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Belatacept

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses

as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Belatacept (Nulojix) **may be considered medically necessary** for:

- Induction prophylaxis of organ rejection in adults receiving a kidney transplant when the following criteria are met:
    - Age 18 or older; and
    - Individual is seropositive for Epstein-Barr Virus (EBV); and
    - Belatacept is used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.
- Maintenance prophylaxis of organ rejection patients with a kidney transplant when the following criteria are met:
    - Age 18 or older; and
    - The individual is seropositive for Epstein-Barr Virus (EBV); and
    - Belatacept is being prescribed by, or in consultation with, a transplant specialist physician or a physician associated with a transplant center; and
    - The individual is converting or has converted from a calcineurin inhibitor to belatacept in their immunosuppressive regimen.

Belatacept (Nulojix) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications, including but not limited to the following:

- In transplant recipients who are Epstein-Barr (EBV) seronegative or with unknown EBV serostatus;
- The prophylaxis of organ rejection in transplanted organs other than the kidney;
- In individuals under 18 years of age as safety and efficacy have not been established.

Policy Guidelines

The FDA label advises of the following warnings and precautions:

- Live vaccines should be avoided during treatment.
- Belatacept is not recommended for use in liver transplant patients.
- Patients should be evaluated for tuberculosis and tested for latent infection prior to initiating belatacept. Treatment of latent tuberculosis infection should be initiated prior to belatacept use.

Description

Solid organ transplantation offers a treatment option for patients with different types of end-stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life. (2) Many advances have been made in the last several decades to reduce perioperative complications. Available data support improvement in long-term survival as well as improved quality of life, particularly for liver, kidney, pancreas, heart, and lung transplants recipients. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by Organ Procurement and Transplantation Network (OPTN) and United Network of Organ Sharing (UNOS).

Kidney Transplant

In 2024, 48,149 transplants were performed in the United States procured from 16,988 deceased donors and 7,030 living donors. (3) Kidney transplants were the most common procedure with 27,759 transplants performed from both deceased and living donors in 2024. Since 1988, the cumulative number of kidney transplants is 609,383. (4) Of the cumulative total, 68.7% of the kidneys came from deceased donors and 31.3% from living donors.

Kidney transplant, using kidneys from deceased or living donors, is an accepted treatment of end-stage renal disease (ESRD). ESRD refers to the inability of the kidneys to perform their functions (i.e., filtering wastes and excess fluids from the blood). ESRD, which is life-threatening, is also known as chronic kidney disease (CKD) stage 5 and is defined as a glomerular filtration rate (GFR) less than 15 mL/min/1.73 m^2. (5) All kidney transplant candidates receive organ allocation points based on waiting time, age, donor-recipient immune system compatibility, prior living donor status, distance from donor hospital, and survival benefit. (6)

Immunosuppressive Therapy

Solid organ transplant recipients receive immunosuppressive therapy to prevent rejection of the allograft. Induction therapy is administered at or around the time of the transplantation and is associated with greater immunosuppression than maintenance therapy, which is usually initiated at the time of transplantation and continued long-term for the duration of the allograft. (7) Induction therapy goals are to prevent acute rejection and permit minimization or avoidance of maintenance immunosuppressive agents that are known to cause toxicity. Induction therapy typically consists of biologic antibodies (rabbit-derived antithymocyte globulin, basiliximab) and high-dose glucocorticoids. Maintenance regimens can include glucocorticoids, calcineurin inhibitors (CNIs: tacrolimus or cyclosporine), antimetabolic agents (mycophenolate mofetil, enteric-coated mycophenolate sodium, or azathioprine), mammalian (mechanistic) target of rapamycin (mTOR) inhibitors (sirolimus or everolimus), or costimulatory blockade agents (belatacept). (7)

In most kidney transplant recipients, a stable maintenance immunosuppression regimen is established within the first 3 months after transplantation. Complete withdrawal of all

maintenance thelike coveragerapy is not recommended since it frequently leads to late acute rejection or accelerated chronic rejection. While CNIs are a fundamental component of maintenance immunosuppression, some patients are unable to tolerate these agents due to nephrotoxicity or other adverse effects. CNI toxicity can cause kidney injury, hypertension, and neurotoxicity; prolonged use may cause permanent fibrosis in the kidney. (7, 8)

Regulatory Status
Belatacept (Nulojix) was approved by the U.S. Food and Drug Administration (FDA) in 2011 as a selective T-cell costimulation blocker indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplantation. It is used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. Per the FDA label, it is to be used only in patients who are Epstein-Barr Virus (EBV) seropositive. Its use has not been established for the prophylaxis of organ rejection in transplanted organs other than the kidney. The safety and efficacy of belatacept in patients under 18 years of age have not been established. (1)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for belatacept (Nulojix).

