

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125288Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

FINAL REMS REVIEW

Date: June 8, 2011

To: Renata Albrecht, MD, Director
Division of Transplant and Ophthalmology Products
(DTOP)

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management (DRISK) *Claudia Karwoski*
6/8/11

From: **Scientific Lead, Risk Management Analyst (RMA)**
Suzanne Robottom, PharmD, DRISK *Suzanne Robottom*
6/8/11

Subject: Review of Risk Evaluation and Mitigation Strategy

Drug Name: Nulojix (belatacept)

Application Type/Number: BLA 125288

Applicant: Bristol-Myers Squibb (BMS)

OSE RCM #: 2009-1396

1 INTRODUCTION

This is the Division of Risk Management's (DRISK) final review of the proposed Risk Evaluation and Mitigation Strategy (REMS) for belatacept (Nulojix).

Belatacept is a selective t-cell costimulation blocker indicated for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. During the clinical trials, an increased risk of post-transplant lymphoproliferative disorder (PTLD), predominantly involving the CNS, was identified in patients treated with belatacept. In addition, two cases of progressive multifocal leukoencephalopathy (PML) were reported.

The Division of Transplant and Ophthalmology Products (DTOP; formerly Division of Special Pathogen and Transplant Products (DSPTP)) sent BMS a Complete Response letter dated May 1, 2010 requiring, among other issues, submission of a REMS consisting of a Medication Guide and Communication Plan (CP) to address these risks. In summary, the CP must include:

- A DHCP letter
- Additional educational materials targeted at prescribers and allied healthcare professionals and settings where patients receive belatacept infusions for dissemination during first product discussions, and dissemination of risk information through professional societies.
- CP materials must be available on the belatacept website.

2 MATERIALS REVIEWED

We reviewed the following submissions:

- Proposed REMS and REMS Supporting Document, submissions of August 16, 2010, November 30, 2010, December 13, 2010, January 20, 2011, March 18, 2011, April 4, 2011, June 1, 2011, and June 3, 2011

DRISK provided written interim reviews dated September 24, 2011 (#1) and February 25, 2011 (#2; both of the August 16, 2010 submission) and April 5, 2011 (#3; March 18, 2011 submission).

The June 3, 2011 submission is the subject of this review.

3 RESULTS OF REVIEW – Risk Evaluation and Mitigation Strategy (REMS)

3.1 Goals

The goals of the REMS are to:

- To inform healthcare providers of the increased risk of post-transplant lymphoproliferative disorder (PTLD), predominantly in the central nervous system (CNS), associated with NULOJIX

- To inform healthcare providers of the increased risk of progressive multifocal leukoencephalopathy (PML), a CNS infection, associated with NULOJIX
- To inform patients of the serious risks associated with NULOJIX

3.2 REMS Elements

3.2.1 Medication Guide

A Medication Guide will be dispensed with each NULOJIX infusion in accordance with 21 CFR 208.24.

Reviewer Comment: [REDACTED] (b) (4)

[REDACTED]. *This requirement can only be required if the REMS includes elements to assure safe use. However, with the guidance of Office of Regulatory Policy, we were able to maintain the expectation that that the Medication Guide should be dispensed before each infusion by including it as a step on the Pre-Infusion Checklist. DRISK believes it is important to review the signs and symptoms of PML and PTLD (particularly in the CNS) with each patient before each infusion.*

3.2.2 Communication Plan

The REMS for belatacept includes a communication plan to healthcare providers expected to prescribe or administer belatacept. This includes transplant physicians, transplant surgeons, transplant pharmacists, nurse practitioners, transplant nurse coordinators, nephrologists, infusion center directors, and infusion center nurses. The communication plan will include the following:

1. A prominent link on the main product webpage that directs healthcare providers to a REMS-specific landing page (www.NULOJIX.com/REMS.aspx). The *NULOJIX REMS landing page* will include links to the most recently approved full Prescribing Information, Medication Guide, and all approved REMS materials. The link, landing page, and all materials will be available within 2 weeks of approval of the REMS [REDACTED] (b) (4)

The *REMS landing page* (www.NULOJIX.com.REMS.aspx) is part of the NULOJIX REMS and is appended.

2. A *webinar* with voiceover and live support will be available [REDACTED] (b) (4)
[REDACTED] In addition, the slides with voiceover will be available on demand fo [REDACTED] (b) (4)

The *webinar slides* are part of the NULOJIX REMS and are appended.

3. A *Dear Healthcare Professional (HCP) Letter* along with HCP Fact sheet, full prescribing information, and Medication Guide will be distributed via direct mail and electronic delivery (b) (4)

(b) (4) The target audience will be all potential prescribers of NULOJIX including transplant nephrologists, transplant surgeons, community nephrologists, transplant nurses/coordinators, transplant clinical pharmacists. (b) (4)

(b) (4)

The *Dear HCP Letter* is part of the NULOJIX REMS and is appended. In addition, BMS will send the DHCP Letter to MedWatch at the same time it is disseminated to the target audience.

4. A *HCP Fact Sheet* will be distributed by BMS field medical liaisons and sales representatives (b) (4)

(b) (4)

The *HCP Fact Sheet* is part of the NULOJIX REMS and is appended.

5. A *Dear Infusion Specialist Letter*, the Full Prescribing Information, Medication Guide, and Pre-Infusion Checklist will be distributed via direct mail and electronic delivery (b) (4) to infusion nurses (b) (4), and infusion center directors. (b) (4)

The *Dear Infusion Specialist Letter* is part of the NULOJIX REMS and is appended.

6. A *Pre-Infusion Checklist* will be distributed with the Infusion Specialist Letter (b) (4)

The *Pre-Infusion Checklist* is part of the NULOJIX REMS and is appended.

7. A *Journal Information Piece* will be circulated in the following journals

(b) (4)

The *Journal Information Piece* is part of the NULOJIX REMS and is appended.

3.2.3 Elements to Assure Safe Use

The belatacept REMS does not include elements to assure safe use.

Reviewer Comment: There was extensive discussion regarding the merits of ETASU- vs a communication-based REMS. Refer to the DRISK review dated April 30, 2010 for a comprehensive discussion of the considerations and agreement with a Medication Guide and Communication Plan option.

3.2.4 Implementation System

The belatacept REMS does not include an implementation system.

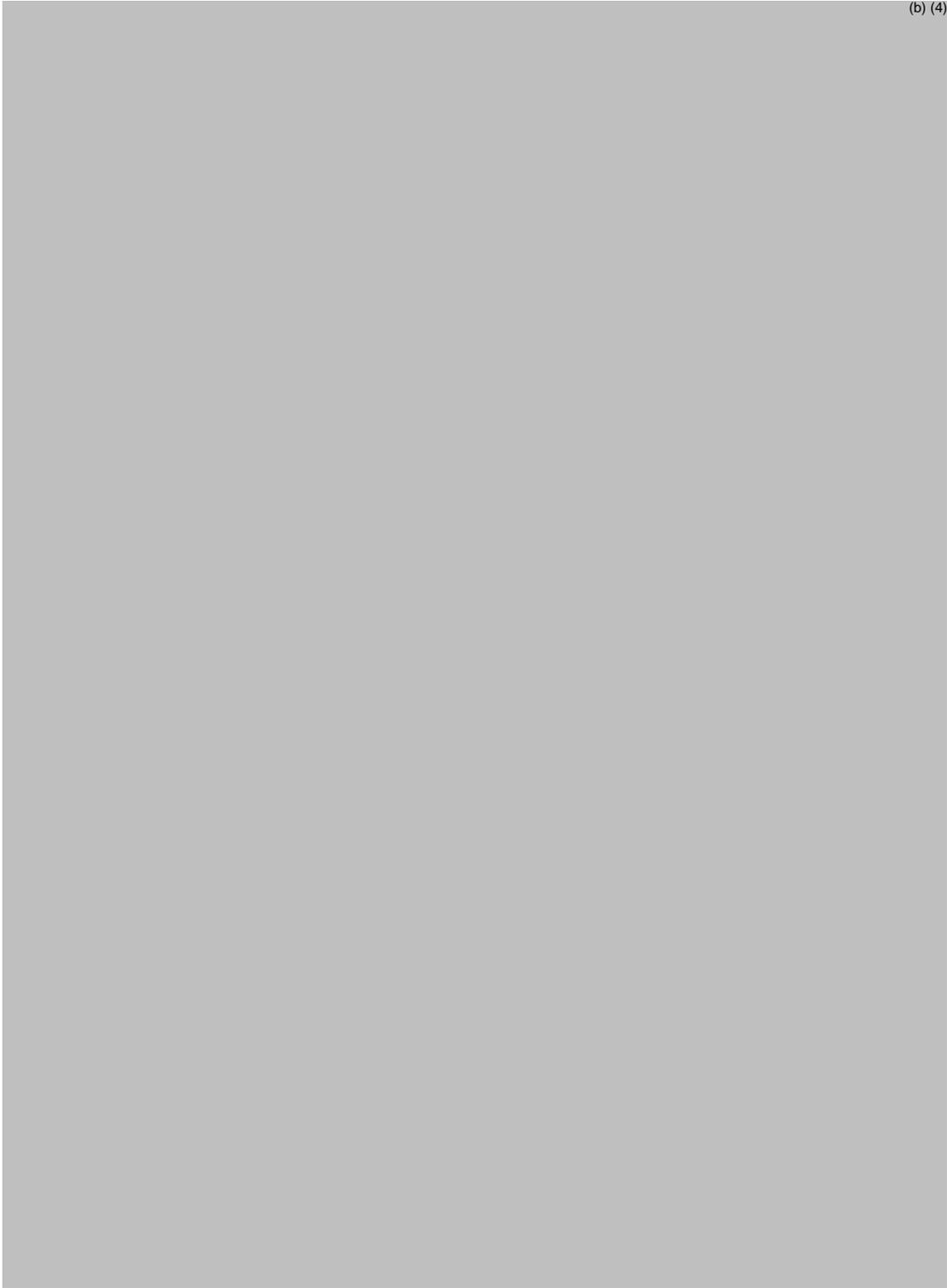
3.2.5 Timetable for Submission of Assessments

BMS will submit REMS Assessments to FDA annually from the date of the initial approval of the REMS for the first 5 years and again 7 years from the initial date of approval of the NULOJIX REMS.

