CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 8-604/S-026

Trade Name: Phenergran VC

Generic Name: phenylphrine HCl, promethazine HCl

Sponsor: Wyeth-Ayerst Research

Approval Date: February 23, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-604/S-026

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-604/S-026

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 8-604/S-026

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 VC (promethazine HCl and codeine phosphate) 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 reflects 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 products are safe and effective for use as recommended in the labeling text submitted August 25, 2000, and with the minor 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 VC Syrup and observed closely.

2. Revise the **"Carcinogenesis, Mutagenesis, Impairment of Fertility"** subsection heading by including the subheading *"Promethazine "* prior to the first sentence of this section.

The final printed labeling (FPL) must be identical to the respective package inserts submitted August 25, 2000, and include the minor 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 8-604-026." 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 05:20:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-604/S-026

APPROVED LABELING

Phenergan® VC
(Promethazine Hydrochloride and Phenylephrine Hydrochloride) Syrup

R_x only

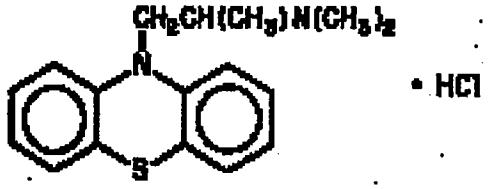
APPROVED
FEB 23 2001

~~Description~~ DESCRIPTION

Each teaspoon (5 mL) of Phenergan VC contains 6.25 mg promethazine hydrochloride and 5 mg phenylephrine hydrochloride 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, FD&C Yellow 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

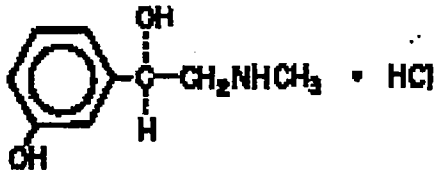
Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S{\cdot}HCl$ and its molecular weight is 320.88.

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 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.

Phenylephrine hydrochloride is a sympathomimetic amine salt. It may be chemically named as 3-hydroxy-α-[(methyl-amino)methyl]-benzenemethanol hydrochloride and has the following chemical formula:



Phenylephrine hydrochloride occurs as white or nearly white crystals, having a bitter taste. It is freely soluble in water and alcohol, with a molecular weight of 203.67. The empirical formula is $C_9H_{13}NO_2{\cdot}HCl$, and the stereochemistry is R-isomer as indicated in

the structure; Specific Rotation—between –42° and –47.5°. Phenylephrine hydrochloride is subject to oxidation and must be protected from light and air.

~~**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 4 to 6 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.

~~PHENYLEPHRINE~~ **Phenylephrine**

Phenylephrine is a potent postsynaptic α-receptor agonist with little effect on β receptors of the heart. Phenylephrine has no effect on β-adrenergic receptors of the bronchi or peripheral blood vessels. A direct action at receptors accounts for the greater part of its effects, only a small part being due to its ability to release norepinephrine.

Therapeutic doses of phenylephrine mainly cause vasoconstriction. Phenylephrine increases resistance and, to a lesser extent, decreases capacitance of blood vessels. Total peripheral resistance is increased, resulting in increased systolic and diastolic blood pressure. Pulmonary arterial pressure is usually increased, and renal blood flow is usually decreased. Local vasoconstriction and hemostasis occur following topical application or infiltration of phenylephrine into tissues.

The main effect of phenylephrine on the heart is bradycardia; it produces a positive inotropic effect on the myocardium in doses greater than those usually used therapeutically. Rarely, the drug may increase the irritability of the heart, causing arrhythmias. Cardiac output is decreased slightly. Phenylephrine increases the work of the heart by increasing peripheral arterial resistance.

Phenylephrine has a mild central stimulant effect.

Following oral administration or topical application of phenylephrine to the mucosa, constriction of blood vessels in the nasal mucosa relieves nasal congestion associated with allergy or head colds. Following oral administration, nasal decongestion may occur within 15 or 20 minutes and may persist for up to 4 hours.

ministration of promethazine has b ı ass

~~PHENYLEPHRINE~~ **Phenylephrine**
Because phenylephrine is an adrenerg
with thyroid diseases, diabetes mellitı
antidepressants.