Nulojix (1)
Prevention of Organ Rejection in Kidney Transplant Recipients
The efficacy and safety of Nulojix in de novo kidney transplantation were assessed in two open-label, randomized, multicenter, active-controlled trials (Study 1 and Study 2). These trials evaluated two dose regimens of Nulojix, the recommended dosage regimen and a regimen with higher cumulative doses and more frequent dosing than the recommended dosage regimen, compared to a cyclosporine control regimen. All treatment groups also received basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids.

<u>Treatment Regimen</u>
The Nulojix recommended regimen consisted of a 10 mg per kg dose administered on Day 1 (the day of transplantation, prior to implantation), Day 5 (approximately 96 hours after the Day 1 dose), end of Weeks 2 and 4; then every four weeks through Week 12 after transplantation. Starting at Week 16 after transplantation, Nulojix was administered at the maintenance dose of 5 mg per kg every four weeks (plus or minus three days). Nulojix was administered as an intravenous infusion over 30 minutes.

Basiliximab 20 mg was administered intravenously on the day of transplantation and four days later. The initial dose of MMF was 1 gram twice daily and was adjusted as needed, based on clinical signs of adverse events or efficacy failure.

The protocol-specified dosing of corticosteroids in Studies 1 and 2 at Day 1 was methylprednisolone (as sodium succinate) 500 mg IV on arrival in the operating room, Day 2,

methylprednisolone 250 mg IV, and Day 3, prednisone 100 mg orally. Actual median corticosteroid doses used with the Nulojix recommended regimen from Week 1 through Month 6 are summarized in the table below (Table 1).

Table 1. Actual Corticosteroid[a] Dosing in Studies 1 and 2

Day of Dosing	Median (Q1-Q3) Daily Dose[b,c]	
	Study 1	Study 2
Week 1	31.7 mg (26.7-50 mg)	30 mg (26.7-50 mg)
Week 2	25 mg (20-30 mg)	25 mg (20-30 mg)
Week 4	20 mg (15-20 mg)	20 mg (15-22.5 mg)
Week 6	15 mg (10-20 mg)	16.7 mg (12.5-20 mg)
Month 6	10 mg (5-10 mg)	10 mg (5-12.5 mg)

Mg: milligram.

[a] Corticosteroid = prednisone or prednisolone.

[b] The protocols allowed for flexibility in determining corticosteroid dose and rapidity of taper after Day 15. It is not possible to distinguish corticosteroid doses used to treat acute rejection versus doses used in a maintenance regimen.

[c] Q1 and Q3 are the 25th and 75th percentiles of daily corticosteroid doses, respectively.

Study 1 enrolled recipients of living donor and standard criteria deceased donor organs and Study 2 enrolled recipients of extended criteria donor organs. Standard criteria donor organs were defined as organs from a deceased donor with anticipated cold ischemia time of <24 hours and not meeting the definition of extended criteria donor organs. Extended criteria donors were defined as deceased donors with at least one of the following: 1) donor age ≥60 years; 2) donor age ≥50 years and other donor comorbidities (≥2 of the following: stroke, hypertension, serum creatinine >1.5 mg/dL); 3) donation of organ after cardiac death; or 4) anticipated cold ischemia time of the organ of ≥24 hours. Study 1 excluded recipients undergoing a first transplant whose current Panel Reactive Antibodies (PRA) were ≥50% and recipients undergoing a re-transplantation whose current PRA were ≥30%; Study 2 excluded recipients with a current PRA ≥30%. Both studies excluded recipients with human immunodeficiency virus (HIV), hepatitis C, or evidence of current hepatitis B infection; recipients with active tuberculosis; and recipients in whom intravenous access was difficult to obtain.

Efficacy data are presented for the Nulojix recommended regimen and cyclosporine regimen in Studies 1 and 2.

The Nulojix regimen with higher cumulative doses and more frequent dosing of belatacept was associated with more efficacy failures. Higher doses and/or more frequent dosing are not recommended.

<u>Study 1: Recipients of Living Donor and Standard Criteria Deceased Donor Kidneys</u>

In Study 1 (NCT00256750), 666 patients were enrolled, randomized, and transplanted: 226 to the Nulojix recommended regimen, 219 to the Nulojix regimen with higher cumulative doses

and more frequent dosing than recommended, and 221 to cyclosporine control regimen. The median age was 45 years; 58% of organs were from living donors; 3% were re-transplanted; 69% of the study population was male; 61% of patients were White, 8% were Black/African-American, 31% were categorized as of other races; 16% had PRA ≥10%; 41% had 4 to 6 HLA mismatches; and 27% had diabetes prior to transplant. The incidence of delayed graft function was similar in all treatment arms (14% to 18%).

Premature discontinuation from treatment at the end of the first year occurred in 19% of patients receiving the Nulojix recommended regimen and 19% of patients on the cyclosporine regimen. Among the patients who received the Nulojix recommended regimen, 10% discontinued due to lack of efficacy, 5% due to adverse events, and 4% for other reasons. Among the patients who received the cyclosporine regimen, 9% discontinued due to adverse events, 5% due to lack of efficacy, and 5% for other reasons.

