DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-819/S-007, S-011

Abbott Laboratories
Attn: Mary O'Sullivan
D-389, Bldg. J45-2
200 Abbott Park Road
Abbott Park, Illinois 60064-6133

Dear Ms. O'Sullivan:

Please refer to your supplemental new drug applications dated April 14, 2000 (S-007) and February 13, 2002 (S-011), received April 17, 2000 (S-007) and February 14, 2002 (S-011), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zemplar (paricalcitol) Injection.

We acknowledge receipt of your submissions dated April 26, August 29, and November 27, 2002 (S-011).

These supplemental new drug applications provide for the following:

> S-007 proposes to revise the Special Populations subsection of the PRECAUTIONS section and the DOSAGE AND ADMINISTRATION section of the package insert to include information on use in patients with hepatic impairment.
>
> S-011 proposes to revise the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection of the package insert to include data from two long-term carcinogenicity studies conducted in rats and mice. The supplement also proposed to revise the ADVERSE REACTIONS section to include events reported post-marketing.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the labeling approved with Supplement –006 on February 1, 2000, revised as follows:

- include the revisions approved with Supplement –003 on February 2, 2000
- include the revisions proposed in Supplement –007
- include the proposed revisions to the ADVERSE REACTIONS section and the following agreed upon text for the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection contained in Supplement –011:

  In a 104-week carcinogenicity study in CD-1 mice, an increased incidence of uterine leiomyoma and leiomyosarcoma was observed at subcutaneous doses of 1 to 10 mcg/kg (<1 to 3 times the maximum recommended human weekly dose of 0.72 mcg/kg, based on body surface area, mg/m^2).

The incidence rate of uterine leiomyoma was significantly different than the control group at the highest dose of 10 mcg/kg. In a 104-week carcinogenicity study in rats, there was an increased incidence of benign adrenal pheochromocytoma at subcutaneous doses of 0.15-1.5 mcg/kg (≤1 time the maximum recommended human weekly dose of 0.72 mcg/kg, based on body surface area, mg/m^2). The increased incidence of pheochromocytomas in rats may be related to the alteration of calcium homeostasis by paricalcitol. In carcinogenicity studies in rats and mice, paricalcitol did not affect the incidences of tumors apart from benign rodent-specific lesions related to the effects of chronic hypercalcemia.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-819/S-007, S-011." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), 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 reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Samuel Wu, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

David G. Orloff, MD
Director
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
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/

David Orloff

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