CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103471

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 23 1993

Our Reference No: 92-0495

Bernardita Mendez, Ph.D.
Chiron Corporation
4560 Horton Street
Emeryville, CA 94608-2916

Dear Dr. Mendez:

Enclosed is a product license which authorizes Chiron Corporation, U.S. License No. 1106, to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce Interferon beta-1b.

Interferon beta-1b is indicated for use in ambulatory patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations. In accordance with approved labeling, your product will bear the tradename Betaseron®, and will be marketed in 0.3 mg (9.6 million IU) fill size single-use vials for subcutaneous injection. The product will be manufactured at the 1400 Fifty-Third Street, Emeryville, CA location. We note that Berlex Laboratories, Richmond, California will be the distributor for Interferon beta-1b.

You are requested to submit samples of each future lot of the product together with protocols showing results of all applicable tests. No lots of product shall be distributed until notification of release is received from the Director, Center for Biologics Evaluation and Research.

The dating period for this product shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated product.

Any changes in the manufacture, packaging or labeling of the product or in the manufacturing facilities will require the submission of an amendment to either your product or establishment license application for our review and written approval prior to implementation.

We acknowledge the written commitments specified in your letters of May 12, June 3, June 7, and July 20, 1993, which include the following:

1. To conduct a randomized, double-blind placebo controlled study in chronic-progressive multiple sclerosis for 4-6 years using disability as measured by Kurtzke Expanded

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Disability Status Scale (EDSS) as a primary endpoint and serial magnetic resonance imaging (MRI) as part of the secondary endpoint. An interim analysis will be conducted in 2-3 years and the study will be initiated during the first or second quarter of 1994.

2. To design and conduct an additional study which will evaluate the usefulness of continued treatment with Interferon beta-1b beyond two years in patients with ambulatory relapsing-remitting multiple sclerosis with the primary efficacy endpoint being rate of exacerbation;

3. To establish the correlation between MRI parameters and clinical parameters (i.e., EDSS, Scripps, and frequency of exacerbation) derived from data from the two studies indicated above;

5. To gather further information in determining the extent of depression or aggravation of pre-existing psychiatric disease as a side effect of treatment with Interferon beta-1b;

6. To conduct ongoing stability studies as specified and to withdraw from the market any lot which fails to meet product specifications. In addition, Chiron will provide updated stability data to CBER at three month intervals;

7. To develop additional lot release specifications;

8. To develop assays that will improve the quantitation and characterization of patient antibodies to Interferon beta-1b.

Furthermore, as discussed during the June 28, 1993 conference call between representatives from CBER, CDER, Chiron and Berlex Laboratories, and agreed in your letter of July 22, 1993, marketing approval of this product is granted under the accelerated approval for biological products regulations, 21 CFR 601.40-.46. These regulations permit the use of certain surrogate endpoints as bases for approvals of products intended for serious or life-threatening illnesses.

Among other things, approval under these regulations requires that you demonstrate through adequate and well controlled studies that differences in CNS lesions, as visualized by MRI scanning, correlate with clinical benefit, and that such studies be carried out with due diligence. If the postmarketing studies fail to

verify clinical benefit associated with the surrogate endpoint and Chiron does not expeditiously remove any labeling claims which have thereby become unsupported, the Agency may, following presentation of data at a hearing, withdraw or modify approval to the extent that approval rests on the surrogate endpoint data.

You are requested to submit adverse experience reports in accordance with the requirements for postmarketing reporting of adverse drug experiences (21 CFR 314.80) until such time that specific reporting requirements for biological products become effective. All experience reports should be prominently labeled as "BIOLOGICAL PRODUCT" and be submitted to the Division of Biostatistics and Epidemiology, HFM-210, Attn: Adverse Experience Reporting, Center for Biologics Evaluation and Research, Food and Drug Administration, Document Control (HFM-99) 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information. In addition, as specified in 21 CFR 601.45, advertising and promotional labeling to be disseminated after 120 days following today's date should be submitted to the Advertising & Promotional Labeling Staff, HFM-202, Center for Biologics Evaluation and Research, Food and Drug Administration, Document Control (HFM-99) 1401 Rockville Pike, Rockville, MD 20852-1448, for review and approval at least 30 days prior to the initial publication of any advertisement or to the initial dissemination of any promotional labeling.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Please acknowledge receipt of the enclosed license to the Director, Division of Applications Review and Policy, HFM-585, Center for Biologics Evaluation and Research.

Sincerely yours,

Janet Woodcock, M.D.
Acting Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure

cc: HF-35 (Orphan Drug)

Dr. Zoon	HFM-1
Dr. Woodcock	HFM-500
Ms. Risso	HFM-585
Dr. Gerrard	HFM-505
Dr. Larner	HFM-505
Dr. Vargo	HFM-205
Dr. Johnson	HFM-207
Dr. Siegel	HFM-570
Ms. Parshall	HFM-230
Mr. Ellengold	HFM-11
Ms. Wion	GCF-1
Dr. Temple	HFD-100
Dr. Leber	HFD-120

HFM-205:JLJohnson:7/9/93
Revised:HFM-585:Risso:7/16/93
Revised:GCF-1:Wion:7/19/93
Revised:HFM-505:Gerrard:HFM-585:Risso:7/21/93
Revised:GCF-1:Wion:HFM-585:Risso 7/22/93