At the end of three years, 25% of patients receiving the Nulojix recommended regimen and 34% of patients receiving the cyclosporine regimen had discontinued from treatment. Among the patients who received the Nulojix recommended regimen, 12% discontinued due to lack of efficacy, 7% due to adverse events, and 6% for other reasons. Among the patients who received the cyclosporine regimen, 15% discontinued due to adverse events, 8% due to lack of efficacy, and 11% for other reasons.

Assessment of Efficacy
Table 2 summarizes the results of Study 1 following one and three years of treatment with the Nulojix recommended dosage regimen and the cyclosporine control regimen. Efficacy failure at one year was defined as the occurrence of biopsy proven acute rejection (BPAR), graft loss, death, or lost to follow-up. BPAR was defined as histologically confirmed acute rejection by a central pathologist on a biopsy done for any reason, whether or not accompanied by clinical signs of rejection. Patient and graft survival was also assessed separately.

Table 2. Efficacy Outcomes by Years 1 and 3 for Study 1: Recipients of Living and Standard Criteria Deceased Donor Kidneys

Parameter	**Nulojix Recommended Regimen N=226 n (%)**	**Cyclosporine (CSA) N=221 n (%)**	**Nulojix-CSA (97.3% CI)**
Efficacy Failure by Year 1	49 (21.7)	37 (16.7)	4.9 (-3.3, 13.2)
Components of Efficacy Failure[a]			
Biopsy Proven Acute Rejection	45 (19.9)	23 (10.4)	
Graft Loss	5 (2.2)	8 (3.6)	
Death	4 (1.8)	7 (3.2)	
Lost to follow-up	0	1 (0.5)	

Efficacy Failure by Year 3	58 (25.7)	57 (25.8)	-0.1 (-9.3, 9)
Components of Efficacy Failure[a]			
Biopsy Proven Acute Rejection	50 (22.1)	31 (14)	
Graft Loss	9 (4)	10 (4.5)	
Death	10 (4.4)	15 (6.8)	
Lost to follow-up	2 (0.9)	5 (2.3)	
Patient and Graft Survival[b]			
Year 1	218 (96.5)	206 (93.2)	3.2 (-1.5, 8.4)
Year 3	206 (91.2)	192 (86.9)	4.3 (-2.2, 10.8)

CI: confidence interval.

[a] Patients may have experienced more than one event.

[b] Patients known to be alive with a functioning graft.

In Study 1, the rate of BPAR at one year and three years was higher in patients treated with the Nulojix recommended regimen than the cyclosporine regimen. Of the patients who experienced BPAR with Nulojix, 70% experienced BPAR by Month 3, and 84% experienced BPAR by Month 6. By three years, recurrent BPAR occurred with similar frequency across treatment groups (<3%). The component of BPAR determined by biopsy only (subclinical protocol-defined acute rejection) was 5% in both treatment groups.

Patients treated with the Nulojix recommended regimen experienced episodes of BPAR classified as Banff grade IIb or higher (6% [14/226] at one year and 7% [15/226] at three years) more frequently compared to patients treated with the cyclosporine regimen (2% [4/221] at one year and 2% [5/221] at three years). Also, T cell-depleting therapy was used more frequently to treat episodes of BPAR in Nulojix-treated patients (10%; 23/226) compared to cyclosporine-treated patients (2%; 5/221). At Month 12, the difference in mean calculated glomerular filtration rate (GFR) between patients with and without history of BPAR was 19 mL/min/1.73 m^2 among Nulojix-treated patients compared to 7 mL/min/1.73 m^2 among cyclosporine-treated patients. By three years, 22% (11/50) of Nulojix-treated patients with a history of BPAR experienced graft loss and/or death compared to 10% (3/31) of cyclosporine-treated patients with a history of BPAR; at that time point, 10% (5/50) of Nulojix-treated patients experienced graft loss and 12% (6/50) of Nulojix-treated patients had died following an episode of BPAR, whereas 7% (2/31) of cyclosporine-treated patients experienced graft loss and 7% (2/31) of cyclosporine-treated patients had died following an episode of BPAR. The overall prevalence of donor-specific antibodies was 5% and 11% for the Nulojix recommended regimen and cyclosporine, respectively, up to 36 months post-transplant.

While the difference in GFR in patients with BPAR versus those without BPAR was greater in patients treated with Nulojix than cyclosporine, the mean GFR following BPAR was similar in Nulojix (49 mL/min/1.73 m^2) and cyclosporine treated patients (43 mL/min/1.73 m^2) at one year. The relationship between BPAR, GFR, and patient and graft survival is unclear due to the limited number of patients who experienced BPAR, differences in renal hemodynamics (and,

consequently, GFR) across maintenance immunosuppression regimens, and the high rate of switching treatment regimens after BPAR.

Assessment of Efficacy in the Epstein-Barr Virus (EBV) Seropositive Subpopulation
Nulojix is recommended for use only in EBV seropositive patients.

