PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

MEDICAL POLICY – 5.01.536

Nulojix (belatacept) for Adults

Effective Date: **Oct. 3, 2025***	RELATED MEDICAL POLICIES:
Last Revised: Jun. 10, 2025	11.01.523 Site of Service: Infusion Drugs and Biologic Agents
Replaces: N/A	
*This policy has been revised. Click here to view the current policy.	

The Site of Service Medical Necessity criteria within this policy DOES NOT apply to Alaska fully-insured members; refer to the infusion and injection drug Medical Necessity criteria only.

Site of Service *and* the infusion and injection drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

Select a hyperlink below to be redirected to that section.

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Nulojix (belatacept) is a drug that suppresses the immune system to prevent the body from rejecting a transplanted kidney. It can be used for both right at the time of transplantation (induction) and long-term as a maintenance therapy. It was shown to be safe and effective in two large studies that compared it to other drugs used to prevent rejection after kidney transplant. In the study and based on the recommendation of the drug manufacturer, the drug needs to be given in combination with basiliximab (induction), mycophenolate mofetil (MMF), and corticosteroids.

Note: The Introduction section is for your general knowledge and is not to be construed as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

This policy does not apply to members who are currently admitted to an acute hospital setting.

Site of Service (SOS) Medical Necessity criteria applies ONLY to medical benefit reviews. SOS Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion and injection drug Medical Necessity criteria only. Please contact Customer Service for more information.

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home.

Drugs subject to site of service review addressed in this policy are:

- Nulojix (belatacept)

Click on the links below to be directed to the related medical necessity criteria:

Epstein-Barr Virus (EBV) seronegative or unknown serostatus

Prophylaxis of organ rejection, kidney

Prophylaxis of organ rejection, organs other than kidney

Site of Service

Site of Service Administration	Medical Necessity
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion and injection therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**IV infusion and injection therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion or injection of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* **Note:** *This does not include when standard dosing between infusions or injections is 6 months or longer **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions or injections of this drug.** **This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions or injections, including any 1 of the following:** • Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC less than or equal to 40%) that may increase the risk of an adverse reaction

Site of Service Administration	Medical Necessity

	• Unstable renal function which decreases the ability to respond to fluids
	• Difficult or unstable vascular access
	• Acute mental status changes or cognitive conditions that impact the safety of infusion or injection therapy
	• A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
	
	This site is considered medically necessary when the individual has cytokine release syndrome (CRS) and all the following are met:
	• CRS is grade 3 or 4 as evidenced by ALL the following:
	  ○ Temperature at least 38 °C
	  ○ Hypotension that requires 1 or more vasopressors
	  ○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation)
	AND
	• The individual will be admitted into an inpatient setting as soon as possible

Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.**

Condition	Medical Necessity
Prophylaxis of organ rejection in adult individuals receiving a kidney transplant	**Nulojix (belatacept) is subject to review for site of service administration.** **Nulojix (belatacept) may be considered medically necessary for induction therapy and prophylaxis of organ rejection in**

Condition	Medical Necessity

	adults receiving a kidney transplant (i.e., immunosuppression immediately post-transplant) when all the following criteria are met:
	• The individual is aged 18 years or older
	AND
	• Has a seropositive test result for Epstein-Barr Virus (EBV)
	AND
	• Nulojix is used in combination with ALL of the following:
	  ○ Simulect (basiliximab)
	  ○ Mycophenolate mofetil (MMF)
	  ▪ Azathioprine can be used for individuals who have tried and did not tolerate mycophenolate mofetil (MMF)
	  ○ Corticosteroids
	
	Nulojix (belatacept) may be considered medically necessary for maintenance therapy and prophylaxis of organ rejection in adults receiving a kidney transplant (i.e., immunosuppression post-induction) when all the following criteria are met:
	• The individual is aged 18 years or older
	AND
	• Has a seropositive test result for Epstein-Barr Virus (EBV)
	AND
	• Nulojix is used in be combination with ALL of the following:
	  ○ Mycophenolate Mofetil (MMF)
	  ▪ Azathioprine can be used for individuals who have tried and did not tolerate mycophenolate mofetil (MMF)
	  ○ Corticosteroids
	
	Note: Individuals should be monitored for new or worsening neurological, cognitive, or behavioral signs and symptoms.

