

Initial REMS Approval: June 2011

BLA 125288

NULOJIX (belatacept)

Selective T-cell costimulation blocker

Bristol-Myers Squibb (BMS) Company

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the NULOJIX REMS are:

1. To inform healthcare providers of the increased risk of post-transplant lymphoproliferative disorder (PTLD), predominantly in the central nervous system (CNS), associated with NULOJIX
2. To inform healthcare providers of the increased risk of progressive multifocal leukoencephalopathy (PML), a CNS infection, associated with NULOJIX
3. To inform patients of the serious risks associated with NULOJIX

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each NULOJIX infusion in accordance with 21 CFR 208.24. The Medication Guide is part of the REMS and is appended.

B. Communication Plan

BMS will implement a communication plan to healthcare providers to support implementation of this REMS.

The communication plan will include:

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 and available for 7 years after approval of the REMS.

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 at the time of launch and at least quarterly during the first year after REMS approval via the REMS landing page. In addition, the slides with voiceover will be available on demand for 7 years after approval of the REMS.

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 within 2 weeks of approval of the REMS and annually for the three subsequent years. This will be a total of four annual distributions of this material. The target audience will be all potential prescribers of NULOJIX including transplant nephrologists, transplant surgeons, community nephrologists, transplant nurses/coordinators, transplant clinical pharmacists. In addition, this letter will be sent to the leadership of the following professional societies and BMS will request that these societies disseminate this information to their members:

- American Society of Transplantation (AST)
- American Society of Transplant Surgeons (ASTS)
- American Society of Nephrology (ASN)
- National Association of Transplant Coordinators (NATCO)
- International Transplant Nurse Society (ITNS, US members only)
- American College of Clinical Pharmacy (ACCP)
- American Society of Health-System Pharmacists (ASHP)

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 during the first discussion of NULOJIX with a transplant center. The transplant centers that account for 80% of the transplant volume based on 2010 UNOS center level data will be visited within the first 90 days of commercial availability of NULOJIX. The remaining centers will be visited within the first 150 days of commercial availability of NULOJIX.

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 within 2 weeks of approval of the REMS to infusion nurses, pharmacists, and infusion center directors. In addition, this letter will be sent to the leadership of the following professional societies and BMS will request that these societies disseminate this information to their members:

- Infusion Nurse Society (INS)
- American College of Clinical Pharmacy (ACCP)
- American Society of Health-System Pharmacists (ASHP)

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 and separately in tear pads within three weeks of the first order of NULOJIX to a transplant center and to infusion centers that BMS is able to identify for the first seven years after approval of the REMS.

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

- American Journal of Transplantation
- Journal of the American Society of Nephrology
- Pharmacotherapy
- American Journal of the Society of Health-System Pharmacists

It will appear every 4 months for a total of 3 years.

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

III. 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. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date of the assessment. BMS will submit each assessment so that it will be received by FDA on or before the due date.

MEDICATION GUIDE
NULOJIX® (noo-LOJ-jiks)
(belatacept)
For Injection, For Intravenous Use

Read this Medication Guide before you start receiving NULOJIX and before each treatment. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about NULOJIX?

NULOJIX increases your risk of serious side effects, including:

- **Post-transplant lymphoproliferative disorder (PTLD).** PTLD is a condition that can happen if certain white blood cells grow out of control after an organ transplant because your immune system is weak. PTLD can get worse and become a type of cancer. PTLD can lead to death.

