

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103471

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

CHIRON

LOG NUMBER 693-003405
REFERENCE NUMBER 92-0495
VOLUME 1 DATE 5/11/93
COPY NUMBER 2 ORIGINAL 10
Return to CBER DCC - HFM-99

May 11, 1993

Kathryn C. Zoon, Ph.D., Director
FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Document Control (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Attn: _____

RE: **Product License Application Ref. No. 92-0495**
Betaseron (Interferon beta-1b)

Dear Dr. Zoon:

Reference is made to the request made to Dr. Suleman Verjee, Berlex Laboratories, by Dr. Jawahar Tiwari, Division of Biostatistics and Epidemiology, CBER, FDA on May 7, 1993. Enclosed is a copy of the cover letter and summary tables of baseline characteristics for patients participating in the third year of the Betaseron study sent on May 10, 1993 by Dr. Verjee in response to Dr. Tiwari's request.

If you have any questions, please call me at (510) 601-2757, or Dr. Sandra Patterson at (510) 601-2785.

Sincerely,

CHIRON CORPORATION



for | Bernardita Méndez, Ph.D.
Vice President, Regulatory Affairs
Responsible Head

000203



May 10, 1993

Berlex Laboratories

Division of Berlex Laboratories, Inc.

Dr. J. Tiwari
FDA/CBER
HRM 215, 400 North
1401 Rockville Pike
Rockville, MD 20852-1448

15049 San Pablo Avenue
P.O. Box 4099
Richmond, CA 94804-0099
(510) 262-5000
FAX: (510) 262-7054

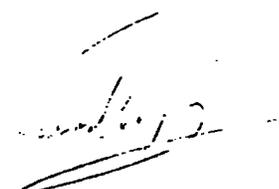
Dear Dr. Tiwari:

Based on the telephone conversation that we had last Friday, enclosed please find the baseline comparisons among treatment groups for patients who participated in the third year of the Betaseron Study. To facilitate your review, I have taken the liberty to attach similar results which were submitted to the Agency earlier and are based on the entire study population.

These results clearly indicate that the baseline characteristics of the subgroup of patients who participated in the third-year of the Study are comparable among the three treatment groups and that these characteristics are similar to those of the entire study population.

Please feel free to call me at (510) 262-5068 if you have further questions.

Sincerely yours,


Suleman S. Verjee, Ph.D.
Senior Director, Biostatistics and Data Management

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Summary of Demographic and Baseline Disease Characteristics
for Patients who were Included in the Three-Year Report
and who participated in the Third-Year of the study.

Parameter		Betaseron			p-value*
		Placebo (n=90)	9 mIU (n=94)	45 mIU (n=94)	
Sex	Female	62	65	65	0.999
	Male	28	29	29	
Race	Caucasian	84	89	89	0.985
	Other	6	5	5	
Age (yr)	Mean	36.0	35.3	35.1	0.692
	Std err	0.7	0.7	0.7	
Baseline weight** (kg)	Mean	68.9	70.4	71.1	0.470
	Std err	1.7	1.7	1.8	
Age at diagnosis	Mean	31.8	30.9	30.4	0.354
	Std err	0.6	0.7	0.6	
Disease duration (yr)	Mean	4.2	4.5	4.7	0.853
	Std err	0.4	0.5	0.4	
Baseline EDSS	Mean	2.8	2.8	3.0	0.888
	Std err	0.1	0.1	0.1	
Baseline Scripps	Mean	81.8	82.4	81.1	0.979
	Std err	1.2	1.2	1.1	
No. Exacerbations	Mean	3.3	3.3	3.3	0.851
	Std err	0.1	0.1	0.2	
Day since last exacerbation	Mean	142.9	142.6	154.1	0.699
	Std err	12.8	12.1	11.7	

mIU = million IU

* Two-sided p-values, for sex, age, and previous exacerbations determined using Cochran-Mantel-Haenszel Chi-square, stratified for site. ANOVA of ranks used for all other variables.

** Placebo n=88, 9 mIU n=93

000205

Summary of Demographic and Baseline Disease Characteristics

Parameter		Placebo (n=123)	Betaseron		p-value*
			9 mIU (n=125)	45 mIU (n=124)	
Sex	Female	88	85	86	0.836
	Male	35	40	38	
Race	Caucasian	116	116	116	0.928
	Other	7	9	8	
Age (yr)	Mean	36.0	35.3	35.2	0.598
	Std err	0.6	0.7	0.6	
Baseline weight (kg)	Mean	68.9**	69.3**	70.3	0.668
	Std err	1.5	1.4	1.5	
Age at diagnosis (yr)	Mean	32.1	30.6	30.5	0.050
	Std err	0.6	0.7	0.6	
Disease duration (yr)	Mean	3.9	4.7	4.7	0.102
	Std err	0.3	0.4	0.4	
Baseline EDSS	Mean	2.8	2.9	3.0	0.721
	Std err	0.1	0.1	0.1	
Baseline Scripps	Mean	81.1	80.8	80.6	0.997
	Std err	1.0	1.1	1.0	
No. Exacerbations in last 2 yrs	Mean	3.6	3.3	3.4	0.704
	Std err	0.1	0.1	0.2	
Days since last exacerbation	Mean	134.9	140.8	157.9	0.326
	Std err	10.3	10.2	10.8	

mIU = million IU

* Two-sided p-values, for sex, race, and previous exacerbations determined using CMH Chi-square, stratified for site. ANOVA of ranked data used for all other variables.

** N=121 for placebo, N=124 for 9 mIU

000206

TB01-3103/TB01-3104
April 8, 1993
Page 26

**Summary of Baseline MRI Comparisons for Patients who were
Included in the Three-Year Report**

		Placebo	Betaseron		p-value
			9 mIU	45 mIU	
All patients (n=372)**	n	119	124	120	0.831
	Mean	2450	2643	2296	
	Std err	210	275	185	
Patients Participating in Third-Year only (n=278)**	n	88	93	92	0.560
	Mean	2372	2386	2337	
	Std err	241	302	204	

mIU-million International Units

*Based on ANOVA performed on ranked data.

**This represents the total of patients. The sum of the number of MRI's will be less than this number because of missing MRI results

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MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE: May 3, 1993

FROM: J. Lloyd Johnson, Pharm.D. JAJ
DEL, HFM-207, 295-9049

TO: Dr. Andy Lerner, Chairman, Interferon beta,
Ref. Nos. 92-0495, 92-0494, DCB HFM-5050

Dr. Theresa Gerrard, Acting Director, DCB, HFM-505

RE: Chiron Revised Interferon Beta Environmental Assessment Report

I have reviewed the revised April 28, 1993 revised Chiron Environmental Assessment Report (EAR). The Office of Orphan Drug Products has given an orphan designation to Chiron's Interferon beta-1b for the treatment of multiple sclerosis. The designation for the treatment of a rare disease exempts Chiron from the requirements specified under 21 CFR 312.31a item 7-11 and therefore review comments on my memo of October 27, 1992 no longer needs to be addressed except for the need to describe procedures regarding proper handling and disposition of used needles and syringes as well as the environmental impact of used drug vial containers resulting from patient administration.

The revised EAR satisfactorily addresses the above remaining comment.