In Study 1, approximately 87% of patients were EBV seropositive prior to transplant. Efficacy results in the EBV seropositive subpopulation were consistent with those in the total population studied. By one year, the efficacy failure rate in the EBV seropositive population was 21% (42/202) in patients treated with the Nulojix recommended regimen and 17% (31/184) in patients treated with cyclosporine (difference=4%, 97.3% CI [−4.8, 12.8]). Patient and graft survival was 98% (198/202) in Nulojix-treated patients and 92% (170/184) in cyclosporine-treated patients (difference=5.6%, 97.3% CI [0.8, 10.4]).

By three years, efficacy failure was 25% in both treatment groups and patient and graft survival was 94% (187/202) in Nulojix-treated patients compared with 88% (162/184) in cyclosporine-treated patients (difference=4.6%, 97.3% CI [−2.1, 11.3]).

Assessment of Glomerular Filtration Rate (GFR)
Glomerular Filtration Rate (GFR) was measured at one and two years and was calculated using the Modification of Diet in Renal Disease (MDRD) formula at one, two, and three years after transplantation. As shown in Table 3, both measured and calculated GFR was higher in patients treated with the Nulojix recommended regimen compared to patients treated with the cyclosporine control regimen at all time points. The differences in GFR were apparent in the first month after transplant and were maintained up to three years (36 months). An analysis of change of calculated mean GFR between three and 36 months demonstrated an increase of 0.8 mL/min/year (95% CI [−0.2, 1.8]) for Nulojix-treated patients and a decrease of 2.2 mL/min/year (95% CI [−3.2, −1.2]) for cyclosporine-treated patients.

Table 3. Measured and Calculated GFR for Study 1: Recipients of Living and Standard Criteria Deceased Donor Kidneys

Parameter	**Nulojix Recommended Regimen N=226**	**Cyclosporine (CSA) N=221**	**Nulojix-CSA (97.3% CI)**
Measured GFR[a] mL/min/1.73 m^2 mean (SD) Year 1 Year 2[b]	63.4 (27.7) (n=206) 67.9 (29.9) (n=199)	50.4 (18.7) (n=199) 50.5 (20.5) (n=185)	13.0 (7.3, 18.7) 17.4 (11.5, 23.4)
Calculated GFR[c] mL/min/1.73 m^2 mean (SD) Year 1	65.4 (22.9) (n=200) 65.4 (25.2)	50.1 (21.1) (n=199)	15.3 (10.3, 20.3)

Year 2	(n=201)	47.9 (23) (n=182)	17.5 (12, 23.1)
Year 3	65.8 (27) (n=190)	44.4 (23.6) (n=171)	21.4 (15.4, 27.4)

CI: confidence interval; GFR: glomerular filtration rate.
[a] GFR was measured using the cold-iothalamate method.
[b] Measured GFR was not assessed at Year 3.
[c] GFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Assessment of Chronic Allograft Nephropathy (CAN)
The prevalence of chronic allograft nephropathy (CAN) at one year, as defined by the Banff '97 classification system, was 24% (54/226) in patients treated with the Nulojix recommended regimen and in 32% (71/219) of patients treated with the cyclosporine control regimen. CAN was not evaluated after the first year following transplantation. The clinical significance of this finding is unknown.

Study 2: Recipients of Extended Criteria Donor Kidneys
In Study 2 (NCT00114777), 543 patients were enrolled, randomized, and transplanted: 175 to the Nulojix recommended regimen, 184 to the Nulojix regimen with higher cumulative doses and more frequent dosing than recommended, and 184 to the cyclosporine control regimen. The median age was 58 years; 67% of the study population was male; 75% of patients were White, 13% were Black/African-American, 12% were categorized as of other races; 3% had PRA ≥10%; 53% had 4 to 6 HLA mismatches; and 29% had diabetes prior to transplantation. The incidence of delayed graft function was similar in all treatment arms (47% to 49%).

Premature discontinuation from treatment at the end of the first year occurred in 25% of patients receiving the Nulojix recommended regimen and 30% of patients receiving the cyclosporine control regimen. Among the patients who received the Nulojix recommended regimen, 14% discontinued due to adverse events, 9% due to lack of efficacy, and 2% for other reasons. Among the patients who received the cyclosporine regimen, 17% discontinued due to adverse events, 7% due to lack of efficacy, and 6% for other reasons.

At the end of three years, 35% of patients receiving the Nulojix recommended regimen and 44% of patients receiving the cyclosporine regimen had discontinued from treatment. Among the patients who received the Nulojix recommended regimen, 20% discontinued due to adverse events, 9% due to lack of efficacy, and 6% for other reasons. Among the patients who received the cyclosporine regimen, 25% discontinued due to adverse events, 10% due to lack of efficacy, and 10% for other reasons.

