CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

8708/S-025

Trade Name: WellSpring Pharmaceutical Corporation

Generic Name: Dibenzyline

Sponsor: phenoxybenzamine hydrochloride

Approval Date: April 3, 2008

Purpose: Changes to the approved package insert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

8708/S-025

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

8708/S-025

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 8-708/S-025

WellSpring Pharmaceutical Corporation
Attention: James Booker
Director, Quality and Regulatory Affairs
9040 Town Center Parkway, Suite 205
Bradenton, FL 34202-4101

Dear Mr. Booker:

Please refer to your supplemental new drug application (NDA) dated September 14, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dibenzyline (phenoxybenzamine hydrochloride), 10 mg Capsules.

We also refer to your submission dated March 20, 2008.

This supplemental new drug application provides for the following changes to the approved package insert:

1. In the **PRECAUTIONS/Carcinogenesis and Mutagenesis** section of the package insert, changing the following text

   FROM

   Carcinogenesis and Mutagenesis
   Phenoxybenzamine hydrochloride showed *in vitro* mutagenic activity in the Ames test and mouse lymphoma assay; it did not show mutagenic activity *in vivo* in the micronucleus test in mice. In rats and mice, repeated intraperitoneal administration of phenoxybenzamine hydrochloride (three times per week for up to 52 weeks) resulted in peritoneal sarcomas. Chronic oral dosing in rats (for up to 2 years) produced malignant tumors of the small intestine and non-glandular stomach, as well as ulcerative and/or erosive gastritis of the glandular stomach. Whereas squamous cell carcinomas of the non-glandular stomach were observed at all tested doses of phenoxybenzamine hydrochloride, there was a no-observed-effect-level of 10 mg/kg for tumors (carcinomas and sarcomas) of the small intestine. This dose is, on a body surface area basis, about twice the maximum recommended human dosage of 20 mg b.i.d.

   TO (underline shows added text)

   Carcinogenesis and Mutagenesis
   Case reports of carcinoma in humans after long-term treatment with phenoxybenzamine have been reported. Hence, long-term use of phenoxybenzamine is not recommended. Carefully weigh the benefits and risks before prescribing this drug.

   Phenoxybenzamine hydrochloride showed in vitro mutagenic activity in the Ames test and mouse lymphoma assay; it did not show mutagenic activity *in vivo* in the micronucleus test in mice. In rats and mice, repeated intraperitoneal administration of phenoxybenzamine hydrochloride (three times per week for up to 52 weeks) resulted in peritoneal sarcomas. Chronic oral dosing in rats (for up to 2 years) produced malignant tumors of the small intestine and non-glandular stomach, as well as ulcerative and/or erosive gastritis of the glandular stomach. Whereas squamous cell carcinomas of the non-glandular stomach were observed at all tested doses of phenoxybenzamine hydrochloride, there was a no-observed-effect-level of 10 mg/kg for tumors (carcinomas and

sarcomas) of the small intestine. This dose is, on a body surface area basis, about twice the maximum recommended human dosage of 20 mg b.i.d.

2. In the **DOSAGE AND ADMINISTRATION** section of the package insert, changing the following text

FROM

DOSAGE AND ADMINISTRATION
The dosage should be adjusted to fit the needs of each patient. Small initial doses should be *slowly* increased until the desired effect is obtained or the side effects from blockade become troublesome. *After each increase, the patient should be observed on that level before instituting another increase.* The dosage should be carried to a point where symptomatic relief and/or objective improvement are obtained, but not so high that the side effects from blockade become troublesome.

Initially, 10 mg of Dibenzyline (phenoxybenzamine hydrochloride) twice a day. Dosage should be increased every other day, usually to 20 to 40 mg 2 or 3 times a day, until an optimal dosage is obtained, as judged by blood pressure control.