3.3 REMS Assessment Plan

The REMS assessment reports will include the following:

(b) (4)



In addition to the list above, the initial assessment should also include the following:

1. Launch date of Nulojix

2. The date the links to the full prescribing information, medication guide, and all approved REMS materials became available on the Nulojix REMS landing page.
3. Number of transplant centers visited within 90 days of launch and within 150 days of launch, and percentage of transplant volume covered by each transplant center visited.
4. The date(s) of distribution of the Dear Infusion Specialist Letter
 - a. The source(s) of the list of infusion specialists
 - b. The number of recipients
 - c. The number of returned items
 - d. A list of the documents included in the mailing

Reviewer Comment: As part of the REMS assessment, data to characterize further the risks will be gathered (b) (4)

BMS stated that the initial prescribing and patient populations would be too small to perform meaningful knowledge, attitude and behavior (KAB) survey results in the first REMS assessment. We agreed to allow BMS to submit the results of the KABs with the 2nd annual REMS assessment.

4 DISCUSSION/CONCLUSION

The risk management strategy for belatacept is communication-based and utilizes a variety of outreach measures via direct and active transplant center and HCP (physicians, pharmacists, nurse practitioners, and nurses) outreach and indirect/passive HCP outreach through mailings, professional journal publications, and the internet. Infusion center staff who will administer belatacept are targeted as well as patients (Medication Guide and Pre-Infusion Checklist tool).

The strategy includes risk communication at launch, ongoing (internet), at time of first order, and periodic re-inforcement (recurring journal information pieces, webinars) of the risk for the (b) (4).

The belatacept REMS is one of the most, if not the most, comprehensive communication plan-based REMS approved to date.

5 RECOMMENDATION

The REMS submitted June 3, 2011 is acceptable. The REMS should be approved.

ATTACHMENTS

- A. REMS and appended materials
- B. DRISK Interim Review #1
- C. DRISK Interim Review #2
- D. DRISK Interim Review #3

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

DRISK INTERIM REMS REVIEW

Date: April 5, 2011

To: Renata Albrecht, MD, Director
Division of Special Pathogen and Transplant Products
(DSPTP)

From: Suzanne Robottom, PharmD, Risk Management Analyst,
Division of Risk Management (DRISK)

Subject: Interim REMS Review

Drug Name: Nulojix (belatacept)

Application Type/Number: BLA 125288

Applicant: BMS

I. Material Reviewed

- BMS proposed REMS materials for belatacept submitted on March 18, 2011

II. Comments to BMS

Please be aware that these are preliminary comments. You will receive additional comments as your REMS undergoes further review. We plan to discuss these comments and answer any questions at an upcoming face-to-face meeting on April 11, 2011. During the meeting, we will discuss the content and timing of your re-submission of these materials.

We have provided revisions to the slide set. We are not providing revisions of the script at this time. We anticipate the script will be revised based on the final agreed upon slides.

REMS Goal

1. We agree with the revised REMS goal as proposed by BMS.

DHCP Letter

1. See attached.

HCP Fact Sheet

1. See attached.

Infusion Specialist Letter

1. See attached.

Pre-Infusion Checklist

1. See attached.

Journal Information Piece

1. See attached.

Slide Set

1. See attached.

REMS Website Landing Page

1.  (b) (4)
2. Include a prominent statement about the risks in conjunction with the header "Risk Evaluation and Mitigation Strategy." For example: "Increased risk of PTLT, predominantly involving the CNS and PML wit Nulojix"
3. Reorganize the website to be more reader/user friendly.

For example:



Link to REMS website

1. The link is acceptable. We have no comments at this time.

REMS Supporting Document

1. Review pages 4 through 11 to ensure the information is consistent with the final approved labeling.
2. Revise "journal ad" to "journal information piece."

**Department of Health and Human Services
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DRISK INTERIM REMS REVIEW

Date: February 25, 2011

To: Renata Albrecht, MD
Director, Division of Special Pathogen and Transplant
Products (DSPTP)

Through: Suzanne Robottom, PharmD,
Team Leader, Division of Risk Management (DRISK)

From: **Kate Heinrich, MS**
Health Education Reviewer, DRISK

Subject: Interim REMS Review **Comments Set # 2**

**Drug Name (Established
Name):** Nulojix (belatacept)

Application Type/Number: BLA 125288

Applicant: BMS

OSE RCM #: 2009-1396

The purpose of this interim review #2 is to provide recommendations and seek clarification on the applicant's proposed Belatacept REMS submitted August 16, 2010. The review includes letter-ready comments for the applicant.

1 MATERIALS REVIEWED

BMS proposed REMS for belatacept submitted August 16, 2010.

2 REMS SUMMARY

2.1 Required REMS

DSPTP sent BMS a Complete Response (CR) letter dated May 1, 2010 requiring, among other issues, submission of a REMS consisting of a Medication Guide and Communication Plan (CP). In summary, the CP must include:

- A DHCP letter
- Additional educational materials targeted at prescribers and allied healthcare professionals and settings where patients receive belatacept infusions for dissemination during first product discussions, and dissemination of risk information through professional societies.
- CP materials must be available on the belatacept website.

BMS submitted a proposed REMS on August 16, 2010. This review addresses the August 16 submission and provides comments to the review division as well as some standard guidance for the applicant.

2.2 APPLICANT'S PROPOSED REMS

In general, the proposed REMS is consistent with what was required. Certain proposed aspects of the program (website, journal information piece, details regarding webinar) were not included in the submission but this is not problematic.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following recommendations on the belatacept REMS be sent to the applicant as soon as possible. In addition to the recommendations in Section 4 below, the following materials including as track changes are appended:

- DHCP Letter
- HCP Fact Sheet
- Infusion Specialist Letter
- Pre-Infusion Checklist

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

Please request that the applicant respond to these comments as soon as possible to facilitate further review in order to meet the action date for this NDA/BLA .

4 RECOMMENDATIONS FOR THE APPLICANT

4.1 REMS

1. All approved REMS materials should include a footnote statement communicating that the material is part of a REMS. For example "This <<piece>> is part of the NULOJIX REMS."
2. We recommend including information on the Registry in the REMS materials to increase its visibility.

3. Revise all materials to ensure information is consistent with the final approved labeling.

4.2 Goals

1. Revise the goals of the REMS as follows:

The goals of the belatacept REMS are:

- To inform healthcare providers of the increased risk of PTLD, predominantly in the CNS, associated with belatacept
- To inform healthcare providers of the increased risk of CNS infections, including PML, associated with belatacept
- To inform patients of the serious risks associated with belatacept

4.3 Medication Guide

Comments on the Medication Guide will be provided under separate cover.

4.4 Communication Plan

4.4.1 DHCP Letter

1. The DHCP Letter will be disseminated with the Fact Sheet. Therefore, revisions to the DHCP letter are provided with this in mind.
2. See attached revised DHCP letter.

4.4.2 HCP Fact Sheet

1. See attached revised HCP Fact Sheet.

4.4.3 Infusion Letter

1. Clarify whether infusion centers/suites that are part of an outpatient transplant clinic will receive the infusion letter.
2. We recommend a copy of the Infusion Checklist accompany the Infusion Specialist Letter. Therefore, revisions to the letter are provided with this in mind.
3. See attached revised infusion letter.

4.4.4 Infusion Center Checklist

1. We do not recommend including the checklist as part of vial carton packaging. We recommend providing tear pads to transplant centers and infusion centers along with making an electronic version available on the belatacept REMS website. We agree that the checklist should be distributed when belatacept is ordered. Transplant centers and infusion centers should be able to order tear pads through various mechanisms (sales rep, phone, website, etc.)
2. The electronic version of the checklist should be in a format that allows it to be incorporated into existing electronic medical records/systems.
3. Ensure the language written to the patient in plain language is consistent with the Medication Guide.

4. See attached revised Checklist.

4.4.5 Journal Information Piece

1. You state that the journal information piece will be based on the Fact Sheet. We recommend that you condense the information for the journal information piece.
2. Submit the proposed journal information piece.

4.4.6 Website

1. Submit the proposed website for review.

4.4.7 Webinar

1. Clarify if the webinar will be a slide set accessible via the web or if you intend to augment the slides with voiceover, video, or other media/technology.
2. Clarify how you plan to use the proposed slides. For example, will these slides be presented as part of a slide presentation or only as a standalone presentation/webinar?
3. Revise the slide set based on the comments and revisions on the other materials and submit a revised proposed slide set.

4.5 Timetable for Submission of Assessments

No comments at this time.

4.6 Supporting Document

Revise the REMS Supporting Document to be consistent with all changes made to the REMS document.