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beta-ea2

000119

Food and Drug Administration
Division of Cytokine Biology
8800 Rockville Pike
Bethesda, MD 20892

Center for Biologics Evaluation and Research
Building 29A, Room 3C22
301-496-0894
301-402-1659 (telefax)

MEMORANDUM

TO: Chairman, PLA committee for the use of Betaseron in MS

FROM: David S. Finbloom, MD

SUBJECT: Review of Safety Update

DATE: 30 April 1993

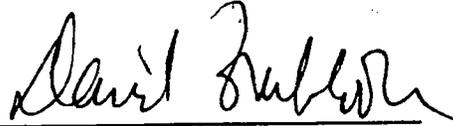
1. The overall percentage of adverse events was similar in the updated material as compared to the initial documents in the PLA. Generally flu-like symptoms such as fever, malaise, myalgias were significantly more in the treatment group. Again injection site reactions were very prominent with 85% of the 45 MU group having some type of injection site event.
2. The sponsor has provided information on notable events (severe and life-threatening). Only two (fever and myalgia) were significantly associated with treatment, occurring in a small percentage of patients (8% and 7%, respectively).
3. Transaminases were elevated in a greater percentage of treatment patients (15% vs 5%), but were generally of grade II severity with 6 patients overall having grade III reactions. Three subjects were withdrawn for elevated liver enzymes (treatment arm unknown). Likewise the percentage of patients with low ANC was greater in the treatment group (18% vs 5%). Again, they were mostly grade II severity, with only two patients overall having grade III severity.
4. There were 17 withdrawals for adverse events for a variety of indications. These included arrhythmia, elevated liver enzymes, nausea, injection site reactions, fatigue, and suicide (1). Five patients had suicide attempts with one death (the only death on study). The treatment arm on all these patients is still blinded.

In summary, the safety profile of the updated report reflects what was submitted previously. These patients have many symptoms some of which are significantly associated with Betaseron treatment. Very few patients overall require dose-reductions (17) and only 17 were discontinued because of toxicity. The 5 patients who had suicide attempts were not separated out by treatment arm. These data should be provided and, if the 5 patients were all on Betaseron, a warning

000211

should be included in the package insert. It is well documented that depression is observed with the alpha interferons. ~~_____~~

~~_____~~ In addition, there should be adequate discussion of the injection site reactions in the package insert.



David S. Finbloom, MD

Food and Drug Administration
Division of Cytokine Biology
8800 Rockville Pike
Bethesda, MD 20892

Center for Biologics Evaluation and Research
Building 29A, Room 3C22
301-496-0894
301-402-1659 (telefax)

MEMORANDUM

TO: Chairman, PLA committee for the use of Betaseron in MS

FROM: David S. Finbloom, MD 

SUBJECT: Safety

DATE: 27 January 1993

This summary represents the review of three volumes 6-8. Upon further examination, it appears that additional data on ADRs are available in vol. 50 and 59-62. These will have to be reviewed to determine if these volumes contain additional useful information.

Of 407 patients who participated in MS studies, there were 20 adverse event withdrawals for a percentage of 5%. Five of the 20 had fatigue while 3 had abnormal liver function, 2 had confusion, and 2 had injection site pain.

Details on the reasons for dose reduction (Table 6, p. 007 069) and adverse event withdrawals by cause (Table 8, p. 007 072) should be supplied by the sponsor. The individual data points for each dose group have not been supplied because it was "censored to preserve blind". Table 10 (007 074) and 12 (007 089) in vol. 7 need to be updated supplying all available information. Table 14, vol 7 (007 092) needs to be broken down by dose of drug or placebo.

As far as laboratory adverse events, there were considerably more patients with elevated transaminases and depressed neutrophil counts in the 45 MU dose group. Elevated SGOT was observed in 15% of placebo and 30% in the 45 MU dose, likewise elevated SGPT was seen in 20% of placebo and 46% of the 45 MU dose group. The portion of patients experiencing a "notable" abnormalities was not provided and should be submitted by the sponsor (Table 12, 007, 090). 40% of the patients in the 45 MU group had low neutrophil counts compared to 12% in the placebo group.

As of the safety cutoff date of 7-31-91, 73% of the patients were still enrolled in the Betaseron

000209

or placebo treated groups. Since this represents a sizable portion of the study patients, we should request an updated safety report prior to labelling.

In conclusion, the overall safety profile is consistent with drugs in the IFN category with adverse events centering around flu-like symptoms of fatigue, fever, myalgia, arthralgia and leukopenia and elevated hepatic enzymes. Since MS patients have these symptoms as part of their disease process, many of these events were also observed in the placebo group. These events seemed to be reasonably well tolerated since there were few (5%) withdrawals from study due to drug toxicity. Of note there is a considerable percentage (63-69%) of patients that experience injection site inflammation. Many of the dose reductions secondary to toxicity were because of injection site reactions. Also of note is the high percentage of antibodies against the drug. By elisa all (99%) patients get antibodies. Of these 40% had neutralizing antibodies. Since as I interpret the data, the safety cut-off date was 7-31-91, an updated safety report should be submitted prior to licensing and labelling.

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JUN 3 1990

DATE:

FROM: Director, Office of Drug Evaluation I, HFD-100
Center for Drug Evaluation and Research

SUBJECT: Betaseron (PLA 92-0495)

TO: Janet Woodcock, M.D.
Director, Office of Therapeutics Research and Review,
Center for Biologics Evaluation and Research, HFM-500

Introduction:

The Director and Deputy Director of the Division of Neuropharmacologic Drug Products have provided memos concluding that the effectiveness of Betaseron in reducing exacerbation rates in MS has been demonstrated. Both have hesitated specifically to assess approvability, as that depends in part on such matters as the need for carcinogenicity studies and the relevant ADR experience for betaseron in non-MS uses, matters for which CBER has knowledge and responsibility. Assuming that other clinical experience with Betaseron indicates an acceptable rate of adverse effects and that carcinogenicity studies are unnecessary/impossible, we would expect CBER to consider these memos as a basis for approval.

Strength of the Evidence:

The HFD-120 conclusion, in agreement with the Peripheral and Central Nervous System Advisory Committee, that effectiveness has been shown should not obscure the difficulties in reaching that conclusion. While NDA's and PLA's may meet a standard that has somewhat different specifics, we all plainly have an interest in a consistent evidentiary standard. By either CDER's usual "replication" standard (one way to describe evidence of adequate strength) or CBER's "strength of the evidence" standard, the direct evidence of clinical benefits is not robust. The effect is fairly small, albeit clinically meaningful; more important, its presence is somewhat analysis-dependent. For example, effectiveness is not demonstrated for the "exacerbation-free" analysis if verified exacerbation events, which were the events contemplated in the protocol, are used, or if patients who were in the study only briefly (less than 6 months) and who would have little likelihood of an

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exacerbation, are excluded. This is also true for the "time to first exacerbation" endpoint. On the other hand, the "exacerbations per subject" endpoint is significant for high dose vs placebo and vs low dose for both verified and total exacerbations, a supportive consistency.

We need, as an Agency, or at least as CDER and CBER, to confront the two studies/strength of the evidence standard. There is no doubt that CDER has relied on a single multi-center study for critical effectiveness conclusions, and the Clinical/Statistical Guideline is explicit on this (p. 15), saying that sometimes studies could not be repeated on ethical grounds. The guideline cites the timolol post-infarction study as an example, noting its very high degree of statistical significance and excellent design; the guideline could have added that there was consistency across study sites and across disease severity subgroups. Given the willingness of Berlex to carry out the additional studies you have asked for (Dr. Latts' letter of May 10, 1993 to Dr. Mendez), it would be hard to argue that there are ethical constraints on the conduct of further studies. But ethical constraints are not the only situations in which we have relied on a single multi-center study. We have recognized, although not consistently, that a multi-center study is not exactly the same as a single-center study and have talked about consistency within clinics, etc. We have explored such devices as randomizing clinics into sub-studies, looking at the first half (in entering time) and the last half of the study separately, etc. While I have contributed to, even encouraged, such discussions, they (now at least) seem rather beside the point. It is obvious that a multi-center study with an extreme p-value will usually stand up to such divisions (you get an extreme p-value because there's a big, consistent difference), unless one large center is carrying the whole study, a special, and easily recognized case. In any event, consistency within a multi-center study is a kind of replication. This is relatively easy when the study is "over-designed" and has several large clinics that show statistical significance by themselves (see Dr. Nevius' discussion of selegiline, an HFD-120 drug for Parkinson's Disease approved on the basis of a single multi-center study a few years ago) but is also a consideration when, as in the case of Betaseron, the sub-studies (U.S. and Canada) are trending favorably. (We have, somewhere, in the past, but I haven't found it yet, talked of "trends", e.g., $p < 0.1$, for the sub-studies; one could also argue that such sub-analyses could use one-sided tests, given the overall two-sided result).

