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.

Belimumab (Benlysta) Clinical Guideline for Home Intravenous Therapy

Section: Clinical Guideline
Compliance: ACHC Infusion Pharmacy
ACHC Standards:
URAC Standards:
Policy ID: CG002
Effective: 10/01/2023
Reviewed: n/a
Revised: n/a
Approved by, Title and Date Approved: Kathleen Patrick, President, 10/1/23

I. BACKGROUND

Belimumab (Benlysta) is a humanized IgG1-lambda monoclonal antibody that prevents the survival of B lymphocytes by blocking the binding of soluble human B lymphocyte stimulator protein (BlyS) to receptors on B lymphocytes. This reduces the activity of B-cell mediated immunity and the autoimmune response. Belimumab is indicated for lupus nephritis and systemic lupus erythematosus (SLE) in patients 5 years and older who are receiving standard therapy. The following outlines the procedures for servicing patients in need of outpatient intravenous (IV) belimumab.

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 the dispensing pharmacy's admission criteria.

B. 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. Age ≥18 years
4. Other relevant social and/or medical history

C. Physician orders for belimumab must include:

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

D. Baseline labs or tests prior to starting therapy (ex: CMP, CBC, autoantibodies, IgG, up to date on vaccinations)

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

III. PHARMACOLOGY OVERVIEW

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

A. Indications

1. Treatment of patients five years or older with active systemic lupus erythematosus (SLE) who are receiving standard therapy
2. Treatment of patients five years or older with active lupus nephritis who are receiving standard therapy

**Subcutaneous dosing and administration will not be discussed in the scope of this guideline*

B. Dosage: Initial: 10 mg/kg IV every 2 weeks for 3 doses Maintenance: 10 mg/kg every 4 weeks

*Dosing is based off actual body weight. Belimumab has not been studied in extremes of body weights

C. Dose Adjustment: No dosage adjustment is recommended in patients with renal or hepatic impairment

D. Duration: Duration of therapy should be dependent on patient response and adverse reaction. No specific duration is noted in package insert.

E. Contraindications: Anaphylaxis to belimumab or any component of the formulation

F. Warnings and Precautions

1. **Serious Infections:** Serious and potentially fatal infections have been reported with belimumab. Use with caution in patients with severe or chronic infections and consider interrupting belimumab therapy in patients who develop a new infection while receiving it and monitor these patients closely.
2. **Progressive Multifocal Leukoencephalopathy (PML):** Cases of progressive multifocal encephalopathy have been reported in patients with SLE receiving immunosuppressants including belimumab. Risks for developing PML include treatment with immunosuppressants and impairment of immune function. Consult with a neurologist for patients presenting with new-onset or deteriorating neurological signs or symptoms.

3. **Hypersensitivity and Reactions including Anaphylaxis:** Acute hypersensitivity reactions including anaphylaxis and death, and infusion-related reactions have been associated with this treatment. Non-acute hypersensitivity reactions including rash, nausea, fatigue, myalgia, headache, and facial edema have also been reported and can occur up to a week following infusion. These events can occur within hours of infusion or in patients who have previously tolerated infusions and will require discontinuation and appropriate medical intervention. Delayed hypersensitivity reactions have been reported following exposure to pharmaceutical products containing polysorbate 80 in certain individuals.
4. **Infusion-Related Reactions:** Infusion-related reactions include symptoms such as angioedema, bradycardia, dyspnea, headache, hypotension, myalgia, pruritus, rash, and urticaria. Due to overlap in signs and symptoms, it was sometimes difficult to distinguish between hypersensitivity reactions and infusion-related reactions. In clinical trials 13% of patients received premedication which may have masked a hypersensitivity response or infusion-related reaction. Monitor patients during infusion and for an appropriate time (30 minutes) after. Slow or temporarily interrupt the infusion if patient develops an infusion reaction and consider administering premedication prior to infusing.
5. **Psychiatric Disorders:** Cases of depression and suicidality were reported in clinical trials. Initial and ongoing assessment of psychiatric status should be conducted. Patients and caregivers should be advised to seek medical attention if patients experience new or worsening depression or anxiety, suicidal ideation or behavior, or other mood changes.
6. **Malignancy:** There is an increased risk of malignancy with the use of immunosuppressants. The exact impact of belimumab on the development of malignancies is not known. A benefit-risk discussion for each individual should be considered.
7. **Vaccinations:** The use of live vaccines should be avoided for 30 days before or concurrently with belimumab as clinical safety has not been stablished. There is no data available regarding secondary transmission of infection from live vaccines.
8. **Concomitant Use with other Biologic Therapies:** In clinical trials, the use of other biologics and IV cyclophosphamide was not permitted. Available data also do not support the safety and efficacy of concomitant use of belimumab with rituximab in patients with SLE. Caution should be exercised if belimumab is administered in combination with other biologic therapies including B-cell targeted therapies.
9. **Patients with Severe Active Disease:** In clinical trials, patients with severe active lupus nephritis and severe active CNS lupus were excluded. Use is not recommended in these patients.
10. **Pregnancy and Lactation:** Available data on the use of belimumab in pregnant women are insufficient to determine whether there is a drug-associated risk of birth defects or miscarriage. Monoclonal antibodies are increasingly transported across the placenta with the largest amount transferred during the third trimester. Based on animal data and the mechanism of action of belimumab, the immune system in infants of treated mothers may be adversely affected. If prevention of pregnancy is warranted, females of reproductive potential should use effective contraception during treatment and for at least 4 months after the final treatment. Due to lack of data available, belimumab is not currently recommended during pregnancy. If pregnancy occurs during treatment, discontinue therapy and enroll in belimumab pregnancy exposure registry for monitoring purposes.
11. No information is available on the presence of belimumab in human milk, the effect of the drug on the breastfed infant, or the effects of the drug on milk production. In animal