4.7 Submission Instructions

1. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document. Provide responses to outstanding questions from the September 29, 2010 comments and this comment set.
2. Format Request:
 - a. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.
 - b. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.
 - c. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document. However, changes must be noted using PDF mark-up tools.

5 ATTACHMENTS

- DHCP Letter
- HCP Fact Sheet
- Infusion specialist letter
- Pre-Infusion checklist

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DRISK INTERIM REMS REVIEW

REMS Comment Set #1

Date: September 24, 2010

To: Renata Albrecht, M.D., Director
Division of Special Pathogen and Transplant Products
(DSPTP)

Through: Suzanne Robottom, Team Leader
Division of Risk Management (DRISK)

From: **Scientific Lead, Risk Management Analyst (RMA)**
Elizabeth A. Donohoe, M.D., DRISK

Subject: Interim REMS Review Comments for Nulojix (belatacept)

**Drug Name
(Established Name):** Nulojix (belatacept)

Therapeutic Class: T-cell Co-stimulation Blocker

Dosage and Route: Lyophilized Powder as 250 mg single-use vial for
Intravenous Infusion

Application Type/Number: BLA 125288

Applicant: Bristol-Meyers Squibb (BMS)

OSE RCM #: 2009-1396

1 Materials Reviewed

- Proposed label received from DSPTP via email September 20, 2010.
- Proposed REMS, Dear Healthcare Provider (DHCP) Letter, Healthcare Provider Fact Sheet (HCPFS), Healthcare Provider Educational Slide Presentation (HCPES), Dear Infusion Specialist Letter (DISL), Infusion Specialist Checklist, and REMS Supporting Document, submitted August 18, 2010.
- Meeting minutes, from the June 11, 2010 meeting with the applicant; provided by DSPTP.
- Complete Response (CR) letter dated May 1, 2010.

2 Introduction and Background

This review is OSE's preliminary review of the proposed REMS for Nulojix (belatacept). Belatacept is a selective T-cell costimulator blocker with a proposed indication for prophylaxis of organ rejection in adult patients receiving a kidney transplant. The original application for belatacept submitted to DSPTP included a voluntarily proposed REMS [REDACTED] (b) (4)

[REDACTED] DRISK subsequently was consulted and completed a review including REMS options; that review was forwarded to DSPTP on April 8, 2010 and was revised April 30, 2010.

DRISK recommended a MG/CP REMS for belatacept to communicate the serious risks of PTLD and progressive multifocal leukoencephalopathy (PML). DRISK further recommended that the CP should be ongoing and should include a multifaceted education approach that is commensurate with increased drug utilization and the anticipated lag time in the clinical presentation of PTLD and PML.

DSPTP sent the applicant a Complete Response (CR) letter dated May 1, 2010 requiring, among other issues, submission of a MG/CP REMS. In summary, the CP must include: A DHCP letter, additional educational materials targeted at prescribers and allied healthcare professionals and settings where patients receive belatacept infusions for dissemination during first product discussions, and dissemination of risk information through professional societies. Further, the CR stated CP materials must be available on the belatacept website. A meeting was held between FDA and the applicant on June 11, 2010 to discuss elements of the CR letter, including some REMS issues.

The applicant submitted a proposed REMS on August 18, 2010. This review addresses the August 18 submission and provides comments to the review division as well as some standard guidance for the applicant. This review is not a comprehensive review of all the REMS materials.

3 Comments for the Review Division

DRISK has reviewed the proposed Nulojix REMS and has the following comments and questions for DSPTP.

- a. Does DSPTP believe that the risk for tuberculosis should be an additional focus of the Nulojix REMS addressing PTLD and PML?
- b. The comments below address the status of the Nulojix REMS:

3.1 REMS

- a. The sponsor has submitted the required elements of the MG/CP REMS:
 1. DHCP Letter
 2. Educational Materials:
 - DHCP Letter
 - HCP Fact Sheet (this will be the basis for the journal information pieces (journal ad) (b) (4)
 - Does DSPTP agree with the information provided in the Fact Sheet?
 - Does DSPTP believe that journal information pieces will be a valuable component of the CP?
 - Does DSPTP agree with placement of these pieces in journals identified by the applicant?
 - Does DSPTP believe that the (b) (4) – should be required in the REMS CP or are the journal information pieces sufficient?
 - HCP Educational Slide Presentation (this will be the basis for personal communications and webinars)
 - Does DSPTP believe that webinars should be required in the REMS CP?
 - Infusion Site Letter (ISL)
 - Does DSPTP agree that the ISL should include instructional aspects regarding treatment? If not, the ISL should be revised to mirror DHCP Letter.
 - Infusion Site Checklist (ISC)
 - Does DSPTP agree with the use of the ISL/ISC as part of the REMS and (generally) agree with the instructional aspects of the letter and the checklist? For example, these pieces include instruction to consult a patient's prescriber before proceeding with the infusion if patient reports signs/symptoms consistent with PML or PTLD.
 - If yes, does DSPTP believe that the ISC should be included with the Nulojix vial along with the MG? [DMEPA consult needed]

- If yes, language in the label and the MG should also include reference to the ISC so that the patient is aware that these questions will be asked and they may not receive treatment.
- If yes, all CP materials should reference the ISC so prescribers are aware.

- b. The above materials will need to be updated with any label changes, including specifics addressing clinical trials.
- c. The Communication Plan section of the REMS Document needs to be expanded.

3.2 Goals

The REMS goals will be revised to be consistent with DRISK language and assessment considerations.

3.3 Medication Guide

Comments on the content and format of the Medication Guide will be provided separately.

3.4 Communication Plan

- a. The sponsor must submit a journal information piece and complete webinar.
- b. DRISK plans to consult with the DRISK Assessment staff regarding the assessment options if the ISC is implemented as a REMS component.

Supporting Document

DRISK requests that DSPTP reviews the SD for clinical accuracy. In particular, parts of the Background section (1.1) seem promotional in tone and not necessary.

3.5 Conveying DRISK Comments to Applicant

We recommend that the following comments in Sections 4 through 6 on the Nulojix REMS proposal be sent to the applicant. Please request that the applicant wait to receive the next set of FDA comments before resubmitting the REMS and related materials.

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

4 Recommendations for the Applicant

We have reviewed the August 18, 2010 submission and have the following general comments. Be aware that we anticipate additional comments as your submission(s)

undergoes further review. We request you receive the next set of comments before resubmitting the REMS and related materials.

4.1 REMS Document

The general elements of the Nulojix REMS outlined in the REMS Document are acceptable. However, considerable edits will need to be made to the REMS document including references to the Attachments (MG and CP materials). Please see the attached template for the REMS document and the REMS Supporting Document.

The CP section needs to be expanded to include specific targeting and outreach efforts (identify audience, frequency of distribution).

4.2 Medication Guide

Comments on the content and format of the Medication Guide will be provided separately.

4.3 Communication Plan Materials

- a. We have the following general comments on the communication plan as described in the REMS:
 1. The timing and frequency you plan to send the CP materials as outlined in Table 1 of the Supporting Document are generally acceptable; additional comments will be forthcoming. This table should be consistent with the information provided in the body of the SD.
 2. The professional societies identified for outreach appear adequate.
 3. The numbers and types of providers you plan to target appear adequate except for the DIS Letter. Consider including additional health care personnel (e.g., Infusion Site administrators) who work at Infusion Sites in this outreach effort.
 4. The databases you plan to use to identify targeted providers appear adequate, however, more information is needed (e.g., see 5.4 below).
 5. A summary of the above information (#1-4) should be included in the REMS Document itself under the CP section.
- b. The DHCP Letter:
 1. You plan to use the (b) (4) to target providers; quantify how many HCPs that will be likely to care for kidney transplant patients, prescribe belatacept and/or infuse belatacept you plan to reach through (b) (4)
- c. The Healthcare Provider Fact Sheet (HCPFS):
 1. The HCPFS is not addressed in this set of comments. You may refer to Victoza's "Highlighted Information for Prescribers" (Appendix D) on the "drugs@fda" website for an example of an appropriate fact sheet.

Although the Victoza Fact Sheet is two pages, one page fact sheets are preferable.

2. It is understood that the HCPFS will be the basis for the “journal ad”. Refer to the “journal ads” as “Journal Information Pieces” in your submission. We recommend that you follow the guidelines below before submitting the Journal Information Piece:
 - Include a heading in large font regarding “Important Information on the Safe Use of Nulojix”
 - Under the heading provide the indication followed by a statement such as:
“The US Food and Drug Administration (FDA) has approved Nulojix with a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of PTLD and PML.”
 - Add the Boxed Warning under the statement in above.
 - Add sections addressing PTLD and PML under the Boxed Warning [wording should be consistent with the label and all CP materials].
 - Include reference to the required REMS program at the bottom of the page, such as: “This journal information piece is required and approved by FDA as part of the Nulojix REMS.”

- d. The HCP Educational Slide Presentation is not addressed in this set of comments. The webinar, when ready, should be submitted with the REMS materials.
- e. The Infusion Site Letter is not addressed in this set of comments.
- f. Infusion Site Checklist (ISC) is not addressed in this set of comments.
- g. Website:

We recommend that you include a prominent link on the product website’s homepage for REMS materials. We remind you that any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a single-click, prominent direct link off the main website that includes REMS-specific materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The REMS-related webpage(s) should not be a means to promote Nulojix or any other BMS product. Only the separate webpage(s) and/or link will be considered a component of the Communication Plan.

