



NDA 19-839/S-043
NDA 20-990/S-009

Pfizer Pharmaceuticals
Attention: Alan Dunbar
Drug Regulatory Affairs
235 East 42nd Street
New York, NY 10017-3184

Dear Mr. Dunbar:

Please refer to your supplemental new drug applications dated December 10, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft (sertraline hydrochloride) 25 mg, 50 mg, and 100 mg tablets (19-839) and 20 mg/ml oral concentrate (20-990).

We additionally refer to an Agency approvable letter dated June 24, 2001 for the above applications.

We acknowledge receipt of your complete response dated September 6, 2002.

These "Prior Approval" supplemental new drug applications provide for revisions to labeling to incorporate the study results from Study A0501007 entitled, "Phase 1 Open Study Designed to Determine the Potential Interaction of Sertraline with Cisapride or Pimozide in Healthy Male and Female Subjects" and also the final study report for Study R-0498 (sertraline-terfenadine interaction study).

We have completed the review of your proposed modifications to our requested labeling revisions, and they are acceptable. Therefore, adequate information has been presented to demonstrate that the drug product is safe and effective for use as agreed upon and stated below. Accordingly, these supplemental applications are approved effective on the date of this letter.

Below are the agreed upon labeling revisions. Double underline font denotes additions to the labeling.

Under **CONTRAINDICATIONS**:

All Dosage Forms of Zoloft:

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**). Concomitant use in patients taking pimozide is contraindicated (see **PRECAUTIONS**).

[Section continues unchanged.]

Under **PRECAUTIONS-Drug Interactions-CNS Active Drugs**

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Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. In a controlled study of a single dose (2 mg) of pimozone, 200 mg sertraline (q.d.) co-administration to steady state was associated with a mean increase in pimozone AUC and C_{max} of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozone dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozone and due to the interaction noted at a low dose of pimozone, concomitant administration of Zoloft and pimozone should be contraindicated (see **CONTRAINDICATIONS**).

[Section continues unchanged.]

Under **PRECAUTIONS-Drug Interactions-Drugs Metabolized by P450 3A4**

In two separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline co-administration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. In three separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (q.d.) induces the metabolism of cisapride (cisapride AUC and C_{max} were reduced by about 35%).

Your proposed Dear Healthcare Practitioner (DHCP) letter to warn practitioners of these important labeling changes is acceptable. However, the Healthcare Provider letter regards a new contraindication. Thus, it would be considered an Important Drug Warning (See 21 CFR § 200.5).

At the time that this letter issues to health care practitioners, we request that you submit a copy of the letter and labeling to this NDA (see paragraph below regarding final printed labeling), the electronic document room, and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Additionally, we note your concern that this interaction may be a selective serotonin reuptake inhibitor (SSRI) class effect with pimozone and, therefore, other marketed SSRIs should be requested to investigate this interaction further. We concur with your concern, and we will request that other SSRI sponsors investigate this interaction. (Please note that the fluvoxamine labeling already carries a contraindication for concomitant pimozone.)

Please submit the copies of final printed labeling (FPL) electronically to each application 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 heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements 19-839/S-043 and 20-990/S-009" Approval of these submissions by FDA is not required before the labeling is used.

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 Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug 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/

Russell Katz
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