TO (underline shows added text)

DOSAGE AND ADMINISTRATION
The dosage should be adjusted to fit the needs of each patient. Small initial doses should be *slowly* increased until the desired effect is obtained or the side effects from blockade become troublesome. *After each increase, the patient should be observed on that level before instituting another increase.* The dosage should be carried to a point where symptomatic relief and/or objective improvement are obtained, but not so high that the side effects from blockade become troublesome.

Initially, 10 mg of Dibenzyline (phenoxybenzamine hydrochloride) twice a day. Dosage should be increased every other day, usually to 20 to 40 mg 2 or 3 times a day, until an optimal dosage is obtained, as judged by blood pressure control.

Long-term use of phenoxybenzamine is not recommended (see **PRECAUTIONS Carcinogenesis and Mutagenesis**).

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the enclosed electronic agreed-upon labeling text. We will transmit the SPL version of the labeling, with minor edits, received on March 25, 2008 to the National Library of Medicine for public dissemination.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Dan Brum, Pharm.D., MBA, Regulatory Health Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge

4/3/2008 07:57:35 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

8708/S-025

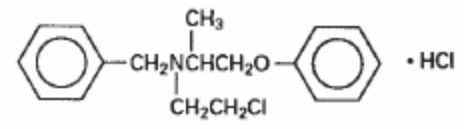
LABELING

DIBENZYLINE®
(phenoxybenzamine
hydrochloride
capsules, USP)
10 mg
adrenergic, *alpha*-receptor-
blocking agent

DESCRIPTION

Each Dibenzyline capsule, with red cap and body, is imprinted WPC 001 and 10 mg, and contains 10 mg of Phenoxybenzamine Hydrochloride USP. Inactive ingredients consist of D&C Red No. 33, FD&C Red No. 3, FD&C Yellow No. 6, Gelatin NF, Lactose NF, Sodium Lauryl Sulfate NF and Silicon Dioxide NF.

Dibenzyline is *N*-(2-Chloroethyl)-*N*-(1-methyl-2-phenoxyethyl)benzylamine hydrochloride:



Phenoxybenzamine hydrochloride is a colorless, crystalline powder with a molecular weight of 340.3, which melts between 136° and 141°C. It is soluble in water, alcohol and chloroform; insoluble in ether.

CLINICAL PHARMACOLOGY

Dibenzyline (phenoxybenzamine hydrochloride) is a long-acting, adrenergic, *alpha*-receptor-blocking agent, which can produce and maintain "chemical sympathectomy" by oral administration. It increases blood flow to the skin, mucosa and abdominal viscera, and lowers both supine and erect blood pressures. It has no effect on the parasympathetic system.

Twenty to 30 percent of orally administered phenoxybenzamine appears to be absorbed in the active form.[1]

The half-life of orally administered phenoxybenzamine hydrochloride is not known; however, the half-life of intravenously administered drug is approximately 24 hours. Demonstrable effects with intravenous administration persist for at least 3 to 4 days, and the effects of daily administration are cumulative for nearly a week.[1]

INDICATION AND USAGE

Dibenzyline is indicated in the treatment of pheochromocytoma, to control episodes of hypertension and sweating. If tachycardia is excessive, it may be necessary to use a *beta*-blocking agent concomitantly.

CONTRAINDICATIONS

Conditions where a fall in blood pressure may be undesirable; hypersensitivity to the drug or any of its components.

WARNING

Dibenzyline-induced *alpha*-adrenergic blockade leaves *beta*-adrenergic receptors unopposed. Compounds that stimulate both types of receptors may, therefore, produce an exaggerated hypotensive response and tachycardia.

PRECAUTIONS

General–Administer with caution in patients with marked cerebral or coronary arteriosclerosis or renal damage. Adrenergic blocking effect may aggravate symptoms of respiratory infections.

Drug Interactions[2]–Dibenzyline (phenoxybenzamine hydrochloride) may interact with compounds that stimulate both *alpha*- and *beta*-adrenergic receptors (i.e., epinephrine) to produce an exaggerated hypotensive response and tachycardia. (See WARNING.)

