

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125288Orig1s000

REMS

Risk Evaluation and Mitigation Strategy (REMS)

NULOJIX™ (belatacept)

Selective Co-Stimulation Blocker

Bristol-Myers Squibb Company

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Contact:

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I. GOAL

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 PML, a CNS infection, associated with belatacept
- To inform patients of the serious risks associated with belatacept

II. REMS ELEMENTS

A. Medication Guide

In accordance with 21CFR 208.24, Bristol-Myers Squibb Co. will ensure that a Medication Guide will be included as part of the secondary packaging for belatacept and

dispensed to the patient at the time of hospital discharge post-transplant and at the time of each monthly infusion.

The Medication Guide will also be available via sales and/or medical representative, the product website and through the sponsor's medical information department.

B. Communication Plan

In accordance with FDCA 505-l(e)(3), Bristol-Myers Squibb (BMS) will implement a communication plan to HCPs who are likely to prescribe or administer belatacept, including transplant surgeons, transplant nephrologists, community nephrologists, transplant coordinators, infusion nurses, transplant pharmacists, and pharmacists who support infusion clinics. The communication plan will extend to professional societies and organizations that have reach and influence in the transplant community and those that support infusion centers.

The communication tools include a Healthcare Provider Letter, a Healthcare Provider Fact Sheet, an Educational Deck presentation, Infusion Specialist Letter, Pre-Infusion checklist, and a Journal Information Piece which will be disseminated to the respective targeted audiences and are included in the appendix. The Health Care Provider Fact sheet will serve as the basis for safety panels at transplant congresses where BMS promotional exhibits are planned and journal advertisements.

The approved REMS communication materials will be available from the BMS product website.

The implementation of the communication plan will begin within 2 weeks of REMS approval and product launch.

C. Elements to Assure Safe Use

The REMS for belatacept does not require elements to assure safe use.

D. Implementation System

An implementation system is not required as a component of the proposed REMS for belatacept as there are no elements to support safe use.

E. Timetable for Submission of Assessments

REMS assessments will be submitted as shown in the following table. Discussions will be held with FDA after the 3rd assessment. The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. The assessments will include an evaluation of the effectiveness of the risk minimization program and recommendations for program improvements or changes, if required. BMS will submit each assessment so that it will be received by the FDA on or before the due date.

Communication Plan Details

Table 1: Proposed REMS Materials Dissemination to Target Audiences

Dissemination Channels

	via Direct mailing or Journal ads				Field-based Representative	Toll-free Medical Information	REMS materials in Transfer Pack	Web-available information
	Transplant HCP	Transplant Coordinator	Pharmacist	Infusion Specialist				
<i>Medication Guide</i>	✓	✓	✓	✓	✓	✓	✓	✓
<i>Dear Healthcare Provider Letter</i>	✓	✓	✓		✓	✓	✓	✓
<i>Healthcare Provider Fact Sheet</i>	✓	✓	✓		✓	✓	✓	✓
<i>Infusion Specialist Letter</i>				✓		✓		✓
<i>Pre-Infusion Checklist</i>			✓*	✓*		✓		✓
<i>Educational Deck</i>					✓	✓		✓

Initial mailing for physicians, pharmacists, and transplant coordinators contain the USPI, Medication Guide, Dear HCP Letter, and HCP Fact Sheet; Infusion Specialists receive USPI, Medication Guide, Infusion Specialist Letter and Pre-Infusion Checklist. Journal ads contain an abbreviated HCP Fact Sheet.

*Provided as part of vial carton packaging

Attachment 1: Healthcare Provider Letter

March X, 2011

IMPORTANT DRUG WARNING

Subject: Increased Risk of Post-transplant Lymphoproliferative Disorder (PTLD), predominantly involving the Central Nervous System (CNS), and Progressive Multifocal Leukoencephalopathy (PML) with NULOJIX™ (belatacept)

Dear Healthcare Professional:

The purpose of this letter is to inform you of important safety information for NULOJIX™ (belatacept), a selective T-cell costimulation blocker recently approved by the Food and Drug Administration (FDA) for prophylaxis of organ rejection in adult patients receiving a kidney transplant. NULOJIX is to be used in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids. NULOJIX is indicated for use only in transplant patients who are Epstein-Barr virus (EBV) seropositive. Use in liver transplant patients is not recommended due to an increased risk of graft loss and death. Use of NULOJIX for the prophylaxis of organ rejection in other transplanted organs has not been established.

