WellMed Doctors helping patients for more than 25 years	**Effective Date:** 08/18/2022	**Revision Date(s):** 11/14/19, 12/10/20, 06/16/22
Department: PHARMACY	**MMC Review/ Approval Date(s):** 12/10/2019, 1/13/2021, 08/09/22	**Total Page(s): 10**

Policy Number: 018.003

Title: Title: Coverage Determination Policy for Belatacept (Nulojix®)

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

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Doctors helping patients for more than 25 years

Title: Coverage Determination Policy for Belatacept (Nulojix®)

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Coverage Policy Number: 018.003

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Belatacept is NOT indicated for the following:

- transplant recipients who are EBV seronegative or with unknown EBV serostatus
- prophylaxis of organ rejection in transplanted organs other than the kidney
- administration in the home setting

Coverage Determination (Initial/New Requests)

According to patient's transplant coverage of benefits and transplant phase, Nulojix will be covered as proven and medically necessary for **prophylaxis of renal transplant rejection when ALL the following criteria are met:**

1. Is prescribed for kidney transplant rejection prophylaxis
2. Patient is immune to the Epstein-Barr virus (i.e., EBV seropositive)
3. Will be used with basiliximab (Simulect®) induction, corticosteroids, and mycophenolate
4. Belatacept dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling for renal transplant rejection

Coverage Determination (Renewal/Continuation of Therapy Requests)

Nulojix is considered medically necessary **for continued use when the ALL the following is met:**

1. Patient continues to meet initial approval criteria
2. Requested dosing is within the approved recommended dosage below

FDA Approved Dose and Indication:

Indication	Approved Dosing
Prophylaxis of Renal transplant rejection, EBV seropositive; in combination with basiliximab induction, mycophenolate mofetil, and corticosteroid	• Initial phase: 10 mg/kg IV on day 1 (day of transplant, prior to implantation), day 5, and end of weeks 2, 4, 8, and 12 • Maintenance phase: 5 mg/kg at end of week 16 of post-transplant and every 4 weeks thereafter

General Background:

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

Belatacept is a fusion protein containing the modified extracellular domain of CTLA-4 linked to a portion of the Fc domain (hinge-CH2-CH3 domains) of human immunoglobulin GI antibody. Belatacept binds to CD80 and CD86 receptors on the antigen-presenting cell and prevents them from binding to CD28 on the T lymphocyte, which prevents the costimulation of T lymphocytes. Stimulated T lymphocytes mediate immunologic rejection. Two amino acid substitutions on the ligand binding of CTLA-4 result in an increased binding affinity for CD80 and CD86 compared with abatacept, the parent molecule from which belatacept is derived.

Warnings:

Increased risk for developing post-transplant lymphoproliferative disorder (PTLD), predominantly involving the CNS. Recipients without immunity to Epstein-Barr virus (EBV) are at a particularly increased risk; therefore, use in EBV-seropositive patients only. Do not use belatacept in transplant recipients who are EBV seronegative or with unknown EBV serostatus.

Only physicians experienced in immunosuppressive therapy and management of kidney transplant patients should prescribe belatacept. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources.

Increased susceptibility to infection and the possible development of malignancies may result from immunosuppression.

Use in liver transplant patients is not recommended due to an increased risk of graft loss and death.

Conversion of patients receiving a CNI based maintenance regimen to a Nulojix based maintenance regimen increases the risk of acute rejection. Conversion of stable kidney transplant recipients from a CNI based maintenance therapy to a belatacept based maintenance therapy is not recommended unless the patient is CNI intolerant.

Clinical Evidence:

Living Donor or Standard Criteria

In the 3-year, multicenter, phase 3, randomized, active-controlled Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT; n=686), at month 12, belatacept (less-intensive regimen) was non-inferior to cyclosporine for patient/graft survival and acute rejection and was superior to cyclosporine for the composite renal impairment endpoint in patients undergoing de novo kidney transplantation (living donor or standard criteria). Patients were randomized 1:1:1 to receive a less-intensive (LI) regimen (n=230; mean age, 42.6 years) of belatacept 10 mg/kg IV over 30 minutes on day 1 (day of transplant, prior to implantation), on day 5, at the end of weeks 2 and 4, then every 4 weeks through week 12, and then a maintenance dose of 5 mg/kg IV every 4 weeks starting at the end of week 16; a more-intensive (MI) regimen (n=225; mean age, 43.6 years) of belatacept 10 mg/kg IV over 30 minutes on day 1 (day of transplant, prior to implantation), on day 5, at the end of weeks 2, 4, 6, 8, 10, and 12, then every 4 weeks through week 24, and then a maintenance dose of 5 mg/kg IV every 4 weeks starting at the end of week 28; or cyclosporine (n=231; mean age, 43.5 years) 4 to 10 mg/kg IV (initial dose), adjusted to 150 to 300 nanograms/milliliter (ng/mL) (month 0 to 1), then adjusted to 100 to 250 ng/mL (month 2 to 12) prior to kidney transplantation. All patients also received basiliximab induction, mycophenolate mofetil, and corticosteroids.

