

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service



Food and Drug Administration

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STN 103628/5021.0

Date: August 14, 2002

From: Melanie Hartsough, Ph.D., DTP

Through: Blair Fraser, Ph.D., DTP *7/14/02 8/28/02*

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(B2R) 8/28/02

Manufacturer: Biogen, Inc

Product: Interferon beta-1a (AVONEX®)

Indication: Relapsing forms of Multiple Sclerosis (intramuscular injection, 30 μ g/ml))

Submission Category: Prior Approval Supplement

Purpose: Addition of an alternate HSA-free liquid formulation in a pre-filled syringe

Reviewers:

- Product: Melanie Hartsough
- Immunogenicity: Gary Kikuchi
- Clinical: Cynthia Rask
- Clinical Pharmacology: Martin Greene
- Pharm/Tox: Anne Pilaro
- Facility: Deborah Trout
- Biostatistics: Clare Gnecco
- RPM: Victoria Tyson-Medlock

Summary:

1. Overview

This supplement requests a change to a product formulation that is free from human serum albumin (HSA). The new formulation is a liquid interferon beta-1a (IFN- β -1a) drug product (BG9418-____) packaged in pre-filled syringes. It is produced from an acetate drug substance, which is manufactured from the commercial phosphate drug substance (BG9418) used to make the current commercial lyophilized product. BG9418-____ was developed as an alternative to currently approved AVONEX lyophilized drug product.

Below is the CMC review

2. Acetate Drug Substance

A. Description

IFN- β -1a is expressed in a Chinese hamster ovary cell line and has one carbohydrate moiety attached at _____. Among ____ cysteine residues, ____ is known to be free, and _____. In addition to the carbohydrate heterogeneity, N- and C-terminal truncation, deamidation, oxidation, and

Table 1.5.2-1 Physical Characteristics of Acetate Drug Substance Compared to Phosphate Drug Substance

	Acetate Drug Substance	Phosphate Drug Substance
Buffer Composition	• Sodium acetate _____ as acetate/acetic acid) _____ arginine HCl	• Sodium Phosphate _____ as phosphate) _____ NaCl
pH	_____	_____

B. Manufacturing

Biogen manufactures the acetate drug from the phosphate drug substance. The phosphate drug substance is manufactured at the currently-approved Biogen, Inc. facilities in Cambridge, MA, and _____ The acetate drug substance is manufactured at the Cambridge, MA facility and then shipped to _____ for final formulation and filling to produce BG9418- _____



C. Process Validation

Process validation was performed on — consecutive batches _____ of acetate drug substance manufactured at the Biogen Cambridge, MA facility. There was a process yield of —

D. Transport Validating

The average transit time from Cambridge, MA to _____ The transport carton was validated to hold the acetate drug substance temperature —) for — , allowing for a significant safety margin for any in-transit delays.

E. Comparability Study (comparison of acetate and phosphate drug substance)

Comparison of validation acetate drug substance batches _____ clinical batch _____ reference standard _____ and phosphate drug substance batches in Table 1.3.7-4 at the end of the review. The analyses were performed using the protein characterization techniques described in PLA No. 95-0979 (Section 4.13.5.1, Vol. 5, September 25, 1996). The comparability study presented in the supplement consisted of a comparison between _____ and reference standard batch _____. The raw data are contained in sections 1.5.2.1-1.5.2.10.

Reviewer's Comment:

_____ was comparable to the reference standard and phosphate drug substance in all assays (see table 1.3.7-4 for summary).

F. Stability

- The approved expiry date of the phosphate drug substance is — months at —
- The sponsor proposes that the expiry date for the acetate drug substance be — months from the date of manufacture. The recommended storage temperature is —
- Biogen has presented results for _____

The drug substances were stored either at — for — months or at — for — months.

• All test results were within specifications. There were no trends observed. One note is that the results of the _____ for the clinical batch increased at — months due to a change in the method, optimized for the acetate drug substance.

- The commercial stability protocol outline is below

Reviewer's Comment:

The results for all acetate drug substances were consistent from lot to lot and were stable over all time points from — months — to — months —. Biogen's proposed expiry date of — months for the acetate drug substance, when stored at — is acceptable.

3. HSA-free drug product

A. Formulation

It was necessary to modify the drug product formulation because IFN- β -1a in the liquid version of the phosphate saline pH 7.2 formulation without HSA showed susceptibility to —. An extensive developmental stability program lead to the final formulation of 60 μ g/ml INF- β -1a, 20 mM acetate, 150 mM arginine hydrochloride, and 0.005% w/v polysorbate 20 at pH 4.8, and is pre-filled in a glass syringe for a 0.5 ml volume (30 μ g) IM injection dose.