Prophylaxis of organ rejection in transplanted organs other than kidney	**The use of Nulojix (belatacept) is considered investigational.** **Use in liver transplant individuals is not recommended by the manufacturer due to increased risk of graft loss and death.**
EBV seronegative or unknown serostatus	**Nulojix (belatacept) is contraindicated for use in individuals who are EBV seronegative or with unknown serostatus because**

Condition	Medical Necessity
	the risk of PTLD (post-transplant lymphoproliferative disorder) is particularly increased in individuals who are EBV seronegative.

Investigational
The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information. **The use of Nulojix (belatacept) in individuals under the age of 18 for any indication is considered investigational because there have been no studies to support use, safety, and efficacy in pediatric individuals.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for Nulojix (belatacept) may be approved up to 12 months.** **All other reviews for Nulojix (belatacept) may be approved up to 6 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for Nulojix (belatacept) may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the type of transplant, EBV serostatus, concurrent medication use, relevant history and physical evaluation

Coding

Code	Description
HCPCS	
J0485	Injection, belatacept (Nulojix), 1 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

For site of service for medical necessity the age described in this policy is 13 years of age or older. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. The age criterion for site of service for medical necessity is based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to individuals above the age of 13.

Nulojix (belatacept) inhibits T lymphocyte proliferation by binding to CD80 and CD86 on antigen-presenting cells, which blocks CD28 co-stimulation of the T cell. It also inhibits the production of interleukin-2&4, interferon-, and TNF-α. Immunologic rejections are mostly mediated by activated T lymphocytes. In primate models, graft survival was extended and anti-donor antibodies were diminished. Nulojix (belatacept) has also been studied and is considered off-label in islet cell transplantation in type 1 diabetic individuals and liver transplant individuals. Use in liver transplant individuals is not recommended due to an increased risk of graft loss and death.

Nulojix (belatacept) has the advantage of not requiring therapeutic drug monitoring, due to its predictable PK profile in trials among both healthy and kidney transplant individuals. Bioavailability is 100%, the PK profile is linear and the exposure increased proportionately to doses of 1 go 20 mg/kg. In an extended phase 2 trial at 5 mg/kg, the measured Cmin was

consistent from year 1 through 5 (Cmin range of 3.43-4.85 mcg/mL). A trend of higher clearance was found among individuals with higher body weight. Subgroups determined to have no effect on clearance included age, gender, race, renal function, hepatic function, diabetes, and concomitant dialysis. Table 5 from the package insert (previous page) summarizes PK variability among healthy and post-transplant individuals. The FDA approved dose is 10mg/kg on day 1, day 5, week 2, week 4, week 8, week 12, and 5 mg/kg every 4 weeks thereafter.

Renal Transplantation

Renal transplant is considered for most individuals when the glomerular filtration rate (GFR) falls below 10 mL/min, while renal failure is considered permanent when the GFR reaches this level or a serum creatinine exceeds 8 mg/dL. After transplantation, the survival of the graft and individual continues to be a challenge, and many therapies are targeted to help prevent rejection of the graft by the host's immune system. Both dialysis and renal replacement therapy are options once the individual reaches end stage renal disease (ESRD). ESRD is most frequently caused by diabetes mellitus, with hypertension, glomerulonephritis, and renal cystic disease following in rank. After transplantation, the primary causes of death are heart disease, sepsis, and stroke (in this order). Compared to the general population, kidney transplant individuals have an increased risk of atherosclerosis and ischemic heart disease and a 50-fold increase in the risk of mortality.

Approximately 360 per million people in the US begin renal replacement therapy each year. While the median age of a new individual is 64 years old, the prevalence and incidence is more pronounced in men and more pronounced among African-American, Hispanic, and Native American than Caucasian or Asian populations. The waiting list in the US for kidney transplantation is exceeds 80,000, while only 10,000 kidneys become available each year. Among those on immunosuppressive drug regimens, it has been estimated that anywhere from 5 to 55% of individuals do not take all of the medications as directed.

Transplant Rejection

Rejection of kidney grafts can be hyperacute, acute cellular, acute humoral, or chronic. Hyperacute rejection occurs within hours after transplantation and contains a marked accumulation of neutrophils within the capillaries, arterioles, and glomeruli, leading to thrombosis, necrosis, and requiring removal of the non-functional organ. Acute rejection occurs from days to years after transplantation and involves humor or cellular immune mechanisms.

Acute cellular rejection appears clinically to resemble renal failure and histologically will show CD4+ and CD8+ T lymphocytes which express activated T cell markers. Tubular damage results from accumulation of mononuclear cells and T cells can also cause endothelitis in the vascular endothelial cells. This rejection can benefit from immunosuppressive therapies.