In the Betaseron data there is a second kind of replication, the MRI results, which are more or less persuasive, depending on one's beliefs. At a minimum, as Dr. Leber says, these data are an independent measurement that supports the clinical finding, a kind of within-study replication. At best, they are evidence of an effect far more important

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than the modest effect on exacerbations. I certainly am not qualified to choose between these interpretations, but our advisors seem to believe the latter, even though all would agree that, strictly, the correlation of improved clinical outcome and improved MRI has not been made.

Conclusion:

On balance, it appears to me that the elements of consistency/replication are sufficient to consider Betaseron effective under CDER, as well as CBER, rules and practices, although, as noted, it is a very close case unless one accepts the MRI data as a surrogate for an important effect on morbidity, a plausible/reasonable view, but one not proved.

It would be possible, I believe, to grant approval under the Accelerated Approval Regulations, which allow this procedure where a surrogate or clinical, but non-ultimate endpoint is the basis for approval. This possibility should be considered, even at this late date, for several reasons:

1. Although the clinical benefit shown is real and of value by itself, and one could argue that the studies conducted as a condition of accelerated approval would not affect that conclusion, even if they were negative, the surrogate did strongly influence the Committee's conclusion that effectiveness had been demonstrated by the single multi-center study. A failure to show benefit in the post-approval studies, Berlex has agreed to shake that conclusion. At a minimum, the present data base would need to be revisited.
2. The agreements already made by Dr. Latts will answer the critical questions about long-term effects on disability and go a long way toward assessing the MRI surrogate. Moreover, pre-clearance of advertising, an extra problem for a drug approved under the accelerated procedure is already part of CBER requirements. The accelerated approval would not add to the sponsor's burden. The only extra burden faced by the sponsor would be the risk of accelerated withdrawal, not very likely unless results are unequivocally bad.
3. If the MRI surrogate is not acknowledged as part of the decision, it seems hard to explain why it could be used at all in promotion. If the surrogate result was part of the basis for approval, it

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would be hard to describe it as a validated surrogate, but easy to describe as a reasonable one. Accelerated approval would easily allow a full, but candid description of the MRI data in labeling and promotion.

I realize this is a very late suggestion and that the Committee did not find the accelerated approval procedure necessary for approval, certainly a basis for declining to invoke the procedure. If conventional approval is granted:

1. The study commitments should be referred to specifically in the approvable letter and the sponsor urged to meet soon with CDER/CBER to firm up the protocols.
2. The sponsor should be reminded that promotion should not emphasize the MRI data until it is validated or until disability effects are documented.

I have made a variety of labeling suggestions.



Robert J. Temple, M.D.

cc:

Dr. Peck
Dr. Leber
Dr. Katz
Dr. Rouzer-Kammeyer

Attachments:

1. Nevius speech on selegiline
2. Letter: Berlex (Latts) to Chiron (Mendez)-May 10, 1993
3. Marked-up labeling

000331

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE: June 24, 1993
FROM: Jay P. Siegel, M.D.
TO: Reference Number 92-0495
SUBJECT: Review MRI Scanning Data

Attached is Dr. Siegel's review of Magnetic Resonance Image Scanning Data for two studies of sequential MRI done as substudies of the Phase III trial of Interferon beta-1b in patients with MS.

Magnetic Resonance Image (MRI) Scanning Data

PLA #92-0495 includes data from two studies of sequential MRI both done as substudies of a Phase III trial (TB01-35686 and TB01-35886) of IFN- β_{ser} in patients with relapsing, remitting multiple sclerosis. One MRI study included all patients enrolled in the trial and involved scanning on admission, at one year, and at two years (as well as after the third extension year). The second MRI study involved only patients enrolled at the University of British Columbia and patients were scanned every 6 weeks. Although patients from all three arms of the trial were studied, data from the from patients in the placebo and 8 m IU arms are summarized here. Data from patients in the 1.6 m IU arm were generally intermediate.

In the first study, all scans on each patient were read in parallel by the same observer after the two year period. Lesions were identified and outlined by this reader and confirmed by neuroradiologists, blinded to the subject's treatment arm. Data were presented as the sum of areas of lesions on all cuts for each patient. Means of these sums and their changes over time were submitted in the PLA but can be misleading because: 1) different study sites used different equipment and took cross-sectional images of different thickness and closeness making comparisons difficult and 2) the range of total lesion areas was not normally distributed and a small number of patients with large lesions areas and large changes had disproportionate impact upon the means. To avoid these problems, MRI data were reanalyzed in terms of percent change from baseline for each patient (excluding the small number of patients with no lesions at baseline) and in terms of the dichotomous outcome variable of improved (less total area) or worsened from baseline. These analyses follow.

	PLACEBO	IFN- β_{ser} 8 m IU	p-VALUE	
Area change*, 1 year	17% \pm 4% [†]	3% \pm 4% [†]	0.03	Student's t
Area change, end [‡]	34% \pm 7% [†]	14% \pm 6% [†]	0.03	Student's t
Area change*, 1 year	9% [§]	-7% [§]	0.0002	Wilcoxon rank
Area change, end [‡]	17% [§]	1% [§]	0.0005	Wilcoxon rank
Patients improved, 1 yr.	39%	54%	0.004	Fisher's exact
Patients improved, end	23%	48%	0.0001	Fisher's exact

N for placebo was 96 at baseline, 95 at 1 yr., and 96 at end; for IFN- β_{ser} , 95 at baseline, 94 at 1 yr., 95 at end

* Area change = (total lesion area/baseline total lesion area) - 1

[†] mean \pm standard deviation

[‡] end = MRI scan at 2 years or last MRI scan prior to two years

[§] median

Data were presented from third year of follow-up on some patients. These data are difficult to interpret because films were not reread in parallel with earlier films and systematic drifting in assessments of lesion size (toward smaller values) appears to have occurred. Also, substantial numbers of patients did not have a year 3 film. Thus, precise analysis is impossible; it is noted

that patients on the IFN- β_{ser} arm who were scanned appeared to do at least as well or better than control patients in the third year.

In the substudy, 17 subjects on the placebo arm and 17 on the IFN- β_{ser} 8 m IU arm received scans every 6 months during the first 2 years of study and were assessed for new enlarging or recurrent lesions. All scans were performed on the same equipment and read by the same reader. The incidences of new lesions, enlarging lesions, recurrent lesions, and active lesions (any of the prior three) were all higher in the placebo arm than in the IFN- β_{ser} 8 m IU arm, typically by 2 to 3 fold.

The significance of MRI scanning data in multiple sclerosis is uncertain. While MRI defined lesions correlate reasonably well with pathological lesions found at autopsy, the extent or development of lesions does not correlate well with the occurrence of an exacerbation. It is felt that MRI scanning identifies cerebral disease while most clinically apparent exacerbations result from extracerebral demyelination. Indeed, some evidence suggests that subtle psychometric or cognitive testing does reflect changes in the cerebral MRI scan. Thus, while changes in MRI scan are not validated as surrogates for changes in clinical status or course, they appear in conjunction with clinical data to provide relevant supportive data regarding the extent of the disease process.

Jay P. Siegel
24 JUN 93

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Department of Health and Human Services
Public Health Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: April 5, 1993

From: Susan A. Vargo, Ph.D., Acting Director, DEL HFM-205 *SMV*

Subject: Chiron Corporation's PLA (92-0495) and ELA (92-0494) submissions for recombinant human interferon beta.

To: Andrew Larner, M.D., Ph.D., LCR, DCB, HFM-508

The following information has not been submitted by Chiron for our review.

PLA (submission of 3/9/93)

1. Pages 7 - 8: Chiron is in the process of identifying the _____ of the High Molecular Weight species. Request for this information should be included in the list of commitments. Lack of this information should not preclude licensure.
2. Page 9: The ELISA assay for interferon beta prior to the _____ stage should be completed by April 1993.
3. Page 11: The assay for aggregates in the final container material has not been developed and release specifications for the percent aggregates allowed have not been determined by Chiron. This could be handled in the commitment letter and submitted as part of the scale-up amendment. The process change may impart on the percent aggregated in the final product. Chiron will need to amend their stability protocol to include percent aggregates.

