Hereditary Angioedema (HAE)

Treatment Plan and Therapy Journal

Plan, prepare, and personalize an effective treatment plan for your HAE attacks

Share your progress with your healthcare provider

Please see full Important Safety Information on pages 34 and 35 and enclosed prescribing information for BERINERT, including the patient product information.
HAE Treatment Plan

Be ready to take action when an HAE attack strikes.

When you have hereditary angioedema (HAE), an attack can happen anytime, anywhere. That’s why it’s so important to work with your doctor to develop a treatment plan that will help prepare you to effectively manage your symptoms at the first sign of attack.

This booklet belongs to: _________________________________

If found, please contact: ________________________________

Connect with BERINERT Connect℠ by calling 1-877-236-4HAE (1-877-236-4423), Monday–Friday, 8 AM–8 PM ET to receive assistance on:

- Insurance coverage or change/lapse in insurance
- Financial assistance
- Peer support or educational resources
- Locating a hospital that has experience with HAE treatment

Learn more at BERINERT.com

Important Safety Information

Do not use BERINERT if you have experienced life-threatening allergic reactions or severe hypersensitivity to the product. Inform your healthcare provider of all medications you are taking and of any medical conditions, especially any history of blood-clotting problems.

This treatment plan is divided into 3 sections to help guide your discussions and record important information.

Together, you and your doctor can determine a personalized approach.

Plan | A planning worksheet helps identify HAE triggers so that you are ready in case of an attack.

An HAE Identification Card is also provided so that you always have key contact information with you. Write your personal information on the card provided, tear it out, and keep it with you at all times.

Prepare | A preparation worksheet helps you recognize HAE symptoms and prepare for what to do when they are beginning or getting worse.

Personalize | A personalized checklist is included that enables you to keep a record of your specific triggers and symptoms, important contact information, and support services.

Please see full Important Safety Information on pages 34 and 35 and enclosed prescribing information for BERINERT, including the patient product information.

[Image of green icon with arrows labeled Plan, Prepare, Personalize]
Plan

Key information to help you be ready to effectively manage HAE. Work with your doctor to plan ahead and be prepared in case of an attack.

Doing Well (No symptoms)

☐ Watch for and manage triggers of HAE attacks, such as:
  • Stress or sickness
  • Mild trauma
  • Any dental work or medical procedures
  • Certain medications, such as ACE inhibitors (for high blood pressure) or estrogen-containing oral contraceptives
☐ Contact your HAE physician before any dental, medical, or surgical procedure(s)

☐ Have 2 to 3 doses of BERINERT available at your home or treatment center
☐ Identify the appropriate treatment location and/or back-up plan for administration assistance
☐ Prepare for treatment while traveling by speaking with your doctor and/or specialty pharmacy in advance
  • Take this HAE Treatment Plan (and your medication) with you and review it with your traveling companion

Important Safety Information

In addition, report immediately any signs or symptoms of allergic reactions to BERINERT, including hives, chest tightness, wheezing, difficulty breathing, turning blue, faintness, facial swelling and fast heartbeat.

HAE Identification Card

Complete the information on the ID card attached to page 35. Be sure to keep the card with you at all times in case of an attack.

The 2018 WAO Guidelines recommend that all patients with HAE have an action plan and product available to treat an attack of HAE.

Please see full Important Safety Information on pages 34 and 35 and enclosed full prescribing information, including the patient product information.
Prepare

Key information to help you be ready to effectively manage HAE. Work with your doctor to plan ahead and be prepared in case of an attack.

Be Prepared to Treat
(Symptoms are starting)

☐ Be aware of symptoms that may indicate the start of an attack, which may include:
  - Sudden mood changes
  - Irritability or aggressiveness
  - Anxiety
  - Extreme fatigue
  - Rash or tingling sensation of the skin where the swelling begins

☐ If your treatment location is outside your home, be sure to bring this HAE Treatment Plan with you, in addition to your BERINERT

Important Safety Information

If you have been trained to self-administer BERINERT, immediately prepare the prescribed dose at the first symptoms of an attack. Seek immediate medical attention and do not begin to self-administer if an HAE attack has progressed to a point where you will be unable to prepare or administer a dose of BERINERT.

Call your doctor right away if swelling is not controlled after use of BERINERT.

Treat Immediately
(Symptoms are getting worse)

☐ Treat immediately if you experience any of the following:
  - Hoarse voice or laryngitis
  - Difficulty swallowing
  - Tightness in throat
  - Voice changes
  - Tongue swelling
  - Face swelling
  - Stomach pain/cramping
  - Swelling of stomach
  - Nausea/vomiting/diarrhea

Important Safety Information

If you self-administer to treat a laryngeal attack, immediately seek medical attention afterward. If you self-administer for an abdominal attack, inform your physician so that other possible causes can be ruled out.