Patients enrolled in the study were recipients of a kidney from a living donor (58%; related, 42%; unrelated, 16%; mean cold ischemia time, 1.4 hours) or a deceased donor following standard criteria (anticipated cold ischemia time of less than 24 hours and did not meet extended criteria; mean cold ischemia time, 16.3 hours).

Three coprimary endpoints were compared at 12 months: composite patient and graft survival (noninferiority test), composite renal impairment (superiority test; percent of patients with GFR less than 60 mL/min/1.73 m(2) at month 12 or a decrease of 10 mL/min/1.73 m(2) or more from month 3 to 12), and the incidence of acute rejection (non-inferiority test; histologically confirmed). Non-inferiority of belatacept to cyclosporine was declared for patient/graft survival if the lower bound of the 97.3% CI of the difference between groups was 10% or less, and for acute rejection if the upper bound of the 97.3% CI was 20% or less. The percentage of patients surviving with functioning graft at month 12 was 209 of 219 (95%; 95% CI, 92.7% to 98.2%) for the MI regimen, 218 of 226 (97%; 95% CI, 94.1% to 98.9%) for the LI regimen, and 206 of 221 (93%; 95% CI, 89.9% to 96.5%) for cyclosporine; both belatacept arms met the non-inferiority criteria (difference from cyclosporine for MI regimen, 2.2%; 97.3% CI, -2.9% to 7.5%; for LI regimen, 3.2%; 97.3% CI, -1.5% to 8.4%). Similarly, although rates of acute rejection at month 12 were higher in both belatacept arms (LI, n=39 of 226 (17%); 95% CI, 12.3% to 22.2%; MI, n=49 of 219 (22%); 95% CI, 16.9% to 27.9%) compared with cyclosporine (n=16 of 221 (7%); 95% CI, 3.8% to 10.7%), belatacept met the non-inferiority criteria for the LI regimen (difference from cyclosporine, 10%; 97.3% CI, 3.3% to 17.1%); however, the MI regimen did not achieve non-inferiority.

Corticosteroid therapy for acute rejection was administered in 21%, 17%, and 7% of patients, respectively, in the belatacept more-intensive, belatacept less-intensive, and cyclosporine groups by month 12. T-cell depleting therapy to treat acute rejection was also more common for patients receiving belatacept (MI, 13%; LI, 10%) compared with cyclosporine (2%). Belatacept was superior to cyclosporine with regards to renal function with a decreased percentage of patients experiencing renal impairment (composite endpoint) for both the MI regimen (115 of 219 (55%); 95% CI, 48.3% to 61.8%; difference from cyclosporine, -22.9%; 97.3% CI, -32.6% to -12.9%; p less than 0.0001) and the LI regimen (116 of 226 (54%); 95% CI, 47.5% to 60.9%; difference from cyclosporine, -23.7%; 97.3% CI, -33.3% to -13.7%; p less than 0.0001) compared with cyclosporine (166 of 221 (78%); 95% CI, 72.4% to 83.5%). Adverse events were similar in all treatment arms; the most common (greater than 25%) included anemia, urinary tract

infection, hypertension, constipation, diarrhea, nausea, and peripheral edema. Acute infusion-related reactions (mild to moderate) were reported in the belatacept arms (4 patients in each arm) and did not occur with cyclosporine therapy. Post-transplant lymphoproliferative disorder (PTLD) at month 12 occurred in 1, 2, and 1 patient, respectively, in the MI, LI, and cyclosporine arms; 2 additional patients developed PTLD after 6 months in the MI arm.

