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APPLICATION NUMBER:

204063Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM TO BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 204063	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	February 27, 2012		
Division:	Division of Neurology Products	**Acting Team Leader:** Tapash Ghosh, PhD	
Applicant:	Biogen Inc.	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	(b) (4)	**Date Assigned:**	February 29, 1012
Generic Name:	Dimethyl fumarate (DMF) Also referred to as BG00012	**Date of Addendum to Review:**	February 12, 2013
Indication:	Treatment of Multiple Sclerosis	**Type of Submission:** 505(b)(1) Original New Drug Application	
Formulation/ strengths	(b) (4) delayed release capsules/ 120 mg and 240 mg		
Route of Administration	Oral		

ADDENDUM TO ORIGINAL BIOPHARMACEUTICS REVIEW DATED 11/19/12:

The original Biopharmaceutics review by Elsbeth Chikhale, Ph.D., dated 11/19/12 included the following recommended language for the action letter:

If approved, the AP letter should include the following two comments:

- We have not made a BCS classification determination for your drug, since the data provided in the NDA are inconclusive with regards to the drug's permeability.

- We are reminding you of your commitment to collect 20 minute (buffer stage) dissolution data for all stability samples of all commercial batches to be released post approval for one year in order to evaluate the possibility of tightening the buffer stage dissolution acceptance criterion to Q= (b) (4) at 20 minutes and to submit the data in a prior approval supplement (PAS) one year after approval for our review.

During an ONDQA internal discussion, it was decided that the above comments (with minor revisions) will be sent to the Applicant by ONDQA in a separate communication.

RECOMMENDATION :

It is recommended that ONDQA conveys the following comments to the Applicant in an separate communication after the action letter is issued:

- We would like to remind you of your commitment to collect 20 minute (buffer stage) dissolution data for all stability samples of all commercial batches to be released post approval for one year and to submit these data to FDA as a prior approval supplement (PAS) 15 months after approval in order to determine if the buffer stage acceptance criterion can be tightened to Q= (b) (4) at 20 minutes.

- We would like to inform you that FDA did not make a determination on the BCS classification of your drug (dimethyl fumarate) at this point, because the provided permeability data for your drug are inconclusive.

From the Biopharmaceutics perspective the overall recommendation included in the original Biopharmaceutics Review dated 11/19/12 for this NDA remains the same.

From the Biopharmaceutics perspective, NDA 204063 for dimethyl fumarate delayed release capsules (120 mg/capsule and 240 mg/capsule) is recommended for APPROVAL.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: SPope, RLostritto

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELSBETH G CHIKHALE
02/12/2013

TAPASH K GHOSH
02/12/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
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Applicant:	Biogen Inc.	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	(b) (4)	**Date Assigned:**	February 29, 1012
Generic Name:	Dimethyl fumarate (DMF) Also referred to as BG00012	**Date of Review:**	November 19, 2012
Indication:	Treatment of Multiple Sclerosis	**Type of Submission:** 505(b)(1) Original New Drug Application	
Formulation/ strengths	(b) (4) delayed release capsules/ 120 mg and 240 mg		
Route of Administration	Oral		

SUBMISSION:

This 505(b)(1) New Drug Application is for an (b) (4) delayed release capsule indicated for the treatment of Multiple Sclerosis (MS). The pharmacological properties of BG00012 are proposed to be mediated through activation of the nuclear factor (erythroid-derived 2)-like 2 (NFE2L2 or Nrf2) antioxidant response pathway, which is the primary cellular defense system for responding to a variety of potentially toxic stimuli. DMF is rapidly and completely hydrolyzed to its active metabolite mono-methyl fumarate (MMF) by esterases present in the GI tract, in the gut wall and in blood before DMF reaches the systemic circulation. The drug product was formulated as (b) (4) a size 0 hard gelatin capsule. The design of the drug product formulation was based on the desired gastro-resistant properties and on the physico-chemical properties of the drug substance. The goal was to develop a delayed release formulation that prevents release of the active ingredient in the gastric environment while allowing for rapid release of the active ingredient in the intestine region. A formulation consisting of a capsule (b) (4) was pursued because such systems are designed to achieve the targeted delivery profile (b) (4)

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