DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Robert B. Clark
Vice-President, US Regulatory
Pfizer Inc.
235 East 42nd Street
New York, New York, 10017

Re: NDA #20-571
Camptosar® (irinotecan hydrochloride injection)
MACMIS ID # 11564

Dear Mr. Clark:

This letter concerns the dissemination of promotional materials for Camptosar (irinotecan hydrochloride injection). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a visual aid (UX0031195) for Camptosar, submitted by Pfizer Inc. (Pfizer) with Form FDA 2253. DDMAC has determined that this visual aid omits material facts with respect to a potentially life-threatening adverse event for Camptosar and contains inaccurate information related to important dose modifications that are needed to manage potentially serious adverse events. These omissions and misrepresentations misleadingly suggest that Camptosar is safer than has been demonstrated by substantial evidence or substantial clinical experience. As a result, they cause Camptosar to be misbranded in violation of the Federal Food, Drug, and Cosmetic Act and FDA implementing regulations. 21 U.S.C. §§ 321(n) and 352(a). Cf. 21 CFR 202.1(e)(6)(i). The visual aid may give healthcare professionals incorrect information on the safety profile of Camptosar and on how to appropriately dose Camptosar when patients are experiencing toxicity during treatment.

Background

According to the approved product labeling (PI), Camptosar Injection is indicated (1) as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum and (2) for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

According to the PI, there are many toxicities and dosing considerations pertinent to treatment with Camptosar. The PI includes a boxed warning regarding severe diarrhea and myelosuppression which states (in pertinent part):

> CAMPTOSAR can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early

> diarrhea and other cholinergic symptoms may be prevented or ameliorated by atropine (see PRECAUTIONS, General). Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide. Patients with diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated or antibiotic therapy if they develop ileus, fever, or severe neutropenia. Administration of CAMPTOSAR should be interrupted and subsequent doses reduced if severe diarrhea occurs (see DOSAGE AND ADMINISTRATION).
>
> Severe myelosuppression may occur (see WARNINGS).

Table 11 in the Dosage And Administration section of the PI (Recommended Dose Modifications for Camptosar/5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedules) states, in bolded font:

> Patients should return to pre-treatment bowel function without requiring anti-diarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to $\geq 1500/mm^3$, and the platelet count has recovered to $\geq 100{,}000/mm^3$, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.

The PI also addresses certain blood disorders. The "Overview of Adverse Events" section of the PI states, "Camptosar commonly causes neutropenia, leukopenia (including lymphopenia), and anemia." With respect to neutropenia, the Warnings section of the PI states (in pertinent part):

> Deaths due to sepsis following severe neutropenia have been reported in patients treated with CAMPTOSAR. Neutropenic complications should be managed promptly with antibiotic support (see PRECAUTIONS). Therapy with CAMPTOSAR should be temporarily omitted during a cycle of therapy if neutropenic fever occurs or if the absolute neutrophil count drops $\leq 1000/mm^3$. After the patient recovers to an absolute neutrophil count $\geq 1000/mm^3$, subsequent doses of CAMPTOSAR should be reduced depending upon the level of neutropenia observed (see DOSAGE AND ADMINISTRATION).

Table 11 also recommends dose modifications for "Other hematologic toxicities," specifically, leukopenia and thrombocytopenia, by stating, "Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also

based on NCI toxicity criteria and are the same as recommended for neutropenia above." As noted in the footnote, Table 11 does not provide dose modification information for alopecia, anorexia, or asthenia.

The dosage of Camptosar may be reduced in patients experiencing continued toxicity. As stated in Table 10 of the PI, "Dose reductions beyond dose level –2 by decrements of –20% may be warranted for patients continuing to experience toxicity. Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit."

Omission of Risk Information About Diarrhea

Page four of the visual aid states, "Camptosar can induce life threatening neutropenia and late diarrhea." The visual aid then states that "Toxicities are generally manageable with appropriate intervention" and cites the medicines that should be administered in the event of such toxicities. This presentation minimizes the risk and consequences of severe diarrhea associated with Camptosar, as described above. The statement that late diarrhea, although life-threatening, is "generally manageable," is misleading given that this adverse event may be fatal if not appropriately managed, as the PI states.

Furthermore, the table titled "Recommended Dose Modifications for Combination Schedules of CAMPTOSAR" on page three of the visual aid fails to convey information regarding necessary dosing modifications, including discontinuations, because of treatment related diarrhea. For example, the table fails to provide accurate dose modifications during a course of therapy for grades 1 and 2 diarrhea. The table states that the dose should be maintained when the patient is experiencing grade 1 diarrhea and decreased one dose level when the patient is experiencing grade 2 diarrhea. FDA is not aware of substantial evidence or substantial clinical experience supporting this dose modification information. According to Table 11 in the PI, for grade 1 diarrhea, the prescriber should "Delay dose until resolved to baseline, then give same dose," and for grade 2 diarrhea, the prescriber should "Omit dose until resolved to baseline, then ↓ 1 dose level." (Emphasis added.)

Additionally, the table in the visual aid states, with respect to dose modifications for grades 3 and 4 diarrhea, that the dose may be continued at a lower dose when the diarrhea has resolved to ≤ grade 2. FDA is not aware of substantial evidence or substantial clinical experience supporting this dose modification information. Table 11 in the PI states for grade 3 diarrhea, "Omit dose until resolved to baseline, then ↓ 1 dose level," and for grade 4 diarrhea, "Omit dose until resolved to baseline, then ↓ 2 dose levels." (Emphasis added.)

The visual aid is also misleading because it does not include dose modification tables for leukopenia and thrombocytopenia, which (as noted above) are also associated with Camptosar. In fact, the visual aid makes no mention of thrombocytopenia, even though over 90% of patients who take Camptosar in combination with bolus 5-FU/LV suffer from this adverse reaction. Your failure to disclose thrombocytopenia misleadingly suggests that this adverse reaction does not occur with Camptosar. The omission of dose modification information for leukopenia and thrombocytopenia misleadingly suggests that these toxicities do not require dose modifications.

Omission of Dose Modifications Information

The visual aid is also misleading because it fails to provide complete dose modification information for a course of therapy for grade 2 other nonhematologic toxicities. The "Recommended Dose Modifications for Combination Schedules of Camptosar" table on page three of the visual aid states that the dose should be decreased one dose level when the patient is experiencing grade 2 other nonhematologic toxicities. FDA is not aware of substantial evidence or substantial clinical experience supporting this dose modification information. The PI states, "Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level" when patients experience grade 2 other nonhematologic toxicities. (Emphasis added.) Moreover, the dosing table in the visual aid omits the footnote (discussed above) containing important contextual information about other nonhematologic toxicities.

This visual aid also omits important information regarding dose modification for patients with continued toxicity. Page three of the visual aid depicts two graphics regarding infusional and bolus regimens for Camptosar + 5-fluorouracil/leucovorin with starting doses and dose modifications but fails to convey that (as discussed above) further dose modifications may be necessary.

Conclusions

The visual aid misbrands Camptosar within the meaning of 21 U.S.C. §§ 321(n) and 352(a) because the presentation and omission of risk information misleadingly suggest the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Requested Action

DDMAC requests that Pfizer Inc. immediately cease the dissemination of this sales aid and of any other promotional materials for Camptosar that contain claims the same as or similar to those described above. Please submit a written response to this letter on or before December 2, 2003, describing your intent to comply with this request, listing all promotional materials for Camptosar that contain claims the same as or similar to those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to me at Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at 301-594-6771. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID # 11564 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Catherine A. Miller
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Catherine Miller

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