Acute humoral rejection involves antidonor antibodies resulting in damaged blood vessels and can present as endothelial necrosis, neutrophil accumulation, deposition of immunoglobulins and fibrin, or thrombosis. B-Cell depleting agents are the typical therapy utilized. Chronic rejection is a large cause of graft loss and is seen with a progressive rise in serum creatinine over 4 to 6 months, often controlled with immunosuppressive therapy. It presents with interstitial fibrosis, tubular atrophy, and vascular changes including vascular lesions and resulting ischemia.

Treatment Alternatives

Immunosuppression involves a combination of targeted therapy. Cyclosporine, a calcineurin inhibitor (CNI) which blocks activation of cytokine transcription factors, was a foundation of therapy early in the last decade but has fallen out of favor to tacrolimus in recent guidelines. Others include azathioprine (inhibits leukocyte development), steroids (block inflammation), rapamycin and mycophenolate mofetil (inhibit lymphocyte proliferation), monoclonal anti-T-cell antibodies, and drugs interrupting T-cell co-stimulatory signaling. While immunosuppression can further survival, individuals become more susceptible to infections and carcinomas. CNIs and corticosteroids can contribute to weight gain, hypertension, and post-transplant diabetes, which can increase the risk of mortality and graft failure. CNIs also have an increased rate of renal function decline, which can further these risks and drug interactions involving CYP3A4 are concerning for this class as well.

Preferred Existing Therapy

For initial maintenance of immunosuppressive therapy, the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends a combination including a CNI (with tacrolimus being first-line) and an anti-proliferative agent (mycophenolate being first-line), with or without corticosteroids (to be discontinued after one week in individuals with low immunological risk). If an mTORi is chosen, it is recommended to be used after surgical wounds are healed and graft function is established. In long-term maintenance, if there has been no acute rejection, the lowest doses of immunosuppressive agents should be reached within 2-4

months. Also, CNIs should be continued and if prednisone is used beyond one week post-transplant, it should be continued as well.

Tacrolimus has been recommended over cyclosporine due to less acute rejection and better graft survival. While mortality, malignancy, infection, delayed onset of graft function, and blood pressure differences between the two agents are not significant, tacrolimus has less incidence of NODAT and lower non-HDL cholesterol. ACR occurrence is typically a top predictor of poor long-term graft survival, but in CNI studies, a decrease in ACR frequency did not increase graft or individual survival rates.

Consideration of Age

In relation to infusion place of service, the age described in this policy for medical necessity of select intravenous and injectable therapy services is 13 years of age or older. The age criteria are based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to individuals above the age of 13.

The ages stated in this policy for which the drugs are considered medically necessary are based on the FDA labeling for this drug.

Evidence Review

In renal transplant individuals, Nulojix (belatacept) was shown to be non-inferior to cyclosporine (CsA) for individual and graft survival and had significantly higher GFRs, a result which held up in long term studies as well. Incidences of acute rejection episodes, defined differently in each study, were often significantly higher in the Nulojix (belatacept) individuals, although without direct correlation to graft loss or death, and these events occurred early in therapy. Secondary outcomes were often focused on the common drawbacks to oral calcineurin inhibitors (CNIs), namely BP, lipid panels, and diabetic complications. For Nulojix (belatacept), blood pressures and reductions in non-HDL cholesterol were significantly better, while fewer incidences of new-

onset diabetes occurred with Nulojix (belatacept) (significant to borderline significant depending on individual population), but long term follow up in one study extension showed these benefits were not preserved over time between agents. Some studies were complicated by individuals being switched to tacrolimus, another more-favored CNI, yet were included in analysis, while other extensions were limited in size.

Nulojix (belatacept) was introduced as an infused alternative to oral CNIs, which can contribute to weight gain, hypertension, post-transplant diabetes (increasing the risk of mortality and graft failure), and a decline in renal function. Belatacept was primarily compared to CsA in studies, as that was the predominant CNI used at the time of most trials' instigation. CsA has fallen out of favor compared to tacrolimus in guidelines, due to greater graft survival and less acute rejection but there is limited evidence available (one small trial) comparing these two agents.