Assessment of Efficacy
Table 4 summarizes the results of Study 2 following one and three years of treatment with the Nulojix recommended dosage regimen and the cyclosporine control regimen. Efficacy failure at one year was defined as the occurrence of biopsy proven acute rejection (BPAR), graft loss,

death, or lost to follow-up. BPAR was defined as histologically confirmed acute rejection by a central pathologist on a biopsy done for any reason, whether or not accompanied by clinical signs of rejection. Patient and graft survival was also assessed.

Table 4. Efficacy Outcomes by Years 1 and 3 for Study 2: Recipients of Extended Criteria Donor Kidneys

Parameter	Nulojix Recommended Regimen N=175 n (%)	Cyclosporine (CSA) N=184 n (%)	Nulojix-CSA (97.3% CI)
Efficacy Failure by Year 1	51 (29.1)	52 (28.3)	0.9 (-9.7, 11.5)
Components of Efficacy Failure[a]			
Biopsy Proven Acute Rejection	37 (21.1)	34 (18.5)	
Graft Loss	16 (19.1)	20 (10.9)	
Death	5 (2.9)	8 (4.32)	
Lost to follow-up	0	2 (1.1)	
Efficacy Failure by Year 3	63 (36)	68 (37)	-1.0 (-12.1, 10.3)
Components of Efficacy Failure[a]			
Biopsy Proven Acute Rejection	42 (24)	42 (22.8)	
Graft Loss	21 (12	23 (12.5)	
Death	15 (8.6)	17 (9.2)	
Lost to follow-up	1 (0.6)	5 (2.7)	
Patient and Graft Survival[b]			
Year 1	155 (88.6)	157 (85.3)	3.2 (-4.8, 11.3)
Year 3	143 (81.7)	143 (77.7)	4.0 (-5.4, 13.4)

CI: confidence interval.

[a] Patients may have experienced more than one event.

[b] Patients known to be alive with a functioning graft.

In Study 2, the rate of BPAR at one year and three years was similar in patients treated with Nulojix and cyclosporine. Of the patients who experienced BPAR with Nulojix, 62% experienced BPAR by Month 3, and 76% experienced BPAR by Month 6. By three years, recurrent BPAR occurred with similar frequency across treatment groups (<3%). The component of BPAR determined by biopsy only (subclinical protocol-defined acute rejection) was 5% in both treatment groups.

A similar proportion of patients in the Nulojix recommended regimen group experienced BPAR classified as Banff grade IIb or higher (5% [9/175] at one year and 6% [10/175] at three years) compared to patients treated with the cyclosporine regimen (4% [7/184] at one year and 5% [9/184] at three years). Also, T cell-depleting therapy was used with similar frequency to treat any episode of BPAR in NULOJIX-treated patients (5% or 9/175) compared to cyclosporine-treated patients (4% or 7/184). At Month 12, the difference in mean calculated GFR between patients with and without a history of BPAR was 10 mL/min/1.73 m^2 among Nulojix-treated

patients compared to 14 mL/min/1.73 m^2 among cyclosporine-treated patients. By three years, 24% (10/42) of Nulojix-treated patients with a history of BPAR experienced graft loss and/or death compared to 31% (13/42) of cyclosporine-treated patients with a history of BPAR; at that time point, 17% (7/42) of Nulojix-treated patients experienced graft loss and 14% (6/42) of Nulojix-treated patients had died following an episode of BPAR, whereas 19% (8/42) of cyclosporine-treated patients experienced graft loss and 19% (8/42) of cyclosporine-treated patients had died following an episode of BPAR. The overall prevalence of donor-specific antibodies was 6% and 15% for the Nulojix recommended regimen and cyclosporine, respectively, up to 36 months post-transplant.

The mean GFR following BPAR was 36 mL/min/1.73 m^2 in Nulojix patients and 24 mL/min/1.73 m^2 in cyclosporine-treated patients at one year. The relationship between BPAR, GFR, and patient and graft survival is unclear due to the limited number of patients who experienced BPAR, differences in renal hemodynamics (and, consequently, GFR) across maintenance immunosuppression regimens, and the high rate of switching treatment regimens after BPAR.

Assessment of Efficacy in the Epstein-Barr Virus (EBV) Subpopulation
Nulojix is recommended for use only in EBV seropositive patients.

In Study 2, approximately 91% of the patients were EBV seropositive prior to transplant. Efficacy results in the EBV seropositive subpopulation were consistent with those in the total population studied.

By one year, the efficacy failure rate in the EBV seropositive population was 29% (45/156) in patients treated with the Nulojix recommended regimen and 28% (47/168) in patients treated with cyclosporine (difference=0.8%, 97.3% CI [−10.3, 11.9]). Patient and graft survival rate in the EBV seropositive population was 89% (139/156) in the Nulojix-treated patients and 86% (144/168) in cyclosporine-treated patients (difference=3.4%, 97.3% CI [−4.7, 11.5]).