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of NULOJIX outweigh the risks of PTLT and PML, both of which can be fatal.

Boxed Warning Includes Increased Risk of PTLT

- Patients treated with NULOJIX are at an increased risk for developing PTLT, predominantly involving the CNS

Increased Risk of PML

- PML has been reported in patients receiving NULOJIX at higher than recommended doses as part of an immunosuppressant regimen

Contraindications

- **NULOJIX is contraindicated in transplant recipients who are EBV seronegative or with unknown serostatus**
- Be sure to verify the patient's EBV status before initiating therapy with NULOJIX

This letter is not intended as a complete description of the benefits and risks associated with the use of NULOJIX. For a more complete description about the risks including PTLT and PML, please see the enclosed NULOJIX™ Fact Sheet, and full Prescribing Information, included with this letter.

XX Registry

To further evaluate the ongoing safety profile of NULOJIX, BMS encourages your center to participate in the XX Registry. XX Registry is intended to enroll all adult patients, regardless of EBV serostatus, who receive NULOJIX following a kidney transplant, including de novo patients and those switched to belatacept. The Primary objective of XX Registry is to determine the incidence rate of PTLT, CNS PTLT, and PML in US adult EBV seropositive kidney transplant recipients treated with NULOJIX. Additional information on the registry can be found at www.clintrials.gov.

Reporting Adverse Events

For any adverse event with the use of NULOJIX, healthcare professionals should contact Bristol-Myers Squibb at 1-800-721-5072 and/or the FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm.

All REMS materials, including a NULOJIX™ REMS webinar, are accessible at www.NULOJIX.com/REMS.aspx. For additional information, please call Bristol-Myers Squibb at 1-800-321-1335 or visit www.NULOJIX.com.

Sincerely,

Laura Bessen, MD
Bristol-Myers Squibb
Vice President, US Medical, Immunoscience and Neuroscience

Enclosure: NULOJIX™ Fact Sheet, Full Prescribing Information and Medication Guide

This letter has been reviewed and approved by the FDA as part of the NULOJIX REMS.

Attachment 2: Healthcare Provider Fact Sheet

IMPORTANT INFORMATION ABOUT NULOJIX™ (belatacept)

Increased Risk of Post-Transplant Lymphoproliferative Disorder (PTLD), predominantly involving the Central Nervous System (CNS), and Progressive Multifocal Leukoencephalopathy (PML) with NULOJIX

NULOJIX is a selective T-cell costimulation blocker indicated for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. NULOJIX is to be used in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids. NULOJIX is indicated for use only in patients who are Epstein-Barr virus (EBV) seropositive. Use in liver transplant patients is not recommended due to an increased risk of graft loss and death. Use of NULOJIX for the prophylaxis of organ rejection in other transplanted organs has not been established.

Increased Risk of Post-Transplant Lymphoproliferative Disorder (PTLD)

NULOJIX treated patients have an increased risk for PTLD, predominantly in the CNS

- The highest risk of PTLD is in EBV seronegative patients, therefore, NULOJIX is contraindicated in transplant recipients who are EBV seronegative or with unknown serostatus.
- In clinical trials of kidney transplant recipients, PTLD was seen in 14 out of 949 NULOJIX treated patients, including patients receiving the recommended dosage regimen and a dosage higher than the recommended regimen.
 - 9 of 14 cases of PTLD in NULOJIX-treated patients presented in the CNS.
 - 6 of those 9 CNS cases were fatal.
- At the recommended clinical dose in the EBV+ population, 4 cases of PTLD were reported.
 - 2 of those 4 cases presented in the CNS; both were fatal.
- Other known risk factors for PTLD include T-cell depleting therapy and cytomegalovirus (CMV) infection.
 - T-cell depleting therapy for the treatment of acute rejection should be used with caution in patients who are on NULOJIX.
 - CMV prophylaxis is recommended for at least 3 months after transplantation.

Increased Risk of Progressive Multifocal Leukoencephalopathy (PML)

Patients in clinical trials exposed to NULOJIX at higher or more frequent dosing than the recommended regimen have developed PML

- 2 cases of PML were reported: 1 case occurred in a renal transplant recipient and 1 case occurred in a liver transplant recipient
- Do not exceed the recommended doses of NULOJIX and concomitant immunosuppressants.