Please see full Important Safety Information on pages 34 and 35 and enclosed full prescribing information, including the patient product information.
**Personalize**

*Keep a record of key information to help in HAE management.*

This page is designed to organize all of your information in case you need treatment—any time of day, at home or away. Keep this checklist in a convenient place, and update it with your doctor as necessary. NOTE: If you do not have your medication, please contact your treatment center in advance to make sure that they have BERINERT for you when you arrive.

**Important Phone Numbers**
- Emergency Contact: ________________________________
- Primary: _____ /____-______  Alternate: _____ /____-______

**My HAE Physician**
- Physician: ________________________________
- Primary: _____ /____-______  Alternate: _____ /____-______

**BERINERT Dose**
- My dose: __________IU (20 IU per kg body weight)
- IV infusion rate: 4 mL/min

**BERINERT Medication** (check all that apply)
- I have BERINERT in my possession
- I visit an infusion center  Location__________________________
- The center has it in stock
- I take my BERINERT to the hospital  Hospital_________________

*Reminder: You should always verify with the hospital that they accept/allow patients to bring their own medication.

**Call your doctor right away if swelling is not controlled after use of BERINERT.**

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**I am enrolled in**
- ☐ BERINERT Co-Pay Program
- ☐ CSL Behring AssuranceSM
- ☐ US Hereditary Angioedema Association (US HAEA)

**My HAE Triggers**
- __________________________________________
- __________________________________________
- __________________________________________
- __________________________________________
- __________________________________________

**My HAE Symptoms**
Use the diagram to indicate the site(s) where you experience symptoms.
- __________________________________________
- __________________________________________
- __________________________________________
- __________________________________________
- __________________________________________

**Please see full Important Safety Information on pages 34 and 35 and enclosed full prescribing information, including the patient product information.**
Specialty Pharmacy Center
Name: ________________________________
Contact Person: _______________________
Phone: _____ / _____ - ________

Specialty Pharmacy Visiting Nurse
Name: ________________________________
Contact Person: _______________________
Phone: _____ / _____ - ________

Treatment Center/Hospital
Name: ________________________________
Contact Person: _______________________
Phone: _____ / _____ - ________
Address: ___________________________________________
__________________________________________________
__________________________________________________

Alternative Plan #1
☐ Home Self-Administration
☐ Home Visiting Nurse
☐ Physician’s Office
☐ Hospital
☐ Other: ________________________________
Primary phone number: _____ / _____ - ________
Secondary phone number: _____ / _____ - ________

Alternative Plan #2
☐ Home Self-Administration
☐ Home Visiting Nurse
☐ Physician’s Office
☐ Hospital
☐ Other: ________________________________
Primary phone number: _____ / _____ - ________
Secondary phone number: _____ / _____ - ________

Other HAE Treatments:
_________________________________________________________________
_________________________________________________________________
_________________________________________________________________
_________________________________________________________________
_________________________________________________________________

Individual responses to therapy may vary. If you self-administer to treat a laryngeal attack, immediately seek medical attention afterward.

Important Safety Information
In addition, report immediately any signs or symptoms of allergic reactions to BERINERT, including hives, chest tightness, wheezing, difficulty breathing, turning blue, faintness, facial swelling and fast heartbeat.

Please see full Important Safety Information on pages 34 and 35 and enclosed full prescribing information, including the patient product information.
Summary

Work with your doctor to develop an effective treatment plan.

HAE is an unpredictable, painful, and life-threatening condition. This provides a summary of how you can plan, prepare, and personalize your treatment plan to best suit your needs.

Plan

Your treatment plan should address:
- Preventive measures
- Home care
- Emergency on-demand treatment
- Self-administration
- Caregiver support

Prepare

You should be prepared with:
- HAE identification card
- On-demand medication
- Instructions on how to use your on-demand medication

Personalize

Your treatment plan should focus on:
- Your symptoms and triggers
- Frequency and location of your attacks
- Your support network

Call your doctor right away if swelling is not controlled after use of BERINERT.

Important Safety Information

If you have been trained to self-administer BERINERT, immediately prepare the prescribed dose at the first symptoms of an attack. Seek immediate medical attention and do not begin to self-administer if an HAE attack has progressed to a point where you will be unable to prepare or administer a dose of BERINERT.

Please see full Important Safety Information on pages 34 and 35 and enclosed prescribing information for BERINERT, including the patient product information.
Ready to take control?

Get started by tracking your HAE attacks.

Use this BERINERT Therapy Journal to track your hereditary angioedema (HAE) attacks, so you can share your progress with your healthcare team.

Make sure you bring your therapy journal to every doctor’s visit. Your healthcare team will find it to be an invaluable resource for monitoring your progress and helping foster successful treatment with BERINERT.

