

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125288Orig1s000

OTHER ACTION LETTERS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125288/0

COMPLETE RESPONSE
May 1, 2010

Bristol-Myers Squibb
Attention: Mary Christian, Pharm.D
Director, Global Regulatory Strategy
PO Box 4000 Mailstop D32-08
Princeton, NJ 08543-4000

Dear Dr. Christian:

Please refer to your biologics license application (BLA) dated June 30, 2009, received July 1, 2009, submitted under section 351 of the Public Health Service Act for belatacept.

We acknowledge receipt of your amendments dated:

July 8, 2009	November 9, 2009	February 12, 2010 (2)
July 31, 2009	November 18, 2009	February 17, 2010
August 6, 2009	November 25, 2009	February 19, 2010 (2)
August 31, 2009	December 14, 2009	February 22, 2010
September 4, 2009	December 18, 2009	February 23, 2010
September 10, 2009	December 30, 2009	February 24, 2010
September 18, 2009	January 6, 2009 (2)	February 25, 2010 (2)
September 25, 2009	January 8, 2009	March 4, 2010
September 30, 2009	January 11, 2010	March 10, 2010
October 15, 2009	January 22, 2010	March 17, 2010
October 21, 2009	January 29, 2010	March 19, 2010
October 29, 2009	February 1, 2010	April 1, 2010
November 3, 2009	February 2, 2010	April 15, 2010
November 6, 2009	February 11, 2010 (2)	April 22, 2010

Your application proposed the following indication: prophylaxis of organ rejection in adult patients receiving renal transplants and preservation of a functioning allograft in adult patients receiving renal transplants.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL DEFICIENCIES

1. Regarding the indication of prophylaxis of organ rejection in adult patients receiving renal transplants, you have not provided sufficient long-term data to evaluate the long-term effect of belatacept on the rate of post-transplant lymphoproliferative disorder (PTLD), renal effects, cardiovascular events, graft and patient survival.

To address this deficiency, provide the 36-month data from your Phase 3 studies, particularly data on outcomes such as mortality, graft loss, GFR, PTLN and other serious adverse reactions.



PRODUCT QUALITY DEFICIENCIES

1. Regarding drug substance manufacturing:



PRODUCT QUALITY MICROBIOLOGY DEFICIENCIES

Regarding product quality from a microbiology perspective the data or information on the (b) (4) (b) (4) the container closure integrity test, (b) (4) validation, shipping validation, drug product endotoxin specification, and the labeling (b) (4) (b) (4) are not adequate.

To address these deficiencies, the following data and information should be provided:

1. Readjust the (b) (4) (b) (4)
The current (b) (4) is not in line with your process capability.

2. The sensitivity (leak volume and the corresponding leak size) of the dye ingress test used to validate the integrity of the drug product container closure was not correlated to a microbial challenge test (using the same vacuum and pressure challenge conditions as the dye ingress test) and evaluated. Correlate the sensitivity of the two tests. In addition, provide information and summary data of the microbial challenge test.

(b) (4)

4. With regard to the validation study for shipping of belatacept from the BMS distribution center to consumers, justify the (b) (4) profile selected. It is not clear the selected profile represents the worst case (b) (4) conditions. The temperature inside the truck during (b) (4) may well be (b) (4) the temperature outside the truck.

5. Because the updated drug product endotoxin specification (b) (4) does not provide a safety margin over the specified limit for parental drugs (5 EU/kg) at the lowest belatacept infusion solution concentration (2 mg/mL), lower the endotoxin specification to include a safety margin.

6. (b) (4)

FACILITY INSPECTIONS

During recent pre-license inspections of the Bristol-Myers Squibb Company facility in East Syracuse, NY by CDER inspectors, and of the Bristol-Myers Squibb facility in Manati, Puerto Rico by an inspector from the SJN-District Office, deficiencies were conveyed to the representatives of the facilities. Satisfactory resolution of the deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
 - Present tabulations of the new safety data combined with the initial data.
 - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.
6. Provide updated exposure information for the clinical trials (e.g. number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS will be necessary for belatacept, if it is approved, to ensure that the benefits of the drug outweigh the risks of post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML). The REMS, once approved, will create enforceable obligations.

We acknowledge receipt of your proposed REMS, included in your submission dated June 30, 2009 and amended on February 17, 2010 which includes a Medication Guide, communication plan, and timetable for submission of assessments of the REMS; we also acknowledge receipt of your amendment dated April 1, 2010 which was not reviewed for this action.

(b) (4)

Your proposed REMS must include the following:

Medication Guide:

As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that belatacept poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of belatacept. FDA has determined that belatacept is a product for which patient labeling could help prevent serious adverse effects, and has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use belatacept.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed belatacept.

Communication Plan:

We have determined that a communication plan targeted to healthcare providers who are likely to prescribe belatacept will support implementation of the elements of your REMS during the first five years after product launch. The communication plan must provide for the dissemination of information about PTLD and PML.

The communication plan must include, at a minimum, the following:

1. A Dear Healthcare Provider (DHCP) Letter that contains the text of the FDA-approved labeling regarding the risk of PTLD and PML associated with the use of belatacept. The DHCP letters should be mailed to healthcare providers at the time of first marketing.
2. Educational materials must be provided to prescribers and all other allied healthcare professionals and healthcare settings where patients receive infusions of belatacept. The educational materials should be distributed by Bristol-Myers Squibb (BMS) representatives during their initial visits to these individuals/sites and during their first discussions of the product with these healthcare providers and at specified intervals thereafter.
3. A plan for dissemination of the risk information and appropriate-use information in conjunction with professional societies and/or their associated medical journals to healthcare providers.
4. A description of the target audience for the communication plan, stating specifically the types and specialties of physicians and other health care providers to whom the communication materials will be directed.
5. A schedule outlining when and how the materials identified above are to be distributed to healthcare providers at the time belatacept is approved and at specified intervals thereafter.
6. The communication materials, along with the professional labeling, and Medication Guide, must be available on the belatacept website.

Timetable for Submission of Assessments:

The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than annually for the first 5 years, and again 7 years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to belatacept (see Appendix A). Include information in the template that is specific to your proposed REMS for belatacept. Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the

approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include, but is not limited to, the following:

- a. A survey of healthcare providers' and patients' understanding of the serious risks of belatacept.
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements of the Medication Guide, and corrective actions taken to address noncompliance.
- d. A summary of all reported cases of PTLD and PML during the preceding reporting period.
- e. An analysis of prescribers' compliance with the labeled contraindication regarding the use of belatacept in EBV negative patients and patients in whom EBV-status is unknown.
- f. A plan to monitor prescription data to evaluate:
 - Number of patients treated, reported by transplant organ received
 - Number of units shipped, reported by year and type of healthcare setting (e.g., transplant center, infusion center, hospital).

Prominently identify all subsequent submissions related to your proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125288
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

POSTMARKETING COMMITMENTS

At this time, we have determined that, if BLA 125288 is approved, we will request that you conduct the postmarketing commitment (PMC) listed below. Whether additional PMCs will be requested will be determined based on our review of your complete response to this letter:

- Provide information and summary data on the container closure integrity test developed in support of finished product on stability in a Prior Approval Supplement.

OTHER

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a

request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings Between FDA and Sponsors or Applicants*, February, 2009 at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

If you have any questions, please call June Germain, M.S. Regulatory Health Project Manager, at (301) 796-4024.

Sincerely,



/Edward Cox/

Edward Cox, MD, MPH

Director

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Enclosure: Appendix A: REMS Template
Appendix B: REMS Supporting Document

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