

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 8-306/S-029

Trade Name: Phenergan w/codeine syrup
Phenergran VC w/codeine

Generic Name: promethazine HCl and codeine phosphate
promethazine HCl, phenylphrine HCl and codeine
phosphate

Sponsor: Wyeth-Ayerst Research

Approval Date: February 23, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-306/S-029

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-306/S-029

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

HFD-093
Jorge

NDA 8-306/S-029

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

Best Available Copy

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 codeine (promethazine HCl and codeine phosphate) Syrup and Phenergan VC with codeine (promethazine HCl, phenylephrine 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.

For Phenergan with codeine (promethazine HCl and codeine phosphate) Syrup:

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 Codeine Syrup and observed closely.

2. At Line 19, remove the hyphen from the phrase "methylnorphinan" such that the revised chemical name for codeine phosphate would read as follows: "(5 α , 6 α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-morphinan-6-0l phosphate (1:1) (salt) hemihydrate"

For Phenergan VC with codeine (promethazine HCl, phenylephrine HCl and codeine phosphate) Syrup:

3. Revise the "Geriatric Use" subsection heading 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 with Codeine Syrup and observed closely.

4. At Lines 108 and 109, use the Greek symbols " α " and " β " in the "CLINICAL PHARMACOLOGY-Phenylephrine" section, as appropriate, in favor of using "a" (for α) and "b" (for β).

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 8-306/S-029." 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 05:39:07 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-306/S-029

APPROVED LABELING

Phenergan®
with codeine
(Promethazine Hydrochloride
and Codeine Phosphate)

5 Syrup

APPROVED

R_x only

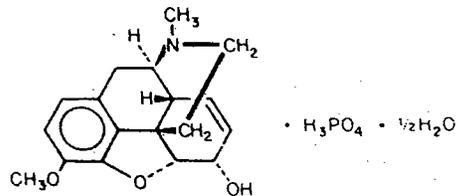
FEB 23 2001

DESCRIPTION

10 Each teaspoon (5 mL) of Phenergan with codeine contains 10 mg codeine phosphate and 6.25 mg promethazine hydrochloride in a flavored syrup base with a pH between 4.8 and 5.4. Alcohol 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C Red 33, FD&C Blue 1, FD&C Yellow 6, glycerine, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

15

Codeine is one of the naturally occurring phenanthrene alkaloids of opium derived from the opium poppy; it is classified pharmacologically as a narcotic analgesic. Codeine phosphate may be chemically named as (5 α ,6 α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol phosphate (1:1) (salt) hemihydrate with the following structural



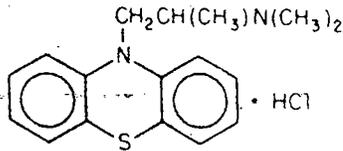
20 formula:

25 The phosphate salt of codeine occurs as white, needle-shaped crystals or white crystalline powder. Codeine phosphate is freely soluble in water and slightly soluble in alcohol, with a molecular weight of 406.37. The empirical formula is C₁₈H₂₁NO₃ · H₃PO₄ · 1/2H₂O, and the stereochemistry is 5 α , 6 α isomer as indicated in the structure.

30 Promethazine hydrochloride is a racemic compound; the empirical formula is C₁₇H₂₀N₂S·HCl and its molecular weight is 320.88.

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

35



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.

40

CLINICAL PHARMACOLOGY

Codeine

Narcotic analgesics, including codeine, exert their primary effects on the central nervous system and gastrointestinal tract. The analgesic effects of codeine are due to its central action; however, the precise sites of action have not been determined, and the mechanisms involved appear to be quite complex. Codeine resembles morphine both structurally and pharmacologically, but its actions at the doses of codeine used therapeutically are milder, with less sedation, respiratory depression, and gastrointestinal, urinary, and pupillary effects. Codeine produces an increase in biliary tract pressure, but less than morphine or meperidine. Codeine is less constipating than morphine.

45

50

Codeine has good antitussive activity, although less than that of morphine at equal doses. It is used in preference to morphine, because side effects are infrequent at the usual antitussive dose of codeine.

55

Codeine in oral therapeutic dosage does not usually exert major effects on the cardiovascular system.

