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Specialty Pharmacy & Infusion Solutions

CLINICAL GUIDELINES FOR INTRAVENOUS ECULIZUMAB (SOLIRIS) AND RAVULIZUMAB (ULTOMIRIS) THERAPY

Section: Nursing
Compliance: ACHC Infusion Pharmacy
ACHC Standards: N/A
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I. Policy

Eculizumab (Soliris) is a monoclonal antibody used for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), myasthenia gravis (anti-acetylcholine receptor positive), and for neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. Eculizumab specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab inhibits terminal complement-mediated intravascular hemolysis in PNH patients and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS. The precise mechanism by which eculizumab exerts its therapeutic effect in MG and NMOSD patients are unknown, but is presumed to involve the reduction of terminal complement complex C5b-9.

Ravulizumab-cwvz (Ultomiris) is a monoclonal antibody therapy used in the treatment of PNH, aUHS, and myasthenia gravis (anti-acetylcholine receptor positive). Ravulizumab specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b preventing the generation of the terminal complement complex C5b9. Ravulizumab inhibits terminal complement-mediated intravascular hemolysis in patients with PNH and TMA in patients with aHUS.

The following outlines the procedures and protocol for coordination of servicing patients in need of outpatient eculizumab and ravulizumab home infusions.

II. Patient Acceptance/Inclusion 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 following criteria:
    1. Prescriber preference
    2. Allergy profile
    3. Ability to secure contracted nursing for subsequent infusions
    4. Other relevant social and/or medical history

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

C. Healthcare provider with enrollment in REMS program
    1. Prescribers must counsel the patient about the risk of meningococcal infection, provide the patient with REMS educational materials, and ensure the patient is vaccinated with a meningococcal vaccine
    2. Enrollment in the eculizumab REMS and Ravulizumab-cwvz REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) and at www.solirisrems.com or https://ultomirisrems.com/ respectively.

D. Patients must receive meningococcal vaccine at least 2 weeks prior to treatment initiation
    1. If urgent eculizumab or ravulizumab initiation is necessary and <2 weeks after vaccination, provide 2 weeks of antibacterial prophylaxis
    2. To reduce the risk for meningococcal disease, consider antimicrobial prophylaxis with oral antibiotics for the duration of eculizumab or ravulizumab therapy

III. Pharmacology Overview

A. Indications and Dosing
    1. Eculizumab
        a. Adults
            i. PNH
                a) 600 mg weekly for the first 4 weeks, followed by
                b) 900 mg for the fifth dose 1 week later, then
                c) 900 mg every 2 weeks thereafter.
            ii. aHUS, generalized myasthenia gravis, and NMOSD
                a) 900 mg weekly for the first 4 weeks, followed by
                b) 1200 mg for the fifth dose 1 week later, then
                c) 1200 mg every 2 weeks thereafter.
        b. Pediatrics (2 months-17 years)
            i. aHUS
                a) Weight based dosing as follows:

Patient Body Weight	Induction	Maintenance
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2 then 300 mg every 3 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2 then 300 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3 then 600 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3 then 900 mg every 2 weeks
40 kg and over	900 mg weekly x 4 doses	1200mg at week 5; then 1200 mg every 2 weeks

    2. Ravulizumab
        a. Adults
            i. PHN and Myasthenia Gravis
                a) Weight based dosing as follows:

Patient Body Weight	Induction	Maintenance
40 kg to less than 60 kg	2400 mg IV infusion	3000 mg IV infusion every 8 weeks beginning 2 weeks after loading dose
60 kg to less than 100 kg	2700 mg IV infusion	3300 mg IV infusion every 8 weeks beginning 2 weeks after loading dose
100 kg or greater	3000 mg IV infusion	3600 mg IV infusion every 8 weeks beginning 2 weeks after loading dose

ii. aHUS

a) Weight based dosing as follows

Patient Body Weight	Induction	Maintenance
20 to less than 30 kg	900 mg IV infusion	2100 mg 2 weeks after loading dose then every 8 weeks
30 to less than 40 kg	1200 mg IV infusion	2700 mg 2 weeks after loading dose then every 8 weeks
40 to less than 60 kg	2400 mg IV infusion	3000 mg 2 weeks after loading dose then every 8 weeks
60 to less than 100 kg	2700 mg IV infusion	3300 mg 2 weeks after loading dose then every 8 weeks
100 kg or greater	3000 mg IV infusion	3600 mg 2 weeks after loading dose then every 8 weeks

b. Pediatrics (≥ 1 month old)

i. aHUS

a) Weight based dosing as follows

Patient Body Weight	Induction	Maintenance
5 kg to less than 10 kg	600 mg IV infusion	300 mg 2 weeks after loading dose then every 4 weeks
10 kg to less than 20 kg	600 mg IV infusion	600 mg 2 weeks after loading dose then every 4 weeks
20 kg to less than 30 kg	900 mg IV infusion	2100 mg 2 weeks after loading dose then every 8 weeks
30 kg to less than 40 kg	1200 mg IV infusion	2700 mg 2 weeks after loading dose then every 8 weeks
40 kg to less than 60 kg	2400 mg IV infusion	3000 mg 2 weeks after loading dose then every 8 weeks
60 to less than 100 kg	2700 mg IV infusion	3300 mg 2 weeks after loading dose then every 8 weeks
100 kg or greater	3000 mg IV infusion	3600 mg 2 weeks after loading dose then every 8 weeks

c. Switching from eculizumab, administer loading dose 2 weeks after last eculizumab infusion, then administer maintenance doses once every 8 weeks, starting 2 weeks after the loading dose

B. Contraindications

1. Unresolved serious Neisseria meningitidis infection
2. Patients not currently vaccinated against Neisseria meningitidis (unless risks of treatment delay outweigh risk of developing a meningococcal infection)

C. Warnings and Precautions
    1. Infections
        a. Serious infections with Neisseria species (other than N. meningitides), including disseminated gonococcal infections, have been reported
        b. In addition to meningitis, the risk of other infections, especially with encapsulated bacteria (e.g., Streptococcus pneumoniae, H. influenzae) is increased – ensure patient is up to date with vaccinations per CDC guidelines
        c. Fungal infections can also occur in immunocompromised patients receiving these medications
    2. Hypersensitivity reactions
        a. Infusion reactions: Infusion reactions, including anaphylaxis or hypersensitivity, may occur; interrupt infusion for severe reaction (e.g., cardiovascular instability, respiratory compromise).

D. Pharmacokinetics
    1. Distribution: 5-8 L
    2. Half-life elimination: ~ 270 to 414 hours (during plasma exchange the half-life is reduced to 1.26 hours)

E. Adverse reactions
    1. Infusion reactions
    2. Infection
    3. Hypertension
    4. Bruising
    5. Nausea/vomiting, diarrhea
    6. Anemia, leukopenia
    7. Headache, back ache
    8. Insomnia
    9. Nasal congestion, nasopharyngitis
    10. Fever

F. Drug interactions
    1. Avoid concurrent use of potent immunosuppressants due to increased risk for infection

IV. Administration Guidelines

A. Preparation
    1. Eculizumab
        a. Dilute required dose to a final concentration of 5 mg/mL by adding to an appropriate amount of 0.9% Normal saline solution

b. Diluent and final infusion volumes are as follows

Eculizumab Dose	Diluent Volume to Add	Final Infusion Volume
300 mg	30 mL	60 mL
600 mg	60 mL	120 mL
900 mg	90 mL	180 mL
1200 mg	120 mL	240 mL

c. Dispensing pharmacy will provide prefilled bags or the nurse will need to remove saline from a stock bag, so the final concentration is 5mg/mL. Exact final infusion volumes are seen in above chart.
d. Draw up eculizumab dose from vials and inject into saline bag
e. Gently invert bag to mix. Do not shake.
f. Discard any portion of unused drug from vial
g. Allow time for infusion to get to room temperature prior to administering the infusion

1. Ravilizumab
   a. Do not mix 100 mg/mL and 10 mg/mL vials together
   b. Dilute 10mg/mL vials to a final concentration of 5 mg/mL by adding to an appropriate amount of Normal saline and dilute 100mg/mL vials to a final concentration of 50mg/mL by adding to appropriate amount of Normal saline
   c. Diluent and final infusion volumes are as follows

Ravulizumab 10mg/mL vials or subsequent 5mg/mL infusions

Ravulizumab Dose	Diluent Volume to Add	Final Infusion Volume
300 mg	30 mL	60 mL
600 mg	60 mL	120 mL
900 mg	90 mL	180 mL
1200 mg	120 mL	240 mL
2100 mg	210 mL	420 mL
2400 mg	240 mL	480 mL
2700 mg	270 mL	540 mL
3000 mg	300 mL	600 mL
3300 mg	330 mL	660 mL
3600 mg	360 mL	720 mL

Ravulizumab 100mg/mL vials or subsequent 50mg/mL infusions

Ravulizumab Dose	Diluent Volume to Add	Final Infusion Volume
300 mg	3 mL	6 mL
600 mg	6 mL	12 mL
900 mg	9 mL	18 mL
1200 mg	21 mL	42 mL
2100 mg	210 mL	420 mL
2400 mg	240 mL	480 mL
2700 mg	270 mL	540 mL
3000 mg	300 mL	600 mL
3300 mg	330 mL	660 mL
3600 mg	360 mL	720 mL

   d. Dispensing pharmacy will provide prefilled bags, or the nurse will need to remove saline from a stock bag, so the final concentration is 5mg/mL or 50mg/mL. Exact final infusion volumes are seen in above charts.
   e. Draw up Ravulizumab dose from vials and inject into prefilled saline bag

f. Gently invert bag to mix. Do not shake.
g. Discard any portion of unused drug from vial
h. Allow time for infusion to get to room temperature prior to administering the infusion

B. Administration
1. Eculizumab
a. Adults:
i. Administer via IV infusion over 35 minutes via gravity, a syringe-type pump, or an infusion pump; infusion may be slowed or stopped due to adverse reactions. Total infusion time should not exceed 2 hours.
b. Pediatrics:
i. Administer via IV infusion over 1 to 4 hours via syringe-type pump, or an infusion pump
c. Do not administer by IV push or IV bolus injection
d. Monitor patients for 60 minutes after infusion is complete
e. In case of missed dose, administer eculizumab at the recommended dosage regimen time points, or within two days of these time points
f. 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.
2. Ravulizumab
a. Administer via IV infusion **with a 0.22-micron filter**
b. See charts below to determine administration rate via ambulatory pump for larger volumes and Freedom 60 Syringe pump for smaller volumes of 60mL or less:
i. Ravulizumab 5mg/mL infusion loading dose:

Body Weight (kg)	Loading Dose (mg)	Total Volume (mL)	Maximum Infusion Rate (mL/hr)
5 to less than 10	600	120	31
10 to less than 20	600	120	63
20 to less than 30	900	180	120
30 to less than 40	1200	240	184
40 to less than 60	2400	480	252
60 to less than 100	2700	540	317
100 or greater	3000	600	333

ii. Ravulizumab 5mg/mL maintenance dose:

Body Weight (kg)	Maintenance Dose (mg)	Total Volume (mL)	Maximum Infusion Rate (mL/hr)
5 to less than 10	300	6	8
10 to less than 20	600	12	16
20 to less than 30	2100	42	33
30 to less than 40	2700	54	49
40 to less than 60	3000	60	65
60 to less than 100	3300	66	99
100 or greater	3600	72	144

iii. Ravulizumab 50mg/mL infusion loading dose:

Body Weight (kg)	Maintenance Dose (mg)	Total Volume (mL)	Maximum Infusion Rate (mL/hr)
5 to less than 10	300	60	31
10 to less than 20	600	120	63
20 to less than 30	2100	420	127
30 to less than 40	2700	540	192
40 to less than 60	3000	600	257
60 to less than 100	3300	660	330
100 or greater	3600	720	327

iv. Ravulizumab 50mg/mL infusion maintenance dose:

Body Weight (kg)	Loading Dose (mg)	Total Volume (mL)	Maximum Infusion Rate (mL/hr)
5 to less than 10	600	12	8
10 to less than 20	600	12	16
20 to less than 30	900	18	30
30 to less than 40	1200	24	46
40 to less than 60	2400	48	64
60 to less than 100	2700	54	92
100 or greater	3000	60	144

c. Monitor patients for 1 hour after infusion is complete

C. Do not administer if solution is discolored or contains particulate matter

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

E. Dose Adjustment: No dosage adjustment is recommended in patient with renal or hepatic impairment

V. Nursing Procedure

A. Supplies for Infusion

1. Supplies for administration of eculizumab via gravity:
    a. Alcohol swabs
    b. Gloves
    c. Tape
    d. Peripheral start kit
    e. Peripheral IV catheter
    f. Central IV-line kit if patient has a central line with corresponding port access needles if needed
    g. 8” extension set
    h. IV injection cap

i. 35 mL lure lock syringes
j. 18-gauge x 1" needles
k. Gravity Tubing
l. IV pole
m. Sharps container

