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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.

CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

Guidelines for Outpatient Rituxan (Rituximab) and its Biosimilars Therapy

Section: Clinical Guidelines
Compliance: Infusion Pharmacy
ACHC Standards: N/A
URAC Standards: N/A
TJC Standards: N/A
Policy ID: NUR259
Effective: 2/13/23
Reviewed:
Revised:
Approved by: Kathleen Patrick, President, 2/13/23

I. BACKGROUND

Rituxan (Rituximab) is a monoclonal antibody that targets CD20 which regulates cell cycle initiation. It is used in the treatment of rheumatoid arthritis, non-Hodgkin lymphoma (NHL), chronic leukemia, and a multitude of other rheumatic disease states. Rituximab binds to the CD20 antigen on the cell surface of B-lymphocytes, activating complement-dependent B-cell cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity. Signs and symptoms of treated autoimmune disorders are reduced by targeting B-cells and the progression of structural damage is delayed. The following outlines the procedures for servicing patients in need of outpatient Rituximab and biosimilar infusions.

Biosimilars: A biosimilar product is highly similar and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from an existing FDA-approved reference product. The manufacturer of a proposed biosimilar product generates data comparing the proposed product to the FDA-approved reference product to demonstrate biosimilarity. A manufacturer that shows its proposed biosimilar product is highly similar may rely in part on FDA's previous determination of safety and effectiveness for the reference product for approval. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients. Biosimilar products may have different inactive or excipient ingredients than the reference product.

Multiple biosimilars for Rituximab are available in the United States (i.e. Ruxience (rituximab-pvvr), Truxima (rituximab-abbs), and Riabni (rituximab-arrx). When dispensing biosimilar products, the four letter suffix (ex: rituximab-**abbs**) must be present after the generic drug name to distinguish which biosimilar product is dispensed. Truxima (rituximab-abbs) is the only biosimilar product that has a labeled indication for rheumatoid arthritis (RA).

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. All patients will be required to receive a first dose of rituximab in a controlled setting due to the high incidence of infusion and anaphylaxis reactions.

C. The decision to administer subsequent doses 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. Patient has a diagnosis of RA or other autoimmune disease state - ***Only patients with RA or autoimmune diagnoses are eligible for home treatment***
    5. Documentation of first dose tolerated in a controlled setting.
    6. Other relevant social and/or medical history

D. Physician orders for Rituximab must include:
    1. Patient height, weight, and BSA
    2. Drug and dose
    3. Route of administration
    4. Frequency of administration
    5. Orders for pre-medications
    6. Line care protocol
    7. Routine lab monitoring, if applicable

E. Baseline labs or tests prior to starting therapy.
    1. CBC, platelet, and CMP
    2. Hepatitis B virus (HBV) screening

F. Vaccination status – Ensure patients are up to date on vaccinations. If possible, the patient should be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Rituximab.

G. For subsequent infusions in the home setting, dispensing pharmacy treatment protocol for anaphylaxis will be instituted unless a more comprehensive patient-specific orders are provided by physician. See policy NUR012 (Appendix A).

III. PHARMACOLOGY OVERVIEW

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

A. Indications and Dosing
    1. **Only autoimmune/inflammation related indications are covered for the purpose of this guideline*

FDA labeled indication	Induction Dosing	Maintenance Dosing	Prophylactic Pre-Medication Recommendations

Rheumatoid Arthritis	No induction phase	Administer 1000mg on day 1 and day 15. Can repeat dosing every 6 months but no sooner than 16 weeks.	Antihistamine, Acetaminophen, and Methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion
Granulatosis with polyangiitis (GPA) and Microscopic polyangiitis (MPA) in adults*	375mg/m^2 once weekly for 4 weeks Alt: 1 gram every 2 weeks for 2 doses	Administer 500 mg on day 1 and 15; followed by 500 mg every 6 months based but no sooner than 16 weeks after induction phase Alt: 500 mg every 6 months starting 16 weeks after induction	
GPA and MPA in pediatrics (2 years old and older) *	375mg/m^2 once weekly for 4 weeks	Administer 250 mg/m^2 on day 1 and 15; followed by 250/m^2 mg every 6 months based but no sooner than 16 weeks after induction phase	
Pemphigus vulgaris (PV)*	Administer 1000mg on day 1 and day 15	Administer 500mg at month 12 and every 6 months thereafter. Do not administer sooner than 16 weeks following previous infusion	

*PCP prophylaxis is **recommended** for patients with GPA and MPA during treatment and for at least 6 months following the last Rituximab infusion. PCP prophylaxis should be **considered** for patients with PV during and following Rituximab treatment.

B. Contraindications
    1. There are no contraindications listed in the manufacturer's US labeling.

C. Warnings and Precautions
    1. Infusion Reactions
        a. Rituximab can cause severe, including fatal, infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes. Rituximab-induced infusion-related reactions and sequelae include urticaria,

hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

b. Premedicate patients with an antihistamine, acetaminophen, and methylprednisolone 100 mg intravenously or its equivalent 30 minutes prior to each infusion. Institute medical management for infusion-related reactions as needed. Depending on the severity of the infusion-related reaction and the required interventions, consider temporarily or permanently discontinuing Rituximab. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved.