60

Narcotic analgesics may cause nausea and vomiting by stimulating the chemoreceptor trigger zone (CTZ); however, they also depress the vomiting center, so that subsequent doses are unlikely to produce vomiting. Nausea is minimal after usual oral doses of codeine.

65

Narcotic analgesics cause histamine release, which appears to be responsible for wheals or urticaria sometimes seen at the site of injection on parenteral administration. Histamine release may also produce dilation of cutaneous blood vessels, with resultant flushing of the face and neck, pruritus, and sweating.

70

Codeine and its salts are well absorbed following both oral and parenteral administration. Codeine is about 2/3 as effective orally as parenterally. Codeine is metabolized primarily in the liver by enzymes of the endoplasmic reticulum, where it undergoes O-demethylation, N-demethylation, and partial conjugation with glucuronic acid. The drug is excreted primarily in the urine, largely as inactive metabolites and small amounts of free and conjugated morphine. Negligible amounts of codeine and its metabolites are found in the feces.

75

Following oral or subcutaneous administration of codeine, the onset of analgesia occurs within 15 to 30 minutes and lasts for four to six hours.

- 80 The cough-depressing action, in animal studies, was observed to occur 15 minutes after oral administration of codeine, peak action at 45 to 60 minutes after ingestion. The duration of action, which is dose-dependent, usually did not exceed 3 hours.

Promethazine

- 85 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 lack (1/10 that of chlorpromazine) of dopaminergic (CNS) action.
- 90 Promethazine is an H1 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.

- 95 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.

100 **INDICATIONS AND USAGE**

Phenergan with codeine is indicated for the temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold.

CONTRAINDICATIONS

- 105 Codeine is contraindicated in patients with a known hypersensitivity to the drug.

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

- 110 Antihistamines and codeine are both contraindicated for use in the treatment of lower respiratory tract symptoms, including asthma.

WARNINGS

Codeine

- 115 Dosage of codeine SHOULD NOT BE INCREASED if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease.

Codeine may cause or aggravate constipation.

120

Respiratory depression leading to arrest, coma, and death has occurred with the use of codeine antitussives in young children, particularly in the under-one-year infants whose ability to deactivate the drug is not fully developed.

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

Head Injury and Increased Intracranial Pressure

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

135 *Asthma and Other Respiratory Conditions*

- Narcotic analgesics or cough suppressants, including codeine, should not be used in asthmatic patients (see "CONTRAINDICATIONS"). Nor should they be used in acute febrile illness associated with productive cough or in chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on the patient's respiratory function.
- 140

Hypotensive Effect

Codeine may produce orthostatic hypotension in ambulatory patients.

145 **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.

- 150 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.
- 155

- 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.
- 160

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

165 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.

170

PRECAUTIONS

Animal reproduction studies have not been conducted with the drug combination—promethazine and codeine. It is not known whether this drug combination can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

175 Phenergan with codeine should be given to a pregnant woman only if clearly needed.

General

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

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

Information for Patients

190 Phenergan with codeine may cause marked drowsiness or may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from Phenergan with codeine therapy. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.

195 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.

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

Codeine, like other narcotic analgesics, may produce orthostatic hypotension in some ambulatory patients. Patients should be cautioned accordingly.

205 Drug Interactions

Codeine

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

210 *Promethazine*

The sedative action of promethazine is additive to the 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.

215

Drug/Laboratory Test Interactions

Because narcotic analgesics may increase biliary tract pressure, with resultant increases in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after a narcotic analgesic has been given.

220

The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:

Pregnancy Tests

225 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.

230

Carcinogenesis, Mutagenesis, Impairment of Fertility

235 Long-term animal studies have not been performed to assess the carcinogenic potential of codeine or of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with these agents. Codeine has been reported to show no evidence of carcinogenicity or mutagenicity in a variety of test systems, including the micronucleus and sperm abnormality assays and the *Salmonella* assay. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.

Pregnancy Category C

240 *Teratogenic Effects—Pregnancy Category C*

Codeine

245 A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120-mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100-mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

250 There are no studies in humans, and the significance of these findings to humans, if any, is not known.

Promethazine

255 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

260 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.