Extended Criteria

In the 3-year, multicenter, phase 3, randomized, active-controlled Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-Extended criteria donors (BENEFIT-EXT; n=578), belatacept (less-intensive regimen) was noninferior to cyclosporine for patient/graft survival and acute rejection at month 12; belatacept (both arms combined) was superior to cyclosporine for the composite renal impairment endpoint in patients undergoing de novo kidney transplantation (extended criteria). Patients were randomized 1:1:1 to receive a less-intensive (LI) regimen (n=193; mean age, 56.1 years +/- 12 years) of belatacept 10 mg/kg IV over 30 minutes on day 1 (day of transplant, prior to implantation), on day 5, at the end of weeks 2 and 4, then every 4 weeks through week 12, and then a maintenance dose of 5 mg/kg IV every 4 weeks starting at the end of week 16; a more-intensive (MI) regimen (n=193; mean age, 56.7 years +/- 13 years) of belatacept 10 mg/kg IV over 30 minutes on day 1 (day of transplant, prior to implantation), on day 5, at the end of weeks 2, 4, 6, 8, 10, and 12, then every 4 weeks through week 24, and then a maintenance dose of 5 mg/kg IV every 4 weeks starting at the end of week 28; or cyclosporine (n=184; mean age, 55.7 years +/- 12 years) 4 to 10 mg/kg IV (initial dose), adjusted to 150 to 300 nanograms/milliliter (ng/mL) (month 0 to 1), then adjusted to 100 to 250 ng/mL (month 2 to 12) prior to kidney transplantation. All patients also received basiliximab induction, mycophenolate mofetil, and corticosteroids. Patients enrolled in the study were recipients of a kidney from a deceased donor following extended criteria (mean donor age, 56.2 years; 60 years or older, 49%; mean cold ischemia time, 20 hours; cerebrovascular accident as cause of donor mortality, 69.8%; donor with cardiac death, 10%). The percentage of patients with delayed graft function (DGF) and CAN (interstitial fibrosis/tubular atrophy) at baseline was similar across groups. Two coprimary endpoints were compared at 12 months: composite patient and graft survival (noninferiority test) and a composite renal impairment endpoint (superiority test; defined as percent of patients with GFR less than 60 mL/min/1.73 m(2) at month 12 or a decrease of 10 mL/min/1.73 m(2) or more from month 3 to 12). Noninferiority of belatacept to cyclosporine was declared if the lower bound of the 97.3% CI for the difference in patient/graft survival between groups was greater than -10%. The percentage of evaluable patients (98%) surviving with a functioning graft at month 12 was 159 of 184 (86%; 95% CI, 81.5% to 91.4%) for the MI regimen, 155 of 175 (89%; 95% CI, 83.9% to 93.3%) for the LI regimen, and 156 of 184 (85%; 95% CI, 79.6% to 90%) for cyclosporine; both belatacept arms met the noninferiority criteria (difference from cyclosporine for MI regimen, 1.6%; 97.3% CI, -6.6% to 9.9%; for LI regimen, 3.8%; 97.3% CI, -4.3% to 11.9%). A decreased percentage of patients experienced renal impairment (composite endpoint) for the belatacept MI regimen (124 of 184 (70.5%); 95% CI, 63.7% to 77.2%; difference from cyclosporine, -14.4%; 97.3% CI, -24 to -4.7%; p=0.0018) compared with cyclosporine (151 of 184 (84.8%); 95% CI, 79.6% to 90.1%); there was no significant difference between the LI regimen and cyclosporine for renal impairment endpoint. Additionally, belatacept was noninferior (declared if upper bound of 97.3% CI for comparison between groups was less than 20%) to cyclosporine with regards to acute rejection at month 12 (secondary endpoint), which occurred in 33 of 184 (17.9%; 95% CI, 12.4% to 23.5%) in the MI arm, 31 of 175 (17.7%; 95% CI, 12.1% to 23.4%) in the LI arm, and 26 of 184 (14.1%; 95% CI, 9.1% to 19.2%) in the cyclosporine arm (difference from cyclosporine for MI regimen, 3.8%; 97.3% CI, -4.7% to 12.4%; for LI regimen, 3.6%; 97.3% CI, -5 to 12.3). T-cell depleting therapy was used in 13 patients in the belatacept MI regimen, 5 patients in the belatacept LI regimen, and 4 patients in the cyclosporine regimen. In the cyclosporine arm, 27 ot 184 (15%) of patients were treated with lymphocyte-depleting therapy (which was not permitted in the belatacept arms) for anticipated DGF; 7% experienced acute rejection compared with 15% who did not receive the therapy. Adverse events were similar in all treatment arms; the most

common (greater than 20%) included anemia, graft dysfunction, constipation, and diarrhea. Acute infusion-related reactions (mild to moderate except 1 case of prolonged hypotension) were reported in the belatacept arms (MI, n=7; LI, n=9) and did not occur with cyclosporine therapy. Post transplant lymphoproliferative disorder (PTLD) at month 12 occurred in 1, 2, and 0 patients, respectively, in the MI, LI, and cyclosporine arms; 2 additional patients developed PTLD after 6 months in the MI and LI arm, respectively.

HCPCS Code:

HCPCS Code:	Description:
J0485	Injection Belatacept (Nulojix)

Acronyms:

Acronyms: EBV= Epstein-Barr virus, CNS = central nervous system, NCD = National Coverage Determination, LCD = Local Coverage Determination, PTLD = posttransplant lymphoproliferative disorder, FDA = Food and Drug Administration, MI = more intense, LI = less intensive, GFR = glomerular filtration rate, CI = confidence interval, CNI: Calcineurin Inhibitor

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