CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

CLINICAL GUIDELINES FOR OUTPATIENT ENZYME REPLACEMENT THERAPY

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I. POLICY

The following outlines the procedures for servicing patients in need of enzyme replacement therapy. Enzyme replacement therapy (ERT) is treatment for patients with specific enzyme deficiencies or enzyme malfunctions. The most common method of enzyme replacement therapy is through intravenous infusions. Some disease states requiring ERT include lysosomal storage diseases (e.g., Lysosomal Acid Lipase deficiency), Fabry disease, Gaucher disease, and Pompe (glycogen storage) disease. ERT is not a cure for these disease states and requires lifelong therapy

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 following intake components will be needed to service a patient needing ERT therapy:
   1. Valid prescription order for ERT. Orders must include the following:
      a. Patient weight for weight based ERT
      b. Drug and dose (weight-dosing for weight-based ERT)
      c. Route of administration
      d. Frequency of administration
      e. Emergency medication orders
      f. Pre-medications, if applicable
      g. Line care protocol
   2. Reimbursement/insurance information
   3. Clinical documentation and past medical history

C. 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 old

4. Ability to secure contracted nursing for ongoing treatments, if required and/or applicable.
5. Other relevant social and/or medical history

D. 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.

Enzyme replacement therapy for Lysosomal disorders or Mucopolysaccharidoses (MPS).

A. Mucopolysaccharidoses comprise a group of lysosomal storage disorders caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG). MPS is generally diagnosed within the first decade of life starting around the first year of life. Different MPS disorders can have different clinical manifestations including developmental delays, skeletal and joint abnormalities, corneal clouding, neurologic decline, aggressive behavior, and death.

B. Indications
   1. MPS I
      a. Laranidase is indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established. Laranidase has been shown to improve pulmonary function and walking capacity. The rationale of Laranidase therapy in MPS I is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of GAG.
   2. MPS II
      a. Hunter syndrome (Mucopolysaccharidosis II, MPS II) is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme iduronate-2-sulfatase. This enzyme cleaves the terminal 2-O-sulfate moieties from the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. Due to the missing or defective iduronate-2-sulfatase enzyme in patients with Hunter syndrome, GAG progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. Idursulfase is intended to provide exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to the M6P receptors on the cell surface, leading to cellular internalization of the enzyme, targeting to intracellular lysosomes and subsequent catabolism of accumulated GAG.
   3. MPS III
      a. Intrathecal ERT for MPS IIIA was ineffective in clinical trials. Early-phase trials for MPS IIIB using IV- or intracerebroventricular (ICV)-delivered ERT are underway. Intrathecal therapy remains experimental.

4. MPS IVA
    a. Mucopolysaccharidosis IVA (MPS IVA, Morquio A Syndrome) is characterized by the absence or marked reduction in N-acetylgalactosamine-6-sulfatase activity. The sulfatase activity deficiency results in the accumulation of the GAG substrates, KS and C6S, in the lysosomal compartment of cells throughout the body. The accumulation leads to widespread cellular, tissue, and organ dysfunction. Elosulfase alpha is intended to provide the exogenous enzyme N-acetylgalactosamine-6-sulfatase that will be taken up into the lysosomes and increase the catabolism of the GAGs KS and C6S. Elosulfase alfa uptake by cells into lysosomes is mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of elosulfase alfa to mannose-6-phosphate receptors. In the absence of an animal disease model that recapitulates the human disease phenotype, elosulfase alfa pharmacological activity was evaluated using human primary chondrocytes from two MPS IVA patients. Treatment of MPS IVA chondrocytes with elosulfase alfa induced clearance of KS lysosomal storage from the chondrocytes.
5. MPS VI
    a. Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome) is characterized by the absence or marked reduction in N–acetylgalactosamine 4-sulfatase. The sulfatase activity deficiency results in the accumulation of the GAG substrate, dermatan sulfate, throughout the body. This accumulation leads to widespread cellular, tissue, and organ dysfunction. Galsulfase is intended to provide an exogenous enzyme that will be taken up into lysosomes and increase the catabolism of GAG. Galsulfase uptake by cells into lysosomes is most likely mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of galsulfase to specific mannose-6-phosphate receptors.
6. MPS VII
    a. Mucopolysaccharidosis VII (MPS VII or Sly syndrome) is a lysosomal disorder characterized by the deficiency of GUS that results in GAG accumulation in cells throughout the body leading to multisystem tissue and organ damage. Vestronidase alfa-vjbk is a recombinant form of human GUS and is intended to provide exogenous GUS enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to cell surface receptors, leading to cellular uptake of the enzyme, targeting to lysosomes and subsequent catabolism of accumulated GAGs in affected tissues.
    b. Lysosomal Acid Lipase (LAL) deficiency is an inherited autosomal recessive disease which is characterized by an impaired lipid metabolism. LAL deficiency refers specifically to a lack in lysosomal glycoprotein enzymes. Lysosomal glycoprotein enzymes are responsible for catalyzing the hydrolysis of esters to free cholesterol and fatty acids. Additionally, these enzymes are responsible for the hydrolysis of triglycerides to glycerol free fatty acids. There are two subtypes known as Wolman disease and cholesterol ester storage disease. Wolman disease presents rapidly and progressively within the first 6 months of life for infant patients. Cholesterol ester storage disease presents later in pediatric (mid-childhood) and adult patients. The clinical presentation of LAL

deficiencies includes an enlarged spleen and liver (i.e., hepatosplenomegaly), inability to gain weight, jaundice, vomiting, diarrhea, fatty stool (i.e., steatorrhea), and malabsorption. Patients ultimately develop the accumulation of lipids in the intestines and blood vessels. Additionally, patients may develop liver dysfunction and dyslipidemia. Affected infants will develop calcium deposits above the adrenal glands, anemia, and developmental delays.

c. Sebelipase alpha binds to cell surface receptors via glycans expressed on the protein and then is internalized into lysosomes. Sebelipase alpha catalyzes the lysosomal hydrolysis of triglycerides and cholesteryl esters into free cholesterol, glycerol, and free fatty acids. Data is not available for pregnant or lactating patients. Safety and efficacy were studied in patients 1 month and older. Data is not available in patients ≥ 65 years old.

