CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

8-708/S023

Trade Name: Dibenzyline 10mg

Generic Name: Phenoxybenzamine HCL

Sponsor: Wellspring Pharmaceutical Corporation

Approval Date: December 30, 2003

Indications: 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.

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APPLICATION NUMBER:

8-708/S023

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APPLICATION NUMBER:

8-708/S023

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 8-708/S-023

Wellspring Pharmaceutical Corporation
Attention: Mr. Drew Karlan
1430 Highway 34
Neptune, NJ 07753-6807

Dear Mr. Karlan:

Please refer to your supplemental new drug application dated August 29, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dibenzyline (phenoxybenzamine HCl) 10 mg Capsules.

We acknowledge receipt of your submissions dated September 4 and November 14 and 18, 2003.

This supplemental new drug application provides for draft labeling revised to remove the following statements from the container label:

> **Warning**: Potent drug- Not to be used except under close supervision of a physician.
>
> **Important**: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

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 agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling dated November 18, 2003.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 8-708/S-023." Approval of this submission by FDA is not required before the labeling is used.

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, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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:

Ms. Melissa Robb
Regulatory Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton
12/30/03 11:59:39 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

8-708/S023

LABELING

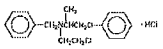
6202-N

Rx only
Prescribing Information

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

DESCRIPTION
Each Dibenzyline capsule, with red cap and body, is imprinted WPC 601 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 levadopa, and blocks hypothermia production by reserpine.

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. Cecalc 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 800 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.

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.

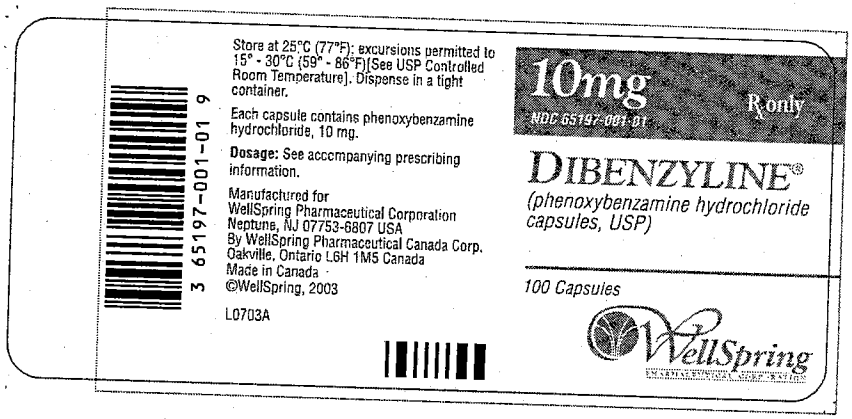
** Available as Levophed® Bitartrate (brand of norepinephrine bitartrate) from Abbott Laboratories.

DATE OF ISSUANCE 2004

Manufactured for
WellSpring Pharmaceutical Corporation
Neptune, NJ 07753-6807 USA
By WellSpring Pharmaceutical Canada Corporation
Oakville, Ontario L6H 1M5 Canada

DIB250L1

Rev. 04/04


3 65197-001-01 9
Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F)[See USP Controlled Room Temperature]. Dispense in a tight container.
Each capsule contains phenoxybenzamine hydrochloride, 10 mg.
Dosage: See accompanying prescribing information.
Manufactured for
WellSpring Pharmaceutical Corporation
Neptune, NJ 07753-6807 USA
By WellSpring Pharmaceutical Canada Corp.
Oakville, Ontario L6H 1M5 Canada
Made in Canada
©WellSpring, 2003
L0703A
10mg
NDC 65197-001-01
Rx only
DIBENZYLINE®
(phenoxybenzamine hydrochloride capsules, USP)
100 Capsules
WellSpring

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

8-708/S023

OTHER REVIEW(S)

RHPM Review of Draft Labeling
NDA 8-708/S-023

Date of Submission:	November 18, 2003
Date of Review:	November 20, 2003
Applicant Name:	Wellspring Pharmaceutical Corporation
Product Name:	Dibenzyline (phenoxybenzamine HCl) 10 mg Capsules

Evaluation:
This submission provides for draft labeling revised to remove the following statements from the container label as they are common sense and have become standard of care:

> **Warning**: Potent drug- Not to be used except under close supervision of a physician.
>
> **Important**: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Recommendation:
An approval on draft letter should be issued for this supplement as set forth under 21 CFR 314.70 (b) (3) [Any change in labeling].

Melissa Robb, RHPM

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/s/

Melissa Robb
12/30/03 03:46:09 PM
CSO

RHPM Review of Final Printed Labeling
NDA 8-708/S-023

Date of Submission:	September 22, 2004
Date of Review:	June 6, 2005
Applicant Name:	Wellspring Pharmaceutical Corporation
Product Name:	Dibenzyline (phenoxybenzamine HCl) 10 mg Capsules

Evaluation:
This submission includes the final printed container labeling in response to the approval on draft letter issued for this supplement dated December 30, 2003.

The following statements were removed from the label as noted in the approval on draft letter:

Warning: Potent drug- Not to be used except under close supervision of a physician.

Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

In addition, the following changes were also noted on the container label:

1. The manufacturing information was changed from:

(b) (4)

To:

Manufactured for
WellSpring Pharmaceutical Corporation
Neptune, NJ 07753-6807 USA
By WellSpring Pharmaceutical Canada Corp.
Oakville, Ontario L6H 1M5 Canada
Made in Canada
©WellSpring, 2003

L0703A

2. The title was changed from:

DIBENZYLINE®
PHENOXYBENZAMINE
HYDROCHLORIDE
CAPSULES

To:

DIBENZYLINE®
(phenoxybenzamine hydrochloride capsules, USP)

Per Dr. Srinivasachar, both of these changes are acceptable. The change in manufacturing site was approved in S-024.

Recommendation:
An acknowledge and retain letter should be issued for this supplement.

Melissa Robb, RHPM

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/s/

Melissa Robb
6/22/05 10:38:57 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

8-708/S023

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 8-708/S-023

WellSpring Pharmaceutical Corporation
Attention: Mr. Drew Karlan
1430 Highway 34
Neptune, NJ 07753-6807

Dear Mr. Karlan:

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 hydrochloride) 10 mg Capsules

NDA Number: 8-708

Supplement number: 023

Date of supplement: August 29, 2003

Date of receipt: September 3, 2003

This supplemental application proposes to remove the following statements from the package insert:

- "**Warning:** Potent drug – not to be used except under the close supervision of a physician."
- "**Important:** Use safety closure when dispensing this product unless otherwise directed by physician or requested by purchaser."

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 2, 2003, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Zelda McDonald
9/9/03 11:00:31 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 8-708\S-023

WellSpring Pharmaceutical Corporation
Attention: Mr. Drew Karlan
Vice President, Regulatory & Quality Affairs
1430 Highway 34
Neptune, NJ 07753-6807

Dear Mr. Karlan:

We acknowledge receipt of your September 22, 2004 submission containing final printed labeling in response to our December 30, 2003 letter approving your supplemental new drug application for Dibenzyline (phenoxybenzamine hydrochloride) 10 mg Capsules.

We have reviewed the container labeling that you submitted in accordance with our December 30, 2003 letter and we find it acceptable.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge
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