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4. Page 18: The _____ has not been resolved and must be prior to licensure. Chiron has completed the _____ validation study. Dr. Lloyd Johnson will call Chiron and ask if any material has been filled and stoppered using the new procedure; and if there is stability data available using the _____ procedure.
5. Page 20: Two issues concerning _____ need to be resolved prior to licensure:
 - A) _____
 - B) _____

It is unclear as to whether _____ is complying with these requirements.

ELA (submission of 3/17/93)

1. Pages 1 - 2: The shipping validation study should be completed in March. This should be reviewed prior to licensure.

All other review responsibilities assigned to me for Chiron's PLA/ELA for interferon beta have been completed and the data submitted by the firm are satisfactory.

cc: _____

Dr. Theresa Gerrard, DCB (HFM-505)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE: October 27, 1992

FROM: J. Lloyd Johnson, Pharm.D. *JLJ*
DPC, HFB-240, 295-8431

TO: Dr. Andy Larner, Chairman, Interferon beta,
Ref. Nos. 92-0495, 92-0494, DCB HFB-800
Dr. Theresa Gerrard, Acting Director, DCB, HFB-800
Dr. Susan Vargo, Deputy Director, DCB, HFB-800

RE: Chiron Interferon Beta Environmental Assessment Report

I have reviewed the May 5, 1992 Chiron Environmental Assessment Report (EAR). In general the report provided insufficient information to meet the requirements specified under 21 CFR 25.31a. Additional information should be provided with respect to estimates of concentrations and quantities of solid and liquid substances used in manufacture, waste deactivation and disposition procedures along with an assessment of the expected environmental impact resulting from administration and use of the product. The EAR should be revised to include the following:

Introduction of substance into the environment:

1. Page 374; In addition to listing gaseous emissions expected to be emitted during the fermentation and purification process, please provide a brief description of the your facility's containment measures and procedures designed to prevent release of viable organism into the environment.
2. Pages 375-376; please provide the estimated quantities by weight or volume of each of the various identified solid and liquid substances that would be discharge to waste treatment facilities as a result of production processes. Quantities for each substance emitted should be estimated per maximum batch size and should not be given merely as percentages.
3. Pages 374-377; a listing and disposition procedures of all materials used and quantities discharge per maximum batch size for substance used in processing equipment, cleaning reagents, solvents, commercial detergents, acid and base cleaning solutions, column resins, buffers, pharmaceutical grade waters etc. should also be included.

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4. Page 376; please describe inactivation and disposal procedures for rejected batches as well returned goods.

Fate of emitted substances and effects of released substances in the environment:

1. Please provide a brief description of how the product is administered and the expected biodistribution, metabolism and excretion profile of this drug.
2. Please provide a description of environmental effects of the product with respect to disposition of used containers and released degradation products resulting from patient administration.
3. Since this product will be patient administered in the home setting, describe procedures regarding proper handling and disposition of potentially infectious materials such as used needles and syringes. Additionally, please provide an estimate of the maximum concentration of product expected to enter the environment as a result of use for treatment of multiple sclerosis and provide an assessment of the environmental effects.

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c:beta-eal

000118

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE : MAR 5 1993

FROM : Inspectors: Margaret A. Tart, Blair A. Fraser, Ph.D. and J. Lloyd Johnson, Pharm D. *Blair A. Fraser*

SUBJECT: Chiron Response to Inspectional Findings
E.I. Dates: February 1-5, 1993; Reference No. 92-0495 - Betaseron (Interferon beta-1b)

TO : Chairperson, Licensing Committee (HFM-805) ² *3/10/93*

THRU : *zmt* Chief, Biological Product Inspections Branch (HFB-655)
Acting Director, Division of Establishment Licensing (HFM-205)
Acting Director, Division of Cytokine Biology (HFM-505)

We have reviewed and evaluated the letter from Chiron, which was in reply to the FDA-483 - List of Observations, dated February 5, 1993.

The written statement of corrective actions, which have been taken to correct the deficiencies noted during the prelicensing inspection, appear adequate and complete.

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**REVIEW AND EVALUATION OF CLINICAL DATA
PLA SAFETY REVIEW**

PLA: _____

Sponsor: Berlex Laboratories/Chiron Corporation

Drug: Betaseron (Recombinant Human Interferon Beta)

Indication: Relapsing-remitting Interferon Beta

Date of Submission: May 22, 1992

Date Review Completed: March 5, 1993

Data Cut-Off Date: July 31, 1991

1.0 Sponsor's Proposed Labeling Indication, Dosage Form, Route of Administration, and Directions for Use

Betaseron is indicated for use in the treatment of relapsing-remitting multiple sclerosis (MS) in patients 18 years or older. Relapsing-remitting MS is characterized by recurrent attacks of neurologic dysfunction followed by complete or incomplete recovery. Controlled studies indicate that Betaseron in the recommended doses results in significant reduction in exacerbation rates in patients with this disease.

Betaseron is a purified, lyophilized protein product manufactured by recombinant DNA techniques and formulated for use by injection. The recommended dose of Betaseron is 45 mIU injected subcutaneously every other day. Each vial contains 0.3 mg of interferon beta. The lyophilized product is reconstituted with 1.2 ml of Sodium Chloride, 0.54% Solution. After reconstitution with diluent, Betaseron vial contain 45 mIU/ml recombinant interferon beta.

2.0 Background

The safety database of Betaseron is large (N=3067), with only a fraction (roughly 15%) contributed by the indication of Multiple Sclerosis. Please refer to Sponsor's Figure 1 for orientation. Because safety experience in MS and non-MS subjects was qualitatively and quantitatively different due to underlying disease, safety data from the MS group is analyzed separately from the non-MS studies.

This summary includes data up to July 31, 1991. To preserve the blind of the ongoing studies, data are censored as necessary. Wherever censoring precludes comparison of the treatment groups, incidence in the total subject group is discussed.

From 1983 to July 31, 1991 (safety cut-off date), the total experience with use of Betaseron in Berlex-sponsored clinical trials encompasses 3067

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subjects (2326 Betaseron, 741 PBO) enrolled in 73 various clinical studies. These studies evaluated Betaseron treatment at a wide range of doses and by both parenteral and non-parenteral routes. Major indication areas were MS, HIV infection, solid tumors, hematologic malignancies, condyloma, and miscellaneous other viral infections. The majority of these patients are derived from open-label and compassionate use studies.

The sponsor has organized the safety summary for Betaseron in the following manner. The integrated summary of safety (ISS) reviews data for all subjects treated in Berlex-sponsored studies, while the integrated safety database (ISD) was limited to studies with systemic routes of administration and generally comparable treatment regimens or populations. Thus, the ISD is comprised of the three MS studies and 52 studies in the non-MS group (1708 subjects), and excludes 21 studies (1359 subjects, 77% of whom were treated intranasally) in the Other Studies group. The Integrated Safety Summary (ISS) is depicted as ordered in strata by indication/analysis groups in Figure 1.

For the integrated safety database (ISD), enrollment by major indication group is as follows: 407 subjects (130 placebo, 277 active drug) in three MS studies; 587 subjects in 28 solid tumor studies; 66 subjects in seven hematologic malignancy studies; 598 subjects (134 placebo, 464 active drug) in nine HIV studies; and 50 subjects (4 placebo, 46 active drug) in three condyloma studies.

An additional 1359 subjects (21 studies) were enrolled in various other trials, including those evaluating Betaseron treatment in rhinovirus and other viral infections. These studies are classified in a group known as "Other Studies" in this application. Investigator-sponsored studies (approximately 1300 subjects in 39 studies) include all data available to Berlex as of July 31, 1991.

The pivotal Phase III MS study began enrollment in June 1988 and enrolled 372 subjects. One interim and a final analysis were completed based on the first 338 subjects enrolled. Safety information for the additional 34 subjects is captured in this integrated safety summary for MS.