By three years, efficacy failure was 35% (54/156) in Nulojix-treated patients and 36% (61/168) in cyclosporine-treated patients. Patient and graft survival was 83% (130/156) in Nulojix treated patients compared with 77% (130/168) in cyclosporine-treated patients (difference=5.9%, 97.3% CI [−3.8, 15.6]).

Assessment of Glomerular Filtration Rate (GFR)
Glomerular Filtration Rate (GFR) was measured at one and two years and was calculated using the Modification of Diet in Renal Disease (MDRD) formula at one, two, and three years after transplantation. As shown in Table 5, both measured and calculated GFR was higher in patients treated with the Nulojix recommended regimen compared to patients treated with the cyclosporine control regimen at all time points. The differences in GFR were apparent in the first month after transplant and were maintained up to three years (36 months). An analysis of change of calculated mean GFR between Month 3 and Month 36 demonstrated a decrease of 0.8 mL/min/year (95% CI [−1.9, 0.3]) for Nulojix-treated patients and a decrease of 2.0 mL/min/year (95% CI [−3.1, −0.8]) for cyclosporine-treated patients.

Table 5. Measured and Calculated GFR for Study 2: Recipients of Extended Criteria Donor Kidneys

Parameter	Nulojix Recommended Regimen N=175	Cyclosporine (CSA) N=184	Nulojix-CSA (97.3% CI)
Measured GFR[a] mL/min/1.73 m^2 mean (SD)			
Year 1	49.6 (25.8) (n=151)	45.2 (21.1) (n=154)	4.3 (-1.5, 10.2)
Year 2[b]	49.7 (23.7) (n=139)	45.0 (27.2) (n=136)	4.7 (-1.8, 11.3)
Calculated GFR[c] mL/min/1.73 m^2 mean (SD)			
Year 1	44.5 (21.8) (n=158)	36.5 (21.1) (n=159)	8.0 (2.5, 13.4)
Year 2	42.8 (24.1) (n=158)	34.9 (21.6) (n=154)	8.0 (1.9, 14)
Year 3	42.2 (25.2) (n=154)	31.5 (22.1) (n=143)	10.7 (4.3, 17.2)

CI: confidence interval; GFR: glomerular filtration rate.

[a] GFR was measured using the cold-iothalamate method.

[b] Measured GFR was not assessed at Year 3.

[c] GFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Assessment of Chronic Allograft Nephropathy (CAN)

The prevalence of chronic allograft nephropathy (CAN) at one year, as defined by the Banff '97 classification system, was 46% (80/174) in patients treated with the Nulojix recommended regimen and 52% (95/184) of patients treated with the cyclosporine control regimen. CAN was not evaluated after the first year following transplantation. The clinical significance of this finding is unknown.

Long-Term Extension (LTE) of Study 1 and Study 2

Although initially designed as three-year studies, Studies 1 and 2 were subsequently extended to seven years to provide descriptive long-term safety and efficacy data. Only patients who completed the assigned treatment for three years and consented to remain on the assigned treatment from three to seven years were eligible for the long-term extension (LTE) studies.

Long-Term Extension of Study 1

In the LTE of Study 1, of the 666 originally randomized and transplanted patients, 457 (69%) patients enrolled into the LTE study: 73% (166/226) in the Nulojix recommended regimen group, 71% (155/219) in the Nulojix non-recommended regimen group, and 62% (136/221) in the cyclosporine group. Fourteen (2%) patients who completed the assigned treatment at the

end of Year 3 did not enroll into the LTE study: 4 in the Nulojix recommended regimen group, 3 in the Nulojix non-recommended regimen group, and 7 in the cyclosporine group.

Of the 457 patients enrolled in the LTE study, 356 (79%) patients completed the assigned treatment at the end of Year 7: 82% (136/166) in the Nulojix recommended regimen group, 83% (128/155) in the Nulojix non-recommended regimen group, and 68% (92/136) in the cyclosporine group. The most common reasons for discontinuation from the LTE study included adverse events and death.

Seven (4.2%) deaths and 2 (1.2%) graft losses were reported in the Nulojix recommended regimen group while 7 (4.5%) deaths and no graft loss were reported in the Nulojix non-recommended regimen group, and 10 (7.4%) deaths and 6 (4.4%) graft losses were reported in the cyclosporine group.

No post-transplant lymphoproliferative disorder (PTLD) was reported in the Nulojix groups while 1 case of non-CNS PTLD was reported in the cyclosporine group, in a patient who was EBV seropositive at the time of transplant.

No progressive multifocal leukoencephalopathy (PML) was reported in the Nulojix groups while 1 case of PML was reported in the cyclosporine group at 82 months post-transplant (56 days after discontinuing therapy).

The higher calculated GFR observed in Nulojix-treated patients compared to cyclosporine-treated patients during the first three years was maintained during the LTE period.