Men with symptomatic, benign prost
when given oral nasal decongestants.

Phenylephrine can cause a decrease i
used when administering the drug, pa
to elderly individuals, and/or to patie
circulation.

Phenylephrine should be used with c
amphetamines or phenylpropanolami
result in serious hypertensive respons

~~Precautions~~ **PRECAUTIONS**
Animal reproduction studies have not
promethazine and phenylephrine. It is
cause fetal harm when administered t
acity. Phenergan VC should be gi to a

~~GENERAL~~ **General**
Promethazine should be used cautiou
impairment of liver function.

Phenylephrine should be used with c
particularly hypertension.

~~INFORMATION FOR PATIENTS~~ **I**
Phenergan VC may cause marked dro
abilities required for the performance
vehicle or operating machinery. Amb
such activities until it is known that tl
VC therapy. Children should be supe
hazardous activities.

The concomitant use of alcohol or ot
narcotic analgesics, sedatives, hypno
and should be avoided or their dosage

Patients should be advised to report a
sitivity to sunlight.

Phenylephrine is irregularly absorbed from and readily metaboliz
tract. Phenylephrine is metabolized in the liver and intestine by n
metabolites and their route and rate of excretion have not been id
pharmacologic action of phenylephrine is terminated at least part
drug into tissues.

~~Indications and Usage~~ **INDICATIONS AND USAGE**
Phenergan VC is indicated for the temporary relief of upper resp
including nasal congestion, associated with allergy or the comm

~~Contraindications~~ **CONTRAINDICATIONS**
Promethazine is contraindicated in individuals known to be hype
an idiosyncratic reaction to promethazine or to other phenothiazi

Antihistamines are contraindicated for use in the treatment of lov
symptoms or asthma.

Phenylephrine is contraindicated in patients with hypertension or
insufficiency (ischemia may result with risk of gangrene or thron
vascular beds). Phenylephrine should not be used in patients kno
to the drug or in those receiving a monoamine oxidase inhibitor (

~~Warnings~~ **WARNINGS**
~~PROMETHAZINE~~ **Promethazine**
Promethazine may cause marked drowsiness. Ambulatory patien
against such activities as driving or operating dangerous machine
they do not become drowsy or dizzy from promethazine therapy.

The sedative action of promethazine hydrochloride is additive to
central nervous system depressants; therefore, agents such as alc
sedatives, hypnotics, and tranquilizers should either be eliminate
dosage in the presence of promethazine hydrochloride. When giv
promethazine hydrochloride, the dose of barbiturates should be r
half, and the dose of analgesic depressants, such as morphine or
reduced by one-quarter to one-half.

Promethazine may lower seizure threshold. This should be taken
administering to persons with known seizure disorders or when g
with narcotics or local anesthetics which may also affect seizure
Sedative drugs or CNS depressants should be avoided in patients
apnea.

Antihistamines should be used with caution in patients with narr
stenosing peptic ulcer, pyloroduodenal obstruction, and urinary b
to symptomatic prostatic hypertrophy and narrowing of the bladd

~~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~~
~~PROMETHAZINE~~ **Carcinogenesis, Mutagenesis, Impairment of Fertility**
Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.

~~PHENYLEPHRINE~~ *Phenylephrine*
A study which followed the development of cancer in 143,574 patients over a four-year period indicated that in 11,981 patients who received phenylephrine (systemic or topical), there was no statistically significant association between the drug and cancer at any or all sites.

Long-term animal studies have not been performed to assess the carcinogenic potential of phenylephrine, nor are there other animal or human data concerning mutagenicity.
A study of the effects of adrenergic drugs on ovum transport in rabbits indicated that treatment with phenylephrine did not alter incidence of pregnancy; the number of implantations was significantly reduced when high doses of the drug were used.

~~PREGNANCY~~ **Pregnancy Category C**
Teratogenic Effects—~~Pregnancy Category C~~
PROMETHAZINE Promethazine
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 of promethazine 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.