B. Manufacturing

There are three _____ manufacturing facilities in _____ (1) the production facility in _____ location _____ (2) the warehouse and packaging area in _____ location _____ and (3) the production facility in _____ maintains a Type V Drug Master File under the Number _____ and has provided Biogen authorization to reference this document.

The acetate drug substance, produced at the Cambridge, MA facility, _____ and shipped to _____ where it is stored at the _____ warehouse facility until use. The acetate drug substance is then transferred to the _____ facility in _____ for manufacturing of the drug product. The _____ acetate drug substance is _____

_____ formulation vessel, _____, and held at _____ before filling into sterilized syringes. For filling, the formulated IFN- β -1a is _____ into _____ sterilized syringe barrels with tip caps. A plunge stopper is then placed into the syringe barrels to form the drug product. Final packaging is then performed at _____. The chemical and analytical laboratories are at the facility in _____. Approximately _____ of formulated solution are required to fill a batch size of _____. syringes.

•Unlabeled Filled Syringes are stored at 2-8 °C prior to packaging. The syringes are stored at _____ or at Biogen's _____ facility / _____

•Labeling and Packaging occurs _____

•The Distributors are _____ and _____ Biogen _____

•Biogen, Inc. stores the pre-filled syringe drug product after manufacture at _____ for US and Canadian production.

1. In process testing

•Testing _____

_____ were performed and outlined in Table 1.4.8-2.

•In process testing for the filled syringes include _____

2. Release Tests (see below)

*Sponsor notes: As per the USP guideline, injections packaged in pre-filled syringes and cartridges are exempt from testing for particulates.

Reviewer's Comment:

The sponsor reported that when measuring the amount of IFN- β -1a in BG9418- _____ by _____ analysis for release testing, _____ were detected, only with syringe lots containing _____. tip caps. Analysis of the _____ cap confirmed that the impurities were a result of the cap. The _____ was found to contain _____

while the _____ was found to contain a compound composed of _____

_____ . The manufacturer of the tip caps has confirmed _____ as ingredients in the tip caps. The sponsor states that the amounts of _____ in the drug product are approximately a million times lower than the corresponding LD₅₀ limits for these compounds, based on animal toxicity data provided in the Material Safety Data Sheet for _____. The amounts of these materials do not seem to be a safety concern.

[] Note: I sent a request for concurrence to the pharm/tox reviewer on 8/16/02. Subsequently, I called Biogen, per pharm/tox reviewer's request, to ask for the quantitation of these impurities expressed as amount per dose (8/21/02). The amounts are as follows: []

Reviewer's Comment:

The sponsor reported that the _____ IFN- β -1a species¹ will not be determined for the liquid drug product "since the processing of the phosphate drug substance to formulate acetate drug substance and ultimately liquid-formulated drug product cannot lead to _____ evident from the consistent level of the _____ in the _____

drug product compared to the phosphate drug substance". The sponsor has provided data for these species in the drug product comparability study, which showed no significant differences between the lyophilized and liquid drug products and in the comparison between the phosphate drug substance and acetate drug substance, which again showed no significant differences (see Table 1.3.7-4). It is important to note that the sponsor will be assaying for these species as a release specification for the _____ as they have done in the past. Total impurities will be a release specification for the _____ and liquid drug product; it will only be used for characterization for the _____. Moreover, *The omission of these specifications from the newly developed acetate drug substance and liquid drug product certificate of analyses is acceptable.*

*Validations were provided for the following assays and samples

TEST	Samples
Identity and Protein Concentration	liquid Avonex
Purity by _____	liquid Avonex
Purity by _____	liquid Avonex +/- Tween 20
Sialylation by _____	liquid and lyophilized Avonex
_____	liquid Avonex
_____	liquid Avonex

C. Process Validation (section 1.4.9)

Process validation was performed on _____ drug product commercial scale lots ranging in size from _____ total filled syringes _____ of final compounded solution), manufactured at _____. Release test results for the _____ process validation lots met release test specifications. However, a contaminant, _____ was observed in _____ µm filtration official compounded solution and the _____ and was found to be an extractable from the _____ filter unit. The _____ is not detectable by the _____ method used for the release testing of the drug product.