Patient Monitoring and Counseling

- Monitor patients for new or worsening neurologic, cognitive, or behavioral signs or symptoms. If detected, consideration should be given to:
 - Appropriate neurologic work-up including consideration for consultation with a specialist (e.g., neurologist and/or infectious disease)
 - Dose reduction or discontinuation of immunosuppressive therapy taking into account the risk to the graft
- Prescribers should counsel patients to:
 - Immediately report changes in thinking, memory, speech, mood or behavior, confusion, weakness, change in vision, episodes of fever, night sweats, prolonged tiredness, weight loss and swollen glands
 - Adhere to all prescribed medications including those for prophylaxis

XX Registry

- To further evaluate these risks ongoing safety profile of NULOJIX, BMS encourages your center to participate in the XX Registry. XX Registry is intended to enroll all adult patients, regardless of EBV serostatus, who receive NULOJIX following a kidney transplant, including de novo patients and those switched to NULOJIX.
- The primary objective of the XX Registry is to determine the incidence rates of PTLD, CNS PTLD, and PML in US adult EBV seropositive kidney transplant recipients treated with NULOJIX.
- Additional information on the registry can be found at www.clintrials.gov.

Adverse events with the use of NULOJIX should be reported to:

- Bristol-Myers Squibb at 1-800-721-5072 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online www.fda.gov/medwatch/report.htm

All REMS materials, including a NULOJIX™ REMS webinar, are accessible at www.NULOJIX.com/REMS.aspx
Please refer to the complete Prescribing Information for further information which is available at www.NULOJIX.com.

This Fact Sheet has been reviewed and approved by the FDA as part of the NULOJIX REMS.

Attachment 3: Infusion Specialist Letter

March X, 2011

IMPORTANT DRUG WARNING

Subject: Increased Risk of Post-transplant Lymphoproliferative Disorder (PTLD), predominantly involving the Central Nervous System (CNS), and Progressive Multifocal Leukoencephalopathy (PML) with NULOJIX™ (belatacept)

Dear Infusion Specialist:

This letter informs you of important safety information for NULOJIX™ (belatacept), a selective T-cell co-stimulation blocker recently approved by the Food and Drug Administration (FDA) for prophylaxis of organ rejection in adult patients receiving a kidney transplant. NULOJIX is to be used in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids. NULOJIX is indicated only for use only in patients who are EBV seropositive. Use in liver transplant patients is not recommended due to an increased risk of graft loss and death. Use of NULOJIX for the prophylaxis of organ rejection in other transplanted organs has not been established.

Important information you should know about NULOJIX:

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of NULOJIX outweigh the risks, including:

- **PTLD**, a type of malignancy. Patients treated with NULOJIX have a higher risk of getting PTLD, predominantly involving the CNS. PTLD can cause death.
- **PML**, a rare, serious brain infection. This rare brain infection has been reported in patients treated with NULOJIX. PML can cause death.

You play an important role by:

- 1) **educating the patient about these risks,**
- 2) **identifying any concerning signs and symptoms associated with these risks, and**
- 3) **alerting the prescriber about any concerning signs and symptoms reported to you.**

For every patient, complete the enclosed PRE-INFUSION CHECKLIST before each infusion, Place the completed checklist into the patient's medical record. You can request more checklists by calling 1-888-NULOJIX or at www.NULOJIX.com/REMS.aspx.

Reporting Adverse Events

For any adverse event with the use of NULOJIX, healthcare professionals should contact Bristol-Myers Squibb at 1-800-721-5072 and/or the FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm.

This letter is not intended as a complete description of the benefits and risks associated with the use of NULOJIX. Please refer to the enclosed complete Prescribing Information and Medication Guide.

All REMS materials, including a NULOJIX™ REMS webinar, are accessible at www.NULOJIX.com/REMS.aspx. For additional information, please call Bristol-Myers Squibb at 1-800-321-1335 or visit www.NULOJIX.com.

Sincerely,

Laura Bessen, MD
Bristol-Myers Squibb
Vice President, US Medical, Immunoscience and Neuroscience

Enclosure: NULOJIX™ (belatacept) Pre-Infusion Checklist, Full Prescribing Information and Medication Guide

This letter has been reviewed and approved by the FDA as part of the NULOJIX REMS.