~~PHENYLEPHRINE~~ Phenylephrine
A study in rabbits indicated that continued moderate overexposure to phenylephrine (3 mg/day) during the second half of pregnancy (22nd day of gestation to delivery) may

contribute to perinatal wastage, prematurity, premature labor, and possibly fetal anomalies; when phenylephrine (3 mg/day) was given to rabbits during the first half of pregnancy (3rd day after mating for seven days), a significant number gave birth to litters of low birth weight. Another study showed that phenylephrine was associated with anomalies of aortic arch and with ventricular septal defect in the chick embryo.

Phenergan VC 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**
Administration of phenylephrine to patients in late pregnancy or labor may cause fetal anoxia or bradycardia by increasing contractility of the uterus and decreasing uterine blood flow.

See also "*Nonteratogenic Effects*."

~~NURSING MOTHERS~~ **Nursing Mothers**
It is not known whether promethazine or phenylephrine are excreted in human milk.

Caution should be exercised when Phenergan VC 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 such 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.

xpe.ence with dialysis

~~id Administration~~ DC
umended adult dose is c
1 24 hours. For childre
)on (2.5 to 5.0 mL) rep
For children 2 years to
1.25 to 2.5 mL) every

VC is not recommend

~~plied~~ HOW SUPPLIE
® VC (Promethazine H
)range-yellow solutio

-0551-02, case of 24
-0551-03, bottle of 1

les tightly closed and
7° F).

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n light-resistant, gla

)oratories Inc.
Ayerst Company
ia, PA 19101

~~Issued July 8, 1996~~

Dermatologic—Rash, rarely photosensitivity.
Hematologic—Rarely leukopenia, thrombocytopenia; agranulocytosis (1 case).

Gastrointestinal—Nausea and vomiting.

~~PHENYLEPHRINE~~ **Phenylephrine**
Nervous System—Restlessness, anxiety, nervousness, and dizziness.

Cardiovascular—Hypertension (see "~~Warnings~~ **WARNINGS**").

Other—Precordial pain, respiratory distress, tremor, and weakness.

~~Overdosage~~ **OVERDOSAGE**
~~PROMETHAZINE~~ **Promethazine**
Signs and symptoms of overdosage with promethazine range from mild depressio central nervous system and cardiovascular system to profound hypotension, respir depression, and unconsciousness.

Stimulation may be evident, especially in children and geriatric patients. Convulsi may rarely occur. A paradoxical reaction has been reported in children receiving s doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmar

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

~~PHENYLEPHRINE~~ **Phenylephrine**
Signs and symptoms of overdosage with phenylephrine include hypertension, hea convulsions, cerebral hemorrhage, and vomiting. Ventricular premature beats and paroxysms of ventricular tachycardia may also occur. Headache may be a symptor hypertension. Bradycardia may also be seen early in phenylephrine overdosage thr stimulation of baroreceptors.

~~TREATMENT~~ **Treatment**
Treatment of overdosage with Phenergan VC is essentially symptomatic and supp Only in cases of extreme overdosage or individual sensitivity do vital signs includ respiration, pulse, blood pressure, temperature, and EKG need to be monitored. Ac charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or contro ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyt losses should be corrected. Note that any depressant effects of promethazine are nc 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 patient: partial adrenergic blockade may further lower the blood pressure.

There is no image file associated with this page.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-604/S-026

MEDICAL REVIEW(s)

MEDICAL OFFICER REVIEW

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

APPLICATION #:	08-604	**APPLICATION TYPE:**	NDA Labeling Supplement
SPONSOR:	Wyeth-Ayerst	**TRADE NAME:**	Phenergan® VC Syrup
CATEGORY:	H1 blocker & alpha agonist	**GENERIC NAME:**	promethazine/phenylephrine
		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 (#26)	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® VC Syrup, an orally administered decongestant for the upper respiratory symptoms of colds and allergy that contains promethazine and phenylephrine 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 [1:2:13-4]:

> "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) 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.

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 [1:2:13-27, 45, 62, 118-9].

III. CLINICAL TRIAL DATABASE REVIEW

The sponsor states that, "Current labeling adequately reflects the database" [2:3:341].

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 [2:4:344].

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) and 21 CFR 201.57(f)(10)(v). 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, 1:1:8]. 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 VC Syrup and observed closely."

