

EXHIBIT 1

December 21, 2006

To: Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061, Rockville, MD 20852

From: Jeanne M. Quivey, M.D., F.A.C.R.

Re: Statement of Expert Opinion in Opposition to MedImmune Oncology, Inc.'s 10/10/06
Citizen Petition Regarding Generic Amifostine (Docket No. 2006P-0410/CP1)

I submit this opinion in response to the Citizen Petition Docket 2006P-0410/CP1 ("Petition" or "Pet.") submitted by MedImmune Oncology, Inc. ("MedImmune"), dated October 10, 2006. In the Petition, MedImmune asks the Food and Drug Administration ("FDA") to refrain from approving any abbreviated new drug application ("ANDA") for an amifostine product that carves-out information in the labeling on the use of the drug to reduce the incidence of xerostomia in head and neck cancer patients being treated with radiotherapy.

I have thoroughly reviewed the Petition. Based upon my extensive knowledge and experience in the fields of radiation oncology and medical oncology in general, I disagree with MedImmune's conclusion in the Petition that "the omission of labeling from the generic product will lead to serious medication errors." Pet. at 1.

Background

I currently am a Professor of Clinical Radiation Oncology at the University of California San Francisco. A full description of my educational, clinical and research and work background can be found in my *curriculum vitae*, which is included as Exhibit A.

Comments

I understand that Sun Pharmaceutical Industries Limited ("Sun") has applied under application ANDA No. 77-126 for a generic amifostine product that cites to MedImmune's brand-name drug Ethyol® as the reference-listed drug. I am fully familiar with amifostine, which is a selective cytoprotective agent that the FDA has approved for two uses: (1) to reduce the incidence of xerostomia associated with receiving radiation to treat head and neck cancer and; (2) to reduce renal toxicity associated with repeated administration of cisplatin (chemotherapy) in patients with advanced ovarian cancer.

I understand that Sun's generic amifostine, if approved, would be labeled exclusively for the second use – *i.e.*, to reduce renal toxicity in ovarian cancer patients undergoing chemotherapy. Sun's label thus would carve-out information on the first use – *i.e.*, to reduce the incidence of xerostomia in head and neck cancer patients being treated with radiotherapy.

In the Petition, MedImmune argues that there is a risk of a serious medication error if a generic amifostine label carved-out information on the use of the drug to reduce the incidence of xerostomia in head and neck cancer patients being treated with radiotherapy. According to MedImmune, this proposed carve-out in the labeling would lead to serious medical errors because health professionals may mistakenly apply the labeled dose for chemotherapy patients to patients seeking the head and neck cancer radiation treatment. Next, MedImmune argues that such confusion could lead to an overdose since the chemotherapy dose is greater than the dose for the radiotherapy indication.

In my expert opinion, MedImmune's arguments overstate health professionals' reliance on generic drug labels, distort the process under which amifostine is prescribed and administered by trained personnel, and ignore the fact that patients who receive amifostine are closely monitored to ensure their safety. Based on my professional experience and knowledge of clinical oncology practice, there is no reason to believe that any reasonable health professional ever would apply the labeled dose for chemotherapy patients to radiotherapy patients. Nevertheless, even if such a mistake occurred, the patient would not be harmed.

I. Sun's Proposed Label Will Not Lead To Confusion As To The Proper Dose For Amifostine Pertaining To Its Use For Radiotherapy Patients

Amifostine is a prescription drug administered only by trained and experienced health care providers. Since patients do not self-administer the drug, there is no risk that patients will be confused by Sun's proposed label. Accordingly, MedImmune argues only that this label will confuse health professionals. Despite MedImmune's argument to the contrary, I do not believe that there is any risk that a trained and experienced health professional simply would assume that the labeled dose for treating *chemotherapy* patients also applies to the drug's use for reducing side effects in *radiotherapy* patients.

First, in my experience, health professionals trained in radiation oncology and radiation therapy for head and neck cancer are intimately familiar with the required dosage regimen and schedule for administering amifostine to reduce the incidence of xerostomia associated with receiving radiation to treat such cancer. Amifostine is prescribed and administered on a daily basis just 15 to 30 minutes prior to radiation treatment for this indication, and health professionals who administer amifostine rely on their knowledge and experience, not the particular labeling on a generic drug to determine its proper dosage for a particular indication. In fact, while the FDA-approved indications for amifostine are for administering the drug only by i.v. (intravenous) infusion, based on my knowledge of amifostine use in the clinical radiation oncology setting, physicians frequently elect to administer 500 mg subcutaneously, a dosage which provides approximately 67% of the area under the curve (AUC) of the FDA-approved dosage values of the active metabolite of amifostine (WR-1065) to minimize the acute toxicity. Schedules that detail this modification have been widely published since 2000 and are particularly favored precisely because of the lower incidence of observed hypotension. These studies were initiated because IV administration on a daily basis creates significant discomfort for patients as well as staff. Multiple catheterization of veins is quite difficult for patients and requires that a specialized nurse be available to the radiotherapy unit to treat the side effects related to the amifostine infusion, including severe nausea and vomiting as well as acute

hypotension. This further demonstrates that health professionals do not rely solely on the drug's label for dosage information.

