Nulojix (belatacept)
Policy Number: C9968-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
12/2016	04/10/2019	04/10/2020
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL**
J0485	RxPA	Q2 2019

PRODUCTS AFFECTED:
Nulojix (belatacept)

DRUG CLASS:
Selective T-Cell Costimulation Blockers

ROUTE OF ADMINISTRATION:
Intravenous

PLACE OF SERVICE:
Buy and Bill, available only through the NULOJIX Distribution Program (NDP) 855-511-6180

AVAILABLE DOSAGE FORMS:
Nulojix SOLR 250MG

FDA-APPROVED USES: indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplantation in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. Belatacept is recommended to be used only in patients who are EBV seropositive

COMPENDIAL APPROVED OFF-LABELED USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS: prophylaxis of organ rejection

REQUIRED MEDICAL INFORMATION:

A. PROPHYLAXIS OF ORGAN REJECTION pre TRANSPLANT:
   1. Documentation of history of renal transplant or scheduled transplant within the next 14 days.
      AND
   2. Documentation patient is Epstein-Barr virus (EBV)- seropositive
      AND
   3. Documentation patient is concurrently taking mycophenolate mofetil and corticosteroids
      AND
   4. Documentation patient was evaluated for tuberculosis and treatment (if needed) for latent infection was initiated prior to Nulojix
      AND
   5. For patients continuing therapy after inpatient- See transplant team approval- PROVIDE REFERRAL DATA

DURATION OF APPROVAL: Initial authorization: 6 months, Continuation of therapy: 12 months

QUANTITY: At the initial phase, Nulojix should be dosed at 10 mg/kg IV on day 1 (day of transplant, prior to implantation), day 5, and end of weeks 2, 4, 8, and 12. Dose at 5 mg/kg at end of week 16 and every 4 weeks thereafter
Conversion from calcineurin inhibitor (off-label dosing) (Grinyo 2012; Grinyo 2016; Rostaing 2011): IV:I nitial phase: 5 mg/kg on transition days 1, 15, 29, 43, and 57, Maintenance phase: 5 mg/kg every 4 weeks beginning 4 weeks after completion of the initial phase. Note: Taper calcineurin inhibitor dose slowly over 1 month (no reduction on day 1, 40% to 60% reduction on day 15, 70% to 80% reduction on day 23; discontinue on day 29 and beyond).

PRESCRIBER REQUIREMENTS: Prescribed by or in consultation with a transplant specialist or nephrologist. Consultation notes required.

AGE RESTRICTIONS: 18 years of age or older

GENDER:
Male and female

CONTINUATION OF THERAPY:
A. PROPHYLAXIS OF ORGAN REJECTION:
   1. Documentation patient is responsive to therapy demonstrated by no signs or symptoms of acute/chronic kidney rejection

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION: All other uses of Nulojix (belatacept) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications include patient who are EBV seronegative or with unknown EBV serostatus.

OTHER SPECIAL CONSIDERATIONS: None

BACKGROUND:
Nulojix powder, lyophilized, for solution for Intravenous injection; a selective T-cell costimulation blocker indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant. It is used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. Some limitations of use are that it can only be used in patients who are EBV seropositive, and it safe use has not been established for the prophylaxis of organ rejection in transplanted organs other than the kidney. Nulojix should never be used in patients with unknown aerostats or EBV seronegative. Use in patients with history of liver transplant is not recommended and only physicians experienced in immunosuppressive therapy and management of kidney transplant patients should prescribe Nulojix. See table 1 below for dosing recommendation. Doses higher than or more frequent than recommended should be avoided due to the increased risk of infection or malignancy. It should only be administered intravenously over a 30 minutes period and only the silicone-free disposable syringe enclosed in the package should be used for administration. Nulojix comes with boxed warning for Post-transplant lymphoproliferative disorder (PTLD), other malignancies, and serious infections. There is an increased risk for Progressive Multifocal Leukoencephalopathy (PML) with Nulojix. Corticosteroid utilization should be consistent with Nulojix clinical trial experience as acute rejection and graft loss might result with corticosteroid minimization

In the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT), 686 recipients of a living or standard-criteria deceased donor kidney transplant were randomly assigned to more intensive (MI) belatacept, less intensive (LI) belatacept, or cyclosporine, in conjunction with mycophenolate and glucocorticoids; all patients received basiliximab as induction therapy [126,128,131,132,134,137]. At 12 months, patients treated with belatacept experienced a higher incidence and grade of acute rejection episodes (22 and 17 versus 7 percent in the MI, LI, and cyclosporine arms, respectively) but had superior renal function, a benefit that was sustained at seven years posttransplant (estimated glomerular filtration rate [eGFR] of 70 and 72 versus 45 mL/min/m2, respectively). In addition, rates of death or allograft loss were significantly lower at seven years in patients assigned to belatacept (12.7 and 12.8 versus 21.7 percent). Posttransplant lymphoproliferative disorder (PTLD) was more common with belatacept, particularly among EBV-seronegative patients.

The BENEFIT-EXT trial compared the efficacy and safety of belatacept with that of cyclosporine in extended criteria donor (ECD) kidney transplant recipients, using the same study design as the one used in BENEFIT [127,128,130,133,138]. At 12 months, acute rejection rates were similar between groups. Similar to BENEFIT, patients treated with belatacept had better renal function at one, two, five, and seven years compared with those treated with cyclosporine. Rates of PTLD were also higher among patients treated with belatacept.

A randomized, controlled trial compared belatacept with a tacrolimus-based, steroid-avoiding maintenance immunosuppression regimen [129]. Recipients of living and deceased donor renal allografts were randomly assigned to treatment with belatacept-mycophenolate mofetil (belatacept-MMF), belatacept-sirolimus, or tacrolimus-MMF. All patients received induction with rabbit antithymocyte globulin (rATG)-Thymoglobulin and a short course of glucocorticoids. Acute rejection rates were highest in the belatacept-MMF arm (12 percent), and the calculated GFR was 8 to 10 mL/min higher with either belatacept regimen than with tacrolimus-MMF.

Another randomized, controlled trial of 40 kidney transplant recipients compared belatacept with a tacrolimus-based, steroid-containing maintenance regimen [139]. Patients were randomly assigned to belatacept or tacrolimus, combined with MMF and prednisolone; all patients received basiliximab as induction therapy. At one year posttransplant, the incidence of acute rejection was higher among patients who received belatacept compared with those who received tacrolimus (55 versus 10 percent, respectively). Graft loss, due to rejection, occurred in three patients, all in the belatacept group. There was no difference in graft function between the two groups.

APPENDIX:

Table 1: Nulojix dosing for Kidney Transplant Recipients

Initial Phase	Dose
Day 1 (day of transplantation, prior to implantation) and Day 5 (approximately 96 hours after Day 1 dose)	10 mg per kg 10 mg per kg
End of Week 2 and Week 4 after transplantation End of Week 8 and Week 12 after transplantation	10 mg per kg
Maintenance Phase	**Dose**
End of Week 16 after transplantation and every 4 weeks (plus or minus 3 days) thereafter	5 mg per kg

REFERENCES:

1. Nulojix® for injection [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; April 2018.
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. Accessed at: https://kdigo.org/wpcontent/uploads/2017/02/KDIGO-2009-Transplant-Recipient-Guideline-English.pdf.
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.