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

cc:
NDA #08-604
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 09:28:23 AM
MEDICAL OFFICER

Marianne Mann
2/23/01 09:57:26 AM
MEDICAL OFFICER

Robert Meyer
2/23/01 03:50:52 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-604/S-026

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Project Manager's Labeling Review

NDA: 8-604/SLR-026 (Geriatric Labeling)

Product: Phenergan VC (promethazine HCl and phenylephrine HCl) 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 July 8, 1996, labeling text in the following ways:

1. The following statement was added at Lines 291-297:

   > **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 package insert.

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. The secondary subsection headings have been reformatted from an all-capital style (e.g. PROMETHAZINE) to an italicized, initial capital style (e.g. *Information for Patients*) and the tertiary subsection headings have been reformatted from an all-capital style (e.g. PROMETHAZINE) to an initial capital style (e.g. Information for Patients).

4. At Line four, the phrase "**R_x only**" has been added.

5. At Line 228, the second level subheading "Promethazine" has been inadvertently deleted.

6. At Line 246, 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.

Comments:

Comments to the above points are as follows, in their respective order:

1. The new "Geriatric Use" section is not in compliance with the Final Rule. To be in compliance with the Final Rule, the following sentence needs to be added as the second sentence of the section:

   > Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

   Additionally, since Phenergan VC is a sedating drug, in accordance with 21 CFR 201.57 (f)(10)(v) the following phrase should be considered for inclusion:

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

   Finally, the drug is inappropriately referred to as [redacted] in the first sentence of the proposed wording.

   Therefore, it is recommended the "Geriatric Use" section read as follows:

   > **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.

2. This minor change in formatting is acceptable.
3. See Comment 2.
4. This change is acceptable.
5. It appears that "Promethazine" was accidentally deleted from Line 228. It should be reinstated on Line 228, using the new second level subheading formatting rules.

6. This change is acceptable.

Recommendation:

With the concurrence of the Medical Officer, this supplement should be approved if the sponsor agrees to revise the labeling to read as follows:

1. Revise the "**Geriatric Use**" section as follows:

> **Geriatric Use**
> Clinical studies of ~~~~ 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.

2. Revise the "**Carcinogenesis, Mutagenesis, Impairment of Fertility**" section by including the subheading "*Promethazine*" prior to the first sentence of this section.

Craig Ostroff, Pharm.D. Date
Project Manager

CONCUR:

Sandy Barnes Date
Chief, Project Management Staff

/s/

Craig Ostroff
2/22/01 01:44:16 PM
CSO

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, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
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 28 2000
HFD-570

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA [illegible]-604

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
	Phenergan® VC

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 NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

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

IF AN ANDA, OR 505(b)(2), 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 ☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION To include geriatric labeling language

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 (Full establishment information should be provided in the body of the Application.)
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. Final dosage form, Stability testing) conducted ction or, if not, when it will be ready.

Pr
lo
os IN nced 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 Microbiology (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 report 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. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

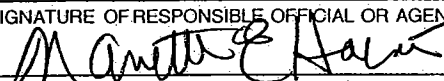
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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 Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 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 Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 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, Associate Director, Worldwide Regulatory Affairs	Aug. 25, 2000
ADDRESS *(Street, City, State, and ZIP Code)* P.O. Box 8299, Philadelphia, PA 19101		Telephone Number (610) 902-3775

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

Form Approved: OMB No. 0910-0297
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® VC Promethazine Hydrochloride and Phenylephrine Hydrochloride

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. 08-604

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)

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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 NO. 8604 REF NO. 026

NDA SUPPL FOR SLR

(Geriatric Labeling)

NDA 08-604
Phenergan® VC
(promethazine hydrochloride and phenylephrine hydrochloride)
Syrup

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 08-604 for Phenergan® VC 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® VC 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® VC 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® VC 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® VC 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:phenvcplain

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

141 CF

NDA 8-604 /S-026

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 ®VC Syrup

NDA Number: 8-604

Supplement Number: S-026

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 8604/S-026
HFD-570/Div. Files
HFD-570/CSO/Mr. Hilfiker

8/30/00

SUPPLEMENT ACKNOWLEDGEMENT