3.0 Source of Studies

3.1 MS Studies

The clinical development program of Betaseron in MS consists of three ongoing double-blind studies which provide safety data for 277 MS subjects.

A total of three studies have now been conducted, with an enrollment of 407 subjects (including PBO): a pilot study, the Phase III trial in the U.S. and in Canada, and the ongoing Phase III studies, TB01-3103 and TB01-3104. Enrollment in TB01-3103 and TB01-3104 was limited to subjects previously enrolled in the pivotal Phase III trial. All studies were double-blind and placebo-controlled, and Betaseron was administered

subcutaneously. Doses ranged from 4.5 to 90 mIU, and were given every other day, or three times weekly.

1986: (Protocol TB01-16486) Phase I placebo controlled pilot study. 31 patients, dose ranging study in relapsing-remitting Multiple Sclerosis (MS). 3 year study, dose levels (4.5, 22.5, 5, 45, 90 mIU). Study amended to allow a fourth year of open-label treatment (placebo subjects were crossed over to receive 45 mIU). 23 patients completed the 2 year study, 19 completed up to 4 years as of March of 1990.

June 1988: 372 subjects, Phase III randomized, double-blind placebo-controlled, multicenter trial (2 year study).

Protocols: US sites---Protocol TB01-35686
 Canadian Sites---Protocol TB01-35886
 Total subjects: 372

Subjects: relapsing-remitting MS randomly assigned to receive 104 weeks (2 years) of therapy by every other day subcutaneous injection with either placebo or 9 or 45 mIU of Interferon beta.

June 1990: 1 year follow up study

Protocols: US sites---TB01-3103
 Canadian sites---TB01-3104

1 year follow up study to evaluate disease progression changes, long term disability of patients enrolled in the 2 year study. Same dosing schedule.

The Pilot study was subsequently converted to open-label and four placebo subjects transferred to active drug. For the analyses presented here, the initial experience for these four subjects is included with the placebo group while experience after crossover is included with medium-dose active drug. Thus, a total of 407 subjects appear in this analysis, four of whom are counted twice.

In January 1989, Berlex initiated protocols for two additional Phase III studies, Study TB01-3103 (U.S.) and TB01-3104 (Canada), with enrollment limited to participants in the initial Phase III trial. Only subjects previously enrolled in either Study TB01-35686 or Study TB01-35886 are eligible to enroll in these additional studies. Studies TB01-3103 and TB01-3104 provide for two cohorts. Group A subjects continue treatment as assigned in either Study TB01-35686 or Study TB01-35886. Group B consists of subjects who either withdrew from the pivotal studies before 104 weeks or completed 104 weeks and chose not to continue treatment in Studies TB01-3103 and TB01-3104. Subjects in Group A are to continue receiving study drug and be followed for at least 48 weeks. At completion of 48 weeks, they may elect to continue dosing and follow-up for another year. Those in Group B will be followed without study therapy for 48 weeks and then terminate.

Enrollment in Studies TB01-3103 and TB01-3104 began in August 1990. As of July, 1991, 273 subjects who completed the pivotal trials had elected to participate in Studies TB01-3103 and TB01-3104. This data is still blinded.

3.2 Non-MS Studies

Sixty-eight non-MS studies, with a total of 2660 subjects, were conducted under Berlex sponsorship. Most of the studies were open-label. Three studies (two Phase II and one Phase III study) were placebo-controlled, and included 286 Betaseron-treated subjects and 138 placebo-treated subjects. In the non-MS studies, Betaseron was administered by intranasal, intravenous, subcutaneous, intramuscular, intracerebral, intraventricular, intravesical, and topical routes. Doses in the clinical trials ranges from 0.1 to 990 mIU. Most subjects were treated on daily, alternating day, five times weekly, or three times weekly schedules.

The non-MS systemically-treated population was composed of a diverse group of subjects, the majority of whom had advanced, usually fatal, disease. Because safety experience in MS and non-MS subjects was qualitatively and quantitatively different due to underlying disease, safety data from the MS group is analyzed separately from the non-MS studies. The non-MS studies were subdivided even further by indication, and the placebo-controlled studies were reviewed separately from the uncontrolled studies.

4.0 Integrated Summary of Safety vs. Integrated Safety Database.

Although the integrated summary of safety (ISS) reviews safety data for all subjects treated in Berlex-sponsored studies, the integrated safety database (ISD) was limited to studies with systemic routes of administration and generally comparable treatment regimens or populations. Thus, the ISD is comprised of the three MS studies and 52 studies in the non-MS group (1708 subjects), and excludes 21 studies (1359 subjects, 77% of whom were treated intranasally) in the Other Studies group.

Five groups of Betaseron studies (Table 1) have been excluded from the Integrated Safety Database. Three groups were excluded because the route of study drug administration (intranasal, topical, and intracerebral) precluded meaningful comparison of effects. The fourth group, titled "Unusual Studies," includes trials conducted in normal volunteers and children, and two studies with unusual dosing regimens involving another agent or modality. The fifth group is made up of one intravesical and three intravenous studies for which methodology did not meet Berlex standards of conduct; these studies are classified as "Not Adequate." Total enrollment for this group of studies was 1359 subjects, 1052 of which represent subjects in intranasal studies.

The Other Studies Group consists of 1359 subjects in 21 clinical trials evaluating treatment in diverse diseases with various doses and routes of administration. These studies were excluded from the ISD for any of the following reasons: the route of drug administration precluded meaningful comparison of effects; the trials included normal volunteers or children;

the study regimens involved another agent or modality; or the methodologies did not meet Berlex standards.

For non-MS studies, the integrated safety database includes a total of 1301 subjects entered in 47 clinical trials evaluating Betaseron treatment. Of these, 1163 subjects received Betaseron. These studies focused on four major disease areas: HIV infection, solid tumors, hematologic malignancies, and condyloma. In three placebo-controlled studies, 138 subjects received placebo and 286 subjects received Betaseron. In 42 Phase I and II open-label studies and two blinded studies that were not placebo-controlled, 877 subjects received Betaseron.

5.0 Dosage and Administration

Multiple Sclerosis

All MS studies employed the subcutaneous route of administration. The Phase I placebo-controlled pilot trial was a dose-ranging study employing multiple dose levels (4.5, 22.5, 45, 90 mIU) in 31 patients. From that experience, two doses, 9 and 45 mIU, were selected for the Phase III multicenter efficacy trial in 111 and 115 subjects, respectively.

6.0 Overview of Clinical Population and Studies which are the Source of MS Safety Data

There are three ongoing studies in MS:

1986: (Protocol TB01-16486) Phase I placebo controlled pilot study. 31 patients, dose ranging study in relapsing-remitting Multiple Sclerosis (MS). 3 year study, dose levels (4.5, 22.5, 5, 45, 90 mIU). Study amended to allow a fourth year of open-label treatment (placebo subjects were crossed over to received 45 MIU. 23 patients completed the 2 year study, 19 completed up to 4 years as of March of 1990.

June 1988: 372 subjects, Phase III randomized, double-blind placebo-controlled, multicenter trial (2 year study).

Protocols: US sites---Protocol TB01-35686
 Canadian Sites---Protocol TB01-35886
 Total subjects: 338

Subjects: relapsing-remitting MS randomly assigned to receive 104 weeks (2 years) therapy by every other day subcutaneous injection with either placebo or 9 or 45 mIU of Interferon beta.

June 1990: 1 year follow up study
 Protocols: US sites---TB01-3103
 Canadian sites---TB01-3104

1 year follow up study to evaluate disease progression changes, long term disability of patients enrolled in the 2 year study. Same dosing schedule.

A total of 403 subjects with relapsing-remitting MS received placebo or Betaseron therapy in three studies: a pilot study, a pivotal Phase III trial in the U.S. and in Canada, and an additional Phase III study, TB01-3103 and TB01-3104, also in the U.S. and Canada (Table 1). Enrollment in studies TB01-3103 and TB01-3104 was limited to subjects previously enrolled in the pivotal Phase III trials. All studies were double-blind and placebo-controlled. The Pilot study was subsequently converted to open-label and four placebo subjects transferred to active drug. For the analyses presented here, the initial experience for these four subjects is included with the placebo group while experience after crossover is included with medium-dose active drug. Thus, a total of 407 subjects appear in this analysis, four of whom are counted twice.

