Public Health Service
Food and Drug Administration
Orphan Products Development

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date April 16, 1996

From Director, Office of Orphan Products Development (HF-35)

Subject Clinical Superiority of Biogen's interferon product, Avonex™

To OOPD Application #91-627

Following the November 14, 1995, meeting concerning Avonex™ and Betaseron™, OOPD evaluated data provided by CBER contained in the PLA for Avonex™. Based on these data, OOPD concluded that Avonex™ is clinically superior to Betaseron™ due to the absence of injection site skin necrosis events reported with Avonex™ compared to the occurrence of same event reported with Betaseron™. The package insert for the Berlex product reported that 85% of patients treated with Betaseron™ experience injection site reactions while only 4% of patients treated with Avonex™ experience injection site reactions. At least 10% of the lesions in patients treated with Betaseron™ required debridement, and some required skin grafting to achieve healing.

OOPD was faced with a similar situation involving two coagulation factor IX products, Mononine™, manufactured by the Armour Pharmaceutical Company, and AlphaNine®, manufactured by Alpha Therapeutic Corporation. AlphaNine® was approved first and had orphan exclusivity. Data submitted in the PLA for Mononine™ provided a reasonable basis to conclude that the viral inactivation process used by Armour for the production of Mononine™ may result in a product less likely to transmit hepatitis C infection than the AlphaNine® product. In view of the prospect of improved viral safety of Mononine™, OOPD concluded that Mononine™ is a safer drug than AlphaNine®. Therefore, since it is a safer drug, Mononine™ was determined to be clinically superior to AlphaNine® and the approval of the PLA for Mononine™ was not blocked by AlphaNine®.

Biogen has submitted data demonstrating that Avonex™ is a safer product because it causes substantially fewer injection site reactions than Betaseron™. Therefore, Avonex™ is clinically superior to Betaseron™ by virtue of its improved safety profile. Since Avonex™ is clinically superior to Betaseron™, under the Orphan Drug Act, Avonex™ is not the same product as Betaseron and approval of the PLA for Avonex™ is not blocked by the orphan exclusivity held by Betaseron™.

cc:
HF-35/Chron file
HF-35/OPD File # 88-318
HF-35/P.Vaccari biogen1.mem 3/16/96

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852

Memorandum

Division of Clinical Trial Design and Analysis
HFM-576

Date: 3/29/96

From: Marc Walton, DCTDA MW

Subject: Clinical Superiority of Interferon beta-1a

Through: Karen Weiss, Acting Director, DCTDA KW

To: David Finbloom, Acting Director, DCB

Per your request, this memorandum summarizes the information regarding the superior safety profile of Interferon beta-1a (Avonex) compared to Interferon beta-1b (Betaseron).

Avonex is clinically superior to Betaseron based upon improved safety, due to the occurrence of injection site skin necrosis with Betaseron (Interferon beta-1b), and the absence of such events with Avonex (Interferon beta-1a).

Analyses of the safety data submitted by Biogen in support of their PLA show that Injection Site Necrosis was not reported at all during the Phase 3 study (0%) in the 158 patients enrolled in the interferon group. In contrast, skin necrosis at the injection sites has become a concerning problem with Betaseron use in clinical practice, prompting a clinical report published in NEJM (332:1584, 1995). Injection Site Necrosis was reported as an adverse event in the Betaseron Phase 3 trial. It is described in the Package Insert, citing the 5% incidence in the 124 patients in the Phase 3 trial. If these incidences are treated as if events in a single trial and statistically comparable, then the difference in incidence rates is statistically significant ($p = 0.007$, Fisher's Exact test).

This has continued to be an ongoing adverse event reported in post-marketing ADR. In the period of 10/93 to 9/15/95, Berlex has received 216 reports of skin necrosis at injection sites. Many reports note multiple skin lesions. Reported lesion sizes range from 0.2 cm diameter to a 20 x 14 cm lesion, with most less than 4 cm diameter. The depth is usually into the subcutaneous fat, with some reports of lesions that extend to the underlying fascia. Little information was reported on management of the lesions, but at least 10% of the lesions required debridement, and some have required skin grafting to achieve healing.