“HAE attacks can be devastating. They can make you feel sick for days and disrupt daily activities. But with BERINERT, you can treat your HAE at the first sign of an attack – and stop missing out on family, work, and life!”

– BERINERT patient

Important Safety Information

BERINERT is used in adults and children to treat swelling and/or painful attacks of hereditary angioedema (HAE) affecting the abdomen, face or throat. The safety and efficacy of BERINERT in preventing HAE attacks have not been established.

Do not use BERINERT if you have experienced life-threatening allergic reactions or severe hypersensitivity to the product. Inform your healthcare provider of all medications you are taking and of any medical conditions, especially any history of blood-clotting problems.

Please see full Important Safety Information on pages 34 and 35 and enclosed prescribing information for BERINERT, including the patient product information.

Self-administer with BERINERT and take control of your next HAE attack

With proper training, you can infuse BERINERT on your own or with the help of a caregiver.

- BERINERT is administered through an intravenous (IV) injection.
- Never attempt to self-administer BERINERT unless you’ve been taught to do so by a healthcare provider.
- One-on-one training from a nurse or other healthcare professional can help you develop the confidence to safely and effectively self-administer BERINERT at the first sign of an HAE attack.
- If you self-administer to treat a laryngeal attack, immediately seek medical attention afterward. If you self-administer for an abdominal attack, inform your physician so that other possible causes can be ruled out.
Benefits of self-administration with BERINERT

When discussing HAE with your physician, recognize the symptoms of an attack and identify your attack triggers. Common triggers include stress or sickness; mild trauma; any dental work or medical procedures; and certain medications, such as ACE inhibitors (for high blood pressure) or estrogen-containing oral contraceptives.

- The ability to self-administer BERINERT means you can get treatment sooner.
- Self-administration with BERINERT can help, whether you’re at home or away.
- Remember, tracking your HAE attacks and sharing your progress with your physician is crucial to your treatment success.

Important Safety Information

BERINERT is used in adults and children to treat swelling and/or painful attacks of hereditary angioedema (HAE) affecting the abdomen, face or throat. The safety and efficacy of BERINERT in preventing HAE attacks have not been established.

Report to your physician or an emergency room any signs and symptoms of a blood clot, including pain and/or swelling or discoloration of an arm or leg, with warmth over affected area; unexplained shortness of breath; chest pain or discomfort that worsens on deep breathing; rapid pulse; and numbness or weakness on one side of the body.

In addition, report immediately any signs or symptoms of allergic reactions to BERINERT, including hives, chest tightness, wheezing, difficulty breathing, turning blue, faintness, facial swelling and fast heartbeat.

Please see full Important Safety Information on pages 34 and 35 and enclosed prescribing information for BERINERT, including the patient product information.
Our BERINERT ConnectSM Network is here to help

Let BERINERT Connect take the hassle out of managing your therapy. With one phone call, BERINERT Connect provides you with convenient access to the following:

- **BERINERT Co-Pay Program** is a financial assistance program designed to cover your eligible out-of-pocket co-pay expenses.*
- **CSL Behring AssuranceSM** provides assistance to some patients who experience a lapse in third-party, private health insurance.
- **CSL Behring Patient Assistance ProgramSM** provides medically necessary therapy to qualified individuals who are uninsured, underinsured, or unable to afford their therapy.

*The BERINERT Co-Pay Program is available to new or existing BERINERT patients. You must be a US resident and insured in the US. Patients must also have insurance coverage for BERINERT under a private health insurance plan. Patients covered by state- or federally funded programs, such as Medicare, Medicaid, and Veterans Health Insurance, are NOT eligible.

The program cannot be used with any other rebate/coupon, free trial, or similar offer. Co-pay assistance under the program is nontransferable. The program only applies in the United States and does not apply where prohibited by law, taxed, or restricted. CSL Behring reserves the right to rescind, revoke, or amend the program at any time without notice. Additional program restrictions may apply.

*Peer advocates are not healthcare professionals or medical experts. For medical questions, please contact your physician. Peer advocates are compensated by CSL Behring for their time and/or expenses.

Important Safety Information

Blood clots have occurred in patients receiving BERINERT. Tell your healthcare provider if you have a history of heart or blood vessel disease, stroke, or blood clots, or if you have thick blood, an indwelling catheter/access device in a vein, or have been immobile for some time. Certain medications, such as birth control pills, may also increase your risk of clotting problems.
Notes on my BERINERT treatment Date 4-23-17

Attack signs and symptoms (check all that apply)³¹

- Cramping
- Muscle aches
- Nonitchy rash
- Diarrhea
- Headache
- Swelling in the throat
- Fatigue
- Nausea
- Tingling of the skin
- Other

Duration of attack

- Time attack began 5:45 AM PM
- Time of treatment 6:15 AM PM
- Time to onset of symptom relief About 50 minutes (minutes)
- Time to complete symptom resolution 4 hours 30 minutes (hours/minutes)

Dose

- No. of BERINERT vials used: 2
- Lot #(s): ______________________________

Site(s) where you experienced symptoms of the attack

Use the diagram to indicate the site(s) where you experienced symptoms and check the severity of your symptoms: □ Mild ✓ Moderate □ Severe

Important Safety Information

BERINERT is used in adults and children to treat swelling and/or painful attacks of hereditary angioedema (HAE) affecting the abdomen, face or throat. The safety and efficacy of BERINERT in preventing HAE attacks have not been established.