1. We recommend a single-click, direct, prominent link off the Nulojix homepage to a REMS landing page. For example, the link could state: “Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)”, or “Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information.”
2. The landing page of the separate REMS link should contain background information on the REMS, as well as safety information, along with the REMS communication materials.

3. We recommend the following language as background information on the REMS landing page:

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

In order for BMS to communicate certain risks about Nulojix, BMS has worked with the FDA to develop materials to communicate the risks of post-transplant lymphoproliferative disorder and progressive multifocal leukoencephalopathy. The REMS program is designed to inform health care providers and patients about the risks with Nulojix. To learn more about serious risks, read the important safety information provided in this link, including the Medication Guide, and discuss it with your patients.

The goals of the Nulojix REMS are:

- o [List goals here]

4. Submit for review the web screenshot(s) for the Nulojix REMS.

- h. All Nulojix CP materials should include statements:

6. In introductory text: “The US Food and Drug Administration (FDA) has approved Nulojix with a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of PTLD and PML.”

7. In bold and centered at the bottom of the page:

This [letter] has been reviewed and approved by the FDA as part of the Nulojix REMS.

- i. Where appropriate, substitute “journal information piece”, “information”, etc. for “letter”.

4.4 Timetable for Submission of Assessments

The timetable for assessments is acceptable. Delete the accompanying chart.

4.5 Information Needed for Assessment - Surveys

Information related to this section will be provided in future comments.

5 REMS Supporting Document

- a. See the attached template for the REMS Document and the Supporting Document.

- b. Revise the Supporting Document to be consistent with the REMS document, based on recommendations included in this communication, as well as any updated labeling changes.
- c. Because you will have a REMS dedicated website in your Communication Plan (CP), please note in the Supporting Document that **only** FDA approved REMS material can be included in the REMS dedicated website.
- d. Distribution of Communication Tools
 - 1. HCP
 - i. Clarify how (b) (4) will assist in broader distribution to specialists, nurse transplant coordinators, transplant and health-system pharmacists, infusion specialists identified through membership of specialty societies. (p.19)
 - ii. Clarify how US postal service addresses will be obtained if email addresses are not available. It appears that it will be through membership in professional societies. (p.20)
 - iii. Clarify the frequency discrepancy of distribution of materials between non-physician and non-pharmacist HCPs and others. (p. 20)
 - iv. AST, ASTS and NATCO have committed to provide links to the Nulojix website and agree to distribute REMS communication materials.(pp.20-21)
 - 1. Consider asking these organizations to post the link to the Nulojix REMS landing page in place of a link to the website so that all the CP materials would be readily accessible.
 - 2. Identify which specific communication materials will be distributed by these organizations.
 - v. Communication tools will be available on the website (b) (4); after REMS approval; specify which tools will be available. (p.21)
- 2. Transplant Centers
 - i. Clarify how the (b) (4) will be determined; based on prior year transplants, past X years, etc. (p.21)
 - ii. How will HCPs be made aware of webinars? Add this type of information to the DHCP Letter and the Fact Sheet.(p.22)
 - iii. Reference is made to (b) (4) these interactions should include REMS-materials as well, as approved by FDA, that are provided to HCPs. (p.22)
- 3. Community Nephrologists
- 4. Infusion Centers
 - i. Consider adding Infusion Site administrators to the distribution for the ISL (with the Infusion Nurses Society). (p.23)

f. Information Needed for Assessment

1. The Information Needed for Assessment (REMS Assessment Plan) section of the SD should specifically address each component as indicated below. Please refer specifically to the language in the Complete Response Letter dated May 1, 2010. Specifically, that letter states that "The REMS assessment plan should include but may not be 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, 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).*

2. Under "b." MG Distribution (b) (4)

[REDACTED] However, because Nulojix will be administered at infusion sites and not self-administered, this requirement does apply regarding distribution and dispensing of the Medication Guides, even though it is "unit-of-use". (p.25)

3. Surveys are not addressed in these comments.

4. Under "Prescription data monitoring", you state: (b) (4)

[REDACTED] This does not tally with your ability to accurately address (e) above regarding analysis of prescribers' compliance with the labeled contraindication regarding the use of belatacept in patients with certain EBV status; please explain.

- g. Regarding Timetable for Assessments:
 - 1. Add: "BMS will submit each assessment so that it will be received by the FDA on or before the due date."

6 Attachments

- a. REMS Document and Supporting Document Template

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Antimicrobial Products
Division of Special Pathogen and transplant Products**

NDA/BLA #s:	BLA 125288
Products:	Belatacept (Nulojix®), Lyophilized Powder for Intravenous Infusion 250 mg single-use vial
APPLICANT:	Bristol-Myers Squibb
FROM:	Edward Cox, MD, MPH <i>Edward Cox 5/1/2010</i>
DATE:	May 1, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (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)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for belatacept to ensure that the benefits of the drug outweigh the risks of Post-transplant Lymphoproliferative Disorder (PTLD) and Progressive Multifocal Leukoencephalopathy (PML). In reaching this determination, we considered the following:

- A. According to the National Health and Nutrition Examination Survey (NHANES) data, approximately 23 million Americans suffer from chronic kidney disease. Of these, around 500,000 receive dialysis and approximately 16,000 patients undergo a kidney transplant each year.
- B. Use of immunosuppressive therapy is vital for patients with a solid organ transplant. Without immunosuppressive therapy, transplantation would cause an immune response and result in destruction of the transplanted organ.
- C. Belatacept is indicated for prophylaxis of organ rejection and preservation of functioning allograft in adult patients receiving renal transplants. Belatacept has been used in combination with an interleukin-2 (IL-2) receptor antagonist, a

mycophenolic acid (MPA), and corticosteroids.

- D. The treatment with belatacept is chronic/lifelong to ensure there is no organ rejection in transplant patients.
- E. The data for the serious known and potential adverse events discussed under this section are derived from the BLA submission dated June 30, 2009.

PTLD is described as an abnormal proliferation of lymphocytes following transplant and includes B-cell neoplasia and hyperplasia. In the 3 clinical trials, the Epstein Barr virus (EBV) serostatus was determined for 95% of the patients prior to enrollment in the clinical trial. PTLT developed in 16 patients: 14 in the belatacept arm and 2 in the cyclosporine (CsA) arm. Of the 14 patients treated with belatacept who developed PTLT, 7 were EBV negative (of 96 total EBV negative patients on belatacept) and 6 were EBV positive (of 805 total EBV positive patients on belatacept) and 1 was of unknown status. EBV serostatus prior to transplant was unknown in 2 of the patients that developed PTLT (one in the belatacept arm and 1 in the CsA arm). Of the 14 patients in the belatacept arm, 8 developed CNS PTLT. Neither of the 2 patients in the CsA arm developed CNS PTLT. Based on the clinical trial results, there was no apparent association between EBV serostatus and development of CNS PTLT. The greatest increase in risk of PTLT was present in patients who were EBV negative.

A patient in the Moderate Intensity (MI) group in the clinical trial (the MI dose was not proposed by the Applicant for approval) was diagnosed with PML in Month 23 of the trial; the patient died shortly after Month 24. A second case of PML was diagnosed in the belatacept liver transplant program in 2009 and that patient also died. The incidence of PML in the general kidney transplant population has been estimated at 14 cases per 100,000 patient-years.¹ Therefore, two occurrences of PML in the context of a drug development program constitute a safety signal.

In addition to the risks described above, belatacept labeling will include information regarding increased susceptibility to infection and possible development of malignancies that may result from immunosuppression in the boxed warning section.

- F. Belatacept is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for belatacept. 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

¹ Neff RT, Hurst FP, Falta EM, et al. Progressive Multifocal Leukoencephalopathy and Use of Mycophenolate Mofetil after Kidney Transplantation. *Transplantation* 2008; 86(10): 1476-8.

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.

The elements of the REMS will be Medication Guide, a communication plan and a timetable for submission of assessments of the REMS.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 8, 2010; *Revised April 30, 2010*

To: Renata Albrecht M.D., Director
Division of Special Pathogen and Transplant Products
(DSPTP)

Through: Claudia Karwoski, Pharm.D., Director *Claudia Karwoski*
Division of Risk Management (DRISK)

From: **OSE Nulojix REMS Review Team**
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Subject: Review of Risk Evaluation and Mitigation Strategy (REMS)
Options

Proprietary/Established Name: Nulojix (belatacept) Intravenous Injection

Therapeutic Class: T-Cell Co-stimulation Blocker

Dosage Form/Strength: Lyophilized Powder as 250 mg single-use vial for Intravenous
Infusion

Type Application/#: BLA 125288

Applicant: Bristol-Myers Squibb Company

OSE RCM #: 2009-1396

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EXECUTIVE SUMMARY

In response to a consult from the Division of Special Pathogens and Transplant Products (DSPTP), the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE) provides a review of the possible risk evaluation and mitigation strategy (REMS) options for a Nulojix.

Nulojix (belatacept) is a T-cell costimulation blocker proposed for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. Nulojix would be a new class of therapeutic biologic in transplantation therapies that differs from existing immunosuppressive therapies. There are a number of factors to weigh in considering the risk management approach for a Nulojix REMS: 1) the healthcare provider expertise of highly trained transplant surgical subspecialists who are well-versed with the serious risks associated with immunosuppressive therapies, similar to those serious risks reported with Nulojix; 2) intra-venous administration of Nulojix provides the opportunity for regular patient evaluation; 3) the benefit of documentation of safe use conditions that could include pre-infusion evaluation and or periodic query of healthcare providers for early signs and symptoms of the serious risks with Nulojix would not outweigh the perceived burden given the current safety review; and 4) the organ transplantation community maintains a unique, required data collection system, the United Network for Organ Sharing (UNOS), which provides data for monitoring the use of and serious risks associated with Nulojix.