Dibenzyline blocks hyperthermia production by levarterenol, and blocks hypothermia production by reserpine.

Carcinogenesis and Mutagenesis

Case reports of carcinoma in humans after long-term treatment with phenoxybenzamine have been reported. Hence long-term use of phenoxybenzamine is not recommended.[3, 4] Carefully weigh the benefits and risks before prescribing this drug.

Phenoxybenzamine hydrochloride showed *in vitro* mutagenic activity in the Ames test and mouse lymphoma assay; it did not show mutagenic activity *in vivo* in the micronucleus test in mice. In rats and mice, repeated intraperitoneal administration of phenoxybenzamine hydrochloride (three times per week for up to 52 weeks) resulted in peritoneal sarcomas. Chronic oral dosing in rats (for up to 2 years) produced malignant tumors of the small intestine and non-glandular stomach, as well as ulcerative and/or erosive gastritis of the glandular stomach. Whereas squamous cell carcinomas of the non-glandular stomach were observed at all tested doses of phenoxybenzamine hydrochloride, there was a no-observed-effect-level of 10 mg/kg for tumors (carcinomas and sarcomas) of the small intestine. This dose is, on a body surface area basis, about twice the maximum recommended human dosage of 20 mg b.i.d.

Pregnancy - Teratogenic Effects– Pregnancy Category C

Adequate reproductive studies in animals have not been performed with Dibenzyline (phenoxybenzamine hydrochloride). It is also not known whether Dibenzyline can cause fetal

harm when administered to a pregnant woman. Dibenzyline should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from phenoxybenzamine hydrochloride, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The following adverse reactions have been observed, but there are insufficient data to support an estimate of their frequency.

Autonomic Nervous System*: Postural hypotension, tachycardia, inhibition of ejaculation, nasal congestion, miosis.

*These so-called “side effects” are actually evidence of adrenergic blockade and vary according to the degree of blockade.

Miscellaneous: Gastrointestinal irritation, drowsiness, fatigue.

OVERDOSAGE

SYMPTOMS - These are largely the result of blocking of the sympathetic nervous system and of the circulating epinephrine. They may include postural hypotension, resulting in dizziness or fainting; tachycardia, particularly postural; vomiting; lethargy; shock.

TREATMENT

When symptoms and signs of overdosage exist, discontinue the drug. Treatment of circulatory failure, if present, is a prime consideration. In cases of mild overdosage, recumbent position with legs elevated usually restores cerebral circulation. In the more severe cases, the usual measures to combat shock should be instituted. Usual pressor agents are *not* effective. Epinephrine is contraindicated because it stimulates both *alpha*- and *beta*- receptors; since *alpha*- receptors are blocked, the net effect of epinephrine administration is vasodilation and a further drop in blood pressure (epinephrine reversal).

The patient may have to be kept flat for 24 hours or more in the case of overdose, as the effect of the drug is prolonged. Leg bandages and an abdominal binder may shorten the period of disability.

I.V. Infusion of levarterenol bitartrate** may be used to combat severe hypotensive reactions, because it stimulates *alpha*- receptors primarily. Although Dibenzyline (phenoxybenzamine hydrochloride) is an *alpha*-adrenergic blocking agent, a sufficient dose of levarterenol bitartrate will overcome this effect.

The oral LD_{50} for phenoxybenzamine hydrochloride is approximately 2000 mg/kg in rats and approximately 500 mg/kg in guinea pigs.

DOSAGE AND ADMINISTRATION

The dosage should be adjusted to fit the needs of each patient. Small initial doses should be *slowly* increased until the desired effect is obtained or the side effects from blockade become troublesome. *After each increase, the patient should be observed on that level before instituting another increase*. The dosage should be carried to a point where symptomatic relief and/or objective improvement are obtained, but not so high that the side effects from blockade become troublesome.