The 5% skin necrosis incidence seen in the Betaseron Phase 3 trial occurred in 124 patients exposed for 2 years each. The phase 3 trial assessment of absence of skin necrosis Avonex is based upon the 158 patients exposed to Avonex in the pivotal trial for periods of 11 months to 2

years. Although the duration of exposure is somewhat less, this appears to be adequate to form a judgement. Among the post-marketing ADR reports of 216 skin necrosis events with Betaseron, the majority occurred within the first 6 months of Betaseron use. Very few of the reported durations-of-use prior to the ADR were greater than 1 year.

The evidence of a difference in skin necrosis incidence is strengthened by the consistency with incidence of Injection Site Reaction in the two pivotal trials. The Betaseron Package Insert cites 85% of patients with Injection Site Reaction (37% in the placebo group). The Biogen PLA reports that only 4% of Avonex patients (6/158) experienced Injection Site Reaction (compared to 1% in the placebo group).

Additionally, Biogen is currently conducting an open label safety study of Interferon beta-1a in multiple sclerosis patients. The study uses the same dose and regimen proposed for licensure, 30μg IM weekly. The product used in this study (C94-801) is the BG9418 material. Biogen submitted a safety update report on this study on March 15, 1996. The data-cutoff date was stated as February 16, 1996.

This report contains information on adverse events in the 274 patients enrolled in study C94-801. These constitute 204 patients previously enrolled in the Biogen pivotal trial (108 from the interferon group, 96 from the placebo group) and 70 patients not previously in the Biogen study (of whom 67 had prior exposure to Betaseron). The duration of treatment in C94-801 ranges from 1 to 29 weeks:

Weeks of Treatment	Number of Patients
1 to 3	3
4 to 7	18
8 to 12	38
13 to 25	116
26 to 29	99

The mean duration of treatment is 18 weeks, median 15 weeks.

In this study, 264 of 274 patients have reported at least one adverse event. Excluding MS exacerbations, there have been 12 Serious Adverse Events in 8 patients. Of these, only a single episode with 2 events (depression and fecal impaction in the setting of an acute exacerbation) was assessed as likely related to the interferon injections by the investigator.

Injection site reaction was reported by 4 patients (1%), and injection site inflammation by 1 patient (<1%). There have been no reports of injection site skin necrosis.

Thus, interferon beta-1a treatment in this study shows a safety profile consistent with that seen in the pivotal trial, and continues to have a better safety profile than interferon beta-1b with regard to the injection site skin necrosis.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

January 4, 1994

Berlex Laboratories, Inc.
Attention: Mr. Anthony Bourdakis
Director, Regulatory Affairs
15049 San Pablo Avenue, P.O. Box 4099
Richmond, CA 94804-0099

Dear Mr. Bourdakis:

Reference is made to your orphan product Betaseron® (interferon beta), which was designated an orphan drug pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 360bb) on November 17, 1988 (application #88-318) for the treatment of multiple sclerosis.

We also refer to the letter of December 14, 1993 from Chiron Corporation notifying us that joint sponsorship of this application has been transferred to you from Chiron.

This letter is to inform you that as the first sponsor of interferon beta to obtain marketing approval for this indication, you are entitled to seven years of exclusive marketing approval pursuant to Section 527 of the FFDCA (21 U.S.C. § 360cc) for the use of interferon beta in the ambulatory patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations. The exclusive seven year approval period began on July 23, 1993, the date of approval of your product licensing application (PLA 92-0495).

Please note that holders of exclusivity for approved orphan products are required to assure the availability of sufficient quantities of an orphan drug to meet the needs of patients. Failure to do so could result in the withdrawal of the drug product's exclusive approval [21 CFR 316.36(b)].

Please also note that the orphan drug regulations [21 CFR 316.27(b)] provide that anyone to whom rights under the Orphan Drug Act are assigned also must assume responsibilities under the Act. Hence, FDA will hold both Berlex and Chiron jointly responsible for compliance with the Act and FDA regulations since Chiron retains rights to exclusive marketing.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Director