People treated with NULOJIX have a higher risk of getting PTLD. If you get PTLD with NULOJIX you are at especially high risk of getting it in your brain. Your risk for PTLD is also higher if you:

- have never been exposed to the Epstein-Barr virus (EBV). Your doctor should test you for EBV. Do not receive NULOJIX unless you are EBV positive (you have been exposed to EBV).
- get an infection with a virus called cytomegalovirus (CMV).
- receive treatment for transplant rejection that lowers certain white blood cells called T lymphocytes.
- **Increased risk of getting cancers other than PTLD.** People who take medicines that weaken the immune system, including NULOJIX, have a higher risk of getting other cancers, including skin cancer. Talk to your doctor about your risk for cancer. See **“What should I avoid while receiving NULOJIX?”**
- **Progressive multifocal leukoencephalopathy (PML).** PML is a rare, serious brain infection caused by JC virus. People with weakened immune systems are at risk for getting PML. PML can result in death or severe disability. There is no known prevention, treatment, or cure for PML.
- **Increased risk of getting other serious infections, including tuberculosis (TB) and other infections caused by bacteria, viruses, or fungi.** These serious infections may lead to death. Also, a virus called BK virus can affect how your kidney works and cause your transplanted kidney to fail.

Tell your doctor right away if you get any of the following symptoms during treatment with NULOJIX:

- change in mood or your usual behavior
- confusion or problems thinking or with memory
- change in the way you walk or talk
- decreased strength or weakness on one side of your body
- change in vision
- fever, night sweats, or tiredness that does not go away
- weight loss
- swollen glands
- flu, cold symptoms, or cough
- stomach-area pain
- vomiting or diarrhea
- tenderness over your transplanted kidney
- change in the amount of urine that you make, blood in your urine, pain or burning on urination
- a new skin lesion or bump, or change in size or color of a mole

See “**What are the possible side effects of NULOJIX?**” for more information about side effects.

Liver transplant patients should not receive NULOJIX because of an increased risk of losing the transplanted liver (graft loss) and death. Talk to your doctor if you would like more information about this risk.

What is NULOJIX?

NULOJIX is a prescription medicine used in adults to prevent transplant rejection in people who have received a kidney transplant. Transplant rejection happens when the body’s immune system senses that the new transplanted kidney is different or foreign, and attacks it. NULOJIX is used with corticosteroids and certain other medicines to help prevent rejection of your new kidney.

It is not known if NULOJIX is safe and effective in children under 18 years of age.

NULOJIX is only used in people who have been exposed to the EBV virus.

It is not known if NULOJIX is safe and effective in people who receive an organ transplant other than a kidney transplant.

Who should not receive NULOJIX?

Do not receive treatment with NULOJIX if you are EBV negative. Your doctor will do a test to see if you were exposed to EBV in the past.

What should I tell my doctor before receiving NULOJIX?

Before receiving NULOJIX, tell your doctor if you:

- plan to receive any vaccines. Talk to your doctor about which vaccines are safe for you to receive during your treatment with NULOJIX. See **“What should I avoid while receiving NULOJIX?”**
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if NULOJIX will harm your unborn baby. If you become pregnant while taking NULOJIX:
 - **Tell your doctor right away.** You and your doctor should decide if you will keep receiving NULOJIX while you are pregnant.
 - Talk with your doctor about enrolling in the National Transplant Pregnancy Registry (NTPR). This Registry collects information about pregnancies in women who have received NULOJIX or if their partner has received NULOJIX, and had a transplant. You can also enroll by calling 1-877-955-6877.
- are breast-feeding or plan to breast-feed. It is not known if NULOJIX passes into your breast milk. You and your doctor should decide if you will receive NULOJIX or breast-feed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine. Do not take any new medicine without talking with your transplant doctor first.

How will I receive NULOJIX?

- To help prevent rejection of your new kidney, you will receive NULOJIX regularly as prescribed by your doctor. It is important for you to keep all your appointments for NULOJIX treatment and follow up.
- You will receive NULOJIX as an intravenous (IV) infusion in your arm. Each IV infusion takes about 30 minutes.
- During treatment with NULOJIX, your doctor will test your blood and urine to check how your kidney is working.
- Take all the medicines prescribed by your doctor to prevent infection or transplant rejection. Take them exactly as your doctor tells you. Talk to your

doctor or pharmacist if you have any questions about how to take your medicines.