Please see full Important Safety Information on pages 34 and 35 and enclosed prescribing information for BERINERT, including the patient product information.
Notes on my BERINERT treatment  Date ________

Attack signs and symptoms (check all that apply)¹

☐ Cramping  ☐ Muscle aches  ☐ Nonitchy rash
☐ Diarrhea  ☐ Headache  ☐ Swelling in the throat
☐ Fatigue  ☐ Nausea  ☐ Tingling of the skin
☐ Other ____________________________

Duration of attack

Time attack began _____________ AM PM  Time of treatment _____________ AM PM
Time to onset of symptom relief ____________________________ (minutes)
Time to complete symptom resolution ____________________________ (hours/minutes)

Dose

No. of BERINERT vials used: ____________  Lot #(s): ______________________________

Site(s) where you experienced symptoms of the attack

Use the diagram to indicate the site(s) where you experienced symptoms and check the severity of your symptoms:

☐ Mild  ☐ Moderate  ☐ Severe

Important Safety Information

Do not use BERINERT if you have experienced life-threatening allergic reactions or severe hypersensitivity to the product. Inform your healthcare provider of all medications you are taking and of any medical conditions, especially any history of blood-clotting problems.

Please see full Important Safety Information on pages 34 and 35 and enclosed prescribing information for BERINERT, including the patient product information.

Place a photo or describe your symptoms

• If your symptoms are external (ie, your swelling attack can be seen), use this space to include a photo

OR

• If your symptoms are internal (eg, an abdominal attack), use these lines to include a description of your attack

_________________________________________________________________
_________________________________________________________________
_________________________________________________________________
_________________________________________________________________
_________________________________________________________________

Other medications

_________________________________________________________________
_________________________________________________________________
_________________________________________________________________

Side effect(s) you may have experienced

_________________________________________________________________
_________________________________________________________________
_________________________________________________________________

Comments about the attack, such as specific triggers

_________________________________________________________________
_________________________________________________________________
_________________________________________________________________

Questions you have for your doctor

_________________________________________________________________
_________________________________________________________________
_________________________________________________________________

Call your doctor right away if swelling is not controlled after use of BERINERT.
Notes on my BERINERT treatment  Date ______

Attack signs and symptoms (check all that apply)¹

☐ Cramping ☐ Muscle aches ☐ Nonitchy rash

☐ Diarrhea ☐ Headache ☐ Swelling in the throat

☐ Fatigue ☐ Nausea ☐ Tingling of the skin

☐ Other ___________________________________________________________________

Duration of attack

Time attack began __________________ AM PM Time of treatment __________________ AM PM

Time to onset of symptom relief ______________________ (minutes)

Time to complete symptom resolution __________________ (hours/minutes)

Dose

No. of BERINERT vials used: ____________ Lot #(s): ______________________________

Site(s) where you experienced symptoms of the attack

Use the diagram to indicate the site(s) where you experienced symptoms and check the severity of your symptoms: ☐ Mild ☐ Moderate ☐ Severe

Important Safety Information

Blood clots have occurred in patients receiving BERINERT. Tell your healthcare provider if you have a history of heart or blood vessel disease, stroke, or blood clots, or if you have thick blood, an indwelling catheter/access device in a vein, or have been immobile for some time. Certain medications, such as birth control pills, may also increase your risk of clotting problems.

Please see full Important Safety Information on pages 34 and 35 and enclosed prescribing information for BERINERT, including the patient product information.

Other medications

____________________________________________________________________________

____________________________________________________________________________

____________________________________________________________________________

Side effect(s) you may have experienced

____________________________________________________________________________

____________________________________________________________________________

Comments about the attack, such as specific triggers

____________________________________________________________________________

____________________________________________________________________________

Questions you have for your doctor

____________________________________________________________________________

____________________________________________________________________________

Call your doctor right away if swelling is not controlled after use of BERINERT.
Notes on my BERINERT treatment  Date ________

**Attack signs and symptoms (check all that apply)**¹

- [ ] Cramping
- [ ] Diarrhea
- [ ] Fatigue
- [ ] Other ____________________________

- [ ] Muscle aches
- [ ] Headache
- [ ] Nausea
- [ ] Other ____________________________

