These Clinical Guidelines have been created using resources that were current as of the "Reviewed" date noted at the beginning of the document. Clinicians should refer to the manufacturer's Prescribing Information (or equivalent) for the most up-to-date information. While CarepathRx has published these Clinical Guidelines after a close review of available literature and a clinical review process, given the evolving nature and complexity of modern pharmaceutical products, CarepathRx does not and cannot warrant or guarantee that these Clinical Guidelines reflect the objectively best or highest standard of care at any given time.

Nothing within these Clinical Guidelines is intended to supersede or interfere with any individual clinician's decision-making or professional judgment with respect to either (1) prescribing or dispensing the drug or product in question or (2) the overall treatment plan for an individual patient.

Belatacept (Nulojix) Clinical Guideline for Home Intravenous Therapy

Section: Clinical Guideline
Compliance: ACHC Infusion Pharmacy
ACHC Standards: N/A
URAC Standards: N/A
Policy ID: CG028
Effective: 6/1/2022
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Revised: 6/1/2025
Approved by, Title and Date Approved: Kathleen Patrick, President, 6/1/22, 6/1/25

I. BACKGROUND

Belatacept (Nulojix) is a fusion protein which acts as a selective T-cell (lymphocyte) co-stimulation blocker by binding to CD80 and CD86 receptors on antigen presenting cells (APC), blocking the required CD28 mediated interaction between APCs and T cells needed to activate T lymphocytes. T-cell stimulation results in cytokine production and activated T-cell proliferation which then facilitates immunologic rejection of the kidney transplant. Belatacept is approved for prophylaxis of organ rejection in adult patients receiving kidney transplant. Belatacept is used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. The following outlines the procedures for servicing patients in need of outpatient belatacept home infusions.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon admission criteria.

B. All patients will be started on belatacept in the inpatient setting prior to being discharged for home infusion therapy.

C. Prescribing physician must be experienced in immunosuppressive therapy and management of kidney transplant patients. Physician orders for belatacept must include:

1. Patient weight
2. Drug and dose (including weight-based dosage)
3. Route of administration
4. Frequency of administration
5. Emergency medications per protocol
6. Orders for pre-medications
7. Line care protocol
8. Routine lab monitoring, if applicable

D. Baseline labs prior to starting therapy (ex: CBC with differential, CMP)

E. Confirmation and documentation of Epstein-Barr virus (EBV) seropositive status.

F. Confirmation and documentation of recent tuberculosis test or Quantiferon gold result.

G. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted unless a more comprehensive patient-specific orders are provided by physician. See Appendix A (Nursing CarepathRx policy on *Management of Allergic/Anaphylactic Reactions*).

III. PHARMACOLOGY OVERVIEW

Refer to manufacturer's full Prescribing Information for most up to date information

A. Indications:

1. Kidney transplant, prophylaxis of organ rejection.

B. Dosing

Dosing of NULOJIX for Kidney Transplant Recipients (2.1)

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

1. The prescribed dose must be evenly divisible by 12.5 mg in order for the dose to be prepared accurately. Evenly divisible increments are 0, 12.5, 25, 37.5, 50, 62.5, 75, 87.5, and 100.
2. The total infusion dose of belatacept should be based on the actual body weight of the patient at the time of transplantation and should not be modified during the course of therapy, unless there is a change in body weight of greater than 10%.
3. Dosing is based off actual body weight. Belatacept has not been studied in extremes of body weights.

C. Dose Adjustments: No dosing adjustment for renal or hepatic impairment. No dose adjustments for advanced age.

D. Duration: Duration of therapy should be dependent on patient response and adverse reactions.

E. Contraindications: Transplant patients who are Epstein-Barr virus (EBV) seronegative or with unknown EBV serostatus due to increased risk for posttransplant lymphoproliferative disorder (PTLD).

F. Warnings and Precautions

1. **Infections:** Immunosuppressive therapy may lead to bacterial, viral (cytomegalovirus [CMV] and herpes), fungal, and protozoal infections, including opportunistic infections which may be fatal. Prophylaxis for CMV is recommended for at least 3 months after transplantation; prophylaxis for *Pneumocystis jirovecii* is recommended after transplantation.

a. Tuberculosis was more frequently observed in patients receiving belatacept than cyclosporine in clinical trials. 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 treatment.
b. Patients receiving immunosuppressive therapy are at an increased risk of activation of latent viral infections, including John Cunningham virus (JCV) and BK (Human polyomavirus 1) virus infection.
    1) Activation of JCV may result in progressive multifocal leukoencephalopathy (PML), a rare and potentially fatal condition affecting the CNS.
    2) Polyoma virus-associated nephropathy (PVAN), primarily from activation of BK virus, may also occur and lead to the deterioration of renal function and/or renal graft loss.
    3) The onset of PML or PVAN may warrant a reduction in immunosuppressive therapy; however, in transplant recipients, the risk of reduced immunosuppression and graft rejection should be considered. Monitor for apathy, ataxia, cognitive deficiencies, confusion, and hemiparesis.