C. Dosing

Brand Name	Generic Name	Dosing
Aldurazyme	Laranidase	0.58mg/kg IV once weekly
Elaprase	Idursulfase	0.5 mg/kg IV once weekly
Vimizim	Elosulfase alpha	2 mg/kg IV once weekly
Naglazyme	Galsulfase	1 mg/kg IV once weekly
MEPSEVII	Vestronidase alpha	4 mg/kg IV every two weeks
KANUMA	Sebelipase alfa	A) Wolman Disease: 1 mg/kg IV every week (May increase to 3mg/kg IV once weekly) B) Cholesterol Ester Storage Disease: 1mg/kg IV once every other week

D. Contraindications
1. None

E. Precautions
1. Hypersensitivity reactions and anaphylaxis
    a. Anaphylaxis can occur with these agents. Pre-treatment with antihistamines/antipyretics are recommended. Anaphylaxis has been observed during and up to 3 hours after infusion for Laranidase.
    b. Patients with known hypersensitivity reactions to eggs or egg products should use caution with sebelipase alpha.
    c. Patients receiving Vestronidase alpha should be observed for 60 minutes after administration. Observe patients during and after the infusion of sebelipase alpha; time limit for observation is not specified.

2. Acute respiratory complications

a. Patients with compromised respiratory function or acute febrile or respiratory illness may be at higher risk of life-threatening complications from hypersensitivity reactions

F. Pharmacokinetics
    1. Laranidase
        a. Onset
            1. Initial response: 3-6 weeks
            2. Peak response: within 26 weeks
        b. Volume of distribution: 0.12-0.6 L/kg
        c. Elimination half-life: 0.3-0.6 hours

    2. Idursulfase
        a. Volume of distribution: 213-829 mL/kg
        b. Elimination half-life: 44-134 minutes
        c. Excretion: 3-7.4 mL/min/kg

    3. Elosulfase alpha
        a. Absorption: 172-202 minutes
        b. Volume of distribution: 39-650 mL/kg
        c. Excretion: 7.08-10 mL/min/kg
        d. Elimination Half Life: 7.52-35.9 minutes

    4. Galsulfase
        a. Volume of distribution: 69 mL/kg
        b. Elimination of half-life: 26 minutes

    5. Vestronidase alpha
        a. Volume of distribution: 260 mL/kg
        b. Metabolism: Proteolytic degradation into small peptides and amino acids
        c. Excretion: 1.3 mL/min/kg

    6. Sebelipase alpha
        a. Volume of distribution: 3.6-5.3 mL/kg (variable by age)
        b. Elimination half-life: 5.4-6.6 minutes (variable by age)
        c. T max: 1.1-1.3 hours (variable by age)

G. Adverse Drug Reactions
    1. Infusion reactions
    2. Anaphylactic reactions
    3. Headache
    4. Urticaria
    5. Chest pain
    6. Fever
    7. Arthralgia
    8. Vomiting
    9. Upper respiratory infection
    10. Abdominal pain
    11. Fatigue
    12. Diarrhea
    13. Ear pain

14. Cough
15. Otitis media
16. Anemia – (infants taking Sebelipase)
17. Hyperlipidemia – (adults and infants taking Sebelipase)

H. Drug interactions
    1. No drug-drug interactions noted

Enzyme replacement therapy for Pompe disease

A. Background and Indication
    1. Acid alpha-glucosidase (GAA, also called *acid maltase*) deficiency (Pompe disease) was the first identified lysosomal storage disease. It is also classified as glycogen storage disease type II (GSD II). GAA deficiency leads to accumulation of glycogen within the lysosome in all tissues. The defect in the lysosomal GAA enzyme affects lysosomal-mediated degradation of glycogenesis, unlike the defects in most other GSDs that affect glycogen synthesis or regulation of energy production. Lysosomal GAA is needed to hydrolyze both alpha-1,4- and alpha-1,6-glucosidic linkages in the low pH environment of the lysosome. Deficiency of the enzyme leads to accumulation of glycogen in lysosomes and in the cytoplasm, resulting in tissue destruction. GAA deficiency has an infantile-onset form presenting with hypertrophic cardiomyopathy, as well as a late-onset (including juvenile and adult presentations) form that typically presents without cardiac manifestations. The advent of enzyme replacement therapy (ERT) has improved clinical outcomes and survival for both early- and late-onset GAA deficiency.
    2. Alglucosidase alpha (Lumizyme), Alglucosidase alpha (Myozyme), and Ayalglucosidase alfa-ngpt are ERT that provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

B. Dosing

Brand Name	Generic Name	Dosing
Lumizyme	Alglucosidase alpha	20 mg/kg IV every two weeks
Myozyme	Alglucosidase alpha	20 mg/kg IV every two weeks
Nexviazyme	Avalglucosidase alfa-ngpt	≥ 30 kg; 20 mg/kg IV every two weeks < 30 kg; 40 mg/kg IV every two weeks