studies, belimumab was detected in the milk of cynomolgus monkeys. However, animal data may not predict drug levels in human milk. The lack of data during lactation makes it difficult to determine the risk of belimumab to an infant during lactation, therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for belimumab, and any potential adverse effects on the breasted child from belimumab or from the underlying maternal condition.

G. Pharmacokinetics

1. Onset of action
2. B cells: 8 weeks
3. Clinical improvement: 16 weeks
4. Volume of distribution: 5 L
5. Half-life: 19.4 days

H. Adverse Reactions

1. GI: Diarrhea 12%; nausea 15%; viral gastroenteritis 3%
2. Hypersensitivity reaction 13%
3. Infection: 71% to 82%, serious infection 6%; Influenza 5%
4. Nervous system: Psychiatric disturbance 16%; serious <1%; Anxiety 4%, depression 5% to 6%; headache ≥3%, insomnia 6%to 7%; migraine 5%; suicidal ideation ≤1%; suicidal tendencies ≤1%
5. Infusion related reaction 17%; injection site reaction 6%; Limb pain 6%
6. Dermatologic: Dermatological reaction ≥3%
7. Genitourinary: Cystitis 4%; UTI >5%
8. Hematologic: Leukopenia 4%
9. Respiratory: Bronchitis 9%; nasopharyngitis 9%, pharyngitis 5%; sinusitis >5%, URTI >5%
10. Miscellaneous: Fever 10%

I. Drug Interactions: No formal drug interactions studies have been performed with belimumab and the effect of belimumab on the pharmacokinetics of other drugs has not been evaluated. Concomitant use of mycophenolate, cyclophosphamide, azathioprine, methotrexate, antimalarials, NSAIDS, aspirin, and/or HMG-CoA reductase inhibitors did not significantly influence belimumab pharmacokinetics. Coadministration of steroids and angiotensin-converting enzyme (ACE) inhibitors resulted in increased clearance of belimumab but this was not clinically significant. Due to lack of data, concomitant use of belimumab and live vaccines and other biologics is not recommended.

IV. ADMINISTRATIVE GUIDELINES

A. Administration- IV infusions should be given immediately after reconstitution and dilution. Use within 4 hours of preparation per current USP Immediate-Use Guidelines. **Administer using a line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron**).

1. Do not co-administer in the same IV line with other agent.

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:
   1. Alcohol Swabs
   2. Gloves
   3. Dressing change kit
   4. IV Pole
   5. IV Start Kit
   6. Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾" for patients needing peripheral access)
   7. Port access needle (ex. 22 Gauge x ¾ to 1" safe step for patients with a port)
   8. Tape
   9. Extension set 8"
   10. IV injection cap
   11. IV administration set (flow regulator [ex: dial-a-flow] or gravity) with in-line or add-on **0.22 micron filter**
   12. Syringes (3-10mL) with needles (20 G x 1")
   13. Sharps container

B. Supplies if utilizing a pole mounted ambulatory infusion pump:
   1. Ambulatory pump tubing with **0.22 micron filter**
   2. Pole mounted ambulatory pump
   3. Batteries for ambulatory pump (Ex: 9 Volt Duracell battery or 4 Double A batteries)
   4. Battery change procedure teaching sheet
   5. Continuous delivery mode teaching sheet
   6. Pump return box

C. Prescription items:
   1. Belimumab vials
   2. Sterile Water for Injection, USP (for reconstitution)
   3. 250mL bag of 0.9% Sodium Chloride for Injection, USP (for dilution) OR for patients whose body weight is $\leq$ 40 kg, a 100mL bag of 0.9% Sodium Chloride for Injection, USP may be used as long as the resulting concentration in the infusion bag does not exceed 4mg/Ml

D. How Supplied: Belimumab for injection is a sterile, white to off-white, preservative-free lyophilized powder in a single-dose vial for reconstitution and dilution prior to IV infusion. It is supplied as 120 mg and 400 mg per vial and requires reconstitution with Sterile Water for Injection, USP (1.5 mL and 4.8 mL, respectively) to obtain a final concentration of 80mg/mL.