Second, at least three health professionals review the dosage regimen for each instance of prescribed amifostine, thus further preventing any chance of a medication error. The Radiation Oncologist who prescribes amifostine must prescribe a particular dosage regimen and specify the specific indication for the drug on the prescription. Next, a trained pharmacist routinely reviews the amifostine prescription to ensure that the dosage information contained in the prescription is accurate, proper and safe for the patient. Pharmacists often seek clarification from the prescribing physician if the prescribed dosage regimen for a particular indication appears to be an error. Once the prescription is filled, one or more nurses, physician assistants and/or other health professionals once again confirm the accuracy of the dosage information before amifostine is administered to the patient. In most instances, the health professional that administers amifostine for patients undergoing radiotherapy treatment (i.e., immediately prior to radiation therapy) does not also administer the drug for patients undergoing chemotherapy treatment and thus would have no reason to be confused about the separate dosage regimen for the drug's two approved indications.

Third, health professionals who provide cancer care are familiar with the differences in chemotherapy versus radiation therapy dosing schedules. Practitioners in oncology practice, as well as medical personnel in oncology practice, know that cisplatin chemotherapy treatments for ovarian cancer patients are typically given once every three weeks for up to six courses (six doses over 18 weeks). In contrast, head and neck cancer patients generally receive radiation treatments four or five days a week for typically three to six weeks. The Petition itself acknowledges these differences in dosing schedules. Pet. at 3. Given the significantly different dosing schedules for chemotherapy treatment versus radiation treatment, there would be no reason for doctors, hospital staff, or any other health professional to assume arbitrarily that the dosing information for chemotherapy patients would apply to patients undergoing radiation treatment for head and neck cancer.

Fourth, health professionals understand that, in general, a dosage pertaining to one indication of a drug does not necessarily apply to a second indication. This is true in the administration of countless other drugs, including countless drugs used in treating cancer patients. For example, Leukeran® (chlorambucil) is indicated in the treatment of chronic lymphatic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. According to the FDA-approved label for Leukeran®, patients with Hodgkin's disease usually require 0.2 mg/kg daily. However, when lymphocytic infiltration of the bone marrow is present, or when the bone marrow is hypoplastic, the labeled daily dose should not exceed 0.1 mg/kg. Again, therefore, it would be unreasonable for a health professional to assume blindly that a dosage regimen for amifostone pertaining to a chemotherapy indication would apply to the drug's radiotherapy indication.

Finally, in my opinion, no reasonable health professional who has a question concerning a proper medication dosage would risk the patient's health by relying on a mere assumption that the labeled chemotherapy dose also applies to the drug's radiotherapy indication. To the contrary, in my opinion, such a provider would consult with other providers and/or reference

materials such as the Physicians' Desk Reference®, or current medical literature, which contains information on the correct dosage regimens and schedules for all uses of amifostine. See Exhibit B.

II. Radiotherapy Patients Would Not Be Harmed Even If Certain Health Care Professionals Mistakenly Assumed That The Labeled Dose For Treating Chemotherapy Patients Also Applied To The Drug's Use For Reducing Side Effects In Radiotherapy Patients And Mistakenly Administered 910 mg/m² Of Amifostine As A 15-minute I.V. Infusion To A Patient Prior To Radiotherapy

A patient would not be harmed even in the extremely unlikely event that a physician prescribed the chemotherapy dosage regimen for amifostine pertaining to a patient undergoing radiotherapy treatment, and neither the pharmacist filling the prescription nor the health professional administering the drug caught the error. MedImmune's argument to the contrary is overly simplistic and has no basis in medical science.

According to MedImmune, radiation oncologists who would use Sun's generic amifostine would mistakenly apply the labeled dose for chemotherapy patients to patients undergoing head and neck cancer radiation treatment, thus resulting in an overdose. Although MedImmune does not specify how such an overdose purportedly would occur, it appears that it posits two potential errors resulting from Sun's proposed label. First, a health professional will mistakenly administer 910 mg/m² of amifostine as a 15-minute i.v. infusion (the labeled dose and infusion schedule for the chemotherapy indication) to a patient prior to radiotherapy therapy. Second, a health professional will mistakenly administer 910 mg/m² of amifostine as a 3-minute i.v. infusion (the labeled dose for the chemotherapy, but the infusion schedule for radiotherapy treatment that was carved-out of the proposed label) to a patient prior to radiation therapy.