Demographics

Ninety-four percent of the placebo and 93% of each of the Betaseron groups were Caucasian, and 72%, 66%, and 67%, respectively, of the placebo, low- and medium-dose, Betaseron groups were female (Table 2). Twenty-eight percent of subjects had received no previous therapy for MS; 61% had received steroid therapy prior to study entry; 5% had miscellaneous other previous treatments. The median age of subjects who received medium doses of Betaseron was 35 years and for the other two groups, 36 years (Attachment B).

Treatment Profile

Betaseron or placebo was self-administered by subcutaneous injection on an alternate-day schedule in 372 subjects and three times weekly in the remaining 35. Approximately one-third of the subjects were in each treatment group: placebo (130), low-dose (130), and medium-dose Betaseron (147). Six subjects in the Pilot Study initially received 90 mIU Betaseron. Of these, four were dose-reduced within 6 weeks of entry and the remaining two within 6 months (see interim report for Study TB01-16486). For this integrated summary, all data for these six subjects are analyzed with the medium-dose group.

7.0 Extent of Exposure to Betaseron

Multiple Sclerosis

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All experience in the three MS studies (TB01-16486, TB01-35686, TB01-35886, TB01-3103, and TB01-3104) through July 31, 1991 yields a total of 407 study subjects: 130 randomized to placebo, 130 to low dose (0 to 44 mIU) Betaseron and 147 to medium dose (45 to 89 mIU) Betaseron. The median duration of treatment for the integrated MS experience is 24 months. Median time on study was 722 days for the placebo group, 724 days for the low-dose group, and 727 days for the medium-dose group. (Table 5). As of the data cutoff date, 19 subjects had been on study for 4 or more years, 300 for more than 2 years, and 361 for at least 1 year).

8.0 Overview of Discontinuations- Multiple Sclerosis Studies

Discontinuations are classified according to the following categories in the following sections:

8.1 Deaths

There were no deaths on study or within 30 days of last dose in the pilot or pivotal Phase III trials or their extension.

8.2 Discontinuations due to ADR

Sixty-five subjects (19%) either withdrew or were withdrawn from treatment for reasons other than study completion. Withdrawals due to adverse events showed a dose-response effect with one, five, and ten withdrawals, respectively, for the PBO, low-dose, and high-dose. Only four adverse event withdrawals were required by protocol; all others were subject initiated. Protocol-required withdrawals were for recurrent LFT elevation, cardiac arrhythmia, urticarial skin reaction to the injections, and dysaesthetic pain at the injection site.

In addition to the 16 subjects who withdrew for adverse events, four other subjects for whom reason for withdrawal was noted as "subject decision for any reason other than adverse events" also had notations at withdrawal that could indicate adverse events. These were mild injection site reaction (Subject 402), recurring flu-like symptoms (Subject 302),

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decreased stamina (Subject 301), fatigue (Subject 506), and events related to disease progression (Subject 249).

The following table depicts the 49 withdrawals for reasons other than the 16 withdrawals due to adverse events:

WITHDRAWAL EVENT	N
Subject decision for perceived increase in disease activity	13
Physician-initiated for increased disease activity	4
Use of steroids beyond protocol limits	11
Use of protocol-restricted concomitant therapy	2
Other subject-initiated reasons	10
Protocol entry violation	3
Lost to follow-up or non-compliant with protocol	6
	<u>49</u>

Maintenance of the blind precludes discussion of treatment assignment for these subjects. With the exception of use of steroids beyond protocol limits, these withdrawals were spread evenly over the treatment arms. The placebo group had significantly more subjects withdraw for use of steroids than the Betaseron groups. The first two categories of perceived disease activity may also be considered lack or loss of efficacy.

8.2 Hospitalizations

When hospitalization for MS-related events are excluded, there were relatively few serious events. In all, 58 subjects had 104 hospitalizations for MS-exacerbation related events (45, 32, and 27 in the PBO, 9 and 45 mIU groups respectively). Frequency of non-exacerbation related hospitalizations (30 subjects, 36 events) was evenly distributed across groups (13, 8, and 14 for the PBO, 9 and 45 mIU groups, respectively) excluding one subject with a hospitalization for pneumonia.

	In-Patient Hospitalizations*			Total
	Placebo	9 mIU	45 mIU	
MS-related				
No. subjects	26	15	17	58
No. events	45	32	27	104
Non-MS				
No. subjects	11	8	10	29**
No. events	13	8	14	35**

* Total subject count exceeds 77 since some subjects experienced events in both categories.

** One subject hospitalized for pneumonia not shown.

8.3 Dose-Reduction

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13/338 subjects (4%) required a dose reduction for toxicity. In 7/13, the dose-limiting event was injection-site related. 10/13 completed the study without further incident.

Of the 407 total subjects, 25 (6%) had a reduction in study drug dose (Table 6). The most common event contributing to dose reduction was injection site necrosis, which occurred in seven subjects. Other injection site events led to, or contributed to, dose reduction in five more subjects. Events that were cited as a reason for dose reduction are summarized in the following table. Subjects with more than one dose-limiting event are counted separately for each event.

**Dose-Limiting Events **
(N=407)**

<u>Event</u>	<u>N*</u>	<u>(%)</u>
Injection site events	12	(3)
Flu-like symptoms	6	(1)
Neurologic symptoms	4	(1)
Subj/physician decision or error	4	(1)
Elevated liver enzymes	3	(1)
Palpitations	1	(<1)
Chest tightness	1	(<1)

* Subjects with multiple dose-limiting events are counted separately for each event

** Blinding in ongoing studies precludes display by treatment group

8.4 Adverse Events

There were two categories of significance: injection site reaction and systemic flu-like syndrome consisting of fever, myalgia, malaise. Discontinuations due to adverse events comparing MS v. other treatment groups are as follows. A higher incidence of adverse event withdrawals occurred in categories other than MS and condyloma, as tabulated below. To a certain extent, this difference reflects association of the events with underlying disease processes rather than with therapy.

Adverse Event Withdrawals by Indication/Analysis Group					
MS	Solid Tumor	Hematologic	HIV	Condyloma	Other
N=407	N=587	N=66	N=464	N=46	N=252
N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
20 (5)	113 (19)	13 (20)	126 (27)	2 (4)	43 (17)

Pilot Study

Over the approximately 3 years of the pilot study (the interim report cut-off), 19/31 subjects continued on treatment. Of 12 withdrawals, two discontinued due to adverse events (fatigue and confusion), both withdrawals occurring within 24 weeks. The small size of placebo group provided limited statistical power for comparison of incidence rates of adverse events between dosage groups. The only adverse events clearly associated with Betaseron treatment ($p < .05$) are those related to the injection site.

Integrated Analysis-Pilot Study Plus Multicenter Study

In the integrated analysis, there were a total of 20 subjects who withdrew for reasons related to adverse events (summarized in the following table). Flu-like symptoms, such as fatigue, "felt sick," flu syndrome, and headache, accounted for 40% of adverse event withdrawals.

Summary of Adverse Event Withdrawals* (N=407)		
Clinical or Laboratory Withdrawal Event	Subjects N	w/Event (%)
Fatigue	5	(1)
Abnormal liver function	3	(1)
Confusion	2	(<1)
Injection site pain	2	(<1)
Allergic reaction	1	(<1)
Cardiac arrhythmia	1	(<1)
Felt sick	1	(<1)
Flu syndrome	1	(<1)
Headache	1	(<1)
Nausea	1	(<1)
Pain	1	(<1)
Unspecified events	1	(<1)
Total	20	(5)

* Blinding precludes display by treatment group in ongoing studies.

