



NDA 8-708/S-022

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 April 3, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dibenzylamine (phenoxybenzamine HCl) 10 mg Capsules.

We acknowledge receipt of your submissions dated July 17, 2002 and October 7, 2002. Your submission of October 7, 2002 constituted a complete response to our July 15, 2002 action letter.

This supplemental new drug application provides for final printed labeling (FPL) revised as follows:

1. The unbolding of the Carcinogenesis and Mutagenesis section of the labeling.
2. The revision of the Carcinogenesis and Mutagenesis section as requested in the approvable letter from the Division dated July 15, 2002 to:

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.

3. The revision of the "Description", "Indications and Usage", and "Carcinogenicity, Mutagenesis, Impairment of Fertility" sections as requested in the Agency's May 27, 1987 letter to SmithKline & French (now GlaxoSmithKline) who had not complied with the Agency's request.

The following additional changes were noted:

1. The addition of a STORAGE section, revised as requested in the approvable letter from the Division dated July 15, 2002 to:

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

2. The second footnote has been changed from:

**Available as Levophed Bitartrate (brand of norepinephrine bitartrate) from Sanofi Winthrop Pharmaceuticals.

To:

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

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling submitted on October 7, 2002.

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, 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, 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
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