2. Severe Mucocutaneous Reactions
    a. Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of Rituximab exposure. Discontinue Rituximab in patients who experience a severe mucocutaneous reaction. The safety of re-administration of Rituximab to patients with severe mucocutaneous reactions has not been determined.
3. Hepatitis B Virus (HBV) Reactivation
    a. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including Rituximab. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).
    b. Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with Rituximab. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during Rituximab treatment.
    c. In patients who develop reactivation of HBV while on Rituximab, immediately discontinue Rituximab and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming Rituximab treatment in patients who develop HBV reactivation. Resumption of Rituximab treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.
4. Progressive Multifocal Leukoencephalopathy (PML)
    a. John Cunningham (JC) virus infection resulting in PML and death can occur in Rituximab -treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received Rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of Rituximab.
5. Tumor Lysis Syndrome (TLS)
    a. Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, sometimes fatal, can occur within 12-24 hours after the first infusion of Rituximab in patients with NHL. A high number of

circulating malignant cells (greater than or equal to 25,000/mm 3) or high tumor burden, confers a greater risk of TLS.

6. Infections
    a. Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of Rituximab -based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia greater than 11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue Rituximab for serious infections and institute appropriate anti-infective therapy. Rituximab is not recommended for use in patients with severe, active infections.
7. Cardiovascular Adverse Reactions
    a. Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur in patients receiving Rituximab. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of Rituximab for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.
8. Renal
    a. May cause fatal renal toxicity in patients with non-Hodgkin lymphomas (NHL). Patients who received combination therapy with cisplatin and rituximab for NHL experienced renal toxicity during clinical trials; this combination is not an approved treatment regimen. Renal toxicity also occurred due to tumor lysis syndrome.
9. Bowel Obstruction and Perforation
    a. Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving Rituximab in combination with chemotherapy. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.
10. Immunization
    a. In the oncology setting, live vaccines should not be given immediately before or during rituximab treatment; the safety of live vaccines following rituximab treatment has not been studied. For non-live vaccines, administer vaccines at least 4 weeks prior to initiating a rituximab course of therapy. Response to some immunizations may be lower in some patients receiving rituximab. For patients treated with Rituximab, physicians should review the patient's vaccination status. If possible, the patient should be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating Rituximab.
11. Embryo-Fetal Toxicity
    a. Based on human data, Rituximab can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving Rituximab and for 12 months after the last dose
12. Concomitant Use with Other Biologic Agents and DMARDS other than Methotrexate in RA, GPA and MPA, PV
    a. Limited data are available on the safety of the use of biologic agents or disease modifying antirheumatic drugs (DMARDs). Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not been studied in GPA or MPA or PV patients exhibiting peripheral B-cell depletion following treatment with Rituximab.

13. Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists
    a. The use of Rituximab in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended.

D. Pharmacokinetics
    1. Vd ~ 3.1 L
    2. Half-life ~ 18-26 days

E. Adverse Reactions
    1. >10%:
        a. Cardiovascular: Cardiac disorder, flushing, hypertension, peripheral edema
        b. Dermatologic: Night sweats, pruritus, skin rash
        c. Endocrine & metabolic: Hypophosphatemia, weight gain
        d. Gastrointestinal: Abdominal pain, diarrhea, nausea
        e. Hematologic & oncologic: Anemia, febrile neutropenia, hypogammaglobulinemia, leukopenia, lymphocytopenia, neutropenia, thrombocytopenia
        f. Hepatic: Hepatobiliary disease, increased serum alanine aminotransferase
        g. Hypersensitivity: Angioedema
        h. Immunologic: Antibody development
        i. Infection: Bacterial infection and viral infection
        j. Nervous system: Chills, fatigue, headache, insomnia, pain, peripheral sensory neuropathy
        k. Neuromuscular & skeletal: Arthralgia, asthenia, muscle spasm
        l. Respiratory: Bronchitis, cough, epistaxis, nasopharyngitis, pulmonary disease, pulmonary toxicity, rhinitis, upper respiratory tract infection
        m. Miscellaneous: Fever, infusion related reaction
    2. <10%:
        a. Cardiovascular: Chest tightness, hypotension, significant cardiovascular event
        b. Dermatologic: Urticaria
        c. Endocrine & metabolic: Hyperglycemia, hyperuricemia, increased lactate dehydrogenase
        d. Gastrointestinal: Dyspepsia, oral candidiasis, upper abdominal pain, vomiting
        e. Genitourinary: Urinary tract infection
        f. Hematologic & oncologic: Hemolytic anemia, pure red cell aplasia
        g. Hepatic: Exacerbation of hepatitis B
        h. Infection: Fungal infection, viral infection
        i. Nervous system: Anxiety, dizziness, migraine, paresthesia, rigors
        j. Neuromuscular & skeletal: Back pain, myalgia
        k. Respiratory: Bronchospasm, dyspnea, sinusitis, throat irritation

F. Drug Interactions
    1. Concurrent use with other immunosuppressants result in increased immunosuppression and an increased risk of infection.

