CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

CLINICAL GUIDELINES FOR BELATACEPT (NULOJIX)

Section: Nursing
Compliance: N/A
ACHC Standards: N/A
URAC Standards: N/A
TJC Standards: N/A
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Reviewed:
Revised:
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I. POLICY

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. The following outlines the procedures and protocol for coordination of 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. Prescribing physician must be experienced in immunosuppressive therapy and management of kidney transplant patients.

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

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

E. The decision to administer a first dose in the home by a field nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:

1. Prescriber preference
2. Allergy profile
3. Ability to secure contracted nursing for subsequent infusions
4. Other relevant social and/or medical history

F. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted unless more comprehensive patient-specific orders are provided by physician. See policy NUR012 (Appendix A)

III. PHARMACOLOGY OVERVIEW

A. Indications:

1. Kidney transplant, prophylaxis of organ rejection
2. Lung transplant, prophylaxis of organ rejection (off-label)
3. Heart transplant, prophylaxis of organ rejection (off-label)

B. Contraindications:

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

C. Precautions:

1. Infections
    a. Immunosuppressive therapy may lead to bacterial, viral (cytomegalovirus [CMV] and herpes), fungal, and protozoal infections, including opportunistic infections which may be fatal.
    b. Tuberculosis (TB) is increased; test patients for latent TB prior to initiation and treat latent TB infection prior to use.
    c. Prophylaxis for CMV is recommended for at least 3 months after transplantation; prophylaxis for *Pneumocystis jirovecii* is recommended after transplantation.

2. Latent Viral Infections
    a. Patients receiving immunosuppressive therapy are at an increased risk of activation of latent viral infections, including John Cunningham virus (JCV) and BK 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.
            - 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.

3. Lymphoproliferative disorders
    a. Risk of post-transplant lymphoproliferative disorder (PTLD) is increased, primarily involving the CNS, in patients receiving Belatacept.
    b. Degree of immunosuppression is a risk factor for PTLD developing - do not exceed recommended dosing.

4. Malignancy
    a. Risk for malignancy is increased
    b. Malignancy, including skin malignancy and PTLS, is associated with the use of Belatacept - patients should be advised to limit their exposure to sunlight/UV light.

5. Liver Transplant

a. Use in liver transplant patients is not recommended due to higher rate of graft loss and death.

6. Coadministration with Anti-Thymocyte Globulin
    a. 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.
    b. If administered concomitantly, a twelve hour interval between the two administrations is recommended.

7. Risk of Rejection with Conversion from a CNI-Based Maintenance Regimen
    a. Conversion of maintenance kidney transplant recipients from a CNI-based regimen increases the risk of acute rejection.
    b. 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.

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

9. Pregnancy/Lactation
    a. Data in pregnant or lactating women is insufficient to inform on drug-associated risk
    b. Pregnant women or their partners receiving Belatacept should be registered in the Transplant Pregnancy Registry International.
    c. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Belatacept and any adverse effects.

10. Prescribing provider
    a. Only physicians experienced in immunosuppressive therapy and management of kidney transplant patients should prescribe Belatacept

D. Pharmacokinetics

1. Distribution: V_{ss}: 0.11 L/kg (transplant patients)
2. Half-life elimination: ~10 days

E. Adverse Reactions

1. Greater than 20%: anemia, diarrhea, **infection**, peripheral edema, constipation, hypertension, pyrexia, graft dysfunction, cough, nausea, vomiting, headache, hypokalemia, hyperkalemia, leukopenia

2. 10-20%: insomnia, hypotension, hypophosphatemia, lipid metabolism disorder, hyperglycemia, hypocalcemia, hypercholesterolemia, arthralgia, proteinuria, dyspnea

3. Less than 10%: atrial fibrillation, dizziness, new onset diabetes, stomatitis, neutropenia, **malignant neoplasm**, antibody development, lymphoproliferative disorder (**CNS PTLD**), **progressive multifocal leukoencephalopathy.**

F. Drug Interactions

1. Increased effect/toxicity: antithymocyte globulin, potent immunosuppressants (denosumab, tacrolimus, etc.)

2. Vaccine-associated infections: live vaccines

3. Diminished therapeutic effect: inactivated vaccines

IV. ADMINISTRATIVE GUIDELINES

A. Administration

1. Administer as an IV infusion over 30 minutes using an infusion set **with a 0.2 micron low protein-binding filter (may use 0.2-1.2 micron filter depending on site availability).**

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

3. Dosing for Belatacept should not be modified during the course of therapy unless there is a change in body weight of greater than 10%

4. The infusion must be completed within 1 hour of reconstitution of the lyophilized powder per current USP Immediate-Use Guidelines - excursion data will be reviewed on a case-by-case basis by clinical management

B. Dosage

1. Kidney transplant and lung (off label) transplant

   a. The prescribed dose must be evenly divisible by 12.5mg in order for the dose to be prepared accurately.