Table 6. Events Reported in Long-Term Extension from 36 to 84 Months Post-Transplant of Study 1: Recipients of Living and Standard Criteria Deceased Donor Kidneys

	Nulojix Recommended Regimen N=166 n (%)	**Nulojix Non-recommended Regimen N=155 n (%)**	**Cyclosporine N=136 n (%)**
Death	7 (4.2)	7 (4.5)	10 (7.4)
Graft Loss	2 (1.2)	0 (0)	6 (4.4)
Death or Graft Loss	9 (5.4)	7 (4.5)	14 (10.3)
PTLD	0 (0)	0 (0)	1[a] (0.7)
PML	0 (0)	0 (0)	1 (0.7)

PTLD: post-transplant lymphoproliferative disorder; PML: progressive multifocal leukoencephalopathy.
[a] This patient was Epstein-Barr Virus (EBV) seropositive at the time of transplant.

Long-Term Extension of Study 2
In the LTE of Study 2, of the 543 originally randomized and transplanted patients, 304 (56%) patients enrolled into the LTE study: 65% (113/175) in the Nulojix recommended regimen group, 57% (104/184) in the Nulojix non-recommended regimen group, and 47% (87/184) in

the cyclosporine group. Nineteen (3.5%) patients who completed the assigned treatment at the end of Year 3 did not enroll into the LTE study: 1 in the Nulojix recommended regimen group, 5 in the Nulojix non-recommended regimen group, and 13 in the cyclosporine group.

Of the 304 patients enrolled in the LTE study, 215 (71%) patients completed the assigned treatment at the end of Year 7: 74% (84/113) in the Nulojix recommended regimen group, 71% (74/104) in the Nulojix non-recommended regimen group, and 66% (57/87) in the cyclosporine group. The most common reasons for discontinuation from the LTE study included adverse events and death.

Twenty-one (18.6%) deaths and 1 (0.9%) graft loss were reported in the Nulojix recommended regimen group while 14 (13.5%) deaths and 2 (1.9%) graft losses were reported in the Nulojix non-recommended regimen group, and 9 (10.3%) deaths and 6 (6.9%) graft losses were reported in the cyclosporine group.

Six cases of PTLD were reported among the three treatment groups: 4 in the Nulojix recommended regimen group, 1 in the Nulojix non-recommended regimen group, and 1 in the cyclosporine group. Three of these cases (1 in each treatment group) occurred in patients who were EBV seropositive at the time of transplant and the other 3 cases (in Nulojix recommended regimen) occurred in patients who were EBV seronegative. No case of PML was reported among the three treatment groups.

The higher mean calculated GFR observed in Nulojix-treated patients compared to cyclosporine-treated patients during the first three years was maintained during the LTE period.

Table 7. Events Reported in Long-Term Extension from 36 to 84 Months Post-Transplant of Study 2: Recipients of Extended Criteria Donor Kidneys

	Nulojix Recommended Regimen N=113 n (%)	**Nulojix Non-recommended Regimen N=104 n (%)**	**Cyclosporine N=87 n (%)**
Death	21 (18.6)	14 (13.5)	9 (10.3)
Graft Loss	1 (0.9)	2 (1.9)	6 (6.9)
Death or Graft Loss	22 (19.5)	16 (15.4)	14 (16.1)
PTLD	4[a] (3.6)	1 (1.0)	1 (1.2)
PML	0 (0)	0 (0)	0 (0)

PTLD: post-transplant lymphoproliferative disorder; PML: progressive multifocal leukoencephalopathy.
[a] Three of these patients were Epstein-Barr Virus (EBV) seropositive at the time of transplant.

Follow-up Data of Patients with Complete 7-Year Patient and Graft Survival

In Study 1, of the original intention-to-treat (ITT) population (N=666), 72% (163/226) of patients in the Nulojix recommended regimen group, 70% (153/219) of patients in the Nulojix non-recommended regimen group, and 60% (132/221) of patients in the cyclosporine group had

complete 7-year patient and graft survival follow-up data. Among these completers, the proportion of patients who died or had graft loss was 17% (27/163) in the Nulojix recommended regimen group, 16% (25/153) in the Nulojix non-recommended regimen group, and 30% (40/132) in the cyclosporine group.

In Study 2, of the original ITT population (N=543), 79% (138/175) of patients in the Nulojix recommended regimen group, 128/184 (70%) of patients in the Nulojix non-recommended regimen group, and 59% (108/184) of patients in the cyclosporine group had complete 7-year patient and graft survival follow-up data. Among these completers, the proportion of patients who died or had graft loss was 39% (54/138) in the Nulojix recommended regimen group, 42% (54/128) in the Nulojix non-recommended regimen group, and 48% (52/108) in the cyclosporine group.