Based on these factors, DRISK recommends that the Nulojix REMS include, in addition to a timetable for submission of assessments, a Medication Guide and communication plan to communicate the serious risks of post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML) associated with the use of Nulojix.

1 INTRODUCTION

This review follows a request from the DSPTP for the OSE/DRISK to review options for a REMS for Nulojix® (belatacept). The applicant's original BLA 125288, dated June 30, 2009, contains a voluntarily proposed Nulojix REMS consisting of a Medication Guide (MG) and communication plan (CP) (b) (4).

Belatacept, a new molecular entity, is a selective T-cell costimulation blocker that binds to CD80 and CD86 domains on the B7 complex on the surface of antigen-presenting cells. This binding interaction is required for T-cell activation. The proposed indication is for the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving a kidney transplant. The proposed formulation is a lyophilized powder as 250 mg per single-use vial for reconstitution with sterile fluid to be administered as an intravenous infusion over 30 minutes. The dosage and administration in the Initial Phase (Days 1, 5, 14, and 28; Month 2 and 3, after transplantation) and in the Maintenance Phase (every month starting at Month 4, after transplantation) is 10 mg/kg and 5 mg/kg, respectively.

1.1 BACKGROUND

Kidney transplantation is the most effective treatment for end-stage renal disease (ESRD). Currently, there are approximately 17,000 kidney transplants performed each year in the United States (US). Following kidney transplant, organ preservation requires lifelong immunosuppressive therapy. Calcineurin inhibitors (CNIs), cyclosporine (CsA) and tacrolimus are the basic regimens used for immunosuppression in kidney transplant patients in the US.

Both CsA and tacrolimus are associated with direct nephrotoxicity, including reversible and non-reversible kidney alterations and damage; metabolic alterations, specifically, new onset diabetes mellitus; and cardiovascular adverse events, specifically, increased blood pressure, stroke, and worsening lipid profiles (non-HDL cholesterol). The primary causes of long-term graft loss are 1)

death, with a functioning graft, most commonly due to cardiovascular disease, and 2) progressive kidney dysfunction due to chronic allograft nephropathy (CAN).

Note: The background information is summarized from the original BLA 125288 application, Module 2.5, Section 1.2 Unmet Medical Need, page 11 of 95.

1.2 REGULATORY HISTORY

Nulojix is currently not FDA approved or approved by any other global regulatory authority for any indication. Nulojix is a second generation, higher affinity variant of abatacept (Orencia) which is approved for rheumatoid arthritis and for moderately to severe polyarticular juvenile idiopathic arthritis.

(b) (4)

(b) (4) Nulojix was granted Fast Track Designation on January 26, 2005 and Orphan-Drug Designation on February 20, 2008 for prophylaxis of organ rejection in kidney allograft recipients.

Cardiovascular and Renal Advisory Committee Meeting

A Cardiovascular and Renal Drug Advisory Committee (CRDAC) meeting was held on March 1, 2010 to discuss Nulojix for use in kidney transplant recipients to prevent graft rejection. The committee voted 13-yes and 5-no, no abstentions, to the Agency's question "given the overall benefits and risks, do you recommend that belatacept be approved for the prophylaxis of acute rejection in *de novo* renal transplant recipients?"

The committee expressed concern about different efficacy endpoint analyses employed by the applicant versus the Agency with regard to acute rejection (AR), and about the non-inferiority comparison between each belatacept regimen and CsA using a 20% non-inferiority margin to exclude the possibility that belatacept is 20% or more worse than CsA.

In regard to safety, the committee communicated a variety of concerns. The committee strongly requested longer-term clinical safety data through at least three years exposure to better characterize serious adverse events (SAEs). These SAEs include PTLD, the preponderance of CNS presentation of PTLD, the increased risk of PTLD in EBV (-) or EBV serostatus unknown recipients, and serious infections including progressive multifocal leukoencephalopathy (PML). The committee questioned if belatacept has a cerebrovascular effect or CNS immunity based on the preponderance of CNS-PTLD and serious infections reported in the CNS. The committee raised concern that risks with belatacept may be insufficiently quantified at this time. Other reported adverse events with fewer observed events with belatacept- compared with CsA-treated patients, specifically, hypertension, dyslipidemias and new onset diabetes, could also be better characterized with longer-term safety data. The committee concurred with the applicant's proposed contraindication of belatacept in EBV (-) serostatus and EBV serostatus unknown recipients.

When asked whether risk management measures are recommended for Nulojix, several committee members suggested a REMS and a "patient registry". Elements to assure safe use (ETASU), as written in the Food and Drug Administration Amendments Act (FDAAA) of 2007, were mentioned as a regulatory pathway to establish a "patient registry". A "patient registry" and observational studies were both discussed as options to monitor the incidence of PTLD and other SAEs. Specific components of how a REMS could be structured were not provided.

2 MATERIAL REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following resources were reviewed:

- BMS submission as a Type-B pre-BLA meeting package (dated on April 15, 2009) to DSPTP and OSE including a proposed REMS for belatacept. The meeting was held on May 20, 2009.
- BMS original submission for BLA 125288 Nulojix (belatacept) dated June 30, 2009.
- BMS submission (dated December 15, 2009) of draft Advisory Committee Briefing Document including 120-Day Safety Updates from November 2009.
- BMS submission (dated February 17, 2010) in response to questions from the Agency including five comments and clarifications from DRISK about the proposed REMS (discussed at the face-to-face meeting with the Agency on January 13, 2010).
- FDA Briefing Document and slides for the Cardiovascular and Renal Drug Advisory Committee Meeting dated March 1, 2010.
- BMS Briefing Document and slides for the Cardiovascular and Renal Drug Advisory Committee dated March 1, 2010.
- BMS submission of Postmarketing Requirement Studies dated June 30, 2009 and March 19, 2010.
- BMS submission of WORD version copies of the REMS document and appended materials dated March 26, 2010.
- BMS submission of amended proposed Nulojix REMS and additional draft mock-up appended materials dated April 1, 2010.

Prescribing Information

- BMS original Proposed Professional Package Labeling submitted on June 30, 2009, revised February 19, 2010.

FDA Reviews

- Cross-Discipline Team Leader Review, BLA 125288 Nulojix (belatacept), Joette Meyer, PharmD., signed April 30, 2010.
- DSPTP, Office of Antimicrobial Products Team Leader Review, BLA 125288 Nulojix (belatacept), Shulal Bala, PhD., March 18, 2010.
- Statistical Review and Evaluation, BLA 125288 (belatacept), Anita Abraham, MS, DrPH, concurring reviewer, LeRee Tracy, MA, PhD, Acting Team Leader, March 26, 2010.

FDA Guidance Documents

- Draft Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications, September 2009.

Publications

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- Graham D, et al. Liver enzyme monitoring in patients treated with troglitazone. *JAMA*. 2001 Aug 15; 286(7):831-3.
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- Weatherby LB, Nordstrom BL, Fife D, Walker AM. The impact of Wording in "Dear Doctor" Letters and in Black Box Labels. *Clin Pharmacol Ther*. 2002; 72:735-742.

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

The risks of Nulojix are summarized from a total of 949 belatacept-treated kidney transplant recipients with a median exposure and follow-up of 24 months. The ongoing clinical trials continue to assess longer-term safety with a total of 77 patients receiving Nulojix for at least 5 years. The primary risks for belatacept are based on three similarly designed clinical trials in *de novo* kidney transplant patients: one Phase 2 trial [IM103100] and two Phase 3 trials [IM103008 and IM103027]. The demographic characteristics of enrolled patients were evenly distributed across treatment groups in both Phase 3 trials.

3.1.1 POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

PTLD is the primary serious risk in the belatacept kidney transplant clinical development program. PTLD represents a spectrum of disease from polyclonal lymphocyte proliferation to malignant lymphoma and may present in different organ systems including the kidney, lymph nodes, intestine, and central nervous system (CNS). It is estimated that less than 15% of PTLD cases affect the CNS. Approximately 15% of the adult population is EBV seronegative. The reported risk factors for PTLD include recipient EBV negative (-) serology at the time of transplantation, CMV disease, and the use of T-cell depleting therapy.¹

A total of 16 cases of PTLD were reported across treatment groups, belatacept more intensive (MI), less intensive (LI) versus the active comparator, CsA. In the belatacept treatment arms, there are 14 PTLD cases (13 PTLD cases before 24 months and one additional PTLD case after 24 months exposure). There are two cases of non-CNS PTLD reported in CsA-treated patients

both within 24 months exposure. No cases of PTLD are reported among recipients of the Phase 2 belatacept LI regimen (0/71 patients).

Two approaches to stratify the observed PTLD cases are: 1) by CNS involvement, and 2) by EBV serostatus.