What should I avoid while receiving NULOJIX?

- Limit the amount of time you spend in sunlight. Avoid using tanning beds or sunlamps. People who take medicines that weaken the immune system, including NULOJIX, have a higher risk of getting cancer, including skin cancer. Wear protective clothing and use sunscreen with a high protection factor (SPF) when you have to be in the sun.
- **Avoid receiving live vaccines during treatment with NULOJIX.** Talk to your doctor to find out which vaccines are safe for you during this time. Some vaccines may not work as well while you are receiving NULOJIX. See **“What should I tell my doctor before receiving NULOJIX?”**

What are the possible side effects of NULOJIX?

NULOJIX increases your risk of serious side effects that can cause death. See **“What is the most important information I should know about NULOJIX?”**

Common side effects of NULOJIX include:

- low red blood count (anemia)
- diarrhea
- kidney or bladder infection
- swollen legs, feet, or ankles
- constipation
- high blood pressure
- fever
- new kidney not working well
- cough
- nausea or vomiting
- headache
- low potassium or high potassium in your blood
- low white blood cell count

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of NULOJIX. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to BMS at 1-800-321-1335.

General information about NULOJIX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about NULOJIX. If you would like more information about NULOJIX, talk with your doctor. You can ask your pharmacist or doctor for information about NULOJIX that is written for healthcare professionals.

For more information, go to www.NULOJIX.com or call 1-800-321-1335.

What are the ingredients in NULOJIX?

Active ingredient: belatacept

Inactive ingredients: monobasic sodium phosphate, sodium chloride, and sucrose

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Bristol-Myers Squibb Company
Princeton, New Jersey 08543

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Iss June 2011

Month DD, 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 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 post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML), both of which can be fatal.

Boxed Warning Includes Increased Risk of PTLD

- Patients treated with NULOJIX are at an increased risk for developing PTLD, predominantly involving the central nervous system (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 PTLD and PML, please see the enclosed NULOJIX® Fact Sheet, and full Prescribing Information, included with this letter.

ENLiST Registry

BMS established the ENLiST Registry to further evaluate the safety profile of NULOJIX. The primary objective of ENLiST is to determine the incidence of PTLD, CNS PTLD, and PML in US adult EBV seropositive kidney transplant recipients treated with NULOJIX. ENLiST is intended to enroll all adult kidney transplant patients who are treated with NULOJIX.

Data collection will include the patients' EBV and CMV serostatus as well as when NULOJIX was initiated relative to time of transplant. BMS encourages your center to participate in the ENLiST Registry. For more information on how to enroll in ENLiST and answers to other questions regarding the registry, please call 1-800-321-1335. Find out more about the protocol at www.clinicaltrials.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

NULOJIX is a registered trademark of Bristol-Myers Squibb.

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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 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 13 out of 949 NULOJIX-treated patients, including patients receiving the recommended dosage regimen and a dosage higher than the recommended regimen
 - 8 of 13 cases of PTLD in NULOJIX-treated patients presented in the CNS
 - 5 of those 8 CNS cases were fatal
- ◆ At the recommended clinical dose in the EBV seropositive population, 3 cases of PTLD were reported
 - 1 of those 3 cases presented in the CNS and that case was 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

ENLIST Registry – Evaluating NULOJIX Long-Term Safety in Transplant


- ◆ BMS established the ENLIST Registry to further evaluate the safety profile of NULOJIX
- ◆ ENLIST is intended to enroll all adult kidney transplant patients who are treated with NULOJIX
- ◆ The primary objective of ENLIST is to determine the incidence of PTLD, CNS PTLD, and PML in US adult EBV seropositive kidney transplant recipients treated with NULOJIX
- ◆ Data collection will include the patients' EBV and CMV serostatus as well as when NULOJIX was initiated relative to time of transplant
- ◆ BMS encourages your center to participate in the ENLIST Registry. For more information on how to enroll in ENLIST and answers to other questions regarding the registry, please call 1-800-321-1335. Find out more about the protocol at www.clinicaltrials.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 at 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.