Initially, 10 mg of Dibenzyline (phenoxybenzamine hydrochloride) twice a day. Dosage should be increased every other day, usually to 20 to 40 mg 2 or 3 times a day, until an optimal dosage is obtained, as judged by blood pressure control.

Long-term use of phenoxybenzamine is not recommended (see **PRECAUTIONS Carcinogenesis and Mutagenesis).**

STORAGE

Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°- 86°F) [See USP Controlled Room Temperature].

HOW SUPPLIED

Dibenzyline (phenoxybenzamine hydrochloride) capsules, 10 mg, in bottles of 100 (NDC 65197-001-01).

REFERENCES

1. Weiner, N.: Drugs That Inhibit Adrenergic Nerves and Block Adrenergic Receptors, in Goodman, L., and Gilman, A., *The Pharmacological Basis of Therapeutics*, ed. 6, New York, Macmillan Publishing Co., 1980, p. 179; p. 182.

2. Martin, E.W.: *Drug Interactions Index 1978/1979*, Philadelphia, J.B. Lippincott Co., 1978, pp. 209-210.

3. Nettesheim O, Hoffken G, Gahr M, Breidert M: Haematemesis and dysphagia in a 20-year-old woman with congenital spine malformation and situs inversus partialis [German]. Zeitschrift fur Gastroenterologie. 2003;41(4):319-24.

4. Vaidyanathan S, Mansour P, Soni BM, Hughes PL, Singh G: Chronic lymphocytic leukaemia, synchronous small cell carcinoma and squamous neoplasia of the urinary bladder in a paraplegic man following long-term phenoxybenzamine therapy. Spinal Cord. 2006;44(3):188-91.

** Available as Levophed® Bitartrate (brand of norepinephrine bitartrate) from Abbott Laboratories.

DATE OF ISSUANCE MARCH 2008

Manufactured for

WellSpring Pharmaceutical Corporation

Bradenton, FL 34202-4101 USA

By WellSpring Pharmaceutical

Canada Corp.

Oakville, Ontario L6H 1M5 Canada

DIB250L1

Rev. 03/08

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

8708/S-025

OTHER REVIEW(S)

PM Review of Draft Electronic Labeling and SPL

Application:	NDA 8-708/S-025 Dibenzyline (phenoxybenzamine HCl) 10 mg Capsules
Applicant:	WellSpring Pharmaceutical Corporation
Original Letter/Receipt Date:	September 14, 2007/September 17, 2007
Amendment Letter/Receipt:	March 20, 2008/March 25, 2008
Submission Type:	Labeling Supplement (CBE)
Date of Review:	March 6, 2008; revised March 12, 2008 & March 31, 2008

Background:

An NDA for Dibenzyline (phenoxybenzamine) was approved on January 26, 1953 and the drug is indicated for the "treatment of pheochromocytoma, to control episodes of hypertension and sweating."

On September 14, 2007, WellSpring submitted a Changes Being Effected (CBE) labeling supplement (S-025) requesting approval to update the **PRECAUTIONS**/**Carcinogenesis and Mutagenesis** section of the package insert. The sponsor provided the Agency with two case reports from the literature describing an association of their drug and human carcinoma to support their recommendations.

Sponsor's proposed changes to the Package Insert

At the end of the **PRECAUTIONS/Carcinogenesis and Mutagenesis** section of the package insert, the sponsor has added the following text:

> "Case reports of carcinoma in humans after long-term treatment with phenoxybenzamine have been reported. Hence, long-term use of phenoxybenzamine is not recommended. The Physician should carefully weigh the benefit to risk ratio before prescribing this drug."