2. **Lymphoproliferative disorders:** Risk of post-transplant lymphoproliferative disorder (PTLD) is increased, primarily involving the CNS, in patients receiving belatacept. Degree of immunosuppression is a risk factor for developing PTLD. Do not exceed recommended dosing. The risk of PTLD was higher in EBV seronegative patients compared to EBV seropositive patients. Other known risk factors for PTLD include cytomegalovirus (CMV) infection and T cell depleting therapy. T cell-depleting therapies to treat acute rejection should be used cautiously.

3. **Immunosuppression:** Only physicians experienced in the management of systemic immunosuppressive therapy and management of kidney transplant patients should prescribe belatacept.

4. **Malignancy:** Risk for malignancy is increased with belatacept. Malignancy, including skin malignancy and PTLS, is associated with the use of belatacept. Patients should be advised to limit their exposure to sunlight and UV light

5. **Progressive Multifocal Leukoencephalopathy:** Progressive multifocal leukoencephalopathy (PML) is an often rapidly progressive and fatal opportunistic infection of the CNS that is caused by the JC virus. In clinical trials, two cases of PML were reported in patients receiving belatacept at higher cumulative doses and more frequently than the recommended regimen, along with mycophenolate mofetil (MMF) and corticosteroids. One case occurred in a kidney transplant recipient and the second case occurred in a liver transplant recipient. As PML has been associated with high levels of overall immunosuppression, the recommended doses and frequency of belatacept and concomitant immunosuppressives, including MMF, should not be exceeded. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive, or behavioral signs or symptoms. PML is usually diagnosed by brain imaging, cerebrospinal fluid (CSF) testing for JC viral DNA by polymerase chain reaction (PCR), and/or brain biopsy. Consultation with a specialist (ex: neurologist and/or infectious disease) should be considered for any suspected or confirmed cases of PML. If PML is diagnosed, consideration should be given to reduction or withdrawal of immunosuppression taking into account the risk to the allograft.

6. **Liver Transplant:** Use in liver transplant patients is not recommended due to higher rate of graft loss and death

7. **Acute Rejection and Graft Loss with Corticosteroid Minimization:** In post marketing experience, use of belatacept in conjunction with basiliximab induction, MMF, and corticosteroid minimization to 5 mg per day between Day 3 and Week 6 post-transplant was associated with an increased rate and grade of acute rejection, particularly Grade III rejection. These Grade III rejections occurred in patients with 4 to 6 HLA (human leukocyte antigen) mismatches. Graft loss was a consequence of Grade III rejection in some patients.

8. **Live Vaccinations:** Avoid concurrent use of live or live-attenuated vaccines in patients who are treated with belatacept. Update vaccinations according to current immunization guidelines prior to initiation of belatacept.

9. **Coadministration with Anti-Thymocyte Globulin:** Coadministration (at the same or nearly the same time) with anti-thymocyte globulin may pose a risk for venous thrombosis of renal allograft in de novo kidney transplant recipients, especially those with other risk factors for venous thrombosis. If administered concomitantly, a twelve-hour interval between the two administrations is recommended.

10. **Risk of Rejection with Conversion from a CNI (Calcineurin Inhibitor) -Based Maintenance Regimen:** Conversion of maintenance kidney transplant recipients from a CNI-based 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

11. **Pregnancy/Lactation:** Data in pregnant or lactating women is insufficient to inform on drug-associated risk. Pregnant women or their partners receiving belatacept should be registered in the Transplant Pregnancy Registry International. Administration of belatacept to pregnant rats and rabbits during the period of organogenesis was not teratogenic at exposures approximately 16 and 19 times greater than that observed at the maximum recommended human dose (MRHD) of 10 mg/kg body weight administered over the first month of treatment, based on area under the concentration-time curve (AUC). In a pre- and post-natal development study in rats, treatment-related infections in dams were associated with increased pup mortality, presumably secondary to deteriorating maternal health, at exposures 3 times higher than that observed at MRHD. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for belatacept and any adverse effects

B. Pharmacokinetics

1. The Cmax was 247 +/- 68mg/mL and 139 +/- 28 mcg/mL following administration of multiple doses of belatacept 10mg/kg and 5 mg/kg IV over 30 minutes in kidney transplant patients.
2. Distribution: 0.11 L/kg (transplant patients)
3. Metabolized by proteolytic enzymes into smaller peptides and amino acids.
4. Half-life elimination: ~10 days