C. Contraindications
    1. None

D. Precautions
    1. Hypersensitivity reactions and anaphylaxis

2. Cardiovascular
    a. Patients susceptible to fluid volume overload or those with acute underlying respiratory illness or compromised cardiac or respiratory function may be at risk for cardiorespiratory failure during infusions. Monitoring is recommended [Alglucosidase alpha (Myozyme) and Avalglucosidase alfa-ngpt]
3. Severe cutaneous and systemic immune mediated reactions involving skin and other organs [(Alglucosidase alpha (Lumizyme) and Alglucosidase alpha (Myozyme)]

E. Pharmacokinetics
1. Alglucosidase alpha (Lumizyme)
    a. Total body clearance: 25 mL/hr./kg
    b. Elimination half-life: 2.3 hrs.
2. Alglucosidase alpha (Myozyme)
    a. Total body clearance: 25 mL/hr./kg
    b. Elimination half-life: 2.3 hrs.
3. Ayalglucosidase alfa-ngpt
    a. Volume of distribution: 3.4 L/kg
    b. Total body clearance: 0.9 L/hr.
    c. Elimination half-life: 1.6 hrs.

F. Drug Interactions
1. None found

Enzyme replacement therapy for Fabry disease: Agalsidase alpha (Fabrazyme)

A. Background and Indication
1. Fabry disease is an X-linked genetic disorder of glycosphingolipid metabolism. Deficiency of the lysosomal enzyme α-galactosidase A leads to progressive accumulation of glycosphingolipids including GL-3, in many body tissues, starting early in life and continuing over decades. Clinical manifestations of Fabry disease include renal failure, cardiomyopathy, and cerebrovascular accidents. Accumulation of GL-3 in renal endothelial cells may play a role in renal failure. Agalsidase Beta is intended to provide an exogenous source of α-galactosidase A in Fabry disease patients. Nonclinical and clinical studies evaluating a limited number of cell types indicate that Agalsidase Beta will catalyze the hydrolysis of glycosphingolipids, including GL-3.

B. Dosing
1. Agalsidase alpha: 1mg/kg IV every two weeks

C. Contraindications
1. None

D. Precautions
1. Hypersensitivity/infusion reactions and anaphylaxis
    a. Pre-treatment with an antihistamine and antipyretic is recommended
    b. Patients with Fabry disease have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions. These patients must be closely monitored during administration.

E. Pharmacokinetics
    1. Volume of distribution
        a. Adult: 81-570 mL/kg
        b. Pediatric: 247-1097 mL/kg
    2. Elimination half-life: 45-102 minutes

F. Adverse Drug Reactions
    1. Cardiovascular
        a. Hypertension
        b. Peripheral edema
    2. Dermatologic
        a. Pruritis
        b. Rash
    3. Immunologic
        a. Antibody development
    4. Musculoskeletal
        a. Backache
        b. Myalgia
        c. Spasms
    5. Neurologic
        a. Dizziness
        b. Headache
        c. Paresthesia
    6. Respiratory
        a. Cough
        b. Lower respiratory tract infection
        c. Nasal congestion
        d. Upper respiratory infection
    7. Fatigue
    8. Fever
    9. Serious
        a. Cardiac arrest

G. Drug interactions
    1. None found

IV. NURSING PROCEDURES

A. Supplies
    1. Alcohol wipes
    2. Tape
    3. IV injection cap
    4. Dressing change kit
    5. Port access needles for patients with port
    6. Peripheral start kit for patients with no central line
    7. Peripheral IV for peripheral start
    8. Sharps container
    9. Gloves
    10. Extension set 8”
    11. Ambulatory pump tubing with 0.2-micron filter

12. Syringes (various sizes depending on product) and 20-gauge 1" needles
13. Ambulatory infusion pump
14. Batteries for infusion pump
15. Pole mount adapter and clamp
16. IV pole
17. Vials of specific ERT product
18. SWFI for products that need reconstituted
19. IV saline bag or IV dextrose bag

B. How Supplied/Storage:

Brand Name	Generic Name	How Supplied	Storage
Aldurazyme	Laronidase	Sterile solution in single use 5mL vials (2.9mg of per 5 mL)	Refrigerate vials. Do not freeze or shake. Protect from light
Elaprase	Idursulfase	Sterile solution 6mg/3mL single use vials	Refrigerate vials. Do not freeze or shake. Protect from light
Vimizim	Elosulfase alpha	Sterile solution 5mg/5mL in single use vials	Refrigerate vials. Do not freeze or shake. Protect from light
Naglazyme	Galsulfase	Sterile solution 5mg/5mL in single use vials	Refrigerate vials. Do not freeze or shake.
MEPSEVII	Vestronidase alpha	Sterile solution 10mg/5mL single dose vial	Refrigerate vials. Do not freeze or shake. Protect from light
KANUMA	Sebelipase alfa	Sterile, nonpyrogenic solution 20mg/10mL single use vials	Refrigerate vials. Do not freeze or shake vials. Protect from light.
Cerezyme	Imiglucerase	Sterile lyophilized powder: 200- unit vial 400-unit vial	Refrigerate
VPRIV	Velaglucerase alpha	Sterile lyophilized powder: 200-unit vial 400-unit vial	Refrigerate vials. Do not freeze or shake. Protect from light.
Elelyso	Taliglucerase alpha	Sterile lyophilized powder. 200-unit vial	Refrigerate vials. Do not freeze or shake. Protect from light.