IV. ADMINISTRATIVE GUIDELINES

A. Administration- IV infusions should be given immediately after dilution. Use within 1 hour of preparation per current USP Immediate-Use Guidelines. **No filter needed for administration.**

B. Patients must receive their first infusion in a controlled setting. All patients will require an anaphylaxis kit in the home for subsequent infusions due to the risk of serious infusion reactions.

C. Do not mix or dilute with other drugs.

D. Interrupt the infusion or slow the infusion rate for infusion-related reactions. Continue the infusion at one-half the previous rate upon improvement of symptoms.

E. **Only patients with RA or autoimmune diagnoses are eligible for home treatment.**

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:
1. Alcohol Swabs
2. Gloves
3. Dressing change kit
4. Tape
5. Port Access Needle (Ex: 22 Gauge x ¾" Safe-step)
6. IV injection cap
7. Dressing change kit
8. Administration tubing
9. Extension set 8"
10. IV start kit for peripheral line
11. IV peripheral catheter (Ex: 24 Gauge x ¾" or 22 Gauge x 1")
12. Pole mounted infusion pump
13. IV pole and pole clamp
14. Batteries for pump administration
15. Syringes (10mL) with needles
16. Sharps container

B. Prescription Supplies
1. rituximab vials
2. 250mL NS or 250mL of D5W
3. NS or D5W flushes

C. How Supplied
1. Rituximab and its biosimilars are supplied as a sterile, preservative-free, clear to opalescent, colorless to pale yellow solution as a 10 mg/mL single-use vial in a 10mL and 50mL single-use vial.

D. Storage and Handling
1. Rituximab and its biosimilars should be kept refrigerated at 2°C to 8°C (36°F to 46°F) and protected from direct sunlight. Do not freeze or shake.

E. Compatibility
1. Compatible in D5W or NS

F. Procedures: Preparation of product, Infusion rates, post infusion monitoring time.
1. Explain the reasoning for visit and use of Rituximab.
2. Don gloves.
3. Establish venous access prior to preparation of drug.
4. After establishing access, it is recommended to premedicate with acetaminophen,

antihistamine, and 100 mg of methylprednisolone or equivalent glucocorticoid 30 minutes prior to the rituximab infusion.

5. Counsel patient on warnings, precautions, and potential side effects including but not limited to infusion-related reactions, TLS, PML, infections, renal toxicity, cardiac adverse effects, and bowel obstruction.
6. Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use vial if particulates or discoloration is present.
7. Withdraw the necessary amount of Rituximab from vial and transfer to an appropriate amount of 0.9% sodium chloride or D5W bag for dilution to provide a final concentration of 1 to 4 mg/mL
8. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Attach pump tubing to compounded product bag and prime tubing. Infuse via electric pump.
9. Infusion Rates
    a. First Infusion: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
    b. Subsequent infusions: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
    c. Slow, interrupt, or discontinue infusion if a reaction develops. Resume at 50% of the previous rate upon improvement of symptoms.
10. Monitor patient and vital signs periodically during the infusion and for 30 minutes after the completion of the infusion per INS guidelines

VI. CLINICAL MONITORING

A. Prior to therapy:
    1. Hep B screening
    2. TB screening
    3. CBC with platelets, CMP
    4. Pregnancy status
    5. Ensure patient is up to date on vaccines

B. During therapy:
    1. Assessment of signs/symptoms of adverse effects:
        a. Mucocutaneous reactions
        b. Hepatitis B virus reactivation
        c. Tumor lysis syndrome
        d. Active infection
        e. Renal toxicity
        f. Progressive Multifocal Leukoencephalopathy (PML)
        g. Cardiac adverse effects- MI, arrhythmias, and angina
        h. Bowel obstruction and perforation
    2. Monitor for infusion related reactions and adjust infusion accordingly. Premedication is recommended to limit infusion reactions.
    3. Monitor necessary lab work including LFTs for Hepatitis and Hepatitis B Virus reactivation, electrolytes for tumor lysis syndrome, BUN/ creatinine for renal toxicity, and CBC/ WBC to monitor for active infection.
    4. Rituximab can cause fetal harm. Advise females of reproductive age of potential risks and to use effective contraception while receiving rituximab and for 12 months after the last dose.

5. Labs:
    a. CBC with differential and platelet counts at two to four month intervals, CMP periodically throughout therapy

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

REFERENCES:

Rituxan [package insert]. San Francisco, CA. Genetech, Inc; 2019.

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

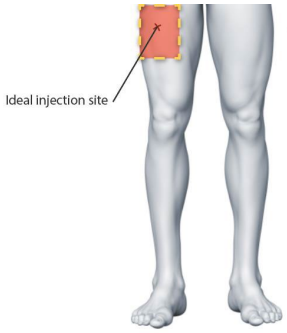
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampule use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampule of epinephrine

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.