DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

FACSIMILE AND
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. William C. Steere, Jr.
Chairman of the Board & CEO
Pfizer, Inc.
235 East 42nd Street
New York, New York 10017 - 5755

APPEARS THIS WAY
ON ORIGINAL

RE: NDA 20-760

Dear Mr. Steere:

The Food and Drug Administration (FDA) was recently alerted through MedWatch and other public sources that Trovan™ I.V. (alatrofloxacin mesylate injection) is incompatible with 0.9% Sodium Chloride Injection, USP, commonly referred as normal saline (NS), and that the labeling for Trovan I.V. fails to contain any reference to this information. As summarized below, FDA believes that you are in violation of Sections 502(a), 502(f), and 201(n) of the Federal Food, Drug and Cosmetic Act (the Act), and federal regulations governing new drug applications and the labeling of new drugs.

(1) The NDA for Trovan I.V. failed to include complete information necessary to assure the stability of the drug, as required by 21 CFR 314.50(d)(1)(i) and (ii).

Information was available prior to NDA submission regarding the compatibility of trofloxacin and alatrofloxacin mesylate in normal saline; nevertheless this information was excluded from the NDA submission. 21 CFR 314.50(d)(1)(i) states that an applicant must provide "...description of the drug substance including ... such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance." In addition, 21 CFR 314.50(d)(1)(ii) states that an applicant must provide "...such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including, for example, specifications relating to...stability data...."

(2) The labeling of Trovan I.V. fails to include all "... essential information on drug incompatibilities if the drug is mixed *in vitro* with other drugs ...," as required by 21 CFR 201.57(j) [Dosage and Administration].

You failed to reveal in the labeling for Trovan I.V. that normal saline is contraindicated as a diluent. Furthermore, you failed to warn that use of Trovan I.V. with normal saline, a commonly used large volume parenteral drug, could result in precipitation of the drug and potentially subtherapeutic levels of Trovan I.V.

In a facsimile correspondence dated September 22, 1998, Pfizer representatives stated that studies evaluating the compatibility of Trovan I.V. with normal saline, were completed in January 1995. These studies indicated that Trovan I.V. had "limited solubility in this diluent. Solubility results of mg/mL and mg/mL (as trovafloxacin) were reported at 5° C and 30° C, respectively. The precipitate isolated from these solubility studies was determined to be the hydrochloride salt of alatrofloxacin." A subsequent exploratory admixture compatibility study using 0.9% Sodium Chloride Injection, USP as a diluent and a 2 mg/mL drug concentration of alatrofloxacin mesylate was also completed, which found that "[a]fter storage under refrigeration for 7 days, this dilution had formed a visibly detectable precipitate . . . Because precipitation had occurred (and therefore incompatibility demonstrated), no additional analyses were conducted . . ."

In the same correspondence, Pfizer representatives admit that "[s]ince the results obtained indicated that normal saline is not an appropriate diluent for [Trovan I.V.], normal saline solution was intentionally excluded from the list of acceptable diluents in the package insert."

It should be noted that information concerning the compatibility of Trovan I.V. with normal saline was included in the European Agency for Evaluation of Medicinal Product's "Summary of Product Characteristics." This would be comparable to U.S. product labeling. Nevertheless, the U.S. labeling failed to include information about the incompatibility of Trovan I.V. with normal saline.

(3) Based on points (1) and (2) above, Trovan I.V. is misbranded within the meaning of Section 502(f) of the Act, in that its labeling fails to bear "...adequate directions for use; and ...adequate warnings...against unsafe dosage or methods or duration of administration..., in such manner and form, as are necessary for the protection of users...". In addition, the drug product is misbranded under 502(a) and 201(n) of the Act in that its labeling is misleading.

The labeling for Trovan I.V. must be modified immediately, by incorporating the following language into your existing label.