- Belatacept-treated patients were observed to be at higher risk for developing CNS-PTLD compared with CsA-treated patients. Of the 14 PTLD cases reported in the belatacept arm, 9 cases (64%) presented with CNS involvement. Neither of the CsA PTLD cases included CNS involvement. Adverse events associated with CNS-PTLD presentation in belatacept-treated patients include seizures, hemiparesis, aphasia, cognitive dysfunction, and behavioral changes. The observed cases of CNS-PTLD presented between 12 and 18 months of belatacept exposure.
- Of the 14 PTLD cases reported among belatacept-treated patients, 5 patients are EBV (+). As stated above, 4 of 9 CNS-PTLD cases are in EBV (+) patients.

In support of these findings, as cited in the FDA Briefing Package, “the preponderance of CNS involvement among the kidney transplant recipients treated with belatacept constitutes the most striking aspect of PTLD presentations.” In a retrospective analysis of 1,094 post-transplant lymphomas reported to the Collaborative Transplant Study Registry (CTSR), the reported CNS involvement was experienced in only 11.7% of cases.¹

The Agency completed “separate and independent analyses of the United Network for Organ Sharing (UNOS) registry data to estimate PTLD incidence by EBV serostatus. The agency concluded that the incidence of PTLD among EBV (+) patients on a comparable calcineurin inhibitor based regimen, to that in the belatacept development program, was lower than the incidence of PTLD among EBV (+) patients maintained on a belatacept regimen.” The applicant proposes to contraindicate belatacept use in EBV (-) or EBV unknown serostatus patients which should reduce the risk but will not eliminate the risk. While the incidence of PTLD is lower among EBV (+) patients compared with EBV (-) patients, among EBV (+) patients alone, the incidence in belatacept regimens is higher compared with the incidence in the CsA control regimen. The occurrence of PTLD in EBV seropositive patients is reported as early as 12 months.

3.1.2 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Progressive multifocal leukoencephalopathy (PML) is a new safety signal beyond one year in the Phase 3 trial (IM103027). One PML case (IM103027) is reported in a 67 year-old female treated with belatacept (MI regimen), mycophenolate mofetil (MMF), and corticosteroids following 23 months exposure. This case was fatal. A second case of PML (IM103045) is reported in a 52 year-old liver transplant recipient maintained on belatacept and MMF after 6 months of exposure to belatacept. Currently, this patient is receiving hospice care. The incidence of PML in the general kidney transplant population is estimated at 14 cases per 100,000 patient-years.² Two cases of PML reported in the pre-market belatacept clinical development program is of concern.

This reviewer completed calculations of the incidence of PML for belatacept in kidney transplant recipients, liver transplant recipients, and the combined kidney and liver recipients. The incidence

¹ Opetz G, Dohler, B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Amer J of Transplantation* 2003; 4:222-230.

² Nef RT, Hurst FP, Falta EM, et al. Progressive Multifocal Leukoencephalopathy and Use of Mycophenolate Mofetil after Kidney Transplantation. *Transplantation* 2008, 86(10);1476-8.

of PML in the kidney transplant program is one case of PML per 1,759 patient-years in belatacept-treated patients, and no cases of PML per 838 patient-years in CsA-treated patients. In the liver transplant recipient program (one clinical trial, n = 146 patients), the incidence of PML is one case of PML per 58 patient-years.

The observed incidence of PML in the combined kidney and liver transplant programs is two cases of PML per 1,817 patient-years. The incidence of PML with belatacept treatment is approximately 1.1 per 909 patient-years. These incidences must be considered in the context of confounding as all patients were exposed to other concomitant immunosuppressive agents. Exposure to belatacept could not be excluded as not contributing to the two PML cases.

This reviewer also completed an assessment of PML with 9 FDA approved products including five immunosuppressive agents (MMF, mycophenolic acid, tacrolimus, rapamycin, and cyclosporine) all indicated for prophylaxis of acute organ rejection in patients receiving kidney transplantation, and four FDA approved products, rituximab, abatacept, natalizumab, and efalizumab, all indicated in non-transplant patient populations, e.g., B-cell non-Hodgkin's lymphoma, rheumatoid arthritis patients, moderate to severe juvenile idiopathic arthritis, relapsing multiple sclerosis, Crohn's disease, and chronic plaque psoriasis.

Currently, this reviewer is not aware of any FDA approved drug or biologic product, regardless of indication, whose pre-market clinical safety database was known to include cases of PML. To balance this discussion, many of the CNIs were originally studied and approved prior to the AIDS pandemic. Cases of PML may have occurred and not been detected for reporting. While these cited products may not have had pre-market PML cases, all are since associated with postmarketing case reports of PML. Therefore, the concern about the pre-market incidence of PML in the belatacept clinical programs is heightened with such a rare and fatal event observed in ongoing clinical trials in transplant recipients.

3.1.3 SERIOUS INFECTIONS

Infections were the most common SAEs reported in this application. There is a lower frequency of serious infections in the belatacept-LI group (23%) than in the belatacept MI and CsA groups (27%). CMV infection, urinary tract infection (UTI), pyrexia, and blood creatinine increased are the most common SAEs and are reported with similar frequencies in the belatacept MI, LI, and CsA groups. The key risks associated with belatacept are serious infections and PTLD, consistent with its immunosuppressant properties. Considering the preponderance of CNS-PTLD cases and two cases of PML, there are concerns about whether belatacept alters CNS immunity.

Central nervous system infections occurred across all three core clinical trials through the 120 Day Safety Update (November 2009): in Study 008, belatacept MI group (219 patients), there are three cases of *Cryptococcus meningitis*, one of which included Chagas Encephalitis and West Nile Virus; in Study 027, belatacept MI group (184 patients), there is one case of cerebral *Aspergillosis* and one case of PML; in Study 100, belatacept MI group (74 patients), there is one case of neurological *Herpes Zoster*. In Study 027, belatacept LI group (174 patients), there is one case of CNS infection as *Cryptococcus meningitis*. In Study 008, CsA group (215 patients), there is one case of *Cryptococcus meningitis*. Overall, a total of 6 cases of CNS infection are reported in belatacept-treated patients compared with one CNS infection in a CsA-treated patient.

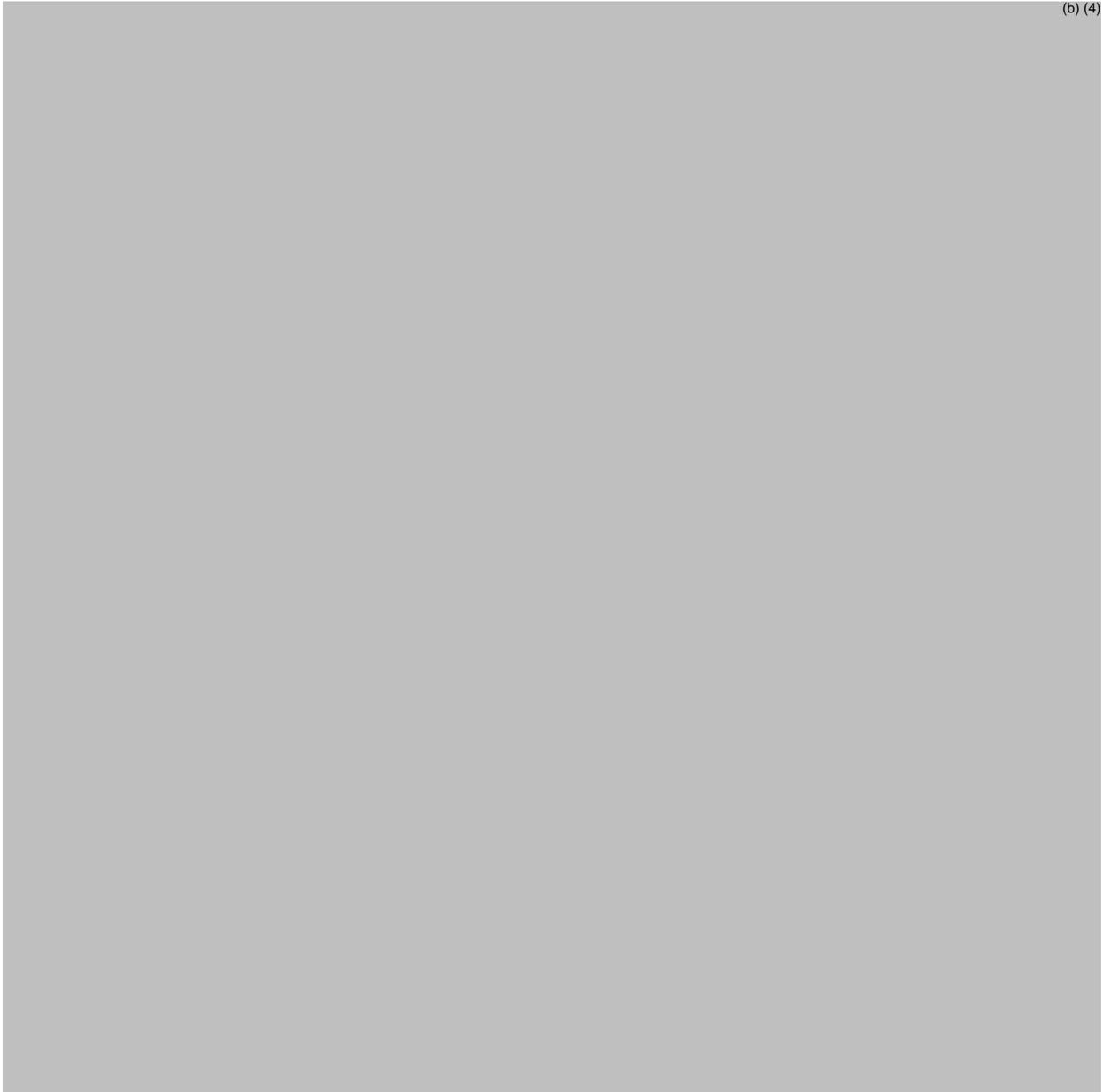
A total of 8 cases of serious tuberculosis are observed across the three trials with all cases in belatacept-treated patients with the exception of one case in a CsA-treated patient. The cases of tuberculosis include disseminated, pulmonary, extra-pulmonary presentation with the majority in

the later category. Among belatacept-treated patients, two cases of disseminated tuberculosis, and one case each of laryngeal, synovial, and gastrointestinal tuberculosis are reported. There was one case of intra-thoracic tuberculosis with lymph node involvement in a CsA-treated patient. There is one death due to disseminated tuberculosis. As the belatacept clinical program is global in scope, the majority of tuberculosis cases are observed in countries where tuberculosis remains endemic, e.g., Brazil, India, and Mali.

