DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-326/S-011, S-013

Attention: Eve Damiano
Senior Director, Regulatory Affairs
MedImmune Oncology, Inc.
One Tower Bridge, Suite 400
West Conshohocken, PA 19428

Dear Ms. Damiano:

Please refer to your supplemental new drug applications dated May 27, 1998 and January 30, 2001, received May 28, 1998 and February 5, 2001, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neutrexin® (trimetrexate glucuronate for injection), 25 mg, 200 mg.

We acknowledge receipt of your submission dated February 15, 2001.

These "Changes Being Effected (CBE)" supplemental new drug applications provide for the following changes to the Neutrexin® labeling. Deleted text is noted by ~~strikethrough~~ and added text is noted by <u>double underline</u>:

1. DESCRIPTION

- The third sentence in the first paragraph was revised to read:

> "Neutrexin is available as a sterile lyophilized powder ~~in multi-dose vials~~, containing trimetrexate glucuronate equivalent to either 200 mg or 25 mg of trimetrexate without any preservatives or excipients."

2. PRECAUTIONS

- In the **General** subsection, the following sentence was deleted, and new text was added to the end of the second paragraph to read:

> ~~An anaphylactoid reaction has been reported in a cancer patient receiving Neutrexin as a bolus injection.~~
> <u>Trimetrexate is a known inhibitor of histamine metabolism. Hypersensitivity/allergic type reactions including but not limited to rash, chills/rigors, fever, diaphoresis and dypsnea have occurred with trimetrexate primarily when it is administered as a bolus infusion or at doses higher than those recommended for PCP, and most frequently in combination with 5FU and</u>

leucovorin. In rare cases, anaphylactoid reactions, including acute hypotension and loss of consciousness have occurred.

3. ADVERSE REACTIONS

- The last sentence in this section was deleted as follows:

~~One case of anaphylactoid reaction has been reported in a cancer patient receiving Neutrexin as a bolus injection.~~

4. DOSAGE AND ADMINISTRATION

- In the **RECONSTITUTION AND DILUTION** subsection, the second paragraph was revised to read:

After reconstitution, the solution ~~is stable for 2 days at room temperature, 5 days at refrigeration (2-8ºC) or 8 days frozen (10-20ºC).~~should be used immediately; however, the solution is stable for 6 hours at room temperature (20 to 25ºC), or 24 hours under refrigeration (2-8°C).

- In the **RECONSTITUTION AND DILUTION** subsection, the third paragraph was revised to read:

~~Reconstituted~~ Prior to administration, the reconstituted solution should be further diluted with 5% Dextrose Injection, USP, to yield a final concentration of 0.25 to 2 mg of trimetrexate per mL. The diluted solution should be administered by intravenous infusion over 60 minutes. Neutrexin should not be mixed with solutions containing either chloride ion or leucovorin, since precipitation occurs instantly. ~~It~~ The diluted solution is stable under refrigeration or at room temperature for up to 24 hours. Do not freeze. Discard any unused portion after 24 hours. The intravenous line must be flushed thoroughly with at least 10 mL of 5% Dextrose Injection, USP, before and after administering Neutrexin.

5. HOW SUPPLIED

- The first sentence in the first paragraph was revised to read:

Neutrexin (trimetrexate glucuronate for injection) is supplied as a sterile lyophilized powder in either 5 mL or 30 mL ~~multi-dose~~ vials.

- The first sentence in the last paragraph was revised to read:

Store at controlled room temperature ~~15° to 30°C (59° to 86°F).~~ 20° to 25°C (68° to 77°F).

6. At the end of the package insert, the names and addresses of the two manufacturing sites were added, and the new corporate name of the marketing company was changed to MedImmune Oncology, Inc.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling submitted on January 30, 2001. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Renata Albrecht

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