265 Phenergan[®] with codeine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

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

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

Labor and Delivery

275 Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see
280 "**OVERDOSAGE**"). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

See also "*Nonteratogenic Effects.*"

285 **Nursing Mothers**

Some studies, but not others, have reported detectable amounts of codeine in breast milk. The levels are probably not clinically significant after usual therapeutic dosage. The possibility of clinically important amounts being excreted in breast milk in individuals abusing codeine should be considered.

290 It is not known whether promethazine is excreted in human milk.

Caution should be exercised when Phenergan with codeine is administered to a nursing woman.

295 **Pediatric Use**

This product should not be used in children under 2 years of age because safety for such use has not been established.

300 **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.

305 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

Codeine

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

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

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

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

325 *Allergic*—Infrequent pruritus, giant urticaria, angioneurotic edema, and laryngeal edema.

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

Promethazine

330 *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).

335 *Cardiovascular*—Increased or decreased blood pressure.

Dermatologic—Rash, rarely photosensitivity.

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

Gastrointestinal—Nausea and vomiting.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

345 Phenergan with codeine is a Schedule V Controlled Substance.

Abuse

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

Dependence

Psychological dependence, physical dependence, and tolerance are known to occur with codeine.

OVERDOSAGE

Codeine

Serious overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. The triad of coma, pinpoint pupils, and respiratory depression is strongly suggestive of opiate poisoning. In severe overdose, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur. Promethazine is additive to the depressant effects of codeine.

It is difficult to determine what constitutes a standard toxic or lethal dose. However, the lethal oral dose of codeine in an adult is reported to be in the range of 0.5 to 1.0 gram. Infants and children are believed to be relatively more sensitive to opiates on a body-weight basis. Elderly patients are also comparatively intolerant to opiates.

Promethazine

Signs and symptoms of overdose 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.

Treatment

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

administered when significant respiratory depression occurs with Phenergan with codeine; any depressant effects of promethazine are not reversed with naloxone.

395 Diazepam may be used to control convulsions. Avoid analeptics, which may cause convulsions. Acidosis and electrolyte losses should be corrected. A rise in temperature or pulmonary complications may signal the need for institution of antibiotic therapy.

400 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.

405 **DOSAGE AND ADMINISTRATION**

The average effective dose is given in the following table:

410	Adults	1 teaspoon (5 mL) every 4 to 6 hours, not to exceed 30.0 mL in 24 hours.
	Children 6 years to under 12 years	1/2 to 1 teaspoon (2.5 to 5 mL) every 4 to 6 hours, not to exceed 30.0 mL in 24 hours.
415	Children under 6 years (weight: 18 kg or 40 lbs)	1/4 to 1/2 teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 9.0 mL in 24 hours.
	Children under 6 years (weight: 16 kg or 35 lbs)	1/4 to 1/2 teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 8.0 mL in 24 hours.
420	Children under 6 years (weight: 14 kg or 30 lbs)	1/4 to 1/2 teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 7.0 mL in 24 hours.
	Children under 6 years (weight: 12 kg or 25 lbs)	1/4 to 1/2 teaspoon (1.25 to 2.5 mL) every 4 to 6 hours, not to exceed 6.0 mL in 24 hours.

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

HOW SUPPLIED

Phenergan[®] with codeine is a clear, purple solution supplied as follows:

430 NDC 0008-0550-02, case of 24 bottles of 4 fl. oz. (118 mL).

NDC 0008-0550-03, bottle of 1 pint (473 mL).

435 **Keep tightly closed—Store at room temperature, between 15° C and 25° C (59° F and 77° F).**

Protect from light.

Dispense in light-resistant, glass, tight container.