Nulojix (belatacept) has a black box warning concerning post-transplant lymphoproliferative disorder (PTLD), which occurred in belatacept individuals who were Epstein-Barr virus (EBV) negative or previously used T-cell depleting therapies. The warning also contains cautions of malignancies, which can be opportunistic due to immunosuppression, and progressive multifocal leukoencephalopathy (PML), which was rare, but reported in studies. While general and serious AEs were similar compared to both CsA and tacrolimus, with more discontinuation of study drug with the latter, malignancies were varied in nature and fairly balanced across all arms in the pivotal studies. Non-life or graft-threatening infusion-related reactions occurred among belatacept individuals, and while infections in general were higher in likelihood among all agents compared, fungal infections tended to be higher in belatacept individuals when compared to tacrolimus.

In 2021, information regarding the risk of rejection with conversion from a CNI based maintenance regimen was added to the prescribing information. Conversion of individuals receiving a CNI based maintenance regimen to a belatacept based maintenance regimen increases the risk of acute rejection. In two randomized controlled studies, kidney transplant recipients at least six months post-transplant and stable on a CNI based regimen who were converted to a belatacept based regimen experienced higher rejection rates mostly during the first year post-conversion than individuals maintained on their CNI based regimens. Conversion of stable kidney transplant recipients from a CNI based maintenance therapy to a belatacept based maintenance therapy is not recommended unless the individual is CNI intolerant.

2013 Update

A literature search of the MEDLINE database conducted from January through December 2012 did not identify any additional published studies that would prompt reconsideration of the policy statements.

In 2-year follow up from a Phase II RCT of belatacept vs. calcineurin inhibitors cyclosporine or tacrolimus (CNI), year 2 data showed a mean cGFR of 62.0 ml/min (belatacept) vs. 55.4 ml/min (CNI). The mean change in cGFR from baseline was +8.8 ml/min (belatacept) and +0.3 ml/min (CNI). Higher cGFR was observed in individuals switched from either cyclosporine (+7.8 ml/min) or tacrolimus (+8.9 ml/min). The frequency of acute rejection in the LTE cohort was comparable between the belatacept and CNI groups by Year 2. All acute rejection episodes occurred during Year 1 in the belatacept individuals and during Year 2 in the CNI group. There were more non-serious mucocutaneous fungal infections in the belatacept group. Switching to a belatacept-based regimen from a CNI-based regimen resulted in a continued trend toward improved renal function at 2 years after switching. The results support the previous hypothesis of a prolonged renal-sparing effect of belatacept, since it avoids some of the toxicities commonly observed with CNI.

Similarly, in the 3-year extension of the Phase III BENEFIT-EXT trial in individuals receiving extended donor criteria kidneys (ECD) where poorer outcomes are normally expected, individual survival with a functioning graft was comparable between groups (80% in MI, 82% in LI, 80% in cyclosporine). Mean calculated GFR (cGFR) was 11 mL/min higher in Nulojix (belatacept)-treated versus cyclosporine-treated individuals (42.7 in MI, 42.2 in LI, 31.5 mL/min in cyclosporine). More cyclosporine-treated individuals (44%) progressed to GFR <30 mL/min (chronic kidney disease [CKD] stage 4/5) than Nulojix (belatacept)-treated individuals (27-30%). Acute rejection rates were similar between groups. Posttransplant lymphoproliferative disorder (PTLD) occurrence was higher in belatacept-treated individuals (two in MI, three in LI), most of which occurred during the first 18 months; four additional cases (3 in LI, 1 in cyclosporine) occurred after 3 years. Tuberculosis was reported in two MI, four LI and no cyclosporine individuals. In conclusion, at 3 years after transplantation, immunosuppression with belatacept resulted in similar individual survival, graft survival and acute rejection, with better renal function compared with cyclosporine. As previously reported, PTLD and tuberculosis were the principal safety findings associated with belatacept in this study population.

2014 Update

A literature search conducted from 1/1/13 through 12/31/13 did not reveal new evidence that would require changes to this policy.

2017 Update

A literature search conducted from 1/1/14 through 9/30/17 did not reveal new evidence that would require changes to this policy. In 2016 Vincenti, et al. reported results of a 7 year follow up study of renal transplant individuals maintained on Nulojix (belatacept). The authors concluded that individual and graft survival and the mean eGFR were significantly higher with than with cyclosporine in the comparator arm of the study.

2018 Update

A literature search conducted from 10/1/17 through 9/28/18 did not reveal new evidence that would require changes to this policy.

2019 Update

Reviewed Nulojix (belatacept) prescribing information and conducted a literature search from 10/1/18 through 11/30/19. No new information was identified that would require changes to this policy.

2020 Update

Reviewed Nulojix (belatacept) prescribing information and conducted a literature search from 12/1/19 through 09/30/20. No new information was identified that would require changes to this policy.

