DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-229/S-004, S-007

Ortho Biotech Products, L.P.
1000 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

Attention: Patricia Capaccione
Sr. Regulatory Associate, Regulatory Affairs

Dear Ms. Capaccione:

Please refer to your supplemental new drug applications dated February 20, 1996 and January 29, 1997, received February 21, 1996 (S-004) and January 29, 1997 (S-007), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Leustatin Injection (cladribine).

We also refer to your final printed labeling (FPL) submitted March 25 and April 2, 1993; February 20, 1996 (S-004); and February 5, 1997 (S-007). We note that the February 5, 1997 FPL supersedes the previous FPLs and that both supplements were submitted as "Special Supplement - Changes Being Effected."

These "Changes Being Effected" (CBE) supplemental new drug applications provide for revisions in the boxed WARNING, DESCRIPTION, CLINICAL PHARMACOLOGY, HUMAN PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections.

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 submitted final printed labeling submitted for S-007 (package insert submitted February 5, 1997). Accordingly, supplemental application 007 is approved effective on the date of this letter. Supplemental application 004 will be retained in your files.

However, we request that at the next printing or within six months, whichever occurs sooner, you make the following changes. These revisions may be submitted as a CBE supplement (with FPL) if you make no revisions to our proposed wording or as a prior approval supplement if you wish to discuss the changes further. The following changes may also be incorporated into other labeling revisions you may have ongoing.

1. In the CLINICAL PHARMACOLOGY section under Human Pharmacology (Pharmacokinetics), paragraph 3, the support for the half-life in leukemic cells is unacceptable. Therefore, the following change should be made:

   Plasma concentrations are reported to decline multi-exponentially after intravenous

infusions with terminal half-lives ranging from approximately 3-22 hours. In general, the apparent volume of distribution of cladribine is very large (mean approximately 9 L/kg), indicating an extensive distribution of cladribine in body tissues. The mean half-life of cladribine in leukemic cells has been reported to be 23 hours.

Should be changed to:

Cladribine plasma concentration after intravenous administration declines multi-exponentially with an average half-life of 7 hours. In general, the apparent volume of distribution of cladribine is approximately 9 L/kg, indicating an extensive distribution in body tissues.

2. The subsection title "Human Pharmacology" should be changed to "Pharmacokinetics."

3. Clinical study reports should be under a separate section titled CLINICAL STUDIES.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" 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 Ann Staten, Project Manager, at (301) 594-0490.

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

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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