2. Supplies for administration of eculizumab/ ravulizumab via ambulatory infusion pump:
    a. Alcohol swabs
    b. Gloves
    c. Tape
    d. Peripheral start kit
    e. Peripheral IV catheter
    f. Central IV-line kit if patient has a central line with corresponding port access needles
    g. 8" extension set
    h. IV injection cap
    i. Luer lock Syringes ranging from 5mL-60mL depending on volume of drug needed
    j. 18-gauge x 1" needles
    k. Ambulatory pump tubing with 0.22-micron filter (**ravulizumab requires filter**)
    l. Ambulatory pump
    m. Batteries for ambulatory pump (Ex: 9 Volt Duracell battery or 4 Double A batteries)
    n. Battery change procedure teaching sheet
    o. Continuous delivery mode teaching sheet
    p. Pump return box
    q. IV pole
3. Supplies for administration of ravulizumab via Freedom 60 Syringe Pump
    a. Alcohol swabs
    b. Gloves
    c. Tape
    d. Peripheral start kit
    e. Peripheral IV catheter
    f. Central IV-line kit if patient has a central line with corresponding port access needles
    g. 8" extension set
    h. IV injection cap
    i. Luer lock Syringes ranging from 5mL-60mL depending on volume of drug needed
    j. 18-gauge x 1" needles
    k. Freedom 60 tubing
    l. 0.22-micron filter
    m. Freedom 60 Syringe pump
    n. Freedom 60 syringe pump delivery mode teaching sheet
    o. Pump return box
4. How Supplied:
    a. Eculizumab
        i. Supplied as 300 mg single-use vials containing 30 mL of 10 mg/mL sterile, preservative-free solution
    b. Ravulizumab
        i. Supplied as 300 mg/30 mL (10 mg/mL) single-dose vials containing a clear to translucent, slight whitish color preservative-free, solution

B. Storage and Handling
1. Eculizumab
    a. Vials must be stored in the original carton until time of use under refrigerated conditions at 2-8º C (36-46º F) and protected from light

2. Ravulizumab
    a. Vials must be stored in the original carton until time of use under refrigerated conditions at 2-8º C (36-46º F) and protected from light
    b. Do not freeze
    c. Do not shake

C. Compatibility
1. Eculizumab
    a. Stable in 0.9% Sodium Chloride, D5W, and Lactated Ringers
2. Ravulizumab
    a. Stable in 0.9% Sodium Chloride only

D. Procedures for infusion
1. Explain the reasoning for visit and use of eculizumab or ravulizumab treatment.
2. Establish venous access prior to preparation of drug.
3. Preparation
    a. See Preparation under section IV Administration Guidelines
4. Administration
    a. See Administration under section IV Administration Guidelines
5. Monitoring
    a. During and at least 60 minutes after eculizumab and ravulizumab infusions have completed. RN will need to monitor vitals and for infusion related reactions. Follow up pharmacy assessment will include:
        i. Life-threatening and fatal meningococcal infections have been reported. Monitor patients for infections and specific s/s of meningitis including headache, fever, and stiff neck
        ii. Infusion or hypersensitivity reactions
        iii. Monitor for adverse effects including
            1) Headache
            2) Nasopharyngitis
            3) Nausea/vomiting
            4) Diarrhea
            5) Back ache
            6) Fatigue
            7) Anemia/leukopenia
            8) Active infection
    b. Follow Protocol for Management of Adult Infusion Reactions (Appendix A)

REFERENCES:

1. Soliris [package insert] Boston, MA. Alexion Pharmaceuticals, Inc.; 2020.
2. Ultomiris [package insert] Boston, MA. Alexion Pharmaceuticals, Inc; 2020.

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

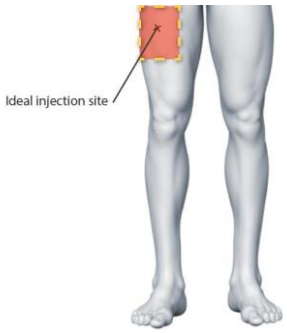
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampul use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampul of epinephrine

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.