2021 Update

Reviewed Nulojix (belatacept) prescribing information and conducted a literature on the management of kidney transplantation in adults. Added additional information to the evidence review per prescribing information regarding the risk of rejection with conversion from a calcineurin inhibitor-based maintenance regimen. No new information was identified that would require changes to this policy.

2022 Update

Reviewed Nulojix (belatacept) prescribing information and conducted a literature on the management of kidney transplantation in adults. No new information was identified that would require changes to this policy.

2023 Update

Reviewed Nulojix (belatacept) prescribing information and conducted a literature search. Added a note to criteria that azathioprine can be used for individuals who have tried and did not tolerate mycophenolate mofetil (MMF).

2024 Update

Reviewed Nulojix (belatacept) prescribing information and conducted a literature search. No new information was identified that would require changes to this policy.

2025 Update

Reviewed Nulojix (belatacept) prescribing information and conducted a literature search. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members pursuant to **Alaska HB 226** (accessed January 3, 2025). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-

service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS). Clarified that the Site of Service Medical Necessity criteria can apply to injection drugs.

References

1. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010 Mar;10(3):535-46.
2. Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant. 2010 Mar;10(3):547-57.
3. Larsen CP, Grinyó J, Medina-Pestana J, et al. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. Transplantation. 2010 Dec 27;90(12):1528-35.
4. Vincenti F, Larsen C, Durrbach A, et al. Costimulation blockade with belatacept in renal transplantation. N Engl J Med. 2005 Aug 25;353(8):770-81.
5. Vincenti F, Blancho G, Durrbach A, et al. Five-year safety and efficacy of belatacept in renal transplantation. J Am Soc Nephrol. 2010 Sep;21(9):1587-96.
6. Ferguson R, Grinyó J, Vincenti F, et al. Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. Am J Transplant. 2011 Jan;11(1):66-76.
7. Rostaing L, Massari P, Garcia VD et al. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. Clin J Am Soc Nephrol. 2011 Feb;6(2):430-9. Epub 2010 Nov 4.
8. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. American Journal of Transplantation 2009; 9(Suppl 3): S1–S157.
9. Vanrenterghem Y, Bresnahan B, Campistol Jet al. Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). Transplantation. 2011May 15;91(9):976-83.
10. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2012 Annual Data Report. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration; 2014. Available at: **https://srtr.transplant.hrsa.gov/annual_reports/2012/pdf/2012_SRTR_ADR.pdf** Accessed January 6, 2025.
11. Posselt AM, Szot GL, Frassetto LA, et al. Islet transplantation in type 1 diabetic patients using calcineurin inhibitor-free immunosuppressive protocols based on Tcell adhesion or costimulation blockade. *Transplantation*. 2010;90(12):1595-1601.
12. Klintmalm GB, Feng S, Lake, JR, et al**.** Belatacept-based immunosuppression in de novo liver transplant recipients: 1-Year experience from a phase II study. Oral presentation at: Annual Meeting of the American Transplant Congress; April 30-May 4, 2011; Philadelphia.
13. NULOJIX (Belatacept) prescribing information. Bristol Meyers Squibb. Princeton, NJ. Revised July 2021.
14. Bremer S, Vethe NT, Rootwelt H, et al. Mycophenolate pharmacokinetics and pharmacodynamics in belatacept treated renal allograft recipients - a pilot study. J Transl Med. 2009 Jul 27;7:64.
15. Martin ST, Tichy EM, Gabardi S. Belatacept: a novel biologic for maintenance immunosuppression after renal transplantation. Pharmacotherapy. 2011 Apr;31(4):394-407. Review. The role of belatacept in transplantation: results and implications of clinical trials in the context of other new biological immunosuppressant agents. Clin Transplant. 2012 Dec 2. doi: 10.1111/ctr.12044 . Transplantation. 2018 Sep;102(9):1440-1452.Heemann U, Viklicky O.

16. Grinyo J, Alberu J, et al. Transpl Int. 2012 Oct;25(10):1059-64. Available online at: Improvement in renal function in kidney transplant recipients switched from cyclosporine or tacrolimus to belatacept: 2-year results from the long-term extension of a phase II study. Available at: **http://www.ncbi.nlm.nih.gov/pubmed/22816557** Accessed January 6, 2025.