Please add to the "**DOSAGE AND ADMINISTRATION**" section, immediately following the "**Compatible Intravenous Solutions:**" subsection in bold typeface the following sentence:

> **TROVAN I.V. should not be diluted with 0.9% Sodium Chloride Injection, USP (normal saline), alone or in combination with other diluents. A precipitate may form under these conditions. The compatibility of TROVAN I.V. and Lactated Ringer's is not known.**

A "Changes Being Effected Supplement" under 21 CFR 314.70(c)(2)(iii) must be submitted to your NDA at the time of your labeling change.

Pfizer representatives have indicated their willingness to notify health care professionals about the incompatibility of Trovan I.V. with normal saline, but have asked to delay this action until additional *in vitro* studies have been completed. This is unacceptable. This information has been available since January 1995. FDA can find no compelling reason why Pfizer should continue to delay notifying health care professionals about this important incompatibility. We therefore request that you issue a Dear Health Care Professional letter as soon as possible with revised labeling. The format for this letter is attached. We also bring your attention to the general provisions for mailing of important information about drugs contained in 21 CFR 200.5. A follow-up to your first letter may be sent when the results of these studies become available.

You have failed to submit information in a complete and timely manner consistent with the regulations. This information is relevant to the safe and appropriate use of this human drug product. Within 15 calendar days of your receipt of this letter, you must notify us in writing of the corrective actions you have taken or plan to take to prevent similar violations.

Your written response and any pertinent documentation must be addressed to:

Stephanie R. Gray, M.P.H.
Director
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place, HFD-300
Rockville, Maryland 20855

Your failure to adequately, and promptly correct, these matters may result in regulatory action without further notice. This letter does not represent a final action and does not preclude any additional regulatory action.

We note that Pfizer has received numerous warning letters for a broad range of problems related to Pfizer drug products. Generally, these problems have been for delays and failure to provide required information to FDA, or for providing misinformation to health professionals. We would like to discuss this matter with you in person. Please contact my secretary, Devota Herbert, at (301) 594-5401, to schedule an appointment.

Sincerely,

/S/

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Enclosure:
Dear Health Care Professional Letter

APPEARS THIS WAY
ON ORIGINAL

[Pfizer Logo/Letterhead]

APPEARS THIS WAY
ON ORIGINAL

IMPORTANT CORRECTION OF DRUG INFORMATION

APPEARS THIS WAY
ON ORIGINAL

December XX, 1998

Dear Health Care Professional:

Recently it has been brought to the attention of the Food and Drug Administration, that the labeling for TROVAN™ I.V. (alatrofloxacin mesylate injection) fails to include information on the incompatibility of alatrofloxacin mesylate injection with 0.9% sodium chloride injection, USP (normal saline solution). Over the next few months while Pfizer continues to conduct *in vitro* studies to better define the issue of incompatibility and to assess the therapeutic impact of this incompatibility, health care professionals should use extra caution when preparing TROVAN™ I.V. for intravenous infusion. In addition, health care professionals should use caution when selecting a solution to flush intravenous tubing following the administration of TROVAN™ I.V.

Based on this information, Pfizer has revised the DOSAGE and ADMINISTRATION section of the TROVAN™ I.V. labeling to include the following information:

> **TROVAN I.V. should not be diluted with 0.9% Sodium Chloride Injection, USP (normal saline), alone or in combination with other diluents. A precipitate may form under these conditions. The compatibility of TROVAN I.V. and Lactated Ringer's is not known.**

Health Care Professionals should follow the instructions included in the attached REVISED LABELING when preparing alatrofloxacin mesylate injection for administration. It should be noted that TROVAN I.V. is compatible in the following intravenous solutions:

Compatible Intravenous Solutions:
5% Dextrose Injection, USP
0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.2% Sodium Chloride Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP

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ON ORIGINAL

[Pfizer Logo/Letterhead]

Please report all adverse events and product problems to (Pfizer Medical Information Department) at 1-800-XXX-XXXX or the FDA MEDWATCH program at 1-800-FDA-1088 or by mail at the following address:

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

Sincerely,

Health/Medical Affairs Director/Contact

APPEARS THIS WAY
ON ORIGINAL

Attachment - REVISED LABELING