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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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.

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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

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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)

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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

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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 PTLD, 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

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