E. Storage and Handling: Refrigerate vials at 36°F to 46°F (2°C to 8°C) in original carton and protected from light. Do not freeze. Avoid exposure to heat.

F. Compatibility:

   1. Compatible with: 0.9% Sodium Chloride Injection, USP, 0.45% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP
   2. Compatible with polyvinylchloride (PVC) or polyolefin bags
   3. Incompatible with Dextrose intravenous solutions

G. Procedures:

1. Explain the reasoning for visit and use of belimumab.
2. Don gloves.
3. Establish venous access prior to preparation of drug.
4. Counsel patient on warnings, precautions, and potential side effects including but not limited to: Infusion site reactions, nausea, diarrhea, fever, nasopharyngitis, bronchitis, insomnia, leg or arm pain, depression, headache (migraine)
5. Prepare Product:
    a. Remove belimumab vial from the refrigerator and allow to stand for 10 to 15 minutes for the vial to reach room temperature.
    b. Reconstitute the belimumab powder with Sterile Water for Injection, USP as follows: 120mg vial with 1.5mL Sterile Water for Injection OR 400mg vial with 4.8mL Sterile Water for Injection. The stream of sterile water should be directed toward the side of the vial to minimize foaming.
    c. Swirl the vial gently for 60 seconds every 5 minutes until the powder is dissolved. *DO NOT SHAKE.* May take up to 10-30 minutes to fully dissolve.
    d. From a 250mL (or 100mL) stock bag of 0.9% Sodium Chloride Injection, USP, withdraw and discard a volume equal to the volume of the reconstituted solution of belimumab required for the patient's dose. Maximum concentration in the infusion bag not to exceed 4mg/mL.
    e. Add the required volume of the reconstituted solution of belimumab into the intravenous infusion bag and gently invert the bag to mix the intravenous infusion solution.
    f. Visually inspect the infusion bag for particulate matter and discoloration prior to administration.
6. Infusion Rates
    a. Administer over a period of 1 hour
    b. The infusion rate may be slowed or interrupted if the patient develops in infusion reaction.
7. Post infusion monitoring- Monitor patient and vital signs periodically during the infusion and 30 minutes after the infusion is complete per CarepathRx Nursing Best Practice Administration Guidelines.

VI. CLINICAL MONITORING

A. Prior to therapy
1. Baseline CBC and CMP
2. Baseline autoantibody levels
3. Baseline IgG level
4. Baseline ESR
5. No current, active infections
6. Psychiatric condition
7. Assessment if patient is up to date on vaccinations

B. During therapy
1. Signs and symptoms of infection
2. New or worsening depression and/or suicidal ideation or behavior
3. Signs and symptoms of hypersensitivity reactions and/or infusion related reactions

4. Monitor for efficacy and disease severity including:
    a. Malar or discoid rash
    b. Photosensitivity
    c. Oral ulcers
    d. Serositis
    e. Arthritis
    f. Renal disorders
    g. Neurological disorders- seizures
    h. Hemolytic anemia
    i. Anti-nuclear antibodies
    j. Laboratory assessment- CBC, ESR, BUN/Creatinine, and LFTs
    k. Disease specific assessment questions to monitor response to treatment and progression

Please refer to the package insert for the most up to date guidance on this medication.

REFERENCES:

Benlysta [package insert]. Philadelphia, PA: GlaxoSmithKline, LLC; 2022.

Fernando, MMA and Isenberg DA. Clinical presentation and monitoring of lupus nephritis. *Annals of the Rheumatic Diseases* 2005;64**:**524-527.

Belimumab. [updated 2023 Jul 10; cited 2023 Aug 27]. In: Lexi-Drugs. Lexicomp Online [Internet]. Available from http://online.lexi.com

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

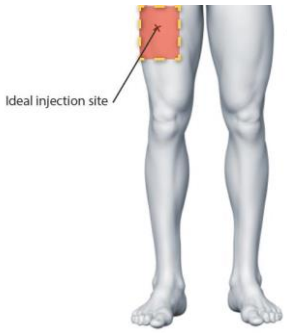
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampul use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampul of epinephrine

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.