DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-571/S-021

Pfizer Inc
235 East 42nd Street
New York, NY 10017

Attention: Kristina Spranger, Senior Manager
US Regulatory Affairs

Dear Ms. Spranger:

Please refer to your supplemental new drug application dated December 22, 2003, received December 24, 2003, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CAMPTOSAR® Injection (irinotecan hydrochloride) to NDA 20-571.

We acknowledge receipt of your submissions dated January 21, February 13, and March 31, 2004. We also acknowledge and retain your final printed labeling submitted May 16, 2002 and resubmitted June 7, 2002.

This supplemental new drug application provides for revisions in the **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** sections of the labeling and was submitted in response to our Pediatric Written Request letter of January 22, 2001.

We completed our review of this supplemental application, as amended. This supplemental application is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. In addition, we have the following recommendations:

1. Information on adverse events (AE) from the Core Data Sheet should be used to update the label, if there are differences. The AE from the Core Data Sheet should be submitted for FDA review and included in the upcoming labeling changes discussions. Please inform the Division of a date by which this data can be submitted to this Division.

2. There appears to be a correlation between the incidence of severe (grade 3 or 4) diarrhea and SN38 area under the concentration curve (AUC) as well as severe (grade 3 or 4) neutropenia and SN38 AUC. However, this relationship was not statistically significant. Pharmacokinetic data was not collected in the majority of the patients. Knowledge of the exposure-toxicity relationship for irinotecan and SN38 would be critical in targeting optimal exposures in future studies. We recommend collection of pharmacokinetic (PK) data to adequately characterize the disposition of irinotecan and SN38 in ongoing as well as future trials when given in combination with other drugs or as a single agent. An optimal sparse sampling approach spanning an appropriate duration post-infusion in all patients should be used.

3. Genotypic differences in UGT1A1, a phase 2 enzyme involved in the glucuronidation of SN38, can result in a decreased rate of elimination of SN38 leading to elevation of SN38 levels and an increased risk of severe toxicity in patients with the less-efficient isoform. Thus, we recommend that you evaluate the relationship between UGT1A1 genotypes on the exposure of SN38 as well as on toxicity:

   - in existing data collected from the phase 2 trial already conducted and/or
   - in future trials to be conducted.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

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 20-571/S-021." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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, call Brenda Atkins, Regulatory Project Manager, at (301) 594-5767.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Richard Pazdur

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