In the pivotal multicenter efficacy trial, a total of 16 subjects withdrew for adverse events. These withdrawals showed a dose-response effect, with one, five, and ten withdrawals, respectively in the PBO, 9 and 45 mIU groups. Except for injection site reactions, incidence for most adverse

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events was equally distributed across groups. The few adverse events that were significantly associated (<0.05) with Betaseron treatment at the effective dose of 45 mIU are summarized in the following table:

Event	Placebo (N=112) N (%)	Betaseron	
		9 mIU (N=111) N (%)	45 mIU (N=115) N (%)
Fever	38 (34)	44 (40)	67 (58)
Chills	20 (18)	22 (20)	51 (44)
Myalgia	27 (24)	27 (24)	47 (41)
Sweating	10 (9)	11 (10)	22 (19)
Malaise	4 (4)	9 (8)	17 (15)

* Excludes injection site events

With time, incidence of treatment-related flu-like symptoms in the 45 mIU group decreased to levels comparable to those in placebo subjects.

Other Serious Adverse Events

Systemic effects were the most common across all strata, encountered in almost 50% of non-MS subjects and 4.7% of the MS subjects. However, these were qualitatively different between the MS and non-MS groups. In non-MS subjects, leading in frequency were systemic symptoms associated with administration of Betaseron: fever, asthenia, chills and headaches. In contrast, attempted suicide emerged as the most common serious adverse event for the MS group, occurring in five subjects (1%). One of these was a Betaseron-treated subject in the unblinded pilot trial; the treatment group for the other 4 subjects remains censored. The only incident of attempted suicide in the non-MS group was in an HIV subject.

Overall, incidence of notable (severe or life-threatening) adverse events was low. Headache and asthenia were the only notable events that occurred in more than 5% of the total population. Notable fever, myalgia and pharyngitis were significantly associated with Betaseron treatment in a three-way comparison of all groups, but there were no notable events that were statistically associated with Betaseron therapy at effective dose in a two-way comparison with placebo.

In all, 77 subjects experienced one or more serious events (total 142 events). Most of these events, 99% (140/142) were classed as serious

because of an associated hospitalization. Of these, 74% (104/140) were hospitalizations for MS exacerbations or symptoms and 26% (36/140) were for conditions not directly related to an MS exacerbation, as detailed in the following table.

In-Patient Hospitalizations*				
Betaseron				
	Placebo	9 mIU	45 mIU	Total
MS-related				
No. subjects	26	15	17	58
No. events	45	32	27	104
Non-MS				
No. subjects	11	8	10	29**
No. events	13	8	14	35**

* Total subject count exceeds 77 since some subjects experienced events in both categories.

** One subject hospitalized for pneumonia not shown.

As in the pivotal studies, notable events were relatively rare for the integrated MS experience. The only events of this severity that were significantly associated with Betaseron treatment were fever, myalgia, and injection site inflammation. Notable pharyngitis was not treatment associated in the pooled MS experience.

Injection site reactions were reported in 222 of 338 subjects. Twelve (12) of 222 subjects had events that were considered severe and only three had events that resulted in withdrawal from the study (allergic reaction, pain, and dysesthetic pain with atrophy). Injection site events, including those significantly associated with treatment at the effective dose, are detailed in the following table.

Injection Site Events in Subjects receiving Betaseron				
Preferred Term	Placebo (N=112) N (%)	Betaseron		
		9 mIU (N=111) N (%)	45 mIU (N=115) N (%)	
Any event	37 (33)	89 (80)	96 (83)	
Inflammation*	7 (6)	70 (63)	79 (69)	
Pain*	17 (15)	27 (24)	39 (34)	
Reaction*	4 (4)	17 (15)	25 (22)	

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Hemorrhage	16 (14)	22 (20)	17 (15)
Hypersensitivity*	3 (3)	13 (12)	17 (15)
Edema	1 (1)	4 (4)	6 (5)
Mass	3 (1)	2 (2)	3 (3)
Necrosis	# (3)	#	# (total 3%)**

* Significantly associated ($p < 0.05$) with Betaseron treatment at the effective dose.

** Treatment group results censored (#) to preserve the blind.

Comment

The firm supplied tabulations of discontinuations due to adverse events which were reviewed. In the opinion of this reviewer, these cases were discontinued for reasons that include common, well-known adverse effects of interferons, effects not related to study drug (concurrent medical illness), or reasons which were otherwise unremarkable from the standpoint of this review.

9.0 Pregnancy

There were two cases of spontaneous abortion, one occurring 14 days after last dose of Betaseron in a female among 1052 subjects in the intranasal studies.

10.0 Overdose

There has been no experience with massive overdose of Betaseron. No evidence or experience suggests that abuse potential or physical or psychological dependence occurs with Betaseron therapy. There is no evidence of deliberate overdosage. Betaseron has been given safely to adults at individual intravenous doses as high as 990 mIU, three times weekly.

11.0 Neutralizing Antibody (NAB)

The development of neutralizing antibody activity did not appear to influence response to therapy as measured by exacerbation rate, time to first exacerbation, or disability scores.

12.0 Laboratory Values

Protocol-defined toxicity grades were used in the safety analysis. The Clinical Scale for Interferon Toxicity was employed to capture laboratory abnormalities. This is a severity scale with four levels of increasing toxicity (1 to 4) for the laboratory categories of hematologic, hepatic, renal, and metabolic. In the event of grade 3 or 4 toxicity on this scale, dosing was to be interrupted. When the toxicity

level had fallen to grade 2 or less, therapy could be reinstated at a 50% reduction for each subsequent dose unless toxicity occurs during doses 1-7 (i.e., patient is terminated from the study). Dosing was to remain at the 50% level unless toxicity increases to Grade 3 or 4 again, at which time the patient must be terminated from the study. Dosage reescalation may not occur following dosage reduction.

Laboratory parameters were examined for change from baseline to last value. Differences among treatment groups in the change from baseline to last value were assessed using the ANOVA of ranks Model 1. For most parameters, frequency of notable events could not be compared among treatment groups because of the paucity of 3 or 4 grade toxicity. Thus, to characterize the safety profile, treatment groups were compared for incidence of events of a severity of grade 2 or greater.

Clinically significant laboratory abnormalities were rare, as were notable (grade 3 or 4) values. In the MS population, leukopenia, neutropenia, notable lymphopenia, and elevated SGOT and SGPT were significantly associated with Betaseron administration.

Lymphopenia was the most pronounced treatment-related effect of Betaseron therapy. Many subjects were mildly lymphopenic at baseline and mean lymphocyte count dropped in all three treatment groups while on-study. However, during study treatment, notable (grade 3/4, 500-999 lymphocytes) lymphopenia was seen in a greater portion of the 45 mIU group as compared to 9 mIU and placebo subjects. Comparison of treatment groups for on-study grade 2 or greater toxicity showed a significantly higher incidence of lymphopenia in Betaseron-treated groups, with the highest incidence in the 45 mIU arm. By last value, incidence of grade 2 or greater lymphopenia had declined in all three treatment groups, although incidence remained highest in the 45 mIU group. The sponsor suggests that on-study lymphopenia was sporadic rather than due to a cumulative effect of Betaseron.

Summary of Lymphopenia

	Betaseron								
	Placebo (N=112)			9 mIU (N=110)			45 mIU (N=115)		
	Grade 2	3/4	Total (%)	Grade 2	3/4	Total (%)	Grade 2	3/4	Total (%)
Baseline	26	4	(27)	26	5	(28)	33	6	(34)
On-study	47	26	(65)	52	32	(76)	42	50	(80)
Last value	30	2	(29)	37	5	(38)	40	11	(44)

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Because of the paucity of notable events, treatment groups were also compared for incidence of grade 2 or greater toxicity (1000-1,499 lymphocytes). Lymphopenia of grade 2 or greater severity was associated with Betaseron treatment. This comparison also showed treatment-related ($p < 0.05$) decreases in WBC and ANC (absolute neutrophil count) and elevations in SGPT and SGOT in Betaseron-treated subjects. However, the mild leukopenia and neutropenia seen was asymptomatic.

Notable liver function abnormalities (see Attachment 1) occurred in five subjects, with only one occurring after a grade 2 event requiring study drug withdrawal. Elevation of LFTs resulted in a protocol-required withdrawal for one subject and subject-initiated withdrawals for two others. Treatment assignment for these subjects remains blinded.