C. Adverse Reactions

1. Greater than 20%: anemia, diarrhea, infections, peripheral edema, constipation, hypertension, pyrexia, graft dysfunction, cough, fever, nausea, vomiting, headache, hypokalemia, hyperkalemia, leukopenia, and urinary tract infections.
2. 10-20%: insomnia, hypotension, hypophosphatemia, lipid metabolism disorder, hyperglycemia, hypocalcemia, hypercholesterolemia, arthralgia, proteinuria, dyspnea, CMV infection, disorder of transplanted kidney, and renal artery stenosis.
3. Less than 10%: atrial fibrillation, dizziness, new onset diabetes, stomatitis, neutropenia, malignant neoplasm, antibody development, lymphoproliferative disorder (CNS PTLD), progressive multifocal leukoencephalopathy, tuberculosis, disease caused by BK virus, Guillain-Barre syndrome, acute renal failure, and malignancies.

D. Drug Interactions

1. Increased effect/toxicity: antithymocyte globulin, potent immunosuppressants (denosumab, tacrolimus, etc.)
2. Vaccine-associated infections: avoid the use of live vaccines.
3. Diminished therapeutic effect: avoid the use of inactivated vaccines.
4. Drug-drug interactions may exist. Consult interaction database for patient specific assessment.

IV. ADMINISTRATIVE GUIDELINES

A. Administration: IV infusions should be given immediately after reconstitution and dilution. Begin infusion within 4 hours of preparation per current USP Immediate-Use Guidelines.

B. Administer infusion with an in-line or add-on 0.2-1.2-micron low protein-binding filter.

C. Belatacept must be reconstituted and prepared using only a silicone-free disposable syringe that is provided with each vial.

D. Do not co-administer other medicinal products in the same infusion line.

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:

1. Alcohol Swabs
2. Gloves
3. Tape
4. IV access supplies as applicable
    a. Peripheral IV access supplies for patients requiring peripheral IV access
        1) IV start Kit
        2) Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾")
        3) Extension set 8" with needless connector
    b. Port access supplies for patients with a port
        1) Port needle (ex. 22 Gauge x ¾ to 1" safe step)
        2) (ii) Needless connector
        3) (iii)Central line dressing change kit
5. IV Pole

6. IV administration set (flow regulator [ex: dial-a-flow] or gravity) with in-line or add-on 0.22 micron filter (may use 0.2-1.2-micron filter depending on site availability)
7. Syringes (20-60 mL) for removal of excess diluent from stock bag and needles (20 G x 1")
8. Sharps container

B. Prescription Items:

1. Belatacept vials with silicone free syringes
2. Vials of Sterile Water for Injection
3. 0.9% sodium chloride 50mL, 100mL, or 250mL IV diluent bag
4. Standard flushes per protocol
5. Anaphylaxis kit per protocol

C. How supplied:

1. Belatacept is supplied as 250 mg lyophilized powder for injection per vial and is also supplied with a silicone-free disposable syringe with each vial.

D. Storage and Handling: Storage and Handling

1. Store vials at 2˚C to 8˚C (36˚F to 46˚F).
2. Protect from light in the original package until time of use.

E. Compatibility:

1. Final diluted product is stable in 0.9% normal saline (NSS) solution or D5W.
2. For reconstitution
    a. Sterile Water for Injection (SWFI) should be further diluted with either NSS or D5W
    b. NSS should be further diluted with NSS
    c. D5W should be further diluted with D5W
3. Do not infuse with other agents.

F. Procedures:

1. Explain the reasoning for visit and use of belatacept.
2. Don gloves
3. Assess for signs and symptoms of infection prior to establishing venous access and preparing medication.
4. Establish venous access prior to preparation of drug.
5. Counsel patient on warnings, precautions, and potential side effects including but not limited to anemia, diarrhea, infections, peripheral edema, constipation, hypertension, pyrexia, graft dysfunction, cough, nausea, vomiting, headache, insomnia, and muscle weakness.
6. Prepare Product: Calculate the number of belatacept vials required to provide the total infusion dose.
7. Reconstitute the contents of each vial with 10.5mL of diluent using the silicone-free disposable syringe provided with each vial and an 18- to 21-gauge needle.
8. Rotate the vial and invert with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. Do NOT shake.
9. Discard any solutions inadvertently prepared using non- siliconized syringes.