NULOJIX is a trademark of Bristol-Myers Squibb.

Attachment 4: Infusion Specialist Checklist

NULOJIX™ (belatacept) PRE-INFUSION CHECKLIST

PATIENT NAME: _____

DATE OF VISIT: _____

Use this checklist **before each infusion** to identify a patient who may be experiencing: new, changed, or worsened neurological, cognitive, or behavioral signs or symptoms. These signs and symptoms could be related to post-transplant lymphoproliferative disorder (PTLD), involving the central nervous system (CNS), or progressive multifocal leukoencephalopathy (PML). Both of these can cause death.

Remember to GIVE CARE (Give, Counsel, Ask, REmind)

CHECK AS COMPLETED:

GIVE	A copy of the NULOJIX Medication Guide must be provided to patients receiving NULOJIX before each infusion.
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Gave Medication Guide

Counsel	Use the Medication Guide to counsel patients about the risks and benefits of NULOJIX, including: <ul style="list-style-type: none">– the increased risk for PTLD, predominantly involving the CNS– increased risk of PML, a CNS infection
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Counseled patient

Ask	Read these questions aloud to the patient before starting each infusion. <ol style="list-style-type: none">1. Over the past month, have you had any new or worsening medical problems such as a new or sudden change in your thinking, memory, speech, mood, behavior, vision, balance, strength, or other problems?2. Over the past month, have you had any new or worsening symptoms such as fever, night sweats, tiredness that does not go away, weight loss, or swollen glands?
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1. Asked Patient Yes
No

2. Asked Patient Yes
No



If any response is YES, notify the prescriber to discuss the patient's symptoms.

REmind	Remind patients to immediately report any new or worsening medical problems such as: <ul style="list-style-type: none">– a new or sudden change in thinking, memory, speech, mood, behavior, vision, balance, strength– fever, night sweats, tiredness that does not go away, weight loss, or swollen glands
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Reminded patient

Infusion Administered

Please file this checklist with the patient's medical record

Reporting Adverse Events

For any adverse event with the use of NULOJIX, healthcare professionals should contact Bristol-Myers Squibb at 1-800-721-5072 and/or the FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm.

This document is not intended as a complete description of the risks associated with the use of NULOJIX. Please refer to the complete Prescribing Information and Medication Guide.

All REMS materials, including a NULOJIX™ REMS webinar, are accessible at www.NULOJIX.com/REMS.aspx. For additional information, please call Bristol-Myers Squibb at 1-800-321-1335 or visit www.NULOJIX.com.

This checklist has been reviewed and approved by the FDA as part of the NULOJIX REMS.



March X, 2011

IMPORTANT SAFETY INFORMATION Regarding NULOJIX™ (belatacept)

Dear Healthcare Professional:

The purpose of this letter is to inform you of important safety information for NULOJIX™ (belatacept), a selective costimulation blocker approved by the Food and Drug Administration (FDA) on Month DD, 20YY for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. NULOJIX has been used in combination with an interleukin-2 (IL-2) receptor antagonist, a mycophenolic acid (MPA), and corticosteroids. NULOJIX has not been studied in patients less than 18 years of age.

CONTRAINDICATIONS

- NULOJIX is contraindicated in transplant recipients who are Epstein-Barr virus (EBV) seronegative or with unknown serostatus
- Be sure to verify the patient's EBV status before initiating therapy with NULOJIX

IMPORTANT INFORMATION ABOUT RISK OF NULOJIX

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of NULOJIX outweigh the potential risks, including:

- **Risk of Central Nervous System Post-transplant Lymphoproliferative Disorder (PTLD) and Progressive Multifocal Leukoencephalopathy (PML)**
 - Patients treated with NULOJIX are at an increased risk for developing PTLD, specifically involving the central nervous system (CNS), which can be fatal
 - In clinical trials with NULOJIX, 2 cases of PML (one in a renal transplant recipient and one in a liver transplant recipient) were reported in patients receiving NULOJIX at doses higher than the recommended regimen along with mycophenolate mofetil (MMF) and corticosteroids
 - Risk factors for PTLD include EBV negative serostatus, cytomegalovirus (CMV) infection and T cell depleting therapy, which was more commonly used to treat acute rejection in NULOJIX-treated patients in Phase 3 clinical trials. T-cell depleting therapies to treat acute rejection should be used cautiously. CMV prophylaxis is recommended for a least 3 months after transplantation
 - Physicians should consider PTLD involving the CNS, and PML in the differential diagnosis in patients with new or worsening neurologic, cognitive, or behavioral signs or symptoms and consider brain imaging. PML may be diagnosed with cerebrospinal fluid (CSF) testing for JC viral DNA by polymerase chain reaction (PCR)