Treatment-related effects were also seen in other hematology values. For change from baseline to last value, differences between treatment groups were significant for hemoglobin, platelet count, WBC, and absolute neutrophil count (ANC). In all three treatment groups, mean values for hemoglobin and platelet count decreased from baseline, with the greatest decrease in the high-dose arm for both parameters. For WBC and ANC, mean values for the placebo group rose while the mean values for the active treatment groups decreased, with the counts for low-dose group decreasing slightly more than those for the high-dose group.

Changes in mean hemoglobin, WBC, ANC, and platelet values were statistically, but not clinically significant. Other than one notable ANC value (a result of improper sample handling), there was only one subject with a notable value for any of these hematologic parameters; this subject had one sample that showed both leukopenia and neutropenia. As compared to placebo, significantly more subjects in the Betaseron groups experienced grade 2 or 3 toxicity for WBC and ANC, again with the highest incidence in the high-dose group. However, there were no grade 4 events and the lower grade of leukopenia and neutropenia seen were not associated with any reported clinically significant events.

For serum chemistry parameters, significant differences among treatment groups for change from baseline to last value were seen for SGOT, SGPT, albumin, bilirubin, and chloride. Significant differences among groups in SGOT and SGPT were a result of mean increases from baseline to last value of 3.5 IU/L for SGOT and 11.1 IU/L for SGPT in the high-dose group. Despite these mean increases, more than 90% of subjects had values within the normal range at last value.

The safety profile for laboratory events was also similar to that seen in the analysis of the pivotal trials. In the integrated experience, abnormalities in six parameters were significantly associated with active-drug treatment: depressed and WBC; elevated SGOT and SGPT; low calcium; and high uric acid. Although incidence of abnormal lymphocyte count was comparable across treatment groups, lymphopenia of notable level was significantly associated with Betaseron administration.

Comment

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Monitoring of CBC should be included in the Laboratory Section of the labeling. Frequency of monitoring needs to be determined.

13.0 Discontinuations due to ADR

The firm supplied tabulations of discontinuations due to adverse events which were reviewed. In the opinion of this reviewer, these cases were discontinued for reasons that include common, well-known adverse effects of study drugs (as discussed later), effects not related to study drugs (concurrent medical illness), or reasons which were otherwise unremarkable from the standpoint of this review.

A higher incidence of adverse event withdrawals occurred in categories other than MS and condyloma. To a certain extent, this difference reflects association of the events with underlying disease processes rather than therapy.

In MS subjects, most adverse event withdrawals (12 of 20) were due to systemic (Body) events. Fatigue accounted for five of the withdrawals. Injection site adverse events resulted in two withdrawals. Other adverse event withdrawals occurred in Gastrointestinal System (elevate liver enzymes (3), nausea (1)), CNS (confusion,(2), Cardiovascular (arrythmia,one), and unspecified (1).

Six subjects attempted suicide while on study: five were MS subjects (1.2%) and one was an HIV subject (0.2%) enrolled in the uncontrolled trial. One suicide attempt occurred in a Betaseron-treated subject in the MS pilot study; the treatment group for the other four MS subjects remains censored.

Spontaneous abortion (2) was the most significant urogenital adverse event reported in the Betaseron trials.

13.0 Safety in Non-MS Studies

Betaseron has been delivered by various routes (subcutaneous, intramuscular, intravenous) over a wide range of doses (0.1 mIU to 990 mIU/dose) for up to 7 days per week. Over 1000 subjects with HIV infection, advanced solid tumors, leukemia or condyloma acuminata have been treated. Qualitatively and quantitatively the adverse events seen with these cohorts appeared to be influenced by certain factors such as underlying disease, dose intensity, route of drug administration.

The only large placebo-controlled, blinded study was carried out in a population of HIV-injected subjects with advanced disease. Similar to the MS-controlled studies, the events significantly associated with Betaseron therapy in the HIV-controlled study were chills, fever, myalgia, and injection site events. Additional treatment-associated events in the HIV population only were tachycardia and dehydration. No grade 3 or 4 laboratory events were associated with Betaseron in these controlled trials.

Ninety (7.7%) subjects died either on study (29 subjects), or off study but within 30 days of last dosing (61 subjects; Table 6). These deaths occurred among 16 of 464 (3%) HIV subjects and 74 of 653 (11%) subjects

with cancer. In the controlled (HIV) studies, deaths in the placebo group slightly exceeded deaths in the treated group (6.0% vs 5.0%). There were no deaths in the condyloma group.

The following tabulation summarizes deaths on study or within 30 days of last dose of study drug. All deaths occurred in subjects with glioma, advanced non-small-cell lung cancer, recurrent brain tumors, renal cell carcinoma, and Kaposi's sarcoma. In order to be consistent with other analyses, some studies were excluded from the following table: intranasal, topical, Study CSC-8984 (bladder cancer), and Study CSV-1184 (chronic hepatitis). There were no deaths on these studies or on Study TB01-23484 (hairy-cell leukemia).

- Deaths occurred exclusively in subjects with cancer and HIV, predominantly as a consequence of disease progression (7% of 1369 Betaseron-treated non-MS subjects). A lower incidence (2% of these subjects) of fatalities was associated with adverse events either related to the underlying disease, drug effects, or other undetermined causes.
- The dropout rate due to adverse events was 21% in the non-MS population (as compared to 5% in the MS population). Although the reasons for study withdrawal varied, the majority were related to systemic adverse events commonly associated with Betaseron.
- Serious adverse experiences occurred in 62% of non-MS subjects (as compared to 11% of MS subjects). The gravity of the underlying diseases in this group probably accounts for the higher incidence of serious adverse events in this population as compared to the MS group.

Many events in these populations were more likely related to underlying or disease-related problems than to drug-related adverse events.

14.0 Summary and Conclusions

It is a difficult task to compare the safety experience of Betaseron in 407 multiple sclerosis patients with such a large, (N=3007) heterogenous study population and types of clinical trials conducted with disparate sets of requirements. What we can learn from examination of that non-MS experience pertains to dose and duration of treatment.

Another factor apart from population demographics that merits consideration in assessing the differences in the incidence of serious adverse events among Betaseron-treated subgroups is dose. MS subjects were dosed for a much longer interval than other indications, while the effective dose was smaller than that used in the other indications. Considering the pooled safety database, the MS (and condyloma) subjects were among those who received the lowest dose (<45 mIU) as compared to the rest of the study population (>45 to 990 mIU). Exclusive of dose intensity, duration of treatment did not appear to have a significant impact on the incidence or spectrum of serious events. The condyloma and

MS groups had the shortest and longest median time on study (26 and 72 days, respectively), yet had the lowest incidence of serious events. The impact of route of administration is demonstrated by the finding of serious injection site reactions almost exclusively in subjects with HIV, hematologic malignancies, and MS. Subcutaneous injection was the principal route of drug administration in nearly all (82% to 100%) these populations.

Due to the heterogeneous study population and types of clinical trials conducted with disparate sets of requirements, the inadequacy of available information, events other than deaths that occurred in the multiagent/modality studies cannot be compared in a quantitative fashion. In general, the disparity in the incidence of serious adverse events between the MS and non-MS subjects can be influenced by the subject age, status of health, nature and severity of the underlying disease.

The safety profile that emerged in this study of Betaseron in MS indicates that the majority of subjects can receive this therapy every other day chronically with very few subjects experiencing serious adverse events. The subject population was young and otherwise relatively healthy, and were treated at medium to low doses. There were no deaths in the two-year study. There was no severe or life-threatening morbidity. Most adverse reactions (aside from those well-known injection site and flu-like events associated with interferons) reported in the pivotal study were evenly distributed across blinded groups, suggesting that they were associated with MS. Hospitalization for MS-exacerbation related events showed a distribution supportive of increased drug benefit, rather than increased risk.

To conclude, the safety profile of Betaseron in multiple sclerosis is favorable. Monitoring of CBC may be useful.


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