DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125288/062

SUPPLEMENT APPROVAL

Bristol-Myers Squibb
Attention: Ashley Pereira, Pharm. D
Director, Global Regulatory Sciences, U.S. Liaison
PO Box 4000
Princeton, NJ 08543

Dear Dr. Pereira:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received June 11, 2014, submitted under section 351(a) of the Public Health Service Act for Nulojix (belatacept).

We acknowledge receipt of your amendment dated September 9, 2014.

This "Prior Approval" supplemental biologics application provides for revisions to the **DRUG INTERACTIONS, CLINICAL PHARMACOLOGY** sections, and various editorial changes of the package insert.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text submitted on September 9, 2014.

LABELING REVISIONS

The revisions to the package insert are as follow (additions are noted with double underline and deletions with ~~strikethrough~~):

1. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, various editorial formatting changes were made.

2. In the **TABLE OF CONTENTS,** the **DRUG INTERACTIONS** sections **7.1** and **7.2** have been updated to reflect the new titles. Section **17 PATIENT COUNSELING INFORMATION** section has been updated to remove the subsections numbering.

In the **FULL PRESCRIBING INFORMATION** section, the following revisions have been made:

3. In the **7 DRUG INTERACTIONS** section, the subsections **7.1** and **7.2** have been reordered to list MMF first and revisions is made to each subsection as follows:

7.1 ~~Cytochrome P450 Substrates~~ Mycophenolate Mofetil (MMF)

~~No formal drug interaction studies have been conducted with NULOJIX. Other biologic therapies that are cytokines or cytokine modulators have been shown to affect the expression and/or functional activities of cytochrome P450 (CYP450) enzymes *in vitro* and/or *in vivo*. *In vitro* studies have shown that NULOJIX inhibits the production of certain cytokines during an alloimmune response. No studies in kidney transplant patients have been conducted to assess if NULOJIX inhibits cytokine production *in vivo*. The potential for NULOJIX to alter the systemic concentrations of drugs that are CYP450 substrates has not been studied; however, in the event that kidney transplant patients receiving NULOJIX exhibit signs and symptoms of altered efficacy or adverse events associated with coadministered drugs which are known to be metabolized by CYP450, the clinician should be aware of potentially altered CYP450 metabolism of these drugs.~~

Monitor for a need to adjust concomitant mycophenolate mofetil (MMF) dosage when patient's therapy is switched between cyclosporine and NULOJIX, as cyclosporine decreases mycophenolic acid (MPA) exposure by preventing enterohepatic recirculation of MPA while NULOJIX does not [see *Clinical Pharmacology (12.3)*]:

- A higher MMF dosage may be needed after switching from NULOJIX to cyclosporine, since this may result in lower MPA concentrations and increase the risk of graft rejection.
- A lower MMF dosage may be needed after switching from cyclosporine to NULOJIX, since this may result in higher MPA concentrations and increase the risk for adverse reactions related to MPA (review the Full Prescribing Information for MMF).

7.2 ~~Use with Mycophenolate Mofetil~~ Cytochrome P450 Substrates

~~In a pharmacokinetic substudy of Studies 1 and 2, the plasma concentrations of mycophenolic acid (MPA) were measured in 41 patients who received fixed mycophenolate mofetil (MMF) doses of 500 mg to 1500 mg twice daily with either 5 mg per kg of NULOJIX or cyclosporine.~~

~~The mean dose-normalized MPA Cmax and AUC0-12 were approximately 20% and 40% higher, respectively, with NULOJIX coadministration than with cyclosporine coadministration.~~
~~Clinicians should be aware that there is also a potential change of MPA exposure after crossover from cyclosporine to NULOJIX or from NULOJIX to cyclosporine in patients concomitantly receiving MMF.~~

No dosage adjustments are needed for drugs metabolized via CYP1A2, CYP2C9, CYP2D6, CYP3A, and CYP2C19 when coadministered with NULOJIX [see Clinical Pharmacology (12.3)].

4. In the **12 CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics** subsection, a new section titled "Drug Interactions" is added as follows:

Drug Interactions

Mycophenolate Mofetil

In a pharmacokinetic substudy of Studies 1 and 2, the plasma concentrations of MPA were measured in 41 patients who received fixed MMF doses of 500 to 1500 mg twice daily with either 5 mg per kg of NULOJIX or cyclosporine. The mean dose-normalized MPA C_{max} and AUC_{0-12} were approximately 20% and 40% higher, respectively, with NULOJIX coadministration than with cyclosporine coadministration [see Drug Interactions (7.1)].

Cytochrome P450 Substrates

The potential of NULOJIX to alter the systemic concentrations of drugs that are CYP450 substrates was investigated in healthy subjects following administration of a cocktail of probe drugs given concomitantly with, and at 3 days and at 7 days following a single intravenous 10 mg per kg dose of NULOJIX. NULOJIX did not alter the pharmacokinetics of drugs that are substrates of CYP1A2 (caffeine), CYP2C9 (losartan), CYP2D6 (dextromethorphan), CYP3A (midazolam), and CYP2C19 (omeprazole) [see Drug Interactions (7.2)].

5. In the **17 PATIENT COUNSELING INFORMATION** section, the numbering of the sub-sections has been eliminated.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Ms. June Germain, Safety Regulatory Project Manager, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MPH, MD
Deputy Director for Safety
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES: Content of Labeling (package insert, medication guide)

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

/s/

OZLEM A BELEN
09/30/2014