Brand Name	Generic Name	How Supplied	Storage
Lumizyme	Alglucosidase alpha	Sterile lyophilized powder: 50 mg vial	Refrigerate vials. Do note freeze or shake. Protect from light
Myozyme	Alglucosidase alpha	Sterile lyophilized powder: 50 mg vial	Refrigerate vials. Do note freeze or shake. Protect from light

Brand Name	Generic Name	How Supplied	Storage
Fabrazyme	Agalsidase Beta	Sterile lyophilized powder: 5mg vial 35mg vial	Refrigerate vials.

C. Compatibility
    1. Normal saline 0.9%
        a. Laranidase
        b. Idursulfase
        c. Elosulfase alpha
        d. Galsulfase
        e. Vestronidase alpha
        f. Sebelipase alpha
        g. Alglucosidase alpha
        h. Imiglucerase
        i. Velaglucerase alpha
        j. Taliglucerase alpha
        k. Agalsidase beta
    2. 5% Dextrose
        a. Ayalglucosidase alfa-ngpt
    3. Do not infuse with other medications

D. Procedures
    1. Explain reasoning for visit and use of enzyme replacement therapy
    2. Don gloves
    3. Counsel patient on warnings, precautions, and potential side effects
    4. Obtain IV access
    5. Prepare product based on Prescribing Information Instructions. Preferred preparation for each ERT medication is a **home mix** unless case-by-case scenarios warrant preparation by the dispensing pharmacy. Administer the product within 1 hour of preparation. Instructions below are reflective of home mix guidelines. Remove vials from refrigerator and allow to come to room temperature. Inspect vials for particulate matter and discoloration. **Each ERT therapy requires a 0.2micron filter for administration.**
    6. Procedures for **Laranidase**:
        a. Prior to drawing up Laranidase, withdraw and discard a volume of 0.9% sodium chloride from IV bag equal to the volume/dose of Laranidase that is to be added.
            i. Patient weighing ≤ 20 kg should utilize a total volume of 100mL.
            ii. Patients weighing greater than 20 kg should utilize a total volume of 250 mL.
        b. Slowly withdraw the calculated dose of Laranidase (2.9mg/5mL) from appropriate number of vials and add to 0.9% saline bag for total volume of either 100 or 250 mL.
        c. Gently rotate the infusion bag. Do not shake.
        d. Infuse as soon as possible over 3-4 hours. Initial infusion rate is 10 µg/kg/hour and may be increased every 15 minutes for the first hour as tolerated. Maximum infusion rate is 200 µg/kg/hr.

Table 1: Incremental Rates for 100 mL ALDURAZYME® Infusion
(For use with Patients Weighing 20 kg or Less)

Infusion Rate	Criteria for Increasing Infusion Rate
2 mL/hr x 15 minutes (10 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
4 mL/hr x 15 minutes (20 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
8 mL/hr x 15 minutes (50 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
16 mL/hr x 15 minutes (100 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
32 mL/hr x ~3 hours (200 µg/kg/hr)	For the remainder of the infusion.

Table 2: Incremental Rates for 250 mL ALDURAZYME® Infusion
(For use with Patients Weighing Greater than 20 kg)

Infusion Rate	Criteria for Increasing Infusion Rate
5 mL/hr x 15 minutes (10 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
10 mL/hr x 15 minutes (20 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
20 mL/hr x 15 minutes (50 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
40 mL/hr x 15 minutes (100 µg/kg/hr)	Obtain vital signs, if stable then increase the rate to…
80 mL/hr x ~3 hours (200 µg/kg/hr)	For the remainder of the infusion.

7. Procedures for **Idursulfase**
    a. Slowly withdraw the calculated dose of Elaprase (2mg/mL) from appropriate number of vials and add to a bag of 100mL of 0.9% saline.
    b. Gently rotate the infusion bag. Do not shake.
    c. Infuse as soon as possible. Start infusion rate at 8mL/hour for the first 15 minutes. If tolerated may increase rate in 8mL/hour increments every 15 minutes. Do not exceed a rate of 100mL/hr.
8. Procedures for **Elosulfase alpha**:
    a. Prior to drawing up Elosulfase alpha, withdraw and discard a volume of 0.9% sodium chloride from IV bag equal to the volume/dose of Elosulfase alpha that is to be added.
        i. Patient weighing < 25 kg should utilize a total volume of 100mL.
        ii. Patients weighing greater than ≥ 25 kg should utilize a total volume of 250mL.
    b. Slowly withdraw the calculated dose of Elosulfase alpha (1mg/mL) from appropriate number of vials and add to 0.9% saline bag for total volume of either 100 or 250mL.
    c. Gently rotate the infusion bag. Do not shake.
    d. Infuse as soon as possible according to the following rates:

For patients who weigh less than 25 kg: initial infusion rate should be 3 mL per hour for the first 15 minutes and, if tolerated, increased to 6 mL per hour for the next 15 minutes. If this rate is tolerated, then the rate may be increased every 15 minutes in 6 mL per hour increments, not to exceed 36 mL per hour. The total volume of the infusion should be delivered over a minimum of 3.5 hours.

For patients who weigh 25 kg or more: initial infusion rate should be 6 mL per hour for the first 15 minutes and, if tolerated, the infusion rate may be increased to 12 mL per hour for the next 15 minutes. If this rate is tolerated, then the rate may be increased every 15 minutes in 12 mL per hour increments, not to exceed 72 mL per hour. The total volume of the infusion should be delivered over a minimum of 4.5 hours.