NULOJIX[®] (belatacept)

Increased Risk of PTLD, CNS PTLD, and PML

Training for Healthcare Professionals

This Educational Deck has been reviewed and approved
by the FDA as part of the NULOJIX REMS

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(belatacept)

NULOJIX and REMS

A risk evaluation and mitigation strategy (REMS) is a strategy to manage known or potential risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh the risks.

BMS has worked with FDA to develop materials to communicate the increased risk of post-transplant lymphoproliferative disorder (PTLD), predominantly in the CNS, and progressive multifocal leukoencephalopathy (PML) associated with NULOJIX.

This Educational Deck has been reviewed and approved by the FDA as part of the NULOJIX REMS

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 **Nulojix**[™]
(belatacept)

NULOJIX Indication and Limitations of Use

- Adult Renal Transplant Recipients
 - 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
- Limitations of Use
 - Use NULOJIX only in patients who are EBV seropositive
 - Use of NULOJIX for the prophylaxis of organ rejection in transplanted organs other than kidney has not been established

This Educational Deck has been reviewed and approved
by the FDA as part of the NULOJIX REMS

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NULOJIX Contraindication

- 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), predominantly involving the central nervous system (CNS)

This Educational Deck has been reviewed and approved
by the FDA as part of the NULOJIX REMS

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Post-Transplant Lymphoproliferative Disorder (PTLD)

- CNS predominant site of presentation of PTLD in patients receiving NULOJIX
 - Eight of 13 cases of PTLD in NULOJIX-treated patients presented in the CNS, and 5 of these 8 CNS cases were fatal.
 - At the recommended clinical dose in the EBV+ population, the frequency of PTLD was 0.7% (3/404)
 - 1 of these 3 cases presented in the CNS and that case was 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

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

This Educational Deck has been reviewed and approved by the FDA as part of the NULOJIX REMS

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Progressive Multifocal Leukoencephalopathy (PML)

- 2 cases of PML were reported in patients receiving NULOJIX at higher cumulative doses and more frequently than the recommended regimen, along with mycophenolate mofetil (MMF) and corticosteroids
 - 1 case occurred in a kidney transplant recipient
 - 1 case occurred in a liver transplant recipient
- Recommended doses and frequency of NULOJIX and concomitant immunosuppressants, including MMF, should not be exceeded
- PML is usually diagnosed by brain imaging, cerebrospinal fluid (CSF) testing for JC viral DNA by polymerase chain reaction (PCR), and/or brain biopsy
 - Consultation with a neurologist and/or infectious diseases specialist should be considered for any suspected or confirmed cases of PML
- If PML is diagnosed, consideration should be given to reduction or withdrawal of 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

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Risk Evaluation and Mitigation Strategies (REMS) Patient Counseling

- **It is important to counsel your patients:**
 - About the increased risk of PTLD, predominantly involving the CNS, and PML in NULOJIX-treated 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
 - To adhere to all prescribed medications including those for prophylaxis
- **Provide patients with a Medication Guide at the time of hospital discharge post-transplant and at the time of each monthly infusion**
- **To download Medication Guides, go to www.nulojix.com/REMS.aspx**
- **To order Medication Guides, go to www.nulojix.com/REMS.aspx or call 1-800-321-1335**

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Risk Evaluation and Mitigation Strategies (REMS) Patient Counseling

- A **PRE-INFUSION Checklist** has been developed to help identify patients who are experiencing new, changed, or worsened neurological, cognitive or behavioral signs and symptoms,
- Transplant and Infusion centers should develop a systematic way to evaluate all patients treated with NULOJIX before each NULOJIX infusion is given.
- To download the **Pre-Infusion Checklist**, go to www.nulojix.com/REMS.aspx
 - The **Checklist** is available as an editable PDF file for easier incorporation into electronic medical record systems.
- To order tear pads of the **Pre-Infusion Checklist**, call 1-800-321-1335
- The **Checklist** is included as part of the NULOJIX packaging.