Reviewer's Comment:

_____ and its related compounds are commonly used in making polymers including _____, _____ and is known to be _____. The amount of _____ carried into the drug product lots is less than _____. European commission's scientific committee has ruled that the tolerable daily intake of _____ A study performed analyzing leaching of _____ from cans showed that the highest levels of _____ were found in cans of peas, with an average of 23 µg per can. *The amount of _____ per dose does not seem to be a safety concern.*

Note: I sent a request for concurrence to the pharm/tox reviewer on 8/16/02. Concurrence was obtained 8/21/02 by email.

D. Transport Validation

Drug product syringes are transported at _____ (with deviations to _____ acceptable for up in _____ containers dedicated to Biogen product. Validation will be executed in an environmental chamber to represent both winter and summer seasonal variation. The validation will demonstrate the ability to transport drug product syringes within the temperature specification _____ °C (with deviations to _____ °C acceptable for up to _____ hours) in _____ containers.

E. Reference Standard

The phosphate drug substance reference standard is used as a reference standard for release testing

and characterization of BG9418-— Biogen states that although the matrices and protein concentrations are different between ————— and drug product, the quality of IFN- β -1a has been shown to be comparable between ————— and drug product.

E. Comparability Study

1. Lot to lot consistency: Acetate liquid AVONEX lots ————— phosphate drug substance lot ————— and lyophilized AVONEX lot ————— were compared ————— (figures 1.4.9-1 and 1.4.9-2, Table 1.5.3-1). **Lots were consistent.**

2. Comparability of drug products [liquid-formulated IFN- β -1a drug product (BG9418-— with currently approved lyophilized drug product (BG9418-—

The comparability analyses were performed using the protein characterization techniques described in PLA No. 95-0979 (Section 4.13.5.1, Vol. 5); the September 25, 1996 Supplement for ————— 108; the August 29, 1997 Supplement for ————— and the December 2000 Supplement for ————— with slight modifications to accommodate the change in the formulation. Where possible, BG9418-— (Lot ————— was analyzed in parallel with the currently approved drug product (Lots —————

—). However, some characterization tests were not applicable to the current drug product due to the presence of a large quantity of HSA in that formulation. In such cases, BG9418-— was compared with drug substance reference lot (Batch —).

Characterization Tests performed for comparability of Liquid AVONEX (BG9418-—) and current AVONEX drug products . The Liquid AVONEX is compared either to current AVONEX or phosphate drug substance (see below)

Reviewer's Comment:

- There is no significant adverse effect of the new formulation (HSA-free) on the active pharmaceutical ingredient (IFN β -1a).

F. Stability**1. Temperature stability**

- The proposed expiration is — months from the date of manufacture. The recommended storage condition is 2-8 °C.
- BG9418- — lots, representing the current commercial process, were placed on the stability protocol.
(note: _____ no data). The stability data include — different syringe configurations, a
— (primary data) and a — (as supportive data).

Table 1.8.1-1: BG9418- Stability Lots – Primary Data



Table 1.8.1-2: BG9418- Stability Lots – Supportive Data



- Biogen commits to place — of BG9418- drug product from each site of manufacture on stability per year as part of the ongoing stability program. *This is acceptable.*

Reviewer's Comment:

- The stability data provided for HSA-free liquid AVONEX includes — lots with — months of data for product stored at 2-8°C. Both lots are completely stable at this temperature (2-8°C) for — months. *Biogen's proposed — month expiration date for product stored at 2-8 °C is acceptable*

- When the product is stored at — C (data are available for — months), there is an upward trend in — , while there is a downward trend — ; however, all results were within specifications.

2. Photostability

Table 1.8.2-1: BG9418- Photostability Study Design

The product was analyzed for appearance, _____

Reviewer's comment:

• There was approximately a _____ for the naked syringe sample, when compared to dark control _____. The other samples remained completely stable. *Biogen's proposed labeling of the drug product as _____ is acceptable.*

Recommendation:

The change from a phosphate buffer to an acetate buffer does not significantly alter the drug substance (the materials are chemically comparable), nor does the change in drug product formulation (HSA-free) adversely alter IFN β -1a. Thus, as far as the product is concerned, I recommend approval of the supplement for the AVONEX HSA-free formulation in pre-filled, 30 μ g (0.5 ml) single-dose syringes with an expiration date of — months at 2-8 °C. I recommend the following be included in the approval letter.

(These are proposed comments for the sponsor to be included in the approval letter. Please edit for style and content to be consistent with policy)

1. The expiration of AVONEX HSA-free formulation in pre-filled, 30 μ g (0.5 ml) single-dose syringes of — months, when stored at 2-8 °C has been approved.
2. The stability protocol for the AVONEX HSA-free formulation is acceptable.
3. Please submit results of ongoing stability studies as they become available.

This page was

Determined

Not to be

Releasable