10. The reconstituted solution contains a concentration of 25 mg/mL and should be clear to slightly opalescent and colorless to pale yellow. Visually inspect the reconstituted solution for opaque particles, discoloration, or other foreign particles, and do not infuse if present.
11. Calculate the total volume of the reconstituted 25 mg/mL solution required to provide the total infusion dose. Volume of 25 mg/mL solution = Prescribed dose ÷ 25 mg/mL
12. Prior to intravenous infusion, the required volume of the reconstituted solution must be further diluted in 0.9% sodium chloride or D5W.
    a. If reconstituted with SWFI, use 0.9% sodium chloride or D5W
    b. If reconstituted with 0.9% sodium chloride, use 0.9% sodium chloride.
    c. If reconstituted with D5W, use D5W
13. Withdraw a volume of diluent from the stock bag that is equal to the volume of the dose of reconstituted solution and discard (ok to use silicone syringes for this step to remove diluent and discard).
14. Withdraw the required amount of belatacept solution from the vial using the silicone-free syringe, inject it into the infusion bag, and gently rotate the infusion bag to ensure mixing. Do NOT shake. The final belatacept concentration in the infusion bag or bottle should range from 2 mg/mL to 10 mg/mL.
15. Visually inspect the infusion for particulate matter and discoloration. Discard the infusion if any particulate matter or discoloration is observed.
16. Administer the infusion over 30 minutes using a sterile, non-pyrogenic, 0.2 or low protein-binding filter (may use 0.2-1.2-micron filter depending on site availability).
17. Post infusion monitoring: Monitor patient and vital signs periodically during the infusion and monitor 30 minutes after the infusion is complete per CarePathRx Nursing Best Practice Administration Guidelines.

VI. CLINICAL MONITORING

A. Prior to therapy initiation:

1. TB screening
2. EBV serostatus
3. Up-to-date on vaccines
4. Baseline labs (CBC with differential and CMP)
5. Ensure prescribing physician is experienced in transplant and immunosuppressive therapy
6. No active infections

B. During therapy, monitor for:

1. New-onset or worsening neurological cognitive, or behavioral signs/symptoms
2. Changes in mood, confusion, problems thinking, loss of memory
3. Changes in walking or talking
4. Decreased strength or weakness on one side of the body
5. Changes in vision
6. Signs/symptoms of cancer, such as suspicious moles or lesions
7. Signs/symptoms of infection
8. GI side effects such as nausea, vomiting, and diarrhea
9. Monitor electrolytes including potassium and magnesium
10. Signs/symptoms of solid organ transplant rejection
11. Change in body weight of greater than 10% (for dosing)

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APPENDIX A: ANAPHYLAXIS KIT INTRUCTIONS

Emergency Medication After Your Infusion

Please call your pharmacy if you have any questions or concerns. In the event of an emergency, always call 911.

Your nurse will tell you when you need to use Emergency Medications.
The epinephrine dose will be noted on the Anaphylaxis Protocol included with your kit.

Start with a clean work surface and clean hands.

Open the supply bag labeled Anaphylaxis Kit Contents.

You will need:

1. **Bag containing Pills** (2 Acetaminophen and 2 Diphenhydramine)
2. **Bag containing Alcohol Prep Pads**
3. **Bag labeled IM Epinephrine**

All other contents will not be needed.

Open the IM Epinephrine Bag

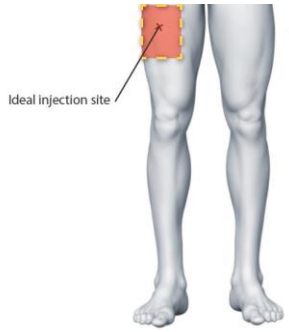
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampule use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampule of epinephrine

Prepare IM (intramuscular) injection of Epinephrine:

1. **Attach the brown filtered needle to syringe**
    a. Be careful to not touch the tip of the syringe or the needle.
2. Using an **alcohol swab, wipe the neck of the epinephrine ampule.**
3. Holding the ampule upright, **swirl and flick the ampule until all fluid flows to the bottom chamber** (the top chamber should be empty).
4. Using a new alcohol wipe, grasp the neck of the ampule and with your other hand grasp the bottom chamber of the ampule. **Quickly snap the top of the ampule off, directing the snap way from you.**
5. **Place the tip of the brown filter needle inside the ampule**. Tilting the ampule, **withdraw dose of medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
6. Remove the needle from the ampule and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
7. **Push the air out of the syringe by gently pushing on the plunger**.
8. Replace the cap on the brown filter needle. Discard remainder in ampule.

9. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection



1. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
2. **Push the needle into your leg muscle straight** in at a 90-degree angle.
3. **Inject the medication** by depressing the plunger in a slow and steady motion.
4. **Remove the needle** and wipe the site with the alcohol wipe.
5. May repeat dose every 5 minutes (**maximum 3 doses**) if ordered per protocol.

Take the pills by mouth.

a. 2 – Acetaminophen
b. 2 – Diphenhydramine

Place all trash in the bag the pills came in and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.

Call 911 or have someone drive you to the emergency department.