draft labeling submitted on August 25, 2000, differs from the previously approved September 6, 1996, labeling text in the following ways:

1. The following statement was added at Lines 210-216:

   Geriatric Use
   Clinical studies of Phenergan did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

   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.

   Language concerning geriatric use was not present in the previous version of the PI.

2. The section titles have been changed from a bold-faced initial capital style (e.g. **Clinical Pharmacology**) to a bold-faced all-capital style (e.g. **CLINICAL PHARMCOLOGY**) and the subsection headings have been reformatted from an all-capital style (e.g. INFORMATION FOR PATIENTS) to a bold-faced, initial capital style (e.g. **Information for Patients**).

3. At Line six, the phrase "**R_x only**" has been added.

4. At Line 180, the "PREGNANCY" subsection heading has been deleted and replaced with "**Pregnancy Category C.**"

Withstanding the above issues, this submission is otherwise identical to the previously approved labeling text.

Geriatric Use

Clinical studies of [redacted] did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Sedating drugs may cause confusion and over-sedation in the elderly. 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.

Craig Ostroff, Pharm.D. Date
Project Manager

CONCUR:

Sandy Barnes Date
Chief, Project Management Staff

/s/

Craig Ostroff
2/22/01 01:46:37 PM
CSO

25 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 11-265 / S-027

Wyeth-Ayerst Research
P. O. Box 8299
Philadelphia, PA 19101-8299

SEP - 1 2000

Attention: Nanette E. Holston
Associate Director Global Brand Management
Regulatory Affairs

Dear Dr. Holston:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Phenergan ®with Dextromethorphan Syrup

NDA Number: 11-265

Supplement Number: S-027

Date of Supplement: August 25, 2000

Date of Receipt: August 28, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 27, 2000 in accordance with 21 CFR 314.101(a). All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Pulmonary Drug Products, HFD-570
Office of Drug Evaluation II
Attention: Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

FOR S.B.

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products, HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 11-265/S-027
HFD-570/Div. Files
HFD-570/CSO/Mr. Hilfiker

8/20/00

SUPPLEMENT ACKNOWLEDGEMENT

WYETH-AYERST RESEARCH

ORIGINAL

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299

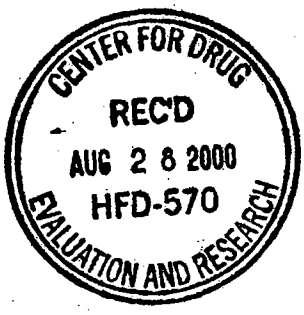
Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

August 25, 2000

NDA 11-265
Phenergan® with dextromethorphan (promethazine hydrochloride and dextromethorphan hydrobromide) Syrup

NDA NO. 11-265 REF NO. 027
NDA SUPPL FOR SLR - Geriatric



Robert Meyer, M.D., Director
Division of Pulmonary Drug Products (HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room 10-B03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

GERIATRIC LABELING SUPPLEMENT

Dear Dr. Meyer:

Reference is made to our approved New Drug Application 11-265 for Phenergan® with dextromethorphan Syrup.

Reference is also made to the Final Rule entitled *"Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in Labeling,"* published in the Federal Register on Wednesday August 27, 1998 (62 FR 45313-45326). This Final Rule amends 21 CFR 201.57, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs" to provide for the addition of a "Geriatric Use" subsection to the **PRECAUTIONS** section of the labeling.

The purpose of this supplemental application is to provide for revisions to the physician's package insert for Phenergan® with dextromethorphan Syrup to comply with the above referenced final rule. The enclosed draft package insert labeling also reflects the addition of the "℞ only" statement. In addition, formatting changes were made to all section headings.

The following material is provided in support of this submission:

Attachment 1: Four draft copies of the revised package insert for Phenergan® with dextromethorphan Syrup. Double-underlined areas indicate additional text and strikeouts indicate deleted text. Four unmarked draft copies of the revised labeling are also included.

Attachment 2: Summary of the geriatric literature search for Phenergan® with dextromethorphan Syrup, followed by a search history and a listing of literature reports reviewed.

Attachment 3: Summary of the review and analysis of in-house data for geriatric patients currently in the clinical trial database.

Attachment 4: Summary of the review and analysis of data received through the post-marketing adverse drug event reporting system.

Attachment 5: Four copies of the currently approved package insert for Phenergan® with dextromethorphan Syrup.

We trust that you will find the enclosed draft labeling acceptable. We will implement these changes as soon as we receive notification that the draft labeling has been approved. If you have any questions regarding this submission, please contact the undersigned at 610-902-3775 or Ms. Christine Rosser at 610-902-3120.

Sincerely,

WYETH-AYERST LABORATORIES

Nanette E. Holston
Associate Director
Global Brand Management
Regulatory Affairs

NEH:CR:jad:phendexgeriatric

9 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-_____

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Wyeth Laboratories	August 25, 2000
TELEPHONE NO. *(Include Area Code)* (610) 902-3775	**FACSIMILE (FAX) Number** *(Include Area Code)* (610) 964-5972

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

P.O. Box 8299
Philadelphia, PA 19101

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 2 8 2000
HFD-570

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously assigned) NDA No. 1[illegible]5

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF
Promethazine Hydrochloride & Dextromethorphan	Phenergan [illegible]thorphan

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* *See Below

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Syrup		Oral

(PROPOSED) INDICATION(S) FOR USE: Temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

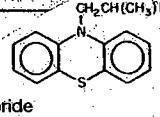
REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 in duplicate — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

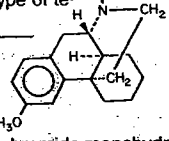
ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., sterile, final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.



• HCl

Promethazine hydrochloride



• HBr • H_2O

Dextromethorphan hydrobromide monohydrate

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
☐	7. Clinical Microbioblogy (e.g. 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
☐	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
☐	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
☐	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
☐	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (k) (3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Nanette E Holston	Nanette E. Holston, Associate Director Worldwide Regulatory Affairs	August 25, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
P.O. Box 8299 Philadelphia, PA 19101	(610) 902-3775

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

FORM FDA 356h (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-02
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Wyeth Laboratories
P.O. Box 8299
Philadelphia, PA 19101

2. TELEPHONE NUMBER *(Include Area Code)*

(610) 902-3775

3. PRODUCT NAME
Phenergan® with dextromethorphan

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER
NDA No. 11-265

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Nanette E. Holston	Nanette E. Holston, Associate Director, Global Brand Management, Worldwide Regulatory Affairs	August 25, 2000

FORM FDA 3397 (5/98)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF