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CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

GUIDELINES FOR CRIZANLIZUMAB-TMCA (ADAKVEO)

Section: Clinical Guidelines
Compliance: Infusion Pharmacy
ACHC Standards: N/A
URAC Standards: N/A
TJC Standards: N/A
Policy ID: NUR257
Effective: 2/13/22
Reviewed:
Revised:
Approved by: Kathleen Patrick, President, 2/13/22

I. BACKGROUND

Crizanlizumab-tmca (Adakveo) is a humanized IgG_2 kappa monoclonal antibody used to reduce the frequency of vascular-occlusive crises in adults and pediatric patients (≥ 16 years of age) with confirmatory sickle cell disease. Crizanlizumab-tmca binds to P-selectin (a mediator for red blood cell aggregation) and blocks its interaction with several ligands. Crizanlizumab-tmca may prevent the cascade of vascular-occlusive crises, decrease platelet aggregation, maintain proper blood flow, and reduce sickle cell-related painful episodes that require hospitalization. Crizanlizumab-tmca is not a cure for sickle cell disease. Maintenance dosing, with or without hydroxyurea, is 5mg/kg (actual body weight) via IV infusion every 4 weeks. The following outlines the procedures for servicing patients in need of outpatient crizanlizumab-tmca 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. 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. Ability to secure contracted nursing for subsequent infusions.
   5. Other relevant social and/or medical history

C. Physician orders for crizanlizumab-tmca must include:
   1. Drug and dose
   2. Patient weight and weight based dosing
   3. Route of administration
   4. Frequency of administration
   5. Line care protocol

6. Orders for pre-medications
7. Emergency medications per protocol
8. Routine lab monitoring, if applicable

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

E. Crizanlizumab-tmca should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

III. PHARMACOLOGIC OVERVIEW

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

A. Indications:
   1. Indicated to reduce the frequency of vasoocclusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

B. Dosing: 5 mg/kg by intravenous infusion at Week 0, Week 2, and every 4 weeks thereafter
   1. These doses have not been studied in extremes of body weight.

C. Contraindications: None

D. Warnings and Precautions
   1. Infusion Reactions
      a. If mild to moderate infusion reactions are noted, then temporarily interrupt or slow the rate of infusion to manage signs and symptoms
      b. Consider premedication(s) and/or reduced infusion rate with further infusions
      c. In the event of a severe infusion reaction then discontinue crizanlizumab and manage signs and symptoms as necessary
      d. Crizanlizumab-tmca may need to be discontinued permanently in this situation

   2. Laboratory test interference
      a. Interference with automated platelet counts has been observed following the administration of crizanlizumab-tmca. Specifically, when blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA)

E. Pharmacokinetics
   1. Volume of distribution: 4.26 L
   2. Half-life: 11.2 days

F. Adverse Reactions
   1. The most common reported adverse drug reactions (>10%) include arthralgia, nausea, back pain, and pyrexia.

G. Drug Interactions
   1. Crizanlizumab-tmca may interfere with automated platelet counts (platelet clumping) particularly with blood samples in tubes containing ethylenediaminetertraacetic acid (EDTA); platelet count may be inconclusive or falsely low.

a. Collect samples in citrate-containing tubes and run samples within 4 hours of collection.

IV. ADMINISTRATIVE GUIDELINES

A. Administration: IV infusions should be given immediately after reconstitution and dilution. Use within 1 hour of preparation per current USP Immediate-Use Guidelines. **Administer with a non-pyrogenic 0.2-micron in-line filter.**

B. Duration: indefinitely unless un-tolerable adverse effects or decreased efficacy

C. Dose Adjustment
   1. If a dose is missed, administer crizanlizumab-tmca as soon as possible
   2. If crizanlizumab-tmca is administered within 2 weeks after the missed dose, continue dosing according to the patient's original schedule
   3. If crizanlizumab-tmca is administered more than 2 weeks after the missed dose, continue dosing every 4 weeks thereafter
   4. Currently, there are no dosage adjustments for renal or hepatic impairment

D. Do not mix or co-administer with other drugs through the same intravenous line.

E. After the infusion is complete, flush the line with ≥ 25ml of NS or D5W.

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:
   1. Alcohol swabs
   2. Gloves
   3. Tape
   4. Peripheral start kit
   5. Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾" for patients needing peripheral access)
   6. Dressing change kit
   7. Port access needle (ex. 22 Gauge x ¾ to 1" safe step for patients with a port)
   8. Extension set 8"
   9. IV injection cap
   10. Luer Lock Syringe (5mL-60mL depending on volume of drug needed)
   11. Needles (ex: 18 gauge x 1")
   12. IV administration set (dial-a-flow or gravity) with an in-line or add-on 0.2 micron filter
   13. IV pole
   14. Sharps container

B. Prescription Items
   1. Vial(s) of crizanlizumab-tmca
   2. 100mL bag of 0.9% Sodium chloride or 5% Dextrose Injection
   3. 25 mL bag of D5W or NS for flushing

C. How Supplied: crizanlizumab-tmca injection is a sterile, clear to opalescent, colorless to slightly brownish-yellow solution for intravenous infusion supplied as:
   1. Carton containing one 100 mg/10 mL (10 mg/mL) single-dose vial

D. Storage and Handling:

1. Store and transport vials at 36 F to 46 F (refrigerated)
2. Do NOT freeze
3. Do NOT shake
4. Store in original carton to protect from light

E. Compatibility: Compatible with 0.9% Sodium chloride and 5% Dextrose in Water injection

F. Procedures:
   1. Explain the reasoning for visit and use of crizanlizumab-tmca
   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:
      a. Infusion related reactions
      b. Arthralgia
      c. Pyrexia
      d. Nausea
   5. Prepare Product
      a. Bring vials to room temperature for a minimum of 30-60 minutes and maximum of 4 hours prior to the start of preparation (piercing the first vial)
      b. Calculate the dose (mg) and the total volume (mL) of crizanlizumab-tmca solution required, and the number of crizanlizumab-tmca vials needed based on the patient's actual body weight according to the following equation:

$$\text{Volume (mL)} = \frac{\text{(patient's body weight (kg))} \times \text{(prescribed dose 5 mg/kg)}}{\text{(Concentration of crizanlizumab-tmca 10 mg/mL)}}$$

      c. One vial is needed for every 10 mL of crizanlizumab-tmca which was determined from the calculation above.
      d. Visually inspect the vials for particulate matter and discoloration. Do not use product if solution is cloudy, discolored, or contains particulate matter. Crizanlizumab-tmca is clear to opalescent, colorless or may have a slightly brownish-yellow tint
      e. Obtain a 100 mL 0.9% Sodium Chloride Injection or 5% Dextrose Injection infusion bag/container - infusion bags/containers must be made of either polyvinyl chloride (PVC), polyethylene (PE), or polypropylene (PP)
      f. Remove a volume of 0.9% Sodium Chloride Injection or 5% Dextrose Injection from the infusion bag/container that is equal to the required volume of crizanlizumab-tmca solution
      g. Withdraw the necessary amount of crizanlizumab-tmca solution and dilute by adding to the infusion bag/container containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection
      h. The volume of crizanlizumab-tmca added to the infusion bag/container should NOT exceed 96 ml
      i. Gently invert the infusion bag to mix the diluted solution. DO NOT SHAKE Single-dose vials. Discard unused portion.
   6. Administer crizanlizumab-tmca diluted solution by intravenous infusion over a period of 30 minutes through an intravenous line, which must contain a **sterile, non-pyrogenic 0.2-micron inline filter.**
   7. After administration of crizanlizumab-tmca, flush the line with at least 25 mL of 0.9% sodium chloride or 5% dextrose injection.
   8. Monitor patients and vital signs periodically throughout infusion and for 30 minutes following the infusion

VI. CLINICAL MONITORING

A. Follow up pharmacy assessment will include:
    1. Assessment of signs and symptoms of adverse effects
    2. Update on previous infusion and if patient experienced an infusion reaction. Infusion reactions may include pain in multiple areas (e.g., oropharyngeal pain), fever, chills, pruritus, rash, bronchospasm, throat irritation, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, headache, dizziness, nausea, vomiting, diarrhea, fatigue, sweating, or tachycardia. Inform patients that infusion reactions can occur up to 24 hours after the infusion.

B. Monitor for frequency and severity of vascular-occlusive occurrences.

C. Counsel patients to report any new signs and/or symptoms along with infusion related reactions.

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

REFERENCES

ADVAKEO [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2019.

ADVAKEO. Lexi-Drugs. Lexi-Comp Online. Hudson, OH: Lexicomp; 2022. Accessed 03/25/22.

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

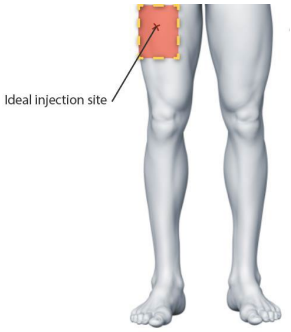
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampul use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1")
    d. 1 ampul of epinephrine

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.