9. Procedures for Galsulfase
    a. Prior to drawing up Galsulfase, withdraw and discard a volume of 0.9% sodium chloride from IV bag equal to the volume/dose of Galsulfase that is to be added.
        i. Patients weighing ≤ 20 kg may utilize a total volume of 100mL.
        ii. Patients weighing greater than > 20 kg should utilize a total volume of 250mL.
    b. Slowly withdraw the calculated dose of Galsulfase (1mg/mL) from appropriate number of vials and add to 0.9% saline bag for total volume of either 100 or 250mL
    c. Gently rotate the infusion bag. Do not shake.
    d. Infuse as soon as possible. For 250mL volume, initial rate should be 6mL/hour for the first hour and then if tolerated can be increased to 80 mL/ hour for the remaining 3 hours. For 100mL volume, the infusion rate should be adjusted so total infusion time is over at least 4 hours.

10. Procedures for Vestronidase alpha:
    a. Due to Vestronidase alpha's intricate compounding instructions, preparation will require a prefilled normal saline bag
    b. Slowly withdraw the calculated dose of Vestronidase alpha (2mg/mL) from appropriate number of vials and add to 0.9% saline bag for total. The final solution should be a 1:1 dilution of Vestronidase alpha and 0.9% sodium chloride
    c. Gently rotate the infusion bag. Do not shake.
    d. Infuse as soon as possible per rates in dosing chart approximately over 4 hours.
    e. Patients should be observed for 60 minutes after Vestronidase alpha administration.

Table 1. Recommended Infusion Rate Schedule by Patient Weight for Administration of MEPSEVII at Recommended Dose of 4 mg/kg

Patient Weight Range (kg)	Total MEPSEVII Dose Range (mg)	Total MEPSEVII Volume (rounded) (mL)	Total Infusion Volume of Drug and diluent (infused over 4 hours) (mL)	Infusion Rate for 1st Hour (2.5%) (mL/h)	Infusion Rate per Hour for Subsequent 3 Hours (97.5%/3) (mL/h)
3.5-5.9	14-23.6	10	20	0.5	6.5
6-8.4	24-33.6	15	30	0.8	9.8
8.5-10.9	34-43.6	20	40	1	13
11-13.4	44-53.6	25	50	1.3	16.3
13.5-15.9	54-63.6	30	60	1.5	19.5
16-18.4	64-73.6	35	70	1.8	22.8
18.5-20.9	74-83.6	40	80	2	26
21-23.4	84-93.6	45	90	2.3	29.3
23.5-25.9	94-103.6	50	100	2.5	32.5
26-28.4	104-113.6	55	110	2.8	35.8
28.5-30.9	114-123.6	60	120	3	39
31-33.4	124-133.6	65	130	3.3	42.3
33.5-35.9	134-143.6	70	140	3.5	45.5
36-38.4	144-153.6	75	150	3.8	48.8
38.5-40.9	154-163.6	80	160	4	52
41-43.4	164-173.6	85	170	4.3	55.3
43.5-45.9	174-183.6	90	180	4.5	58.5
46-48.4	184-193.6	95	190	4.8	61.8
48.5-50.9	194-203.6	100	200	5	65
51-53.4	204-213.6	105	210	5.3	68.3
53.5-55.9	214-223.6	110	220	5.5	71.5
56-58.4	224-233.6	115	230	5.8	74.8
58.5-60.9	234-243.6	120	240	6	78
61-63.4	244-253.6	125	250	6.3	81.3
63.5-65.9	254-263.6	130	260	6.5	84.5
66-68.4	264-273.6	135	270	6.8	87.8
68.5-70.9	274-283.6	140	280	7	91

11. Procedures for **Sebelipase alfa**:
    a. Determine the number of vials required per patient's weight
        i. 1mg/kg or 3mg/kg
        ii. Total dose (mg) = Patient's weight (kg) x Recommended dose (mg/kg).
        iii. Total number of vials = Total dose (mg) divided by 20mg/vial
    b. Round to next whole vial and remove required number of vials from the refrigerator and allow them to reach room temperature
        i. Volume (mL) of calculated total dose = Total dose (mg) divided by the 2mg/ml concentration
        ii. Volume (mL) of 0.9% Sodium Chloride for dilution = Total Infusion volume (mL) for patient's weight (See Table 1 below) – Volume (mL) of calculated total dose.

Table 1: Total Infusion Volumes*

Weight Range (kg)	1 mg/kg dose	3 mg/kg dose**
	Total Infusion Volume (mL)	Total Infusion Volume (mL)
1 to 10.9	10	25
11 to 24.9	25	50
25 to 49.9	50	100
50 to 99.9	100	250
100 to 120.9	250	500

* The infusion volume should be based on the prescribed dose and should be prepared to a final KANUMA concentration of 0.1 mg/mL to 1.5 mg/mL.