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

CI 4868-2 Revised July 22, 1998 Printed in USA

445

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-306/S-029

MEDICAL REVIEW(s)

MEDICAL OFFICER REVIEW

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

APPLICATION #: 08-306	APPLICATION TYPE: NDA Labeling Supplement
SPONSOR: Wyeth-Ayerst	TRADE NAME: Phenergan® VC with Codeine Syrup and Phenergan® with Codeine Syrup
CATEGORY: H1 blocker & antitussive	GENERIC NAME: promethazine/ phenylephrine/ codeine and promethazine/ codeine
	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 (#29)	08/28/2000	NDA supplement	geriatric labeling

RELATED APPLICATIONS

DOCUMENT DATE	APPLICATION TYPE	COMMENTS

REVIEW SUMMARY:

There appears to be 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: _____

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I. EXECUTIVE SUMMARY

This is a fairly routine geriatric labeling supplement of Phenergan® VC (phenylephrine) With Codeine and Phenergan® With Codeine Syrups, orally administered decongestants and antitussives for the upper respiratory symptoms of colds and allergy that contain promethazine, codeine ± phenylephrine as active components [1:1:2-5]. 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 [1:2:18-9]:

"There appears to be 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:

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

cc:

NDA #08-306

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 09:33:46 AM
MEDICAL OFFICER

Marianne Mann
2/23/01 09:58:23 AM
MEDICAL OFFICER

Robert Meyer
2/23/01 05:00:59 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 8-306/S-029

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

Project Manager's Labeling Review

NDA: 8-306/SLR-029 (Geriatric Labeling)

Product: Phenergan with codeine (promethazine HCl and codeine phosphate) 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 22, 1998, labeling text in the following ways:

1. The following statement was added at Lines 300-306:

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. At Line seven, the phrase "**R_x only**" has been added.
3. At Line 19, the phrase "methyilmorphinan" is incorrect; it should be "methyl-morphinan."
4. At Line 239, 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.

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. At Line 19 of the draft labeling submitted August 25, 2000, remove the hyphen from the phrase "methyilmorphinan" such that the revised chemical name for codeine phosphate would read as follows: "(5• , 6•)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-morphinan-6-01 phosphate (1:1) (salt) hemihydrate"

Craig Ostroff, Pharm.D.
Project Manager

Date

CONCUR:

Sandy Barnes
Chief, Project Management Staff

Date

/s/

Craig Ostroff
2/22/01 01:38:10 PM
CSO

Wyeth

Wyeth Pharmaceuticals Inc.
P.O. Box 8299
Philadelphia, PA 19101-8299

Tracy Rockney
Director
Worldwide Regulatory Affairs
484-865-5879

ORIGINAL

SLR 029 FA
NDA SUPPL AMENDMENT

July 23, 2003

**Phenergan[®] with Codeine (promethazine HCl and codeine phosphate) Syrup
and Phenergan[®] VC with Codeine (promethazine HCl, phenylephrine HCl,
and codeine phosphate) Syrup
NDA No. 08-306**

Badrul Chowdhury, M.D., Ph.D.
Division of Pulmonary and Allergy Drug Products (HFD-570)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room 10B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

RECEIVED
JUL 24 2003
FDR/CDER

**“Changes Being Effected Supplement”
“FPL for Approved Supplement NDA 08-306/S-029”**

Dear Dr. Chowdhury:

Reference is made to our approved New Drug Application No. 08-306 for Phenergan[®] with Codeine (promethazine HCl and codeine phosphate) Syrup and Phenergan[®] VC with Codeine (promethazine HCl, phenylephrine HCl, and codeine phosphate) Syrup.

We are submitting final labeling for approved supplement NDA 08-306. This supplement provides revisions to the text of the CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections along with formatting changes throughout.

Wyeth

Information in this supplement is provided in duplicate sets of individual binders.
Each binder contains the following information:

Tab 1: Final labeling for Phenergan[®] with codeine (promethazine HCl and codeine phosphate) syrup physician's insert (W10428C002 ET01).

Tab 2: Final labeling for Phenergan VC with codeine (promethazine HCl, phenylephrine HCl, and codeine phosphate) syrup physician's insert (W10435C002 ET01).

Tab 3: Marked copy of Phenergan[®] with codeine (promethazine HCl and codeine phosphate) syrup physician's insert (W10428C002 ET01). Identical changes have been made to the labeling for Phenergan VC with codeine (promethazine HCl, phenylephrine HCl, and codeine phosphate) syrup.

Tab 4:

~~_____~~

Tab 5: Most current FDA-approved label for Phenergan (promethazine HCl) Injection (CI 4807-2).

Tab 6: FDA correspondence dated February 21, 1997.

Tab 7: Most current FDA-approved label for Phenergan (promethazine HCl) Tablets and Suppositories (CI 4679-8).