4 APPLICANT'S PROPOSED RISK EVALUATION AND MITIGATION STRATEGY

BMS submitted a proposed REMS (submitted with the original BLA and amended April 1, 2010) that includes a Medication Guide and Communication Plan (CP) (b) (4)

Each proposed element is described below.



4.7 PROPOSED POSTMARKETING STUDIES

The applicant submits the following (b) (4) proposed postmarketing (b) (4) studies:

- **Pattern of Use of Belatacept in US Transplant Recipients (Study IM103074)**

The primary objective would be to describe the pattern of use of belatacept and of CNI use at transplantation and at one year post-transplantation. (b) (4)

- **Belatacept and PTLD in US Renal Transplant Recipients (Study IM103075)**

The primary objective would be to estimate the incidence rates of PTLD in adult kidney-only transplant recipients treated with belatacept at the time of transplantation, compared with the rates in patients treated with CNI-based regimens at the time of transplantation.

(b) (4)

(b) (4)

(b) (4)

(Study IM103076)

(b) (4)

(b) (4)

Two of these (b) (4) studies propose to gather data regarding PTLD and Nulojix use through the United Network of Organ Sharing (UNOS). Transplantation provides a unique opportunity in that a framework for long term data collection is established, required, and active. It is not known how rigorous compliance is with information beyond the basic transplantation data, e.g., organ, matching criteria, etc. For example, in evaluating belatacept use, data on patients who start belatacept at transplantation may be accounted for whereas patients who are switched at some point, post-transplantation, may be missed. As with any data collection, whether part of REMS, in a controlled clinical trial or in an observational study, the decision to report information such as treatment changes, adverse events, etc. relies on the healthcare provider's professional responsibility and discretion.

5 REMS OPTIONS

For the purposes of the discussion below, we will focus on the advantages and disadvantages of a REMS that includes a CP only versus ETASU in conjunction with a CP to address the serious risk of PTLD and the serious infection, PML. Based on discussions DRISK and DSPTP, there is agreement that a Medication Guide would be necessary because "the drug product is one that has serious risks, relative to benefits, of which patients should be made aware of because information concerning the risk(s) could affect patients decision to use or discontinue to use the product."³

5.1 COMMUNICATION PLAN

Implementing only a Communication Plan in addition to the Medication guide is the less burdensome REMS option. PTLD and PML are known risks to healthcare providers who care for transplant recipients and manage their immunosuppression. Additional outreach measures to

³ 21 CFR 208.1(c).

communicate the increased risk of PTLD and PML associated with Nulojix would be important, particularly, to community-based healthcare providers in considering whether Nulojix is appropriate for their patients. However, there is limited experience on the effectiveness of education alone in improving the safe use of a product. Traditional risk communication tools such as prescriber labeling and DHCP letters have been shown to have little effect on impacting prescribing behavior or on increasing compliance with labeled laboratory monitoring recommendations.^{4, 5, 6, 7} Neither of the serious risks associated with Nulojix have regular laboratory monitoring to aid in risk mitigation and it is not clear if early detection through clinical presentation will result in better outcomes. The transplant physician will specify that EBV serostatus will need to be determined prior to initiating therapy with Nulojix. While REMS with ETASU would assure that this laboratory testing is conducted, it may not be necessary to implement an ETASU for this purpose. EBV serostatus is routinely checked in all pre-transplant patients because the risks of PTLD are higher in EBV (-) patients irrespective of the immunosuppressive therapy.

5.2 ELEMENTS TO ASSURE SAFE USE

ETASU may be employed to implement mandatory certification of prescribers and or dispensers, e.g. hospitals, transplant centers, infusion centers, and or to implement some form of mandatory monitoring and counseling of patients. A REMS can include one or more element(s) and may or may not be linked to drug distribution. Each element is presented with various advantages and disadvantages based on a variety of considerations including the route of Nulojix administration, the nature and presentation of PTLD and PML, and the structure and organization of post-transplantation patient care.

5.2.1 PRESCRIBER CERTIFICATION

Overview

Prescriber certification may include attestation of their understanding of the risks and benefits of Nulojix and importance of EBV (+) serostatus/EBV unknown serostatus prior to prescribing Nulojix. This ETASU may include attestation that the HCP can diagnose and treat the SAEs reported with Nulojix, and report these events under a Nulojix REMS.

How could this be accomplished?

- Prescriber reviews FDA approved REMS education materials including web-based courses, a brochure, fact sheet, or other written materials
- Prescribers signs an attestation form acknowledging their understanding of the belatacept risks, including verifying EBV serostatus as (+) prior to prescribing Nulojix and , if applicable, agreement to monitor their patients closely for potential SAEs.

⁴ Willy M, et al. A Study of Compliance with FDA Recommendations for Pemoline (Cylert). J Am Acad Child Adolesc Psychiatry. 2002 Jul; 41 (7): 785-90.

⁵ Graham D, et al. Liver enzyme monitoring in patients treated with troglitazone. JAMA. 2001 Aug15;286(7): 831-3.

⁶ Smalley W, Shatin D, Wysowski D, Gurwitz J, Andrade S, et al. Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action. JAMA 2000; 284(23):3036-3039.

⁷ Weatherby LB, Nordstrom BL, Fife D, Walker AM. The Impact of Wording in "Dear Doctor" Letters and in Black Box Labels. Clin Pharmacol Ther. 2002;72:735-742.

Advantages	Disadvantages
<ul style="list-style-type: none"> • Passive approach <ul style="list-style-type: none"> ○ Required for applicant ○ “Voluntary” for HCPs based on professional responsibility (in the absence of restricting the distribution of the drug) • If selected alone, has no impact on drug distribution • Assessment of HCP knowledge of risks of Nulojix treatment including appropriate monitoring 	<ul style="list-style-type: none"> • No incentive for prescribers to become certified • Requires additional ETASU to successfully support compliance of HCPs; the applicant would need to establish a certification process with appropriate documents for HCPs to complete. • No active risk mitigation or prevention steps would be part of prescriber certification. Elements would further reinforce safe use but without additional ETASU, would not require it. <ul style="list-style-type: none"> ○ No patient monitoring/data, e.g., EBV (+)/EBV unknown serostatus, SAEs. To monitor a lab would require a added ETASU and increase the burden to the healthcare system. • Difficult to assess impact, e.g., prescriber adherence with EBV (+)/EBV unknown serostatus prior to Nulojix treatment. To assess impact with patient data could require additional ETASU.

While healthcare professionals who regularly care for transplant recipients are highly trained in immunosuppression and its consequences, community-based nephrologists who may care for a smaller number of transplant recipients may not be as familiar with the serious risks of immunosuppressive therapy including Nulojix. Requiring certification would attempt to ensure all prescribers have similar baseline knowledge of the serious risks with Nulojix. As Nulojix is not distributed directly by a physician to a patient, certification of prescribers alone would not serve to restrict Nulojix distribution.

5.2.2 CERTIFICATION OF DISPENSER

Overview

The certification of the dispenser, e.g., central hospital pharmacy in tertiary center with a transplant center, community infusion center, home health agency, would require attestation of a responsible person, e.g., director of pharmacy services, director of a department of surgery/transplant surgery, or director of an infusion center to understand the serious risks of Nulojix. The attestation includes agreement to develop and implement appropriate policies and procedures to ensure that Nulojix is dispensed after receiving a prescription order from a certified prescriber and confirming EBV (+) serostatus.

A certified dispenser would be responsible for the education of their staff about the serious risks with Nulojix.

- Periodic recertification and re-enrollment of the dispenser may be required.

How could this be accomplished?

- Dispenser reviews the FDA approved REMS education materials via web-based “course”, a brochure, fact sheet, or other written materials
- Dispenser attests to having the appropriate policies and procedures to ensure the following steps:
 - Educate staff about the risks and required monitoring
 - Dispenser, e.g., central pharmacy, infusion center, etc., only accepts prescription orders from a certified prescriber
 - Verify a patient’s EBV serostatus as (+) before dispensing Nulojix
- Manufacturer, wholesaler, specialty distributor only ships Nulojix to certified dispensers. Wholesalers distribute Nulojix to certified hospitals, transplant centers and community hospitals. Specialty distributors distribute Nulojix to certified non-hospital settings, e.g. infusion centers, physician offices, and specialty pharmacies supporting home health agency infusion of Nulojix.