- Consultation with a specialist (e.g., neurologist, and/or infectious disease specialist) should be considered for any suspected cases of PTLD or PML
 - As PTLD and PML have been associated with high levels of overall immunosuppression, the recommended doses of NULOJIX and concomitant immunosuppressive, including MMF or mycophenolic acid, should not be exceeded
- **Increased susceptibility to serious infections**
 - Patients receiving immunosuppressants, including NULOJIX are at increased risk of developing bacterial, viral (cytomegalovirus [CMV] and herpes), fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes
 - CMV prophylaxis is recommended for at least 3 months after transplantation
 - Pneumocystis pneumonia prophylaxis is recommended for at least 6 months following transplantation

PATIENT COUNSELING

Patients should be counseled about the risks and benefits of NULOJIX, including:

- The potential risks for PTLD, PML, and other serious infections

Patients should be reminded to contact their doctor immediately to report any:

- New or worsening neurological, cognitive, or behavioral changes, such as changes in memory, speech, mood or behavior, confusion, weakness, or change in vision
- Episodes of fever, night sweats, prolonged tiredness, weight loss and swollen glands

Patients should be counseled on the importance of adherence to their medication including belatacept infusion visits, and prophylactic medications such as those utilized for CMV prophylaxis after initial transplantation, and following T cell depleting therapy for treatment of rejection episodes

The NULOJIX Medication Guide must be provided to patients before each infusion

The medication Guide contains information to support patient counseling regarding the risks and benefits of treatment with NULOJIX. Additional copies of the NULOJIX Medication Guide may be obtained from the web site at www.NULOJIX.com or by calling Bristol-Myers Squibb at 1-800-321-1335

The Important Safety Information in the NULOJIX Full Prescribing Information includes a **BOXED WARNING CONTAINING THE FOLLOWING INFORMATION:**

**WARNING: POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER
AND IMMUNOSUPPRESSION**

NULOJIX-treated patients are at an increased risk for developing post-transplant lymphoproliferative disorder (PTLD), specifically involving the central nervous system (CNS). Recipients without immunity to Epstein-Barr virus (EBV) are at a particularly increased risk; therefore, transplant recipients who are EBV seronegative or with unknown serostatus should not receive TRADENAME [see Contraindications (4), WARNINGS AND PRECAUTIONS (5.1)].

Increased susceptibility to infections and the possible development of malignancies may result from immunosuppression [see WARNINGS AND PRECAUTIONS (5.2, 5.4)].

Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should prescribe NULOJIX. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient [see WARNINGS AND PRECAUTIONS (5)].

REPORTING ADVERSE EVENTS

For any adverse events with or coincident with the use of NULOJIX healthcare professionals should contact Bristol-Myers Squibb at 1-800-321-1335 and/or the FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

This letter is not intended as a complete description of the benefits and risks associated with the use of NULOJIX. Please refer to the enclosed complete Prescribing Information and Medication Guide.

For additional information, please call Bristol-Myers Squibb at 1-800-321-1335 or visit www.NULOJIX.com.

Sincerely,

Laura Bessen, MD
Vice President, US Medical, ImmunoScience

Enclosure: NULOJIX™ (belatacept) Full Prescribing Information and Medication Guide

NULOJIX is a trademark of Bristol-Myers Squibb.

IMPORTANT INFORMATION ABOUT NULOJIX™ (belatacept)

Do not prescribe NULOJIX for transplant recipients who are EBV seronegative or with unknown EBV serostatus

WARNING: POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER AND IMMUNOSUPPRESSION

NULOJIX-treated patients are at an increased risk for developing post-transplant lymphoproliferative disorder (PTLD), specifically involving the central nervous system (CNS). Recipients without immunity to Epstein-Barr virus (EBV) are at a particularly increased risk; therefore, transplant recipients who are EBV seronegative or with unknown serostatus should not receive NULOJIX [see Contraindications (4), *WARNINGS AND PRECAUTIONS* (5.1)].