Tab 8: Referenced literature on Neuroleptic Malignant Syndrome.

Tab 9: FDA correspondence dated November 1, 1994.

Tab 10: FDA correspondence dated February 23, 2001.

Tab 11: Justification document: promethazine HCl overdose reports.

Tab 12:

~~_____~~

Phenergan[®] with Codeine (promethazine HCl and codeine phosphate) Syrup and Phenergan[®] VC
with Codeine (promethazine HCl, phenylephrine HCl, and codeine phosphate) Syrup

NDA No. 08-306

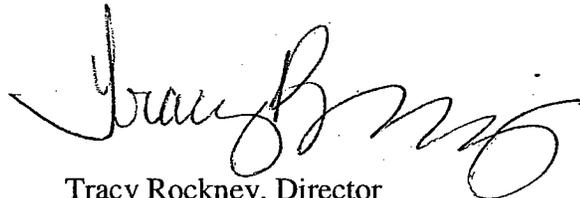
Page 3

Wyeth

To facilitate distribution of the FPL into the Division files, twenty samples of final labeling (W10428C002 ET01 and W10435C002 ET 01) are included in this submission. If you have any questions regarding this supplement, please contact me at (484) 865-5879 or Harris Rotman, PhD, Regulatory Coordinator, at (484) 865-5935.

Sincerely,

WYETH PHARMACEUTICALS INC.



Tracy Rockney, Director
Worldwide Regulatory Affairs
(484) 865-5879

HR/lw092

13 Page(s) Withheld

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

 X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

WORLDWIDE REGULATORY AFFAIRS

August 25, 2000

NDA NO. 8-306 REF NO. 009
NDA SUPPL FOR SLP Geriatric
Labeling

NDA 08-306

Phenergan® with codeine
(promethazine hydrochloride and codeine phosphate) Syrup
and Phenergan® VC with codeine (promethazine hydrochloride, phenylephrine
hydrochloride and codeine phosphate) 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 08-306 for Phenergan® with codeine Syrup and Phenergan® VC with codeine 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 codeine Syrup and Phenergan® VC with codeine Syrup to comply with the above referenced final rule. The enclosed draft package insert labeling also reflects the addition of the "Rx only" statement.

The following material is provided in support of this submission:

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

Robert Meyer, M.D., Director
NDA 08-306
August 25, 2000
Page 2

- Attachment 2:** Summary of the geriatric literature search for Phenergan® with codeine Syrup and Phenergan® VC with codeine 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 codeine Syrup and Phenergan® VC with codeine 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:phencodvcgeriatric



11-1 (F)

Food and Drug Administration
Rockville MD 20857

NDA 8-306 /S-029

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 Codeine
NDA Number:	8-306
Supplement Number:	S-029
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,

Sandy Barnes 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

NDA 8306/S-029
Page 2

cc:

Original NDA 8306/S-029

HFD-570/Div. Files

HFD-570/CSO/Mr. Hilfiker

AA 8/30/99

SUPPLEMENT ACKNOWLEDGEMENT



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

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

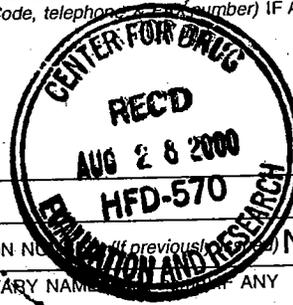
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Wyeth Laboratories	DATE OF SUBMISSION 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 number) IF APPLICABLE



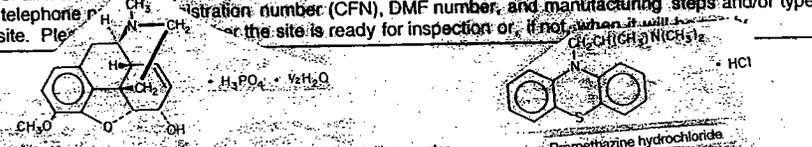
PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA No. 08-306	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name)	PROPRIETARY NAME (if any) Phenergan with codeine
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) • See Below	CODE NAME (if any)
DOSAGE FORM: Syrup	ROUTE OF ADMINISTRATION: 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)	<input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input type="checkbox"/> 505 (b)(1)	<input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION	Holder of Approved Application	
TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION
	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> PRESUBMISSION
	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> EFFICACY SUPPLEMENT	<input checked="" type="checkbox"/> LABELING SUPPLEMENT
	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY	<input type="checkbox"/> CBE	<input type="checkbox"/> CBE-30
	<input type="checkbox"/> Prior Approval (PA)	
REASON FOR SUBMISSION	To include geriatric labeling language	
PROPOSED MARKETING STATUS (check one)	<input type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED 1 in duplicate	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> 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 (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate the site is ready for inspection or, if not, when it will be.



Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and D)

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (k)(3))
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

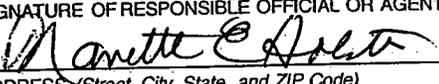
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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 Nanette E. Holston, Associate Director, Worldwide Regulatory Affairs	DATE Aug. 25, 2000
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 8299, Philadelphia, PA 19101	Telephone Number (610) 902-3775	

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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.

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

3. PRODUCT NAME
Phenergan[®] with codeine (Promethazine Hydrochloride and Codeine Phosphate)

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).

2. TELEPHONE NUMBER (Include Area Code)

(610) 902-3775

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER
NDA No. 08-306

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 COMMERCIALY (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.

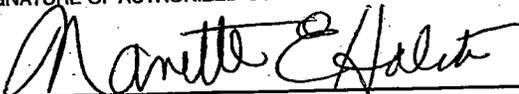
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments 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

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

DATE

August 25, 2000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Wyeth Pharmaceuticals Inc.	DATE OF SUBMISSION July 23, 2003
TELEPHONE NO. (Include Area Code) 484-865-5879	FACSIMILE (FAX) Number (Include Area Code) 484-865-6465
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 19101-8299	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE P.O. Box 8299 Philadelphia, PA 19101-8299

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA No. 08-306

ESTABLISHED NAME (e.g., Proper name, USP/USAN name): Promethazine HCl and Codeine Phosphate; Promethazine HCl, Phenylephrine HCl and Codeine Phosphate	PROPRIETARY NAME (trade name) IF ANY: Phenergan® with Codeine; Phenergan VC with Codeine	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) (5a, 6a)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-morphinan-6o1 phosphate (1:1) (salt) hemihydrate	CODE NAME (If any)	
DOSAGE FORM: Syrup	STRENGTHS: 75 mg to 125 mg	ROUTE OF ADMINISTRATION: 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 31.94)
 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 add safety information and provide FPL for S-029

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 at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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

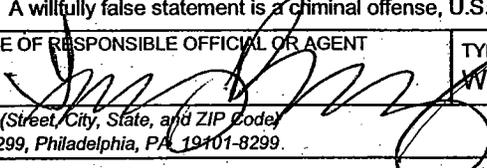
This application contains the following items: (Check all that apply)	
<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input checked="" type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50(c))
<input type="checkbox"/>	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)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k) (1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50(k) (3))
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	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 and 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 review 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: Tracy D. Rockney, Director Worldwide Regulatory Affairs	DATE July 23, 2003
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 8299, Philadelphia, PA 19101-8299.	Telephone Number (484) 865-5879	

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services Food and Drug Administration BER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	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.
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USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdofa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Wyeth Pharmaceuticals, Inc. P.O. Box 8299 Philadelphia, PA 19101-8299	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA No. 08-306
2. TELEPHONE NUMBER (Include Area Code) (484) 865-5879	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO 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: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Phenergan with Codeine, Phenergan VC with Codeine	6. USER FEE I.D. NUMBER

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

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> 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.)	<input type="checkbox"/> 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.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

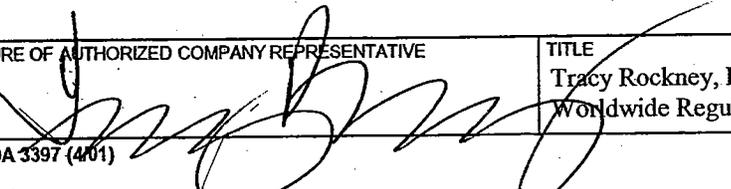
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Tracy Rockney, Director Worldwide Regulatory Affairs	DATE July 23, 2003
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