Table 8. Events Reported in Patients with Complete 7-Year Patient and Graft Survival Follow-up Data

	Nulojix Recommended Regimen n (%)	**Nulojix Non-recommended Regimen n (%)**	**Cyclosporine n (%)**
Study 1	**N=163**	**N=153**	**N=132**
Death	17 (10%)	17 (11%)	26 (20%)
Graft Loss	11 (7%)	10 (7%)	17 (13%)
Death or Graft Loss	27 (17%)	25 (16%)	40 (30%)
Study 2	**N=138**	**N=128**	**N=108**
Death	37 (27%)	37 (29%)	29 (27%)
Graft Loss	23 (17%)	21 (16%)	29 (27%)
Death or Graft Loss	54 (39%)	54 (42%)	52 (48%)

Conversion from Calcineurin Inhibitors to Belatacept for Immunosuppression
In 2022, the American College of Clinical Pharmacy, American Society of Transplantation, and the International Society for Heart and Lung Transplantation all endorsed consensus recommendations for the use of maintenance immunosuppression in solid organ transplantation. The level 2B kidney recommendation indicates that it is safe to convert stable, living, or deceased donor, low immunologic risk transplant recipients from CNI to belatacept. This guidance is supported by one randomized controlled trial (RCT) with long-term follow-up and three large observational studies, several of which are described in more detail below. (9)

The RCT evaluated belatacept conversion at 6 to 36 months post-transplant. Belatacept 5mg/kg on days 1, 15, 29, 43, and 57 with subsequent 28-day dosing thereafter was added to CNI, antimetabolite, and corticosteroids and compared to a CNI-continuation group (split between tacrolimus and cyclosporine containing regimens). Patients were of low immunologic risk (predominantly white, first-time transplants, with PRAs <20%, and without recent history of rejection). At 12 and 36 months, kidney function was improved in the belatacept group, but rejection rates were higher with the majority occurring early post-conversion. At 12 months,

blood pressure tended to be lower in the belatacept group compared to the CNI group. At 36 months, more viral and fungal infections occurred in the belatacept group.

Two observational studies found similar results. A cohort of 219 patients converted to belatacept found an increase in mean eGFR (32 ± 16.4 at baseline to 38 ± 20 ml/min per 1.73 m^2 at follow-up, p<0.0001), with conversion <3 months post-transplant being the largest predictive factor of an increase in GFR >10 ml/min per 1.73 m^2 at 12 months. Acute rejection rate was 8.2% post-conversion. Similarly, another cohort of 280 patients found a significant improvement in eGFR in those converted <6 months post-transplant (12.7 ± 15.4 vs. 6.4 ± 11.9 ml/min per 1.73 m^2, p = 0.009). Considering infections, the same cohort found a 1-year opportunistic infection (OI) rate of 12.1% in belatacept-treated patients with the most common being CMV (18/42 OI; 42.9%) and *Pneumocystis* pneumonia (12/42 OI; 28.6%). Similarly, among 181 belatacept-treated patients matched to 181 controls, 17.7% experienced CMV disease versus 2.8% of controls. CMV disease cumulative incidences were 6.33 and 0.91/100 person-years (p-y) in belatacept and control groups, respectively. CMV disease risk was highest in those >70 years and with eGFR <30ml/min; cumulative incidences were 18.4 and 5.2/100 p-y, respectively.

Summary of Evidence

Based on review of the clinical studies provided to the U.S. Food and Drug Administration for approval, and consensus recommendations concerning the efficacy and safety of converting kidney transplant recipients from a calcineurin inhibitor-based immunosuppressive regimen to a belatacept-based regimen, belatacept (Nulojix) may be considered medically necessary when the criteria in the policy are met for induction prophylaxis or maintenance prophylaxis. Per the FDA label, belatacept (Nulojix) is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. It is not to be used in transplant recipients who are EBV seronegative or with unknown EBV serostatus, individuals under the age of 18, or for the prophylaxis of organ rejection in transplanted organs other than the kidney.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0485

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

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Other:

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
08/15/2025	Document updated with literature review. The following change was made to Coverage: Added “non-Food and Drug Administration approved” to the existing experimental, investigational and/or unproven statement. Added reference 9; others removed/revised.
11/01/2024	Document updated with literature review. Coverage was revised to include induction therapy prophylaxis in patients receiving a kidney transplant for patient age 18 or older; and maintenance prophylaxis or organ rejection patients with a kidney transplant when the following criteria are met: age 18 or older; the patent is seropositive for Epstein-Barr Virus (EBV); and Belatacept is being prescribed by, or in consultation with, a transplant specialist physician or a physician associated with a transplant center; and, the patient is converting or has converted from a calcineurin inhibitor to belatacept in their immunosuppression regimen. References 9-14 added; others revised.
04/01/2024	New medical document. Belatacept (Nulojix) may be considered medically necessary for prophylaxis of organ rejection in adult patients receiving a kidney transplant when the following criteria are met: Patient is seropositive for Epstein-Barr Virus (EBV); and, When used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. Belatacept (Nulojix) is considered experimental, investigational and/or unproven for all other indications, including but not limited to the following: In transplant recipients who are Epstein-Barr (EBV) seronegative or with unknown EBV serostatus; The prophylaxis of organ rejection in transplanted organs other than the kidney; In patients under 18 years of age as safety and efficacy have not been established.