Agency Reviews:

- Dr. Williams suggests adding the following text to the PI: "Prolonged use of this drug may predispose to malignancy in humans". He recommends adding the text either to the clinical section or perhaps to a section other than the **Carcinogenesis and Mutagenesis** section of the label *(Note: There is no "Clinical Section" in the label).*

- Dr. DeFelice recommends adding the text to the **Carcinogenesis and Mutagenesis** section of the labeling, however, he notes that the text should precede the animal findings.

- Dr. Southworth's review, dated March 6, 2008, recommends adding the sponsor's proposed text to the beginning of the **Carcinogenesis and Mutagenesis** section of the labeling as well as adding the following sentence to the **DOSAGE AND ADMINISTRATION** section of the PI: "Long-term use of phenoxybenzamine is not recommended." Her review included a search of the AERS database that identified three additional cases of cancer in patients taking phenoxybenzamine (the sponsor provided the Agency with two cases unique from those found in AERS). It should be noted that phenoxybenzamine is classified as "reasonably anticipated to be a human carcinogen" by the National Toxicology Program of the Department of Health and Human Services.

- Drs. Karkowsky and DeFelice concur with the comments in Dr. Southworth's review. During an internal meeting held March 6, 2008, we further suggested removing the following three words from the sponsor's original proposal, "The Physician should…" (please see below for details).

Agency's proposed changes to the PI

1. In the **PRECAUTIONS/Carcinogenesis and Mutagenesis** section of the package insert, the Agency proposes changing the text

   FROM

   Carcinogenesis and Mutagenesis
   Phenoxybenzamine hydrochloride showed *in vitro* mutagenic activity in the Ames test and mouse lymphoma assay; it did not show mutagenic activity *in vivo* in the micronucleus test in mice. In rats and mice, repeated intraperitoneal administration of phenoxybenzamine hydrochloride (three times per week for up to 52 weeks) resulted in peritoneal sarcomas. Chronic oral dosing in rats (for up to 2 years) produced malignant tumors of the small intestine and non-glandular stomach, as well as ulcerative and/or erosive gastritis of the glandular stomach. Whereas squamous cell carcinomas of the non-glandular stomach were observed at all tested doses of phenoxybenzamine hydrochloride, there was a no-observed-effect-level of 10 mg/kg for tumors (carcinomas and sarcomas) of the small intestine. This dose is, on a body surface area basis, about twice the maximum recommended human dosage of 20 mg b.i.d.

   TO (underline shows added text)

   Carcinogenesis and Mutagenesis
   Case reports of carcinoma in humans after long-term treatment with phenoxybenzamine have been reported. Hence, long-term use of phenoxybenzamine is not recommended. Carefully weigh the benefits and risks before prescribing this drug.

   Phenoxybenzamine hydrochloride showed in vitro mutagenic activity in the Ames test and mouse lymphoma assay; it did not show mutagenic activity *in vivo* in the micronucleus test in mice. In rats and mice, repeated intraperitoneal administration of phenoxybenzamine hydrochloride (three

times per week for up to 52 weeks) resulted in peritoneal sarcomas. Chronic oral dosing in rats (for up to 2 years) produced malignant tumors of the small intestine and non-glandular stomach, as well as ulcerative and/or erosive gastritis of the glandular stomach. Whereas squamous cell carcinomas of the non-glandular stomach were observed at all tested doses of phenoxybenzamine hydrochloride, there was a no-observed-effect-level of 10 mg/kg for tumors (carcinomas and sarcomas) of the small intestine. This dose is, on a body surface area basis, about twice the maximum recommended human dosage of 20 mg b.i.d.

2. In the **DOSAGE AND ADMINISTRATION** section of the package insert, the Agency proposes changing the text

FROM

DOSAGE AND ADMINISTRATION
The dosage should be adjusted to fit the needs of each patient. Small initial doses should be *slowly* increased until the desired effect is obtained or the side effects from blockade become troublesome. *After each increase, the patient should be observed on that level before instituting another increase*. The dosage should be carried to a point where symptomatic relief and/or objective improvement are obtained, but not so high that the side effects from blockade become troublesome.