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

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:

- increased risk for PTLT, predominantly involving the CNS
- increased risk of PML, a CNS infection

Ask

Read these questions aloud to the patient before starting each infusion.

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?

REmind

Remind patients to immediately report any new or worsening medical problems such as:

- 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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ENLIST Registry: Evaluating Nulojix Long-term Safety in Transplant

- BMS established the ENLiST Registry to further evaluate the safety profile of NULOJIX.
- The primary objective of ENLiST is to determine the incidence rate of PTLD, CNS PTLD, and PML in US adult EBV seropositive kidney transplant recipients treated with NULOJIX.
- ENLiST is intended to enroll all adult kidney transplant patients who are treated with NULOJIX.
- Data collection will include the patients' EBV and CMV serostatus as well as when NULOJIX was initiated relative to time of transplant.
- BMS encourages your center to participate in the ENLiST Registry.
- For more information on how to enroll in ENLiST and answers to other questions regarding the registry please call 1-800-321-1335. Find out more about the protocol at www.clinicaltrials.gov

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Healthcare Professional Information

- Additional resources for you include:
 - Dear Healthcare Professional Letter
 - Healthcare Professional Fact Sheet
 - Infusion Specialist Letter
 - Pre-Infusion Checklist
 - Infusion Specialists are reminded to ask patients about new or worsening neurologic, cognitive, and behavior signs or symptoms prior to start of infusion
 - Infusion Specialists are instructed to alert the prescriber if any changes are observed or reported
- Visit www.NULOJIX.com/REMS.aspx

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Adverse Event Reporting

- 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 at www.fda.gov/medwatch/report.htm

Month DD, 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 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 patients who are Epstein-Barr virus (EBV) seropositive. 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:

- Post-Transplant Lymphoproliferative Disorder (PTLD)**, a type of malignancy. Patients treated with NULOJIX have a higher risk of getting PTLD, predominantly involving the central nervous system (CNS). PTLD can cause death
- Progressive Multifocal Leukoencephalopathy (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.**

To help identify patients who are experiencing new, changed, or worsened neurological, cognitive, or behavioral signs and symptoms, a **PRE-INFUSION CHECKLIST** is available. For every patient, complete the enclosed **PRE-INFUSION CHECKLIST** before each infusion. Transplant and infusion centers should develop a systematic way to evaluate all patients treated with NULOJIX before each NULOJIX infusion is administered.

- **To download the PRE-INFUSION CHECKLIST**, go to www.NULOJIX.com/REMS.aspx. The checklist is available as an editable PDF file for easier incorporation into electronic medical record systems
- **To order tear pads of the Checklist**, call Bristol-Myers Squibb at 1-800-321-1335

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

NULOJIX is a registered trademark of Bristol-Myers Squibb.



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.	<input type="checkbox"/> Gave Medication Guide
Counsel	Use the Medication Guide to counsel patients about the risks and benefits of NULOJIX, including: ♦ increased risk for PTLD, predominantly involving the CNS ♦ increased risk of PML, a CNS infection	<input type="checkbox"/> Counseled patient
Ask	Read these questions aloud to the patient before starting each infusion. 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?	1. Asked patient Yes <input type="checkbox"/> No <input type="checkbox"/> 2. Asked patient Yes <input type="checkbox"/> No <input type="checkbox"/> <small>If any response is YES, notify the prescriber to discuss the patient's symptoms.</small>
REmind	Remind patients to immediately report any new or worsening medical problems such as: ♦ 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	<input type="checkbox"/> Reminded patient



Please file this checklist in the patient's medical record.

Infusion administered

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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.