** For patients with LAL deficiency presenting within the first 6 months of life who do not achieve an optimal clinical response with a dose of 1 mg/kg.

        iii. Mix gently by inversion. Do NOT shake the vials or the prepared infusion.
        iv. The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear to slightly opalescent, colorless to slightly, colored solution. Thin, translucent particles or fibers may be present in the vials or diluted solution. Do not use if the solution is cloudy or if other particulate matter is observed.
        v. Vials are for single use only. Discard any unused product. Do not freeze.
        vi. Administer the diluted solution as an IV infusion using a low-protein infusion set with an in-line, low-protein binding **0.2-micron filter.**
        vii. Infuse over at least 2 hours.
            1) Consider further prolonging the infusion time for patients receiving the 3mg/kg dose or those who have experienced hypersensitivity reactions.
            2) A 1-hour infusion may be considered for patients receiving the 1mg/kg dose who tolerate the infusion
        viii. **Sebelipase alpha contains no preservatives and should be used immediately after preparation**
        ix. If immediate use is not possible, the diluted product may be stored

up to 24 hours in the refrigerator.

x. Do not freeze or shake.

12. Procedures for **Imiglucerase**
    a. Prior to drawing up Imiglucerase, withdraw and discard a volume of 0.9% sodium chloride from IV bag equal to the volume/dose of Imiglucerase that is to be added.
    b. Reconstitute 200-unit vials with 5.1mL of SWFI and 400-unit vials with 10.2mL of SWFI for a total concentration of 40 units/mL.
    c. Slowly withdraw the calculated dose of Imiglucerase (40 units/mL) from appropriate number of vials and add to 0.9% saline bag for total volume between 100-200 mL.
    d. Gently rotate the infusion bag. Do not shake.
    e. Administer as soon as possible after dilution over 1-2 hours

13. Procedures for **Velaglucerase alpha**
    a. Reconstitute Velaglucerase alpha 200-unit vials with 2.2 mL of SWFI and 400-unit vials with 4.3 mL of SWFI for a total concentration of 100uits/mL
    b. Slowly withdraw the calculated dose of Velaglucerase alpha (100 units/mL) from appropriate number of vials and add to 0.9% 100mL normal saline bag
    c. Gently rotate the infusion bag. Do not shake.
    d. Administer as soon as possible after dilution over 60 minutes.

14. Procedures for **Taliglucerase alpha**
    a. Reconstitute Taliglucerase alpha 200-unit vials with 5.1 mL of SWFI for a total concentration of 40 units/mL
    b. Slowly withdraw the calculated dose of Taliglucerase alpha (40 units/mL) from appropriate number of vials and dilute in normal saline to a final volume of 100-120 mL for pediatric patients and a final volume of 130-150mL for adult patients
    c. Gently rotate the infusion bag. Do not shake.
    d. Administer as soon as possible after dilution.
    e. For pediatric patients, infuse over at least an hour. Initial infusion rate 1mL/min and may be increased up to 2mL/min as tolerated
    f. For adult patients, infuse over at least an hour. Initial rate is 1.2mL/ min and may be increased up to 2.2mL/min as tolerated.

15. Procedures for **Alglucosidase alpha (Lumizyme)**
    a. Due to Alglucosidase alpha intricate compounding instructions, preparation will require a prefilled normal saline bag
    b. Reconstitute vial with 10.3mL of SWFI for a concentration of 5mg/mL.
    c. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection opaque particles are observed or if the solution discolored do not use. The reconstituted solution may occasionally contain some alglucosidase alfa particles (typically less than 10 in a vial) in the form of thin white strands or translucent fibers after the initial inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa and may appear after the initial reconstitution

step and increase over time

d. Withdraw volume of Alglucosidase alpha from vial and add to prefilled 0.9% Normal saline bag for a final concentration between 0.5-4mg/mL.

e. Gently rotate the infusion bag. Do not shake.
f. Infuse as soon as possible, per rates in dosing chart below, approximately over 4 hours

The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours. Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. If the patient is stable, alglucosidase alfa may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed or temporarily stopped in the event of mild to moderate hypersensitivity reactions. In the event of anaphylaxis or severe hypersensitivity reaction, immediately discontinue administration of alglucosidase alfa, and initiate appropriate medical treatment. See *Table 1* below for the rate of infusion at each step, expressed as mL/hr based on the recommended infusion volume by patient weight.

Table 1: Recommended Infusion Volumes and Rates

Patient Weight Range (kg)	Total infusion volume (mL)	Step 1 1 mg/kg/hr (mL/hr)	Step 2 3 mg/kg/hr (mL/hr)	Step 3 5 mg/kg/hr (mL/hr)	Step 4 7 mg/kg/hr (mL/hr)
1.25–10	50	3	8	13	18
10.1–20	100	5	15	25	35
20.1–30	150	8	23	38	53
30.1–35	200	10	30	50	70
35.1–50	250	13	38	63	88
50.1–60	300	15	45	75	105
60.1–100	500	25	75	125	175
100.1–120	600	30	90	150	210
120.1–140	700	35	105	175	245
140.1–160	800	40	120	200	280
160.1–180	900	45	135	225	315
180.1–200	1,000	50	150	250	350

16. Procedures for **Alglucosidase alpha (Myozyme)**

a. Due to Alglucosidase alpha's intricate compounding instructions, preparation will require a prefilled normal saline bag
b. Reconstitute 50 mg vial with 10.3mL of SWFI for a concentration of 5mg/mL.
c. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection opaque particles are observed or if the solution discolored do not use. The reconstituted solution may occasionally contain some alglucosidase alfa particles (typically less than 10 in a vial) in the form of thin white strands or translucent fibers subsequent to the initial inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa and may appear after the initial reconstitution step and increase over time

d. Withdraw volume of Alglucosidase alpha from vial and add to prefilled 0.9% Normal saline bag for a final concentration between 0.5-4mg/mL.
e. Gently rotate the infusion bag. Do not shake.
f. Infuse as soon as possible per rates in dosing chart below approximately over 4 hours:

Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. If the patient is stable, MYOZYME may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed and/or temporarily stopped in the event of infusion reactions. See Table 1 below for the rate of infusion at each step, expressed as mL/hr based on the recommended infusion volume by patient weight.