**Duration of attack**

- Time attack began ____________ AM PM  Time of treatment ____________ AM PM
- Time to onset of symptom relief ___________________________ (minutes)
- Time to complete symptom resolution ___________________________ (hours/minutes)

**Dose**

- No. of BERINERT vials used: ____________  Lot #(s): ____________________________

**Site(s) where you experienced symptoms of the attack**

Use the diagram to indicate the site(s) where you experienced symptoms and check the severity of your symptoms:  □ Mild  □ Moderate  □ Severe

**Important Safety Information**

Report to your physician or an emergency room any signs and symptoms of a blood clot, including pain and/or swelling or discoloration of an arm or leg, with warmth over affected area; unexplained shortness of breath; chest pain or discomfort that worsens on deep breathing; rapid pulse; and numbness or weakness on one side of the body.

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**Place a photo or describe your symptoms**

- If your symptoms are external (ie, your swelling attack can be seen), use this space to include a photo

  **OR**

- If your symptoms are internal (eg, an abdominal attack), use these lines to include a description of your attack

  ______________________________________________________

**Other medications**

_________________________________________________________

**Side effect(s) you may have experienced**

_________________________________________________________

**Comments about the attack, such as specific triggers**

_________________________________________________________

**Questions you have for your doctor**

_________________________________________________________

**Call your doctor right away if swelling is not controlled after use of BERINERT.**
Notes on my BERINERT treatment  Date ________

**Attack signs and symptoms (check all that apply)**
- Cramping
- Diarrhea
- Fatigue
- Other ____________________

**Duration of attack**
- Time attack began __________ AM PM  Time of treatment __________ AM PM
- Time to onset of symptom relief __________ (minutes)
- Time to complete symptom resolution __________ (hours/minutes)

**Dose**
- No. of BERINERT vials used: __________  Lot #: ______________________________

**Site(s) where you experienced symptoms of the attack**
Use the diagram to indicate the site(s) where you experienced symptoms and check the severity of your symptoms:
- □ Mild
- □ Moderate
- □ Severe

**Important Safety Information**
In addition, report immediately any signs or symptoms of allergic reactions to BERINERT, including hives, chest tightness, wheezing, difficulty breathing, turning blue, faintness, facial swelling and fast heartbeat.

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**Place a photo or describe your symptoms**
- If your symptoms are external (ie, your swelling attack can be seen), use this space to include a photo
  OR
- If your symptoms are internal (eg, an abdominal attack), use these lines to include a description of your attack

**Other medications**
___________________________________________________________
___________________________________________________________
___________________________________________________________
___________________________________________________________

**Side effect(s) you may have experienced**
___________________________________________________________

**Comments about the attack, such as specific triggers**
___________________________________________________________

**Questions you have for your doctor**
___________________________________________________________

Call your doctor right away if swelling is not controlled after use of BERINERT.
Notes on my BERINERT treatment  

Date ________

Attack signs and symptoms (check all that apply)¹

☐ Cramping  ☐ Muscle aches  ☐ Nonitchy rash
☐ Diarrhea  ☐ Headache  ☐ Swelling in the throat
☐ Fatigue  ☐ Nausea  ☐ Tingling of the skin
☐ Other ________________________________

Duration of attack

Time attack began ___________ AM  PM  Time of treatment ___________ AM  PM

Time to onset of symptom relief ________________________________ (minutes)

Time to complete symptom resolution ________________________________ (hours/minutes)

Dose

No. of BERINERT vials used: ____________  Lot #(s): ______________________________

Site(s) where you experienced symptoms of the attack

Use the diagram to indicate the site(s) where you experienced symptoms and check the severity of your symptoms:  ☐ Mild  ☐ Moderate  ☐ Severe

Important Safety Information

If you have been trained to self-administer BERINERT, immediately prepare the prescribed dose at the first symptoms of an attack. Seek immediate medical attention and do not begin to self-administer if an HAE attack has progressed to a point where you will be unable to prepare or administer a dose of BERINERT.

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Place a photo or describe your symptoms

- If your symptoms are external (ie, your swelling attack can be seen), use this space to include a photo

  OR

- If your symptoms are internal (eg, an abdominal attack), use these lines to include a description of your attack

Other medications


Side effect(s) you may have experienced


Comments about the attack, such as specific triggers


Questions you have for your doctor


Call your doctor right away if swelling is not controlled after use of BERINERT.
Notes on my BERINERT treatment

Date __________

**Attack signs and symptoms (check all that apply)**

- [ ] Cramping
- [ ] Muscle aches
- [ ] Nonitchy rash
- [ ] Diarrhea
- [ ] Headache
- [ ] Swelling in the throat
- [ ] Fatigue
- [ ] Nausea
- [ ] Tingling of the skin
- [ ] Other ___________________________