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Important Information on the Safe Use of



NULOJIX and INCREASED RISK of PTLD, CNS PTLD, and PML

FDA has required a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits outweigh the following risks:



Boxed Warning Includes Increased Risk of Post-Transplant Lymphoproliferative Disorder (PTLD)

- ◆ Patients treated with NULOJIX are at an increased risk for developing PTLD, predominantly involving the central nervous system (CNS)



Increased Risk of Progressive Multifocal Leukoencephalopathy (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 Epstein-Barr virus (EBV) seronegative or with unknown serostatus**
- ◆ Be sure to verify the patient's EBV status before initiating therapy with NULOJIX

Patient Monitoring and Counseling

- ◆ Monitor patients for new or worsening neurologic, cognitive, or behavioral signs or symptoms

ENLiST Registry—Evaluating NULOJIX Long-Term Safety in Transplant

- ◆ BMS established the ENLiST Registry to further evaluate the safety profile of NULOJIX
- ◆ ENLiST is intended to enroll all adult kidney transplant patients who are treated with NULOJIX
- ◆ The primary objective of ENLiST is to determine the incidence of PTLD, CNS PTLD, and PML in US adult EBV seropositive kidney transplant recipients treated with NULOJIX
- ◆ Data collection will include the patients' EBV and CMV serostatus as well as when NULOJIX was initiated relative to time of transplant
- ◆ BMS encourages your center to participate in the ENLiST Registry. For more information on how to enroll in ENLiST and answers to other questions regarding the registry, please call 1-800-321-1335. Find out more about the protocol at www.clinicaltrials.gov

NULOJIX Indication

NULOJIX is a selective T-cell costimulation blocker indicated for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. Use in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. NULOJIX is indicated for use only in patients who are EBV seropositive. Use of NULOJIX for the prophylaxis of organ rejection in other transplanted organs has not been established.

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 at www.fda.gov/medwatch/report.htm

This is not intended as a complete description of the benefits and risks associated with the use of NULOJIX. For a more complete description, please see the full Prescribing Information **which is available at www.NULOJIX.com/REMS.aspx.**

Risk Evaluation and Mitigation Strategy

for increased risk of PTLD, predominantly involving the CNS, and PML with NULOJIX

A Risk Evaluation and Mitigation Strategy 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.

BMS has worked with the FDA to develop materials to communicate the increased risk of post-transplant lymphoproliferative disorder, predominantly involving the CNS, and progressive multifocal leukoencephalopathy (PML) associated with NULOJIX.

Ongoing Evaluation of NULOJIX Safety Profile

BMS established the ENLIST (Evaluating Nulojix Long-Term Safety in Transplant) Registry to further evaluate the safety profile of NULOJIX.

ENLIST is intended to enroll all adult kidney transplant patients who are treated with NULOJIX regardless of when NULOJIX is initiated. The primary objective of ENLIST is to determine the incidence rate of PTLD, CNS PTLD, and PML in US adult EBV seropositive kidney transplant recipients treated with NULOJIX. BMS encourages you to participate in the ENLIST registry.

To enroll Patients in the ENLIST Registry, call BMS at 1-800-321-1335.

For additional information about the ENLIST Registry visit www.clinicaltrials.gov.

To order Pre-Infusion Checklist tear pads call BMS at 1-800-321-1335.

This presentation is not intended as a complete description of the risks and benefits associated with the use of NULOJIX. Please see the Full Prescribing Information.

THE ELEMENTS OF THE NULOJIX REMS

MATERIALS FOR HEALTHCARE PROFESSIONALS

NULOJIX REMS VIDEO

Posted August 10, 2010 | Length 7:53



[Live REMS Webinars >](#)

[REMS Educational Deck](#)

[Dear Healthcare Professional Letter >](#)

[Healthcare Professional Fact Sheet >](#)

[Infusion Specialist Letter >](#)

[Pre-Infusion Checklist \(PDF\) >](#)

[Pre-Infusion Checklist \(PDF for electronic health records\) >](#)

[Medication Guide >](#)

MATERIAL FOR PATIENT

[Medication Guide >](#)