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/kg
End of week 2 and week 4 after transplantation	10 mg/kg
End of week 8 and week 12 after transplantation	10 mg/kg

Dosing for Maintenance Phase	Dose
End of week 16 after transplantation and every 4 weeks (plus or minus 3 days) thereafter	5 mg/kg

2. Heart transplant (off-label) – based on length of initiation phase
   a. 1-month initial phase
      - 10 mg/kg on days 0, 4, 14, and 28; followed by 10 mg/kg monthly

b. 2-month initial phase
    - 10 mg/kg on days 1, 5, 15, 29, 45, and 59; followed by 5 mg/kg monthly
c. 3-month initial phase
    - 5 mg/kg every 2 weeks for 6 doses, followed by 5 mg/kg monthly thereafter

C. Duration

1. Duration of therapy should be dependent on patient response and adverse reaction

2. No specific duration is noted in the package insert

D. Dose Adjustment

1. No dosing adjustment is recommended for impaired kidney or hepatic function or advanced age.
2. Safety and efficacy in pediatric patients or neonates have not been established

E. Patient Monitoring

1. Prior to therapy, monitor for:
    a. TB screening
    b. EBV serostatus

2. During therapy, monitor for:
    a. New-onset or worsening neurological cognitive, or behavioral signs/symptoms
    b. Signs/symptoms of infection or malignancy
    c. GI side effects
    d. Potassium
    e. Magnesium
    f. Signs/symptoms of solid organ transplant rejection

3. Treatment for hypersensitivity reactions should be available via anaphylaxis kit

V. NURSING PROCEDURE

A. Supplies

1. Alcohol Swabs
2. Gloves
3. Vial(s) of Belatacept (250mg per vial) **with silicone free syringes**
4. Vials of Sterile Water for Injection
5. 0.9% NaCl 50mL, 100mL, or 250mL IV Bag
6. Dressing change kit
7. IV Pole
8. IV Start Kit
9. Peripheral IV catheter (ex. 22 Gauge x 1" and 24 Gauge x ¾" for patients needing peripheral access)
10. Port access needle (ex. 22 Gauge x ¾ to 1" safe step for patients with a port)
11. Tape
12. Extension set 8"
13. IV injection cap

14. IV administration set (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)**
15. Sharps container

B. 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**

C. 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.
3. Reconstituted product must be infused within 1 hour of preparation. Excursion data will be reviewed on a case-by-case basis by clinical management.

D. Compatibility

1. Final diluted product is stable in NS or D5W
2. Do not infuse with other agents

E. Procedures

1. Explain the reasoning for visit and use of Belatacept.

2. Calculate the number of Belatacept vials required to provide the total infusion dose.

3. 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.
    a. To reconstitute, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of diluent (SWFI, NS, or D5W) to the glass wall of the vial.
    b. Rotate the vial and invert with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. Do **NOT** shake.
    c. Discard any solutions inadvertently prepared using siliconized syringes.

4. 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.

5. Calculate the total volume of the reconstituted 25 mg/mL solution required to provide the total infusion dose
    a. Volume of 25 mg/mL solution = Prescribed dose ÷ 25 mg/mL

6. Prior to intravenous infusion, the required volume of the reconstituted solution must be further diluted in NS or D5W.
    a. If reconstituted with SWFI, use NS or D5W
    b. If reconstituted with NS, use NS
    c. If reconstituted with D5W, use D5W

7. Withdraw a volume of infusion fluid that is equal to the volume of the reconstituted solution and discard. 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.

8. Visually inspect the infusion for particulate matter and discoloration. Discard the infusion if any particulate matter or discoloration is observed.

9. 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)** in a separate line.

F. Infusion Rates

1. Infusion should be administered continuously over a period of 30 minutes through a dedicated IV line.
2. Do not infuse other agents concomitantly with Belatacept in the same IV line.
3. Follow Protocol for Management of Adult Infusion Reactions (Appendix A).

G. Clinical Monitoring

1. Patients/providers should monitor for:
   a. Changes in mood or usual behavior
   b. Confusion, problems thinking, loss of memory
   c. Changes in walking or talking
   d. Decreased strength or weakness on one side of the body
   e. Changes in vision
   f. Signs/symptoms of skin cancer, such as suspicious moles or lesions
   g. Signs/symptoms of infection
   h. Other adverse drug reactions

2. Treatment for hypersensitivity reactions should be available via anaphylaxis kit (Appendix A)

VI. REFERENCES

Belatacept [package insert]. Princeton, NJ; Bristol Myers Squibb Company; 2021.

USP General Chapter <797>: Pharmaceutical Compounding- Sterile Preparations. Rockville, MD: United States Pharmacopeia Convention; 2008.

Launay M, Guitard J, Dorent R, Prevot Y, Prion F, Beaumont L, Kably B, Lecuyer L, Billaud EM, Guillemain R. Belatacept-based immunosuppression: A calcineurin inhibitor-sparing regimen in heart transplant recipients. Am J Transplant. 2020 Feb;20(2):553-563. doi: 10.1111/ajt.15584. Epub 2019 Sep 26. PMID: 31452337.

Timofte I, Terrin M, Barr E, Sanchez P, Kim J, Reed R, Britt E, Ravichandran B, Rajagopal K, Griffith B, Pham S, Pierson RN 3rd, Iacono A. Belatacept for renal rescue in lung transplant patients. Transpl Int. 2016 Apr;29(4):453-63. doi: 10.1111/tri.12731. Epub 2016 Feb 8. PMID: 26678245.

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

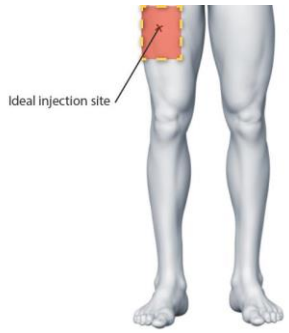
1. **Remove 1 of each item**
   a. 1 -syringe
   b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampul use only**
   c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1")
   d. 1 ampul of epinephrine

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 ampul.**
3. Holding the ampul upright, **swirl and flick the ampul 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 ampul and with your other hand grasp the bottom chamber of the ampul. **Quickly snap the top of the ampul off, directing the snap way from you.**
5. **Place the tip of the brown filter needle inside the ampul**. Tilting the ampul, **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 ampul 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 ampul.
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.