Even assuming, for the sake of argument, that the first error could realistically occur (which I dispute), such an error would not harm the patient. The recommended starting dose of amifostine for administration prior to chemotherapy (910 mg/m² administered once daily as a 15-minute i.v. infusion, starting 30 minutes prior to chemotherapy) already has been approved by the FDA as a safe dosage regimen for patients scheduled to receive chemotherapy. Patients, therefore, would not be harmed if this same dosage regimen (910 mg/m² administered as a 15-minute i.v. infusion) were mistakenly administered to a patient prior to receiving radiation therapy.

MedImmune's argument also ignores that all patients who receive amifostine are constantly monitored by trained health professionals for adverse signs, such as a decrease in the patient's blood pressure, nausea or vomiting. Health professionals would be able to discontinue use of amifostine if there were any adverse changes in the patient's blood pressure. In fact, Sun Pharma's proposed label, in the "Dosage and Administration" section, expressly states that a patient's blood pressure should be monitored "every 5 minutes during the infusion, and thereafter as clinically indicated."

Sun's proposed amifostine label further recommends that antiemetic medication be administered prior to, and in conjunction with, the amifostine injection. This co-administration of an antiemetic agent helps assure that if the generic amifostine injection were administered

prior to radiation treatment, potential side effects including nausea and vomiting would be diminished.

III. A Health Professional Would Not Mistakenly Administer 910 mg/m² Of Amifostine As A 3-Minute I.V. Infusion To A Patient Prior To Radiotherapy Under Sun's Proposed Label

In my opinion, the second possible error discussed above – *i.e.*, a health professional will mistakenly administer 910 mg/m² of amifostine as a 3-minute i.v. infusion – would simply not occur under any circumstances. As discussed above, Sun's proposed generic label would indicate that the recommended starting dose of amifostine is 910 mg/m² administered once daily as a 15-minute i.v. infusion, starting 30 minutes prior to chemotherapy. Thus, there would be no information on the proposed label about any infusion time other than the clearly labeled 15-minute i.v. infusion. It appears, however, that MedImmune is arguing that, if Sun's proposed label were approved, health professionals would mistakenly administer the 910 mg/m² dosage regimen as a 3-minute i.v. infusion prior to radiation therapy. No health professional could make this medication error based on Sun's proposed label.

First, Sun's proposed label does not mention a 3-minute i.v. infusion dosage regimen. This proposed medication error logically would be more possible under the labeling for MedImmune's Ethyol®, which discusses both the 910 mg/m² dose and the 3-minute infusion schedule. Nevertheless, such an error has not been reported anywhere in clinical practice with Ethyol® itself. Accordingly, there is no reason to believe that this error would occur under a label that makes no mention whatsoever of a 3-minute infusion schedule.

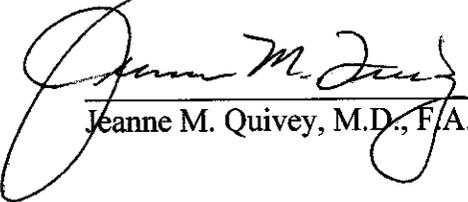
Second, health professionals are completely aware of calculating the dose for an individual depending on the body surface area of that individual. The average surface area of a 70 Kg adult with a height of 165 cm is about 1.7 m². Therefore, 910 mg/m² will be equivalent to a dose of 1547 mg for a 70 Kg adult. This would require an administrator to reconstitute four vials of an amifostine injection, each vial containing 500 mg of amifostine. Amifostine has not been studied in pediatric populations, but assuming that it were administered to a 25 Kg child having a height of 120 cm, the amount to be administered would be about 828 mg – an amount that would require reconstitution of two vials. A health professional would find the need to use more than one vial unusual because in head and neck cancer the approved dose is 200 mg/m², which is equivalent to 340 mg for a 70 Kg adult, and only one vial is ever used even for adults having a higher weight. Consequently, a health professional could not reasonably administer 910 mg/m² over 3 minutes at a rate of about 303.33 mg/m²/min under any circumstances.

Finally, I have also reviewed the John Santell article cited by MedImmune on page 8 of the Petition. In my expert opinion, the Santell article is irrelevant to the use of amifostine because the article deals entirely with errors that may occur in diagnostic radiological settings, As any medical practitioner or health professional knows, however, amifostine is not used as a treatment in a radiographic imaging setting but, rather, is used in a chemotherapy setting or a radiotherapy setting. In this latter situation, the patient is seen for daily treatment and evaluation and is well known to the treatment team.

Conclusion

For the reasons discussed above, I do not believe that FDA should credit any of MedImmune's medical arguments.

Respectfully submitted,



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