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RESEARCH**

*APPLICATION NUMBER:*

**125288Orig1s000**

**OFFICE DIRECTOR MEMO**

## Office Director Decisional Memo

<b>Date</b>	June 15, 2011
<b>From</b>	Edward M. Cox, MD MPH <i>Edward Cox</i>
<b>Subject</b>	Office Director Decisional Memo
<b>NDA/BLA #</b>	BLA 125288
<b>Supplement #</b>	
<b>Applicant Name</b>	Bristol-Myers Squibb (BMS)
<b>Date of Submission</b>	June 30, 2009
<b>Date of Receipt</b>	July 1, 2009
<b>Complete Response Letter Date</b>	May 1, 2010
<b>Resubmission Date</b>	December 15, 2010
<b>PDUFA Goal Date</b>	June 15, 2011
<b>Proprietary Name / Established (USAN) Name</b>	Nulojix belatacept
<b>Dosage Forms / Strength</b>	Lyophilized powder for intravenous infusion 250 mg/mL
<b>Proposed Indication(s)</b>	Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving a kidney transplant
<b>Actions:</b>	Approval for BLA 125288 for prophylaxis of organ rejection in adult patients receiving kidney transplants

BMS submitted BLA 125288 for belatacept in support of the proposed indication for the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving a kidney transplant. Belatacept is a selective T-cell costimulation blocker. It is used as part of a regimen to prevent rejection that includes basiliximab induction, mycophenolate mofetil, and corticosteroids.

This application was originally submitted/received on June 30, 2009/July 1, 2009. As part of the initial review cycle, the application was presented to the FDA's Cardiovascular and Renal Drugs Advisory Committee. On May 1, 2010 a Complete Response (CR) letter was issued that included both product quality and clinical deficiencies. The product quality deficiencies enumerated in the letter included deficiencies related to the drug substance manufacturing process, specifications for the drug substance and drug product, deficiencies related to the qualification of new reference standards, deficiencies for stability studies, a deficiency related to the use of an (b) (4), a deficiency related to the immunogenicity assay. There were also product quality microbiology deficiencies regarding the (b) (4) the container closure integrity test, (b) (4) validation, shipping validation, drug product endotoxin specification limits, and the proposed (b) (4). The clinical deficiencies were the lack of 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 (b) (4).

The May 2010 CR letter also notes necessary revisions to the proposed REMS which includes

a Medication Guide and a Communication Plan, along with a timetable for assessments of the REMS.

For a detailed discussion of BLA 125288, the reader is referred to the individual discipline specific reviews from the initial cycle and the current resubmission. In addition Drs. Meyer, Taylor, and Belen's Cross-Discipline Team Leader (CDTL) Memorandum and Dr. Albrecht's Division Director's Memo summarize key issues in BLA 125288. I concur with the recommendations of the review team, the CDTLs and the Division Director that the information on safety, efficacy and product quality for belatacept support approval. This memorandum will focus on selected issues from the resubmission for BLA 125288.

The product quality issues have been reviewed by the Division of Therapeutic Proteins (DTP) and they are recommending approval based upon the data submitted in the application addressing the deficiencies. The information provided supports that the manufacturing is well controlled and the product is pure and potent. DTP has specified dating periods for the drug product and drug substance and a stability protocol for extending the expiration dating periods. The approval letter will also include a postmarketing requirement (PMR) and postmarketing commitments (PMC) for additional manufacturing/product quality information.

From the standpoint of CMC sterility assurance, the product is recommended for approval; the applicant has addressed the deficiencies from the May 2010 CR letter. There is also a PMC for additional information on the container closure integrity test. The Therapeutic Biologics Establishment Evaluation Request summarizing the status of the manufacturing facilities found each of the seven sites to be Acceptable.

With regard to the first clinical deficiency, the 36 month data from the phase 3 clinical trials were submitted to evaluate the long-term effects of belatacept in kidney transplant patients. The findings on the results for patient and graft survival and the biopsy proven acute rejection endpoint (BPAR) including graft loss, death, and loss to follow-up when assessed at 36-months are consistent with the results from the 12-month (primary analysis timepoint for the FDA primary endpoint of BPAR) and 24-month timepoints.

Review of safety information at 36 months is consistent with the findings at the 12 and 24 month timepoints. For PTLD in the core belatacept trials, 13 of the 14 cases (8 in the belatacept MI arms and 6 in the belatacept LI arms) developed in the first 18 months of follow-up. In the belatacept patients with PTLD, 9 of the 14 cases were CNS PTLD (6 in the MI arms and 3 in the LI arms). In the core belatacept trials there were 2 cases of PTLD in the CsA arms; neither was CNS PTLD. (Note: the numbers for PTLD provided here include safety data through the safety cut-off date for the resubmission; the numbers in the labeling are for 3 year follow-up data.) The one PML case in a belatacept kidney transplant patient was in a patient receiving the MI regimen and was reported at month 23. There was an additional case of PML in a liver transplant patient reported at month 6. During months 24 to 36, one patient that was diagnosed with CNS PTLD prior to month 24, and one patient that was diagnosed with PML prior to month 24 died. In addition to PTLD and PML events, analyses of cases of tuberculosis found that in trial IM103008 that there were 4 cases in the belatacept MI arm, 2 cases in the belatacept LI arm, and 1 case in the CsA arm; in trial IM103027 there were 2 cases

in the belatacept MI arm, 4 cases in the belatacept LI arm, and 0 case in the CsA arm. The labeling includes a Boxed Warning that describes risks for PTLD, other malignancies and serious infections. In addition, there is also a Warnings and Precautions statement on PTLD, other malignancies, PML, and other serious infections.

EBV seronegative status is a factor associated with PTLD (independent of belatacept) and belatacept appears to further increase the risk of PTLD, particularly in EBV seronegative recipients. Because of the greater risk of PTLD in patients who are EBV seronegative, belatacept is contraindicated in patients who are EBV negative or when EBV serostatus is unknown. Information on the increased risks of PTLD is provided in the boxed warning for belatacept and in the Warnings and Precautions section of the labeling. In addition, the product labeling includes a limitation of use statement, that the product should only be used in patients who are EBV seropositive.

Data from an ongoing trial in liver transplant recipients found increased rates of graft loss and death in the belatacept arms of the trial compared to the tacrolimus control arms. Based upon this finding, the Data Monitoring Committee recommended stopping the study. The product labeling will include information in the Boxed Warning and in the Warnings and Precautions section of the product labeling describing these adverse outcomes in patients receiving a liver transplant.

The LI (less intense) regimen is the regimen that will be approved. Review of data from the MI (more intense) regimen found numerically higher rates of PTLD, CNS infections (including PML), and biopsy proven acute rejection (BPAR) in comparison to the LI regimen. The MI regimen will not be included in the labeling. In addition, the labeling also provides cautionary wording about the risks of using higher or more frequent dosing of belatacept.

(b) (4)



A revised REMS proposal was submitted that includes a Medication Guide and a Communication Plan. The materials for the REMS and for the assessments have been developed through working with the Division of Risk Management (DRISK). The purpose of the REMS is to inform of the increased risk of PTLD (predominantly CNS PTLD) and CNS infections including PML and to raise awareness of the contraindication for use in patients who are EBV serostatus negative or unknown in order to reduce usage in this population. The REMS Communication Plan includes a Dear Healthcare Provider Letter, a Healthcare Provider Fact Sheet, a Dear Infusion Specialist Letter, a pre-infusion checklist, an informational piece