Initially, 10 mg of Dibenzyline (phenoxybenzamine hydrochloride) twice a day. Dosage should be increased every other day, usually to 20 to 40 mg 2 or 3 times a day, until an optimal dosage is obtained, as judged by blood pressure control.

TO (underline shows added text)

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The dosage should be adjusted to fit the needs of each patient. Small initial doses should be *slowly* increased until the desired effect is obtained or the side effects from blockade become troublesome. *After each increase, the patient should be observed on that level before instituting another increase*. The dosage should be carried to a point where symptomatic relief and/or objective improvement are obtained, but not so high that the side effects from blockade become troublesome.

Initially, 10 mg of Dibenzyline (phenoxybenzamine hydrochloride) twice a day. Dosage should be increased every other day, usually to 20 to 40 mg 2 or 3 times a day, until an optimal dosage is obtained, as judged by blood pressure control.

Long-term use of phenoxybenzamine is not recommended (see **PRECAUTIONS Carcinogenesis and Mutagenesis**).

Conclusion: On March 12, 2008, the sponsor agreed to the Agency's proposed modifications to the original supplement (via electronic correspondence). Therefore, the sponsor submitted revised SPL on March 20, 2008 which will be transmitted to the NLM. An approval letter with the agreed-upon labeling changes has been drafted for Dr. Stockbridge's signature.

Dan Brum, Pharm.D.
Regulatory Health Project Manager
Revised: March 31, 2008

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/s/

Dan Brum
4/2/2008 11:07:49 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

8708/S-025

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE/DDRE/Cheryl Wiseman**	FROM: Dan Brum, Regulatory Project Manager Division of Cardiovascular and Renal Products (DCRP)

DATE January 9, 2008	IND NO.	NDA NO. 8-708/S-025	TYPE OF DOCUMENT Labeling Supplement	DATE OF DOCUMENT 9/14/07

NAME OF DRUG Dibenzyline (phenoxybenzamine)	PRIORITY CONSIDERATION Medium	CLASSIFICATION OF DRUG Alpha-blocker	DESIRED COMPLETION DATE 2/15/08

NAME OF FIRM: sanofi-aventis

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
X OTHER *(SPECIFY BELOW)*:
AERS search

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
X CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor submitted a CBE labeling supplement to update the **Carcinogenesis and Mutagenesis** section under the **PRECAUTIONS** section of the Debenzyline (phenoxybenzamine HCl) package insert. The sponsor states that there have been reports of carcinoma in humans with long-term use of phenoxybenzimine (two literature case reports of carcinoma in humans). DCRP had a meeting on 1/8/08 to discuss the sponsor's proposal. The Division agrees that the information should be added to the label, but has not determined the most appropriate place for such information (e.g., Warnings section). In addition to the 2 case reports cited by the sponsor, are we able to find other reports of cancer associated with chronic use of this drug? Also, is MEA associated with these cancers?

Please let me know what else you may need. Thanks!

SIGNATURE OF REQUESTER Daniel Brum, 301-796-0578	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Dan Brum
1/9/2008 02:45:10 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 08-708/S-025 **CBE-30/CBE-0 SUPPLEMENT**

WellSpring Pharmaceutical Corporation
Attention: James Booker
Director, Quality and Regulatory Affairs
9040 Town Center Parkway, Suite 205
Bradenton, FL 34202-4101

Dear Mr. Booker:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Dibenzyline® (phenoxybenzamine HCI)

NDA Number: 08-708

Supplement number: S-025

Date of supplement: September 14, 2007

Date of receipt: September 17, 2007

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes to change the Carcinogenesis and Mutagenesis section under the Precautions section of the Dibenzyline® (phenoxybenzamine HCI) package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 16, 2007 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Mr. Dan Brum, Pharm.D.
Regulatory Health Project Manager
(301) 796 0578

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm

10/30/2007 10:41:06 AM