Table 1: Recommended Infusion Volumes and Rates

Patient Weight Range (kg)	Total infusion volume (mL)	Step 1 1 mg/kg/hr (mL/hr)	Step 2 3 mg/kg/hr (mL/hr)	Step 3 5 mg/kg/hr (mL/hr)	Step 4 7 mg/kg/hr (mL/hr)
1.25 -10	50	3	8	13	18
10.1 - 20	100	5	15	25	35
20.1 – 30	150	8	23	38	53
30.1 – 35	200	10	30	50	70
35.1 – 50	250	13	38	63	88
50.1 – 60	300	15	45	75	105
60.1 – 100	500	25	75	125	175
100.1 – 120	600	30	90	150	210
120.1 – 140	700	35	105	175	245
140.1 – 160	800	40	120	200	280
160.1 – 180	900	45	135	225	315
180.1 – 200	1000	50	150	250	350

17. Procedures for **Avalglucosidase alfa-ngpt**:
    a. Due to Avalglucosidase alfa-ngpt intricate compounding instructions, preparation will require a prefilled normal D5W bag
    b. Reconstitute 100 mg vial with 10.0 mL of SWFI for a concentration of 10mg/mL.
    c. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection particles are observed or if the solution discolored do not use.
    d. Withdraw volume of Avalglucosidase alfa-ngpt from vial and add to prefilled Dextrose 5% in Water bag for a final concentration between 0.5-4mg/mL.
    e. Gently rotate the infusion bag. Do not shake
    f. Infuse as soon as possible per rates in dosing chart below approximately over 4 to 7 hours
    g. After infusion is complete, flush with D5W

2. Administer the infusion incrementally, as determined by the patient's response and comfort.
   When the recommended dose is 20 mg/kg
   - *Initial and Subsequent Infusions:* The recommended starting infusion rate is 1 mg/kg/hour. If there are no signs of infusion-associated reactions (IARs), gradually increase the infusion rate every 30 minutes in each of the following three steps: 3 mg/kg/hour, 5 mg/kg/hour, and then 7 mg/kg/hour; then, maintain the infusion rate at 7 mg/kg/hour until the infusion is complete. The approximate total infusion duration is 4 hours to 5 hours.

   When the recommended dose is 40 mg/kg
   - *Initial Infusion:* The recommended starting infusion rate is 1 mg/kg/hour. If there are no signs of IARs, gradually increase the infusion rate every 30 minutes in each of the following three steps: 3 mg/kg/hour, 5 mg/kg/hour, and then 7 mg/kg/hour; then, maintain the infusion rate at 7 mg/kg/hour until the infusion is complete (4-step process). The approximate total infusion duration is 7 hours.
   - *Subsequent Infusions:* The recommended starting infusion rate is 1 mg/kg/hour, with gradual increase in infusion rate every 30 minutes if there are no signs of IARs. The process may use either the above 4-step process or the following 5-step process: 3 mg/kg/hour, 6 mg/kg/hour, 8 mg/kg/hour, and then 10 mg/kg/hour; then, maintain the infusion rate at 10 mg/kg/hour until the infusion is complete. The approximate total 5-step infusion duration is 5 hours.

Table 1: Projected Intravenous Infusion Volume for NEXVIAZYME Administration According to Patient Weight

Patient Weight Range (kg)	Total Infusion Volume (mL) for 20 mg/kg	Total Infusion Volume (mL) for 40 mg/kg
5 to 9.9	N/A	100
10 to 19.9	N/A	200
20 to 29.9	N/A	300
30 to 34.9	200	N/A
35 to 49.9	250	N/A
50 to 59.9	300	N/A
60 to 99.9	500	N/A
100 to 119.9	600	N/A
120 to 140	700	N/A

18. Procedures for **Agalsidase Beta**
    a. Prior to Agalsidase Beta reconstitution, withdraw and discard a volume of 0.9% sodium chloride from IV bag equal to the volume/dose of Agalsidase Beta that is to be added.
    b. Reconstitute Agalsidase Beta 5 mg vial with 1.1 mL of SWFI and 35 mg vial with 7.2mL of SWFI for a concentration of 5mg/mL in each vial
    c. Visually inspect the reconstituted vials for particulate matter and discoloration. Do not use the reconstituted solution if there is particulate matter or if it is discolored.
    d. Withdraw volume of Agalsidase Beta from vial and add to 0.9% Normal saline bag for a total volume based on dosing weights in below chart:

Patient Weight (kg)	Minimum Total Volume (mL)
≤ 35	50
35.1 – 70	100
70.1 – 100	250
> 100	500

e. Gently rotate the infusion bag. Do not shake.
f. Infuse as soon as possible per dosing rates below. Infusion should be at least 1.5 hours long

The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of infusion reactions. After patient tolerance to the infusion is well established, the infusion rate may be increased in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) with each subsequent infusion. For patients weighing < 30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr). For patients weighing ≥ 30 kg, the administration duration should not be less than 1.5 hours (based on individual patient tolerability).

Patients who have had a positive skin test to Fabrazyme or who have tested positive for anti-Fabrazyme IgE may be successfully re-challenged with Fabrazyme. The initial re-challenge administration should be a low dose at a lower infusion rate, e.g., 1/2 the therapeutic dose (0.5 mg/kg) at 1/25 the initial standard recommended rate (0.01 mg/min). Once a patient tolerates the infusion, the dose may be increased to reach the approved dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/min), as tolerated.