**Duration of attack**

- Time attack began __________ AM PM Time of treatment __________ AM PM
- Time to onset of symptom relief __________ (minutes)
- Time to complete symptom resolution __________ (hours/minutes)

**Dose**

- No. of BERINERT vials used: __________ Lot #(s): __________________________

**Site(s) where you experienced symptoms of the attack**

Use the diagram to indicate the site(s) where you experienced symptoms and check the severity of your symptoms:

- [ ] Mild
- [ ] Moderate
- [ ] Severe

**Important Safety Information**

If you self-administer to treat a laryngeal attack, immediately seek medical attention afterward. If you self-administer for an abdominal attack, inform your physician so that other possible causes can be ruled out.

Please see full Important Safety Information on pages 34 and 35 and enclosed prescribing information for BERINERT, including the patient product information.

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**Place a photo or describe your symptoms**

- If your symptoms are external (ie, your swelling attack can be seen), use this space to include a photo
- OR
- If your symptoms are internal (eg, an abdominal attack), use these lines to include a description of your attack

**Other medications**

…………………………………………………………………………………………………………………………………………………

**Side effect(s) you may have experienced**

…………………………………………………………………………………………………………………………………………………

**Comments about the attack, such as specific triggers**

…………………………………………………………………………………………………………………………………………………

**Questions you have for your doctor**

…………………………………………………………………………………………………………………………………………………

Call your doctor right away if swelling is not controlled after use of BERINERT.
Important Safety Information

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Blood clots have occurred in patients receiving BERINERT. Tell your healthcare provider if you have a history of heart or blood vessel disease, stroke, or blood clots, or if you have thick blood, an indwelling catheter/access device in a vein, or have been immobile for some time. Certain medications, such as birth control pills, may also increase your risk of clotting problems.

Report to your physician or an emergency room any signs and symptoms of a blood clot, including pain and/or swelling or discoloration of an arm or leg, with warmth over affected area; unexplained shortness of breath; chest pain or discomfort that worsens on deep breathing; rapid pulse; and numbness or weakness on one side of the body.

In addition, report immediately any signs or symptoms of allergic reactions to BERINERT, including hives, chest tightness, wheezing, difficulty breathing, turning blue, faintness, facial swelling and fast heartbeat.

If you have been trained to self-administer BERINERT, immediately prepare the prescribed dose at the first symptoms of an attack. Seek immediate medical attention and do not begin to self-administer if an HAE attack has progressed to a point where you will be unable to prepare or administer a dose of BERINERT.

Call your doctor right away if swelling is not controlled after use of BERINERT.

In clinical studies, the most serious adverse reaction reported in subjects who received BERINERT was an increased severity of the pain associated with HAE. In the placebo-controlled clinical trial, the most common adverse reaction reported more often among subjects who received BERINERT than those receiving placebo was dysgeusia (a bad taste in mouth). Tell your healthcare provider about any side effect that bothers you or does not go away.

Because BERINERT is made from human blood, the risk that it may transmit infectious agents, including viruses and theoretically, the agents of Creutzfeldt-Jakob Disease (CJD) and its variant form (vCJD), cannot be completely eliminated.

Please see enclosed prescribing information for BERINERT, including the patient product information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

HAE Identification Card

Complete the information on the tear-off card below. Be sure to keep the card with you at all times in case of an attack.

Call 911 or head to the nearest emergency room in the event of a life-threatening attack.

Phone: __________________________

Physician: ________________________

Relationship: ____________________

Emergency Contact: _______________

______/____________-_____________

Specialty Pharmacy: __________________________

Phone: __________________________

Hospital: ________________________

Phone: __________________________

Nurse: __________________________

Phone: __________________________

Important Contacts

Phone: __________________________

Physician: ________________________

Relationship: ____________________

Emergency Contact: _______________

______/____________-_____________

Important Contacts

Phone: __________________________

Physician: ________________________

Relationship: ____________________

Emergency Contact: _______________

______/____________-_____________

Important Contacts

Phone: __________________________

Physician: ________________________

Relationship: ____________________

Emergency Contact: _______________

______/____________-_____________

Important Contacts

Phone: __________________________

Physician: ________________________

Relationship: ____________________

Emergency Contact: _______________

______/____________-_____________
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BERINERT safely and effectively. See full prescribing information for BERINERT.

BERINERT® [C1 Esterase Inhibitor (Human)]
For intravenous use. Freeze-Dried Powder for Reconstitution.
Initial U.S. Approval: 2009

INDICATIONS AND USAGE
BERINERT is a plasma-derived C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric patients.

The safety and efficacy of BERINERT for prophylactic therapy have not been established.

For intravenous use only.