Advantages	Disadvantages
<ul style="list-style-type: none"> • Because Nulojix distribution is effected <ul style="list-style-type: none"> ○ Ensures that only HCPs/ facilities with knowledge/ understanding of Nulojix risks and monitoring would dispense/administer Nulojix • Supports prescriber certification • Supports safe use strategies, e.g. documentation of EBV (+) serostatus, (critical if patient is started on Nulojix, post-transplantation) 	<ul style="list-style-type: none"> • Drug distribution is effected • Without additional elements does not ensure patient monitoring or data collection regarding: <ul style="list-style-type: none"> ○ EBV serostatus (+) or (-), ○ SAEs • Difficult to assess REMS program impact <ul style="list-style-type: none"> ○ No tracking of prescriber or dispenser adherence with verification of EBV serostatus (+) prior to Nulojix treatment

BMS would only ship Nulojix to certified dispenser which serves to establish a link between certification and drug distribution. With this element, infusion centers and hospitals that administer Nulojix are responsible for developing and implementing procedures to ensure all of their staff are trained and the EBV (+) serostatus is verified prior to initial dispensing. However, unless patients are enrolled in the program, documentation of EBV serostatus under the REMS would not be required. EBV (+) serostatus data would be collected via UNOS. Certification of dispensers would be more effective if certification of prescribers is also required.

5.2.3 DOCUMENTATION OF SAFE USE CONDITIONS / PATIENT ENROLLMENT/ PATIENT MONITORING

Overview

Documentation of safe use conditions may include documentation of EBV (+) and or periodic documented monitoring for signs and symptoms of PTLD and PML, and or periodic query of HCPs for cases of PTLD and PML. The periodic monitoring could be similar to the Tysabri TOUCH Program or the Nplate and Promacta REMS programs. (b) (4)

How could this be accomplished?

<ul style="list-style-type: none"> • Prescribers, transplant centers, hospitals and infusion centers enroll in REMS program • Patients presents for kidney transplant • Verify patient’s EBV serostatus • Transplant surgeon determines if patient is appropriate for Nulojix • Patient is counseled and is enrolled by prescriber, signs patient agreement • Prescriber sends enrollment form with documentation of EBV serostatus to company • Pharmacy verifies EBV serostatus before dispensing Nulojix • Patient is transplanted, stable, and discharged → Transfers care to enrolled community nephrologists and enrolled infusion centers <ul style="list-style-type: none"> ○ Monitor each patient prior to each Nulojix infusion for new or early signs and symptoms of PTLD and or PML via “Pre-Infusion Checklist” ○ Periodically query HCPs, e.g., q 6 months or annually, requesting reports of SAEs of concern via the FDA approved Nulojix REMS form for each treated patient, HCP completes monitoring form • Each monitoring form is submitted to the Nulojix REMS system, if concerning signs and symptoms are reported by a patient, the enrolled prescriber is alerted. • Patient discontinuation and reason for discontinuation is captured. 	
Advantages	Disadvantages
<ul style="list-style-type: none"> • Active risk mitigation steps • One time documentation of EBV (+) serostatus for Nulojix treatment with, particularly for the risks of PTLD <ul style="list-style-type: none"> ○ EBV serostatus verified at time of kidney transplantation or if Nulojix initiated post kidney transplantation ○ Detection of any new or worsening signs and symptoms of PTLD/PML ○ Periodic query of cases of PTLD and PML • Supports adherence with Nulojix label, including contraindications, and overall safety. • Facilitates transfer of patient from transplant center to community infusion center • Increased assessment capabilities <ul style="list-style-type: none"> ○ Capture all patients treated with Nulojix, <i>de novo</i> transplant and post-transplantation. ○ Monitor SAEs ○ Track prescriber adherence with EBV (+) serostatus pre-treatment • Minimal impact on patient 	<ul style="list-style-type: none"> • Requires prescriber and dispenser certification to implement Nulojix REMS <ul style="list-style-type: none"> ○ Drug distribution would be effected ○ Effects drug distribution ○ No additional steps from required dispenser certification • Increases the burden on HCPs, healthcare delivery systems at tertiary transplant centers, community hospitals, infusion centers, and home health care agencies, and on the applicant.

6 REMS DISCUSSION

At this time, in considering the most appropriate risk management approach for Nulojix, a number of factors were considered.

Healthcare Provider Expertise

Transplant specialists are well versed in immunosuppression. Although Nulojix represents a new class of therapeutic biologic agents in transplant immunosuppression, Nulojix (pre-market) and approved maintenance immunosuppressants for kidney transplantation, e.g., CsA, tacrolimus, MMF/MPA, sirolimus, corticosteroids, share serious risks such as serious infection, malignancy and the more relevant risks to this discussion, PTLD and PML. As long as patients are immunosuppressed, they are continually at-risk for these serious adverse events. Therefore, while the serious risks of PTLD and PML are augmented with Nulojix, they are not new to healthcare providers specializing in transplantation. However, given that the clinical presentation of PTLD and PML in the belatacept clinical trials occurred at 12 months or later after transplantation, the role and level of expertise of non-transplantation specialists, e.g., community-based nephrologists and infusion centers, must be considered in conjunction with the purported expertise of transplantation specialists.

Route of Administration

Nulojix is the first maintenance transplant immunosuppressive administered as a monthly intravenous infusion. At present, all maintenance transplantation immunosuppression is administered orally.⁸ The intravenous route of administration provides for regular interaction and potential evaluation by a healthcare provider for any concerning signs or symptoms of PTLD and or PML. Because Nulojix treatment cannot be reversed once it is infused, if a patient begins to experience adverse immunosuppressive effects, it will be prudent to evaluate the patient prior to each infusion.

Risks and Utility of Intervention

Not all risks can be mitigated through monitoring a laboratory parameter. REMS do not require that the risk(s) must have a simple mitigation tool to “qualify” for a REMS. Mitigation may come in the form of periodic query by the healthcare provider for signs and symptoms of SAEs and prompt discontinuation, if appropriate. Mitigation may also be in the form of periodic assessment of the appropriateness of continuing treatment. This approach is employed with Tysabri (natalizumab) for PML, Nplate (romiplostim) and Promacta (eltrombo-pag) for malignancy. In discussion with the review division, they did express confidence at this time that early diagnosis of PTLD and PML, or periodic drug reauthorization would not have a significant impact or benefit on patient outcomes because prompt discontinuation may not be possible. Because treating patients that are EBV (-) or EBV unknown serostatus will be a labeled contraindication and accounts for less than 15% of patients, compliance with the labeled contraindication is expected to be high.

Established Monitoring and Follow-Up

The organ transplantation community maintains a unique, required data collection system. To address the nation’s organ donation shortage and improve the organ matching and placement process, the US Congress passed the National Organ Transplant Act (NOTA) in 1984. The Act called for a unified transplant network named the Organ

⁸ We note that cyclosporine, tacrolimus, and mycophenolate mofetil are available as intravenous infusions but this route of administration is not the primary route for maintenance immunosuppression.

Procurement and Transplantation Network (OPTN). The United Network for Organ Sharing (UNOS) was awarded the initial and current OPTN contract. The OPTN regulations state that “to receive organs for transplantation, a transplantation program...shall abide by these rules and shall: Be a transplant program approved by the Secretary for reimbursement under Medicare; or Be an organ transplant program which has adequate resources to provide transplant services to its patients and agrees to promptly notify the OPTN and patients waiting transplants if it becomes inactive...”

The regulations further state that “All Organ Procurement Organizations (OPOs) and transplant programs shall maintain such records pertaining to each potential donor identified, each organ retrieved, each recipient transplanted and such other transplantation-related matters as the Secretary deems necessary to carry out her/his responsibilities under the Act. The OPO or transplant program shall maintain these records for seven years.”⁹

Therefore, in the absence of a specific Nulojix patient registry, UNOS captures EBV serostatus, post-transplant malignancies including PTLD at 6 months, one year and annually, thereafter up to 5 years. UNOS also captures events of acute rejection and patient and graft survival at the same follow-up intervals until graft failure or patient death. While these data do not provide active risk mitigation, these data provide a basis for monitoring the use of and serious risks associated with Nulojix.

Considering all the factors discussed above, a reasonable case could be made to conclude the need for restricted distribution or the need for a robust educational effort. Restricted distribution in the context of solid organ transplantation has deleterious consequences if drug distribution is limited unnecessarily. However, Nulojix has serious risks. Given these considerations, most importantly, the familiarity of the transplant community with these risks of all transplant immunosuppressive therapies, the lack of proven benefit, to date, of early clinical detection for the serious risks of PTLD and PML, and the established monitoring capability unique to transplantation, a robust education effort seems a practical first step. If further safety concerns arise, restricted distribution must again be carefully considered.

7 CONCLUSION

If Nulojix (belatacept) is approved with the current safety profile, DRISK recommends a Nulojix REMS to consist of a Medication Guide and communication plan. The communication plan should be ongoing, versus limited to the time of initial product approval, and should include a multifaceted education approach that is commensurate with increased drug utilization and the anticipated lag time in the clinical presentation of PTLD and PML.

We believe Nulojix should be monitored closely through UNOS, postmarketing requirements, and ongoing clinical studies. If accumulating data reflects additional risk beyond what is anticipated based on the current data for PTLD, PML or any other serious risks, we would then recommend a low threshold for requiring restricted distribution measures if it is believed that the benefits would continue to outweigh the risks.

There remain outstanding issues in the most recently submitted proposed Nulojix REMS document and in the appended REMS materials (April 1, 2010). Specific comments on the proposed Nulojix REMS will be sent as a separate review.

⁹ 42 CFR Part 121.