To: BLA STN 103628/5021 (Biogen Avonex, Interferon beta-1a for MS)
From: Gary Kikuchi
Through: Elizabeth Shores, Chief LI, DTP, Barry Cherney, Deputy Director, DTP, Amy Rosenberg, Director, DTP EWS
Date: September 4, 2002

Immunogenicity Review for Avonex HuSA-Free Liquid Presentation Supplement

I. Administrative

sBLA Chairperson:	Melanie Hartsough
Immunogenicity Reviewer:	Gary Kikuchi
Clinical Review Team:	Cynthia Rask, Marc Walton
Pharm/Tox:	Dave Green, Anne Pilaro
Biostatistics:	Clare Gnecco
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Action due date: September 8, 2002

II. Summary

This sBLA submission (103628/5021) (HuSA-free supplement) is for a HuSA-free liquid presentation of Avonex, (Interferon beta-1a for multiple sclerosis). The following table summarizes the status of commercial preparations of interferon-beta:

Company	Trade Name	Generic name	Host cell	1o sequence	Glycos-ylated	Route	US license
Biogen	Avonex	IFN-beta-1a	CHO	Native	Yes	IM	Approved
Berlex/Chiron	Betaseron	IFN-beta-1b	E.Coli	Ser17Cys	No	SubQ	Approved
Serono	Rebif	IFN-beta-1a	CHO	Native	Yes	Sub Q	Approved

The immunogenicity assay used in this HuSA-free supplement is the one fully described in another supplement, STN 103628/5008 (NAB supplement), which is currently under review with an action due date of November 12, 2002. A two part screening method is used, an ELISA screening assay and a neutralization assay. Complete assay methods and validation are described in a review dated August 21, 2002 of the NAB supplement.

The immunogenicity information contained in the HuSA-free supplement is from clinical trial C98-844. This was a multi-center, single-arm, open label study of 153 MS patients (intent-to-treat basis) treated with serum-free Avonex at 30 mcg weekly IM. Presence of antibodies was determined using the assays described briefly below. The sponsor stated that the incidence of immunogenicity observed in this clinical trial with the liquid formulation was similar to the incidence found in previous clinical trials found with the lyophilized formulation of Avonex (BG9418). There were no revisions in the immunogenicity section of the label submitted with this sBLA.

Overall Problems/Caveats/Comments regarding this supplement.

There are no overall revisions to the immunogenicity section of the label recommended by the sponsor in this supplement, and revisions have been submitted to sBLA STN 103628/5008. The only immunogenicity information is contained within interim analysis of clinical trial C98-844. The rate stated by the sponsor differs from that determined by independent CBER analysis of the database, and this discrepancy should be discussed with the sponsor. A milestone for submission of the complete database should be set.

III. Summary of Immunogenicity assay information

The assays used to assess product immunogenicity are described in reviews dated January 24, 2002 and August 21, 2002 of the NAB supplement. The Biogen assay uses two steps, a screening ELISA and a neutralization assay. These assays are briefly summarized as follows:

1. Biogen Screening ELISA. [redacted]

2. Biogen Neutralization Assay. Neutralizing antibody is detected by its ability to neutralize the protective effect of interferon beta in a cytopathic effect (CPE) assay. [redacted]

Complete methods and validation for these assays have been submitted to sBLA STN 103628/5008 (NAB supplement) and are reviewed in a document dated August 21, 2002.

VI. Clinical Immunogencity information

153 MS patients were enrolled in clinical study C98-844 and were to receive Avonex pre-filled syringes (30 mcg IM weekly) for up to three years. Key demographics of the patient population were 79% female, mean age 39.6 years, median time since onset of MS symptoms 6 years, 2.4 relapses during the 3 years prior to study entry, and mean EDSS score at entry 2.4. Interim data is reported in the sBLA, including 127 patients that had NAB data up to 12 months. 12 months is stated by the sponsor to be adequate to evaluate the immunogenicity of Avonex.

In the clinical summary, the sponsor states that 5/150, (3.3%) of the patients had neutralizing titers >=5 at some time during the course of the study.

Problems/Caveats/Comments:

Close examination (in collaboration with the statistical reviewer) of the clinical database, ——— provided by the sponsor, yields an incidence rate that differs slightly from that stated by the sponsor. The following table shows all neutralizing titers greater than zero for the clinical trial:

Neutralizing titers greater than zero in C98-844 by month						
	Month					
	9	12	15	18	21	24
102003	0	0	0	30	270	ND
106003	ND	0	0	4	0	ND
106007	ND	5	30	13	13	ND
106009	0	0	30	0	0	ND
204001	0	23	270	810	810	ND
301014	2	0	0	0	0	ND
307006	0	0	4	0	ND	ND
307007	0	0	0	30	ND	ND

Five patients, 102003, 106007, 106009, 204001, and 307007, had positive titers greater than or equal to 5 during the trial.

