DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Hanne Johansen, Ph.D.
Senior Director, Regulatory Affairs
MedImmune Oncology, Inc.
35 West Watkins Mill Road
Gaithersburg, Maryland 20878

RE: NDA # 20-221
Ethyol® (amifostine) for Injection
MACMIS ID# 11751

This letter notifies MedImmune Oncology Inc. (MedImmune) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has received a patient-directed video tape ("the video tape"), submitted by MedImmune to FDA with a Form FDA 2253, titled, "It's not just about lifestyle, it's about livelihood" (ETH-036-02). DDMAC has determined that the video tape is in violation of Section 502(a) the Federal Food, Drug, and Cosmetic Act (the "Act"), 21 U.S.C. § 352(a), and FDA's implementing regulations, in that it overstates the efficacy of Ethyol therapy and its impact on a patient's physical functioning and quality of life related to preserving sensory functions such as the ability to taste and smell, and thereby misrepresents the usual patient experience while taking Ethyol. Our specific objections follow:

Background

Efficacy

Ethyol was approved on June 24, 1999, "to reduce the incidence of moderate to severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands."

The effects of Ethyol on mucositis (i.e., inflammation of the mucous membranes) and xerostomia (i.e., dryness of the mouth from salivary dysfunction) caused by radiation therapy for head and neck cancer were evaluated in a clinical trial using the Radiation Therapy Oncology Group Acute Morbidity Scoring Criteria and a patient questionnaire. While the study results demonstrated a statistically significant difference in the incidence of acute and late xerostomia between the Ethyol arm and the control arm, a longitudinal assessment of unstimulated saliva production did not show a difference between treatment groups. There was no difference noted between treatment arms for all grade 1 or higher acute xerostomia.

Additionally, with respect to specific parameters concerning physical functional well-being, general dryness, and the use of external aids, there was no statistically significant difference between the treatment groups at seven months and one year. And, although a lower

percentage of Ethyol treated patients developed grade 3 or higher mucositis compared with control patients, no statistically significant difference was noted between the Ethyol and control arms.

The approved product labeling (PI) also includes a warning regarding the serious risk of hypotension, nausea, and vomiting associated with Ethyol when used for this indication. Consequently, the PI recommends that antiemetic medication should be administered prior to and in conjunction with Ethyol. In addition, serious allergic reactions have been observed during or after Ethyol administration.

Overstatement of Efficacy

The testimonial in your video tape misleadingly implies that patients taking Ethyol in conjunction with radiation therapy for head and neck cancer are: 1) less likely to have olfactory perceptions affected by radiation therapy; 2) less likely to experience the effects from mucositis or xerostomia, or loss of taste; 3) very likely to experience a preservation of their physical functioning and quality of life related to their sensory perceptions such as their senses of smell and taste, and 4) better able to eat and have a decreased likelihood of weight loss compared with not using Ethyol. FDA is not aware of any data that supports these claims. If, at some future time, you develop such evidence that would support any of these claims, please submit that data in a supplemental NDA to FDA for review.

First, the video tape describes the patient as a vintner whose profession wholly depends on his ability to taste and smell. He speaks of wine making as an “art” and “entirely a sensory matter” involving the olfactory system and taste. The video goes on to make the following claims:

> “He’s not the typical patient who would receive this kind of medication. But because he is a vintner, and his sense of taste and the preservation of the normal moisture in the mouth was very important to him, we talked about the idea of using Ethyol. And he understood that we were doing something different. But he was motivated to try anything to keep his sense of taste, because without that he’d lose his livelihood and really, an important part of his quality of life.” [Physician.]
>
> “And then as soon as the radiation stopped, then the ability to taste sweetness slowly came back.” [Patient.]
>
> “And now that the treatment’s over, his preservation of mouth moisture and his sense of taste is dramatically better than anything I would’ve expected.” [Physician.]
>
> “My quality of life is as good as can be. I have all functions restored. All sensory perceptions restored.” [Patient.]

These claims, in addition to pictorial representations (e.g., the patient sniffing and tasting a glass of wine), imply that Ethyol therapy will preserve or contribute to the restoration of a patient’s olfactory perception, sense of taste, and other unspecified sensory "functions," as well the patient’s quality of life (and, with the patient portrayed, ability to perform job

responsibilities) related to use of those sensory functions. Such claims have not been demonstrated to FDA by substantial evidence or substantial clinical experience.

Second, the patient states, "The really remarkable effect, the one that —even to this day—I look at as a marvel, was the elimination of the severe sore throat." The treating physician expands and reinforces this claim by stating "...The lining of his mouth did not become sore or inflamed. He was not having significant discomfort, and he both subjectively as well as in my opinion had a significantly better degree of moisture, a lack of dryness of mouth, throughout the whole course of treatment." These claims imply that Ethyol will improve mucositis, or prevent any degree of xerostomia. Such effects have not been demonstrated to FDA by substantial evidence or substantial clinical experience. Furthermore, data submitted to FDA in support of Ethyol's approval showed that Ethyol was not associated with a statistically significant difference in overall mucositis experienced at grade 0 compared with control.

Third, the physician concludes, "That made it a lot easier for him to tolerate the treatment, because he was able to eat better than patients typically do, and he didn't lose the same degree of weight that most patients do." The patient reinforces this claim by stating, "I could continue to eat. I could continue to drink. I had no pain whatsoever. And then as soon as the radiation stopped, then the ability to taste sweetness slowly came back. And by a month later I could taste everything." These claims imply that Ethyol will allow patients to eat better and not lose the same amount of weight as compared to patients who receive radiation therapy for head and neck cancer without the addition of Ethyol, and that Ethyol will prevent the permanent deterioration of the sense of taste. These effects have not been demonstrated by substantial evidence or substantial clinical experience. Moreover, FDA is not aware of any substantial evidence or substantial clinical experience that support the claim that Ethyol therapy will allow patients to "taste everything" within a month of their treatment.

Therefore, the video tape gives false or misleading information about the efficacy of Ethyol therapy and its impact on physical functioning and quality of life related to sensory functions. FDA is not aware of substantial evidence or substantial clinical experience substantiating these claims. The slide at the beginning of the video tape that states "The uses of Ethyol under discussion in this document has [sic] not been approved by the FDA except for the reduction of the incidence of moderate to severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands," does not counteract the misleading statements in the video tape, which primarily discusses effects for which you have not provided FDA with substantial evidence or substantial clinical experience. The experience of a patient whose livelihood depends on protection and restoration of his olfactory and taste senses, given via his testimonial, implies a greater efficacy of Ethyol than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

MedImmune should immediately cease the distribution of this and other similar promotional materials for Ethyol that contain the same or similar claims or presentations. Please submit a written response to DDMAC on or before November 10, 2003, describing your intent and

plans to comply with the above. In MedImmune's letter to DDMAC, MedImmune should include the date on which this and other similarly violative materials were discontinued.

MedImmune should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID #11751 in addition to the NDA number. DDMAC reminds MedImmune that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
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
10/28/03 11:33:14 AM
Signed for Joseph A. Grillo, Pharm.D.

It's not just
about *lifestyle*,

it's about
livelihood

For David Jones, xerostomia was not an option. As the winemaker at California's Lava Cap Winery, David relied on a sense of taste for his livelihood. So, when he was diagnosed with head and neck cancer, radiation treatment was a scary proposition—if his salivary glands were badly damaged, his days as a winemaker would be over. His doctor prescribed medication that helped reduce radiation damage to his salivary glands. Today, David and his excellent sense of taste are back on the job, making great wines high in the foothills of the magnificent Sierra Nevada. This is his story...

lifestyle

livelihood

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