DOSAGE AND ADMINISTRATION
For intravenous use only.
- Store the vial in the original carton in order to protect from light. Store at 2-25°C (36-77°F). Do not freeze.
- Administer 20 International Units per kg body weight.
- Reconstitute BERINERT prior to use using the Sterile Water for Injection, USP provided.
- Use a silicone-free syringe for reconstitution and administration.
- Administer at room temperature within 8 hours of reconstitution.
- Inject at a rate of approximately 4 mL per minute.
- Do not mix BERINERT with other medicinal products or solutions.
- Appropriately trained patients may self-administer upon recognition of an HAE attack.

DOSE FORMS AND STRENGTHS
- 500 International Units lyophilized concentrate in a single-use vial for reconstitution with 10 mL of Sterile Water for Injection, USP.

CONTRAINDICATIONS
- Do not use in patients with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.

WARNINGS AND PRECAUTIONS
- Hypersensitivity reactions may occur. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions following discontinuation of administration.
- Serious arterial and venous thromboembolic (TE) events have been reported at the recommended dose of C1 Esterase Inhibitor (Human) products, including BERINERT, following administration in patients with HAE. Risk factors may include the presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives or certain androgens, morbid obesity, and immobility. Benefits of treatment of HAE attacks should be weighed against the risks of TE events in patients with underlying risk factors. Monitor patients with known risk factors for TE events during and after BERINERT administration.
- TE events have also been reported following administration of a C1 Esterase Inhibitor (Human) product when used for unapproved indications at higher than recommended doses.
- Because BERINERT is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.
- Laryngeal HAE attacks: Following self-administration of BERINERT for laryngeal HAE attacks, advise patients to immediately seek medical attention.

ADVERSE REACTIONS
The most serious adverse reaction reported in subjects who received BERINERT was an increase in the severity of pain associated with HAE.

The most common adverse reaction reported in greater than 4% of the subjects who received BERINERT was dysgeusia.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USES IN SPECIFIC POPULATIONS
- Pregnancy: Use only if clearly needed.
- Compared to adults, when adjusted for baseline, the half-life of BERINERT was shorter and clearance (on per kg basis) was faster in children. The clinical implication of this difference is not known.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: April 2019

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### CSL Behring
**FULL PRESCRIBING INFORMATION**

**BERINERT® [C1 Esterase Inhibitor (Human)]**
**Freeze-dried powder**

#### 1 INDICATIONS AND USAGE
BERINERT® is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric patients. The safety and efficacy of BERINERT for prophylactic therapy have not been established.

#### 2 DOSAGE AND ADMINISTRATION

**For Intravenous Use Only.**

Administer BERINERT at a dose of 20 International Units (IU) per kg body weight by intravenous injection. Doses lower than 20 IU/kg body weight should not be administered. BERINERT is provided as a freeze-dried powder for reconstitution with the Sterile Water for Injection, USP provided. Store the vial in the original carton in order to protect from light. Do not freeze.

##### 2.1 Preparation and Handling
- Check the expiration date on the product vial label. Do not use beyond the expiration date.
- Prepare and administer using aseptic techniques [see Dosage and Administration (2.2)].
- Use a silicone-free syringe for reconstitution and administration of BERINERT.
- After reconstitution and prior to administration, inspect BERINERT visually for particulate matter and discoloration. The reconstituted solution should be colorless, clear, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.
- The BERINERT vial is for single use only. BERINERT contains no preservative. Any product that has been reconstituted should be used promptly. The reconstituted solution must be used within 8 hours. Discard partially used vials.
- Do not freeze the reconstituted solution.

##### 2.2 Reconstitution and Administration

Each BERINERT® vial containing 500 IU of C1 esterase inhibitor as a lyophilized concentrate for reconstitution with 10 mL of Sterile Water for Injection, USP provided. Use either the Mix2Vial® transfer set provided with BERINERT® [see How Supplied/ Storage and Handling (16.1)] or a commercially available double-ended needle and vented filter spike.

**Reconstitution**

The procedures below are provided as general guidelines for the reconstitution and administration of BERINERT.