Clear discernment of the denominator on which to base the incidence rate is made more difficult by the fact that only interim analysis is provided. The sponsor states that 12 months is an appropriate interval for monitoring neutralizing titers; however only 1/5 patients had a positive titer at 12 months. All of the 5 patients had positive titers within the 18 month time period. However, because only interim analysis is provided, only 128 patients had data available at 18 months. Based on this, a more appropriate estimate of the incidence rate for titer >=5 is 5/128 (as treated basis, 18 months) or 3.9%, which differs slightly from the sponsor's stated rate of 3.3%. However, this is a minimum estimate, and patients may need to be followed for a longer time period.

The sponsor then compares the incidence of immunogenicity of the liquid formulation with the incidence observed in previous clinical trials. In all of the following trials, the patients were treated with BG9418, rather than BG9015, and the Biogen, rather than the ——— assay was performed:

Sponsor Analysis					
Study	# of subjects	Study Name	Formulation	Titer >=5	Titer >=20
C98-844	150	Antigenicity of liquid formulation	Pre-filled syringe	3.9%	3.3%
C94-801	83	Safety extension	Lyophilized	8.4%	6.0%
———	———	———	———	———	———
C95-812	178	Monosymptomatic	Lyophilized	3.4%	1.7%

[ ]

C95-812 is a study to determine if Avonex is beneficial in delaying onset of symptoms in patients experiencing a first and recent demyelinating event. The clinical study has been fully reviewed. However, the final form of labeling, including potential revisions to the Avonex indication, are currently in dispute resolution with Biogen. In addition, according to the medical reviewer for this study, ———

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C98-801 is an ongoing open-label study in patients from the phase 3 trial that were not treated with Avonex, in which subjects with MS are treated up to 56 months. This is the most appropriate study for comparing the incidence rates. In sBLA 103628/5008/5004 page 14 and 971 the sponsor states that the immunogenicity incidence rate for trial C98-901 was 7%. Based on a 95% confidence interval, the incidence is 2-14%. The rate observed in C98-44 lies within the 95% confidence interval for C98-801. Based on this, it can be concluded that the observed immunogenicity rate for C98-44 is not significantly different that observed in C98-801. However, the rate is different from that described using the ——— assay on BG9015, which is the incidence rate currently described in the label.

V. Labeling

Since the incidence of immunogenicity in clinical trial C98-844 was similar to that found previously, there were no revisions to the immunogenicity section recommended by the sponsor with this supplement. The immunogenicity information is not changed from the previous version, which cites a 24% incidence of immunogenicity, based on data from the phase 3 Roswell Park clinical trials using the BG9015 interferon beta-1a product that predates BG9418 (Avonex.) The text of this section reads:

SERUM NEUTRALIZING ACTIVITY
Throughout the placebo-controlled multiple sclerosis study, serum samples from patients were monitored for the development of Interferon beta-1a neutralizing activity. During the study, 24% of AVONEX®-treated patients were found to have serum neutralizing activity at one or more time points tested. Fifteen percent of AVONEX®-treated patients tested positive for neutralizing activity at a level at which no placebo patient tested positive. The significance of the appearance of serum neutralizing activity is unknown.

Since revisions to the text of the immunogenicity section are the subject of sBLA 103628/5008 (the NAB supplement), approval of any final changes to the Avonex label should be contingent on approval of that supplement.

Comments to Sponsor:

1. The Biogen assay for antibodies to Avonex used in clinical trial C98-844 in this supplement consists of a screening ELISA, using a [redacted] and a neutralizing antibody assay. The [redacted] may have the potential for steric hinderance of antibodies from patients treated with interferon beta-1a. This concern is supported by data you have published that the capture antibody neutralizes anti-viral activity of interferon beta-1a, and that at least one clinical sample is not positive in the [redacted] ELISA but positive in an ELISA of different design. To address this issue, please provide to the BLA quantitative information regarding the following:

    a. The percentage of IFN-β1a treated individuals (defined using appropriate statistics) whose sera contain antibodies that are blocked by the anti-Avonex [redacted] antibody.

    b. Within those individuals whose antibodies are blocked or partially blocked, the proportion of patient [redacted] antibodies that are blocked by the [redacted] antibody.

2. You have stated that 5/150 patients in clinical trial C98-844 were positive for antibodies to Avonex, based on interim12-month data. However, our analyses of the database reveal that

    a. 4/5 of these patients had titers that were positive only at 15 months or after, and that 128 patients in the trial had antibody data collected at 15 months. Therefore, we calculate the incidence rate of patients with antibody titers >=5 as 5/128 or 3.9%.

    b. the incidence rate of antibodies in patients treated with interferon-beta 1a should be expressed based on analysis of samples collected at a minimum of 18 months of treatment.

    Please comment.

3. Please provide a milestone for submission to CBER of the final immunogenicity results from clinical trial C98-844.