Increased susceptibility to infections and the possible development of malignancies may result from immunosuppression [see *WARNINGS AND PRECAUTIONS* (5.2, 5.4)].

Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should prescribe NULOJIX. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient [see *WARNINGS AND PRECAUTIONS* (5)].

Prescribers should also be aware of other important information

- Post Transplant Lymphoproliferative Disorder (PTLD)
 - Risk factors include EBV-negative serostatus, CMV disease and T cell depleting therapy
 - CMV prophylaxis is recommended for at least 3 months after transplantation
 - T cell depleting therapies used to treat acute rejection should be used cautiously
- Progressive Multifocal leukoencephalopathy (PML) has been reported in patients receiving NULOJIX at higher than recommended dose as part of an immunosuppressant regimen
 - Do not exceed recommended doses of NULOJIX and concomitant immunosuppressives
- Patients should be monitored for new or worsening neurologic, cognitive or behavioral signs or symptoms
 - PTLD and PML should be considered
 - Consideration should be given to:
 - Brain imaging and consultation with a specialist
 - Reduction or discontinuation of immunosuppressive therapy taking into account the risk to the graft

Prescribers should counsel patients to:

- Immediately report any new or worsening neurologic, cognitive, or behavioral signs or symptoms
- Adhere to all prescribed medications including those for prophylaxis

NULOJIX is selective costimulation blocker indicated for:

- Prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.

Adverse events with or coincident with the use of NULOJIX should be reported to:

- Bristol-Myers Squibb at 1-800-321-1335 and/or FDA MedWatch program by phone at 1-800-FDA-1088 or online <https://www.accessdata.fda.gov/scripts/medwatch/>

Please refer to complete Prescribing Information for further information which is available at www.NULOJIX.com

NULOJIXTM (belatacept)

Training for Healthcare Professionals

NULOJIX Indication and Contraindication

- **Adult Renal Transplant Recipients**
 - NULOJIX is a selective costimulation blocker indicated for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. NULOJIX has been used in combination with an interleukin-2 (IL-2) receptor antagonist, a mycophenolic acid (MPA), and corticosteroids

- **Contraindications**
 - NULOJIX is contraindicated in transplant recipients who are Epstein-Barr virus (EBV) seronegative or with unknown EBV serostatus due to the risk of post-transplant lymphoproliferative disorder (PTLD), specifically involving the central nervous system (CNS)

EBV serology should be ascertained before administering NULOJIX

Transplant recipients who are EBV seronegative or serostatus unknown should not receive NULOJIX

Post-Transplant Lymphoproliferative Disorder (PTLD)

- NULOJIX treated patients have an increased risk for PTLD predominantly in the CNS
 - Nine of 14 cases of PTLD in NULOJIX-treated patients presented in the CNS and 6 of these 9 CNS cases were fatal.
 - At the recommended clinical dose in the EBV+ population, 4 cases of PTLD were reported
 - 2 CNS cases, both were fatal
- Highest PTLD risk in EBV-seronegative patients
- Additional risk include CMV infection and T cell depleting therapy
 - T-cell depleting therapy for the treatment of acute rejection should be used with caution
- The total burden of immunosuppression is a risk factor for PTLD
 - Higher than recommended doses of both belatacept and concomitant immunosuppressive therapy should be avoided

Consider PTLD in the differential diagnosis in patients with new or worsening neurological, cognitive or behavior signs or symptoms

Progressive Multifocal Leukoencephalopathy (PML)

- Progressive multifocal leukoencephalopathy (PML) is a rare, often rapidly progressive and fatal, opportunistic infection of the CNS that is caused by the JC virus
- 2 cases of PML were reported in patients receiving NULOJIX at doses higher/more frequently administered than the recommended regimen along with mycophenolate mofetil (MMF) and corticosteroids
 - 1 case occurred in a renal transplant recipient and 1 case occurred in a liver transplant recipient
- The total burden of immunosuppression is a risk factor for PML
 - Higher than recommended doses of both belatacept and concomitant immunosuppressive therapy should be avoided
- PML is usually diagnosed by brain imaging and cerebrospinal fluid (CSF) testing for JC viral DNA by polymerase chain reaction (PCR)
 - Consultation with a neurologist and/or infectious diseases specialist should be considering
- If PML is diagnosed, reduction or withdrawal immunosuppression, taking into account the risk to the graft

Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavior signs or symptoms

Serious Infections

- Patients receiving immunosuppressants, including NULOJIX, are at increased risk of developing bacterial, viral (cytomegalovirus [CMV] and herpes), and opportunistic infections including fungal, and protozoal infections
- These infections may lead to serious, including fatal, outcomes
- Post-transplant patients should receive appropriate prophylactic antimicrobial and antiviral therapy
 - CMV prophylaxis for at least 3 months after transplantation or administration of lymphocyte depleting therapy

Risk Evaluation and Mitigation Strategies (REMS)

Patient Information

- **It is important to counsel your patients:**
 - About the overall risk of PTLD, especially CNS PTLD, and serious infections including PML in NULOJIX-treated patients
 - To immediately report any new onset or worsening neurological, cognitive or behavioral signs and symptoms to their HCP
 - To adhere to antimicrobial and antiviral prophylaxis regimens, particularly at times of enhanced immunosuppression
- **Provide patients with a Medication Guide with each monthly infusion**

Medication Guide

- The NULOJIX Medication Guide should be used to educate patients on the risks of NULOJIX and must be given to patients with each monthly infusion
 - A copy is included with each single-use vial carton in compliance with 21 Code of Federal Regulations (CFR) 208.24
 - Additional copies are available for healthcare professionals and patients upon request at www.NULOJIX.com or by calling 1-800-321-1335

Healthcare Professional Information

- Additional resources for you include:
 - Healthcare Professional Letter
 - Healthcare Professional Fact Sheet
 - Infusion Specialist Letter
 - Infusion Specialist Checklist

 - Visit www.NULOJIX.com
 - Call Bristol-Myers Squibb at 1-800-321-1335

Adverse Event Reporting

Report all adverse events associated with use of NULOJIX to:

Bristol-Myers Squibb
1-800-321-1335

OR

FDA
1-800-FDA-1088 (1-800-332-1088)
or by mail using Form 3500 at
www.fda.gov/medwatch

[Bristol-Myers Squibb letterhead]

IMPORTANT SAFETY INFORMATION ABOUT NULOJIX™ (belatacept)

Dear Infusion Specialist:

This letter informs you of important safety information for NULOJIX™ (belatacept), a selective co-stimulation blocker approved by the Food and Drug Administration (FDA) on Month DD, 20YY for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants. NULOJIX has not been studied in patients less than 18 years of age.

Important information you should know about NULOJIX:

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of NULOJIX outweigh the potential risks, including:

- **PTLD (post-transplant lymphoproliferative disorder)**, a type of malignancy. Patients treated with NULOJIX have a higher risk of getting PTLD, specifically involving the CNS. PTLD can cause death or severe disability.
- **PML (progressive multifocal leukoencephalopathy)**, a rare, serious brain infection. This rare brain infection has been reported on patients treated with NULOJIX. PML can cause death or severe disability.

You play an important role in risk mitigation. Before each infusion, GIVE CARE (Give, Counsel, Ask, Remind)

<u>G</u>IVE	A copy of the NULOJIX Medication Guide must be provided to patients receiving NULOJIX before each infusion.
<u>C</u>ounsel	Use the Medication Guide to counsel patients about the risks and benefits of NULOJIX, including: <ul style="list-style-type: none">– the risk for PTLD, specifically involving the central nervous system– the risk for serious infections including PML
<u>A</u>sk	Read these questions aloud to the patient before starting each infusion. <ol style="list-style-type: none">1. Have either you or your family members noticed any changes in your memory, speech, mood or behavior, confusion, weakness or change in vision in the past month?2. Have you had any fever, night sweats, prolonged tiredness, or unexplained weight loss or swollen glands in the last month? If the patient answers YES to either of these questions, consult the patient's prescriber (or designee) BEFORE proceeding with the infusion.
<u>R</u>emind	Remind patients to: <ul style="list-style-type: none">– Contact their doctor immediately to report any signs and symptoms of:<ul style="list-style-type: none">– nervous system or motor function disorders such as memory lapse, speech or communication difficulty, mood or behavior change, confusion, weakness on one side of the body or vision changes– fever, night sweats, prolonged tiredness, weight loss or swollen glands– Continue to take all medications including NULOJIX as prescribed

The Important Safety Information in the NULOJIX Full Prescribing Information includes a **BOXED WARNING CONTAINING THE FOLLOWING INFORMATION**.