V. CLINICAL MONITORING

A. Nursing monitoring
1. Monitor vital signs prior to starting infusion and after infusion is complete. Refer to manufacturer information for most up-to-date and detailed monitoring and titration protocols. Monitor vital signs with every rate increase per the following recommended intervals for therapies below:
    a. Every 15 minutes
        i. Laronidase
        ii. Elosulfase alpha
        iii. Idursulfase
    b. Every 15-30 minutes
        i. Imiglucerase
        ii. Velaglucerase alpha
        iii. Taliglucerase alpha
        iv. Sebelipase alfa
    c. Every 30 minutes
        i. Alglucosidase alpha
        ii. Avalglucosidase alfa-ngpt
        iii. Galsulfase
        iv. Vestronidase alpha
    d. Patients should be observed for 60 minutes after Vestronidase alpha administration
    e. Unless otherwise specified, monitor patient for 30 minutes after the

completion of the infusion per INS guidelines

2. Do not infuse other agents concomitantly with ERT in the same IV line.
3. If a minor reaction is observed, the infusion may be slowed or temporarily interrupted.
4. If anaphylaxis occurs, immediately discontinue the infusion, and initiate appropriate medical treatment. Follow CarepathRx Protocol for Management of Adult Infusion Reactions (Appendix A). Patients with history of severe infusion reactions should only be considered for home infusion after a thorough discussion of safety for the patient and risk vs. benefit with physician. If home infusion continues, a slower infusion rate will be utilized, and pre-medication may be required prior to starting the ERT infusion. Pre-treatment with antipyretics and/or antihistamines may prevent subsequent reactions.

B. Clinical monitoring
    1. With all therapeutic proteins, there is potential for immunogenicity
    2. Laranidase
        a. Monitor for improvement in pulmonary function for efficacy
        b. Monitor for improvement with walking capacity for efficacy
    3. Idursulfase
        a. Monitor for acute respiratory complications including hypoxia, cyanosis, and seizure with loss of consciousness
        b. Monitor walking capacity for efficacy
        c. Monitor reduction in spleen volume in patients older than 16 months for efficacy
        d. Monitor cardiac and respiratory function
    4. Elosulfase alpha
        a. Inform patients of the Morquio A Registry (MARS) established to better understand the variability and progression of the disease in the population as a whole, and to monitor and evaluate long term effectiveness and safety of Elosulfase alpha.
        b. Monitor sleep apnea and respiratory function
        c. Spinal or cervical cord compression (SCC) is a known and serious complication of MPS IVA and may occur as part of the natural history of the disease. Monitor patients with back pain, paralysis of limbs below the level of compression, urinary and fecal incontinence
    5. Galsulfase
        a. Monitor for improvement in walking or stair-climbing for efficacy
        b. Monitor sleep apnea and respiratory function
        c. Monitor signs and symptoms of spinal or cervical cord compression including back pain, paralysis of limbs below the level of compression, and urinary and fecal incontinence
    6. Vestronidase alpha
        a. Monitor improvement in walking for efficacy
        b. **Monitor for anaphylaxis closely during infusion and for 60 minutes after the infusion has completed.**
    7. Sebelipase alfa
        a. Monitor for improvement in signs and symptoms (e.g., improvement in liver function)
        b. Monitor for anaphylaxis closely during and after the infusion
        c. Monitor for anaphylaxis in patients with known systemic hypersensitivity reactions to eggs or egg products.

    d. Monitor for development of anti-drug antibodies
8. Imiglucerase
    a. Monitor normalization of Hemoglobin and platelet counts for efficacy
    b. Monitor improvement in bone disease for efficacy
    c. Monitor reduction in liver and spleen size in patients with Type I Gaucher disease
9. Velaglucerase alpha
    a. Monitor normalization of Hemoglobin and platelet counts for efficacy
    b. Monitor reduction in liver and spleen size in patients with Type I Gaucher disease
10. Taliglucerase alpha
    a. Monitor normalization of Hemoglobin and platelet counts for efficacy
    b. Monitor reduction in liver and spleen size in patients with Type I Gaucher disease
11. Alglucosidase alpha (Lumizyme)
    a. Monitor for improvements in Pompe disease including walking capacity
    b. Monitor IgG antibody formation every 3 months for 2 years, and annually thereafter
    c. Monitor liver enzymes; baseline and periodically
    d. Monitor urinalysis; periodically
    e. Monitor for systemic immune complex-mediated reactions involving skin and other organs. Can occur weeks to years after initiation
12. Avalglucosidase alfa-ngpt
    a. Monitor for improvements in Pompe disease including walking capacity
13. Agalsidase Beta
    a. Monitor for the improvement of symptoms or prevention of disease progression of Fabry's disease may indicate efficacy
        i. Numbness, tingling, burning in hands in feet
        ii. Pain during physical activity
        iii. Heat or cold intolerance
        iv. Dizziness
        v. Flu-like symptoms
        vi. Opacity of the eye

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

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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.

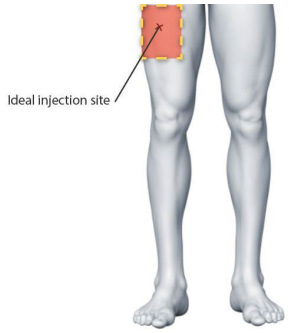
Open the IM Epinephrine Bag

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 hold 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.