17. Pestana JO, Grinyo JM, et al. Three-year outcomes from BENEFIT-EXT: a Phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys. Am J Transplant. 2012 Mar;12(3):630-9. **https://www.ncbi.nlm.nih.gov/pubmed/22300431** Accessed January 6, 2025.

18. Bassil N, Rostaing L, Mengelle C, et al. Prospective monitoring of cytomegalovirus, Epstein-Barr virus, BK virus, and JC virus infections on belatacept therapy after a kidney transplant. Exp Clin Transplant. 2014 Jun;12(3):212-9.

19. Vincenti F1, Rostaing L, Grinyo J, et al. Belatacept and Long-Term Outcomes in Kidney Transplantation. N Engl J Med. 2016 Jan 28;374(4):333-43.

20. Schwarz C, Mahr B, Muckenhuber M, Belatacept/CTLA4Ig: an update and critical appraisal of preclinical and clinical results. Expert Rev Clin Immunol. 2018 Jul;14(7):583-592. doi: 10.1080/1744666X.2018.1485489. Epub 2018 Jun 25.Perez CP, Patel N, Mardis CR, Belatacept in Solid Organ Transplant: Review of Current Literature Across Transplant Types.

21. Hardinger K, Brennan D. Kidney transplantation in adults: Maintenance immunosuppressive therapy. UpToDate. Accessed January 6, 2025.

22. McDonald R. Kidney transplantation in children: Immunosuppression. UpToDate. Accessed January 6, 2025.

History

Date	Comments
02/27/12	New Policy. Add to Prescription Drug section. Reviewed by P&T January 24, 2012.
02/13/13	Replace policy. Policy updated with literature review; no change in policy statements. HCPCS code J0485 added (new code 1/1/13); C9286 deleted effective 12/31/12.
03/25/14	Replace policy. Policy updated with literature review; no change to policy statement.
08/11/15	Annual Review. A literature search was conducted from 3/1/14-6/30/15. No new studies were found that would require changes to this policy. One new reference added. HCPCS codes J3490, J3590 and J7599 removed; these are non-specific codes – the specific code J0485 remains on the policy.
06/01/16	Annual Review, approved May 10, 2016. Inclusion of the "Site of Service" criteria to the existing policy. Format of the "Policy" section re-structured to include tabulated view of the medical necessity criteria.
08/19/16	Converted to new policy format; no changes in content or coverage.
11/01/16	Interim Review, approved October 11, 2016. Clarified age criteria language indicating that site of service review is applicable to only those age 13 and older; drug criteria review applies to all ages.
01/01/17	Interim Review, approved December 13, 2016. Added Consideration of Age Requirements to policy.

Date	Comments
07/01/17	Formatting update; added hyperlinks to medical necessity criteria sections.
09/25/17	Interim Review, approved September 22, 2017, effective September 25, 2017. Policy statement added to indicate that Nulojix (belatacept) is investigational for use in pediatric patients because there have been no studies to support use in this group.
11/01/17	Annual Review, approved October 3, 2017. Clarified site of service exception criterion related to access: There is no outpatient infusion center within 50 miles of the patient's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug. Added 7-year results of a long term follow up study.
02/14/18	Interim Review, approved February 13, 2018. Update hospital based outpatient coverage from 30 days to 90 days.
11/01/18	Annual Review, approved October 26, 2018. No changes to policy statement. References added.
01/01/19	Minor update. Clarified Consideration of Age information.
06/01/19	Interim Review, approved May 23, 2019. Clarified Nulojix (belatacept) criteria when used for induction therapy versus maintenance therapy.
01/01/20	Annual Review, approved December 10, 2019. No changes to policy statement.
12/01/20	Annual Review, approved November 3, 2020. No changes to policy statement.
10/01/21	Annual Review, approved September 23, 2021. No changes to policy statement.
11/01/22	Annual Review, approved October 10, 2022. No changes to policy statement. Changed the wording from "patient" to "individual" throughout the policy for standardization.
05/01/23	Annual Review, approved April 11, 2023. Reviewed Nulojix (belatacept) prescribing information and conducted a literature search. Added a note to criteria that azathioprine can be used for individuals who have tried and did not tolerate mycophenolate mofetil (MMF).
06/01/24	Annual Review, approved May 24, 2024. No changes to policy statement.
02/01/25	Annual Review, approved January 27, 2025. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members; only Medical Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS).
07/01/25	Interim Review, approved June 10, 2025. The following policy changes are effective October 3, 2025, following 90-day provider notification. Clarified that the Site of Service Medical Necessity criteria can apply to injection drugs.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.