BE SURE TO READ THIS CAREFULLY.

**WARNING: POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER
AND IMMUNOSUPPRESSION**

NULOJIX is contraindicated in transplant recipients who are EBV seronegative or with unknown EBV serostatus due to the risk of post-transplant lymphoproliferative disorder (PTLD), specifically involving the central nervous system (CNS) [see *Boxed Warning and Warnings and Precautions (5.1)*].

NULOJIX-treated patients are at an increased risk for developing post-transplant lymphoproliferative disorder (PTLD), specifically involving the central nervous system (CNS). Recipients without immunity to Epstein-Barr virus (EBV) are at a particularly increased risk; therefore, transplant recipients who are EBV seronegative or whose serostatus is unknown should not receive NULOJIX [see *WARNINGS AND PRECAUTIONS*].

Increased susceptibility to infections and malignancies may result from immunosuppression [see *WARNINGS AND PRECAUTIONS*].

Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should prescribe NULOJIX. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient [see *WARNINGS AND PRECAUTIONS*].

Reporting Adverse Events

For any adverse event with or coincident with the use of NULOJIX, healthcare professionals should contact Bristol-Myers Squibb at 1-800-321-1335 and/or FDA MedWatch program at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm.

This letter is not intended as a complete description of the benefits and risks associated with the use of NULOJIX. Please refer to the enclosed complete Prescribing Information and Medication Guide.

For additional information, please call Bristol-Myers Squibb at 1-800-321-1335 or visit www.NULOJIX.com.

Sincerely,

Laura Bessen, MD
Vice President, US Medical, ImmunoScience

Enclosure: NULOJIX™ (belatacept) Full Prescribing Information and Medication Guide

NULOJIX is a trademark of Bristol-Myers Squibb

Appendix F: Infusion Specialist Checklist NULOJIX™ INFUSION CHECKLIST

PATIENT NAME: _____

DATE OF VISIT: _____

Use this checklist **before each infusion** to identify a patient who may be experiencing early neurological signs or symptoms related to post-transplant lymphoproliferative disorder (PTLD), specifically involving the central nervous system, or progressive multifocal leukoencephalopathy (PML).

Remember to GIVE CARE (Give, Counsel, Ask, REmind)

CHECK AS COMPLETED:

GIVE	A copy of the NULOJIX Medication Guide must be provided to patients receiving NULOJIX before each infusion.
Counsel	Use the Medication Guide to counsel patients about the risks and benefits of NULOJIX, including: – the risk for PTLTD, specifically involving the central nervous system – the risk for PML and other serious infections
Ask	<p>Read these questions aloud to the patient before starting each infusion.</p> <ol style="list-style-type: none"> 1. Have either you or your family members noticed any changes in your memory, speech, mood or behavior, experienced confusion, weakness on one side of the body or change in vision in the past month? 2. Have you had any fever, night sweats, prolonged tiredness, or unexplained weight loss or swollen glands in the last month? <p style="text-align: center;">If the patient answers YES to either of these questions, contact the patient’s prescriber (or</p>
REmind	<p>Remind patients to:</p> <ul style="list-style-type: none"> – Contact their doctor immediately to report any signs and symptoms of: <ul style="list-style-type: none"> – memory lapse, speech, mood or behavior, confusion, weakness on one side of the body, or change in vision – fever, night sweats, prolonged tiredness, or unexplained weight loss or swollen glands – Continue to take all medications including NULOJIX as prescribed

Gave Medication Guide

Couseled patient

1. Asked Patient Yes
 No

2. Asked Patient Yes
 No



**If any response is YES, notify prescriber before proceeding.
Reminded patient**

Reminded patient

Infusion Administered

Please file this checklist in the patient’s chart.

NULOJIX™ INFUSION CHECKLIST

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WARNING: POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER AND IMMUNOSUPPRESSION

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Increased susceptibility to infections and malignancies may result from immunosuppression [see WARNINGS AND PRECAUTIONS].

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This document is not intended as a complete description of the risks associated with the use of NULOJIX. Please refer to the complete Prescribing Information and Medication Guide.

For additional information, please call Bristol-Myers Squibb at 1-800-321-1335 or visit www.NULOJIX.com.