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ensure that the BERINERT® vial and diluent vial are at room temperature.</td>
</tr>
<tr>
<td>2.</td>
<td>Place the BERINERT® vial, diluent vial and Mix2Vial® transfer set on a flat surface.</td>
</tr>
<tr>
<td>3.</td>
<td>Remove the flip caps from the BERINERT® and diluent vials. Wipe the vial stoppers with the alcohol swab provided. Allow to dry prior to opening the Mix2Vial® transfer set package.</td>
</tr>
<tr>
<td>4.</td>
<td>Open the Mix2Vial® transfer set package by peeling away the lid (Figure 1). Leave the Mix2Vial® transfer set in the clear package.</td>
</tr>
<tr>
<td>5.</td>
<td>Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial® transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial® transfer set firmly through the center of the stopper of the diluent vial (Figure 2).</td>
</tr>
<tr>
<td>6.</td>
<td>Carefully remove the clear package from the Mix2Vial® transfer set. Make sure that you pull up only the clear package, and not the Mix2Vial® transfer set (Figure 3).</td>
</tr>
<tr>
<td>7.</td>
<td>With the BERINERT® vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial® transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the BERINERT® vial (Figure 4). The diluent will automatically transfer into the BERINERT® vial.</td>
</tr>
<tr>
<td>8.</td>
<td>With the diluent and BERINERT® vial still attached to the Mix2Vial® transfer set, gently swirl the BERINERT® vial to ensure that the BERINERT® is fully dissolved (Figure 5). Do not shake the vial.</td>
</tr>
<tr>
<td>9.</td>
<td>With one hand, grasp the BERINERT®-side of the Mix2Vial® transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial® transfer set and unscrew the set into two pieces (Figure 6).</td>
</tr>
<tr>
<td>10.</td>
<td>Carefully look at reconstituted solution in each vial of BERINERT®. It should be colorless, clear, and free from visible particles. Do not use the vial if the liquid looks cloudy, contains particles, or has changed color. Do not use if the expiration date on the label has expired.</td>
</tr>
<tr>
<td>11.</td>
<td>Draw air into an empty, sterile syringe. Use a silicone-free syringe. While the BERINERT® vial is upright, screw the syringe to the Mix2Vial® transfer set. Inject air into the BERINERT® vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Figure 7).</td>
</tr>
<tr>
<td>12.</td>
<td>Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial® transfer set (Figure 8). Attach the syringe to a suitable intravenous administration set.</td>
</tr>
<tr>
<td>13.</td>
<td>If patient requires more than one vial, pool the contents of multiple vials into one syringe. A new unused Mix2Vial® transfer set should be used for each BERINERT® vial.</td>
</tr>
<tr>
<td>14.</td>
<td>Do not refrigerate after reconstitution. When reconstitution is carried out using aseptic technique, administration may begin within 8 hours, provided the solution has been stored at up to 30°C (86°F). Do not refrigerate or freeze the reconstituted solution. Only store the reconstituted product in the vial.</td>
</tr>
</tbody>
</table>

**Administration**

- Do not mix BERINERT® with other medicinal products. Administer BERINERT® by a separate infusion line.
- Use aseptic technique when administering BERINERT®.

---

**Figure 1**
**Figure 2**
**Figure 3**
**Figure 4**
**Figure 5**
**Figure 6**
**Figure 7**
**Figure 8**
• Use a silicone-free syringe.
• Follow recommended venipuncture guidelines for initiating intravenous therapy.
• Administer BERINERT by slow intravenous injection at a rate of approximately 4 mL per minute. Please refer to the illustration in step 6 of the self-administration section in the Patient Product Information (PPI) section.
• For self-administration, provide the patient with instructions and training for intravenous injection outside of a clinic setting so patients may self-administer BERINERT upon recognition of symptoms of an HAE attack (see Patient Counseling Information (17)).
• After administration, immediately discard any unused product and all used disposable supplies in accordance with local requirements.

3 DOSAGE FORMS AND STRENGTHS
• BERINERT is available in a single-use vial that contains 500 IU of C1 esterase inhibitor as a lyophilized concentrate.
• Each vial must be reconstituted with 10 mL of Sterile Water for Injection, USP provided.

4 CONTRAINDICATIONS
BERINERT is contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity
Severe hypersensitivity reactions may occur. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reaction (see Patient Counseling Information (17)). The signs and symptoms of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and/or anaphylaxis during or after injection of BERINERT.
Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment methods should be carefully considered. In case of suspected hypersensitivity, immediately discontinue administration of BERINERT and institute appropriate treatment.

5.2 Thromboembolic Events
Serious arterial and venous thromboembolic (TE) events have been reported at the recommended dose of C1 Esterase Inhibitor (Human) products, including BERINERT, following administration in patients with HAE. Risk factors may include the presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives or certain androgens, morbid obesity, and immobility. Benefits of treatment of HAE attacks should be weighed against the risks of TE events in patients with underlying risk factors. Monitor patients with known risk factors for TE events during and after BERINERT administration.
TE events have also been reported following administration of a C1 Esterase Inhibitor (Human) product when used for unapproved indications at higher than recommended doses1,2 (see Overdosage (10) and Nonclinical Toxicology (13.2)).

5.3 Transmissible Infectious Agents
Because BERINERT is made from human blood, it may carry a risk of transmitting infectious agents (eg, viruses, the variant Creutzfeldt-Jakob disease ie, [vCJD] agent and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk that such products will transmit an infectious agent has been minimized by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by processes demonstrated to inactivate and/or remove a wide range of viