CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Transplantation – Nulojix Utilization Management Medical Policy
- Nulojix® (belatacept intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 08/20/2025

OVERVIEW

Nulojix, a selective T-cell co-stimulation blocker, is indicated for **prophylaxis of organ rejection** in patients ≥ 18 years of age receiving a kidney transplant.[1] Nulojix is to be used in conjunction with basiliximab, mycophenolate mofetil, and corticosteroids. Limitations of Use: Use only in patients who are Epstein-Barr virus (EBV) seropositive. Use has not been established for the prophylaxis of organ rejection in transplanted organs other than the kidney.

A prospective, randomized, open-label, Phase III trial evaluated the efficacy of conversion of kidney allograft recipients from calcineurin inhibitors- to Nulojix-based maintenance immunosuppression.[4] Patients were stable adult kidney transplant recipients (n = 446) who were 6 months to 60 months post-transplantation and were randomized to switch to Nulojix or continue therapy with their established calcineurin inhibitor. All patients were EBV seropositive and had received calcineurin inhibitor-based immunosuppression for 1 month or longer. A key inclusion criterion was stable renal function. Most patients were receiving tacrolimus at study entry (89%). The time from transplant to randomization was around 21 months. At 24 months, 98% of patients in the Nulojix conversion group and 97% of patients in the calcineurin inhibitor continuation group were alive with a functioning graft. The 24-month estimated glomerular filtration rate was higher for patients who were transitioned to Nulojix compared with patients who remained on calcineurin inhibitor-based immunosuppression (55.5 mL/minute/1.73 m^2 vs. 48.5 mL/minute/1.73 m^2).

Dosing Information

For its indicated use, dosing of Nulojix for the initial phase is 10 mg/kg by intravenous infusion on Day 1 (day of transplantation, prior to implantation) and Day 5 (approximately 96 hours after the Day 1 dose); at the end of Week 2 and Week 4 after transplantation; and at the end of Week 8 and Week 12 after transplantation.[1] Dosing for the maintenance phase at the end of Week 16 after transplantation and once every 4 weeks (plus or minus 3 days) thereafter is 5 mg/kg by intravenous infusion. The prescribed dose must be evenly divisible by 12.5 mg. Use of higher than recommended doses or more frequent administration is not recommended due to the increased risk of post-transplant lymphoproliferative disorder predominately of the central nervous system (CNS), progressive multifocal leukoencephalopathy, and serious CNS infections. The dose is based on actual body weight of the patient at the time of transplantation and should not be modified during the course of treatment unless the patient's weight changes by > 10%.[1] In the study involving stable kidney transplant recipients in which patients were transitioned from their calcineurin inhibitor-based maintenance immunosuppression to Nulojix, the dose of Nulojix was 5 mg/kg by intravenous infusion once every 2 weeks (Days 1, 15, 29, 43, and 57) for the first 8 weeks and then once every 28 days thereafter as a maintenance regimen.[4]

Guidelines

Nulojix is not included in the guidelines. In 2009, the Kidney Disease Improving Global Outcomes published extensive clinical practice guidelines for the care of kidney transplant recipients.[2] For maintenance therapy, it is recommended to employ a combination of immunosuppressive medications including a calcineurin inhibitor and an anti-proliferative agent, with or without corticosteroids. Compared

to cyclosporine, tacrolimus reduces the risk of acute rejection and improves graft survival within the first year of transplantation. Tacrolimus is the first-line calcineurin inhibitor and it is suggested that tacrolimus (or cyclosporine) be initiated before or at the time of transplantation, rather than delayed until the onset of graft function. Mycophenolate should be used first-line as an anti-proliferative agent. Patients who are at low immunological risk and who receive induction therapy should have corticosteroid therapy discontinued during the first week post-transplantation. If a mammalian Target of Rapamycin (mTOR) inhibitor (Zortress® [everolimus], Rapamune® [sirolimus]) is used, it should not be commenced until graft function is established and surgical wounds are healed. In the case of no reported acute rejection, the lowest doses of maintenance immunosuppressive medications should be maintained 2 to 4 months post-transplant. Calcineurin inhibitors should be continued. Of note, many of the medications require the monitoring of levels (e.g., calcineurin inhibitor, mycophenolate mofetil, mTOR inhibitors).

Safety

Nulojix labeling contains a Boxed Warning for post-transplant lymphoproliferative disorder; other malignancies and serious infections; and use in liver transplant recipients.[1] Patients receiving Nulojix are at increased risk of developing post-transplant lymphoproliferative disorder, particularly those without immunity to EBV. Nulojix should only be used in individuals who are EBV seropositive; do not use in individuals who are EBV seronegative or with unknown EBV status. Individuals receiving Nulojix are at increased risk of developing infections or malignancies due to immunosuppression. Nulojix should not be used in liver transplant recipients due to an increased risk of graft loss and death.

Liver Transplantation

Nulojix has a Boxed Warning stating that use in liver transplant recipients is not recommended due to an increased risk of graft loss and death.[1]

In a partially-blinded, active-controlled, parallel group, Phase II trial (n = 260), patients receiving the first liver transplant were randomized 1:1:1:1:1 to basiliximab + Nulojix high-dose + mycophenolate mofetil; or Nulojix high-dose + mycophenolate mofetil; Nulojix low-dose + mycophenolate mofetil; tacrolimus + mycophenolate mofetil; or tacrolimus alone.[3] The primary endpoint was the composite of acute rejection, graft loss, and death at 6 months. Secondary endpoints included the incidence, severity, treatment, and outcome of acute rejection at 12 months; graft loss and death at 12 months; and change in renal function over time. At 6 months, the frequency of the composite endpoint was higher in the Nulojix groups (42% to 48%) compared with the tacrolimus groups (15% to 38%), driven mostly by a higher rate of acute rejection with Nulojix. An external Data Monitoring Committee stopped further enrollment in the Nulojix low-dose arm due to an increase in graft loss and death compared to the other arms of the study; however, patients already on Nulojix low-dose were allowed to continue at the discretion of the investigator. At 12 months, there was a higher rate of acute rejection and death in the Nulojix groups compared with tacrolimus + mycophenolate mofetil. The long-term extension phase was terminated early when the Data Monitoring Committee determined there was continued graft loss and death in the Nulojix high-dose group.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Nulojix. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nulojix as well as the monitoring required for

adverse events and long-term efficacy, approval requires Nulojix to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nulojix is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Kidney Transplantation – Prophylaxis of Organ Rejection.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is Epstein-Barr virus (EBV) seropositive; AND
   - **C)** Nulojix is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

   Dosing. Approve the following dosing regimens (A and/or B):
   - **A)** Initial Dosing: Approve ONE of the following (i or ii):
     - **i.** Up to 10 mg/kg administered by intravenous infusion no more than four times in the first 4 weeks, followed by no more frequently than once every 4 weeks for the next 8 weeks; OR
     - **ii.** Up to 5 mg/kg administered by intravenous infusion no more frequently than once every 2 weeks for up to 8 weeks; AND/OR
   - **B)** Maintenance Dosing: Up to 5 mg/kg administered by intravenous infusion no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

2. **Solid Organ Transplantation Other Than Kidney – Prophylaxis of Solid Organ Rejection in a Patient Currently Receiving Nulojix.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is Epstein-Barr virus (EBV) seropositive; AND
   - **C)** Nulojix is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

   Dosing. Approve up to 5 mg/kg administered by intravenous infusion no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nulojix is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nulojix® intravenous infusion [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; July 2021.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Am J Transplant*. 2009;9(Suppl 3):S1-S157.

3. Klintmalm GB, Feng S, Lake JR, et al. Belatacept-Based Immunosuppression in *De Novo* Liver Transplant Recipients: 1-Year Experience From a Phase II Randomized Study. *Am J Transplant*. 2014;14:1817-1827.
4. Budde K, Prashar R, Haller H, et al. Conversion from calcineurin inhibitor- to belatacept-based maintenance immunosuppression in renal transplant recipients: a randomized Phase 3b trial. *J Am Soc Nephrol.* 2021;32:3252-3264.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/16/2023
Annual Revision	No criteria changes.	08/21/2024
Annual Revision	**Kidney Transplantation – Prophylaxis of Organ Rejection:** Dosing was changed to divide into Initial Dosing and Maintenance therapy, with the option to approve both cited regimens for up to 1 year. For Initial Dosing, the dosing is either up to 10 mg/kg by intravenous infusion no more than four times in the first 4 weeks, followed by no more frequently than once every 4 weeks for the next 8 weeks; AND/OR up to 5 mg/kg by intravenous infusion no more frequently than once every 2 weeks for up to 8 weeks. Maintenance Dosing is up to 5 mg/kg administered by intravenous infusion no more frequently than once every 4 weeks. Previously, dosing was that each individual dose must not exceed 10 mg/kg administered by intravenous infusion; AND Nulojix is administered no more than four times in the first 4 weeks (day of transplant, Day 5, end of Week 2, and end of Week 4), and then no more frequently than once every 4 weeks. **Organ Transplantation Other Than Kidney – Prophylaxis of Solid Organ Rejection in a Patient Currently Receiving Nulojix:** Dosing was changed to up to 5 mg/kg administered by intravenous infusion no more frequently than once every 4 weeks. Previously, dosing was that each individual dose must not exceed 10 mg/kg administered by intravenous infusion; AND Nulojix is administered no more than four times in the first 4 weeks (day of transplant, Day 5, end of Week 2, and end of Week 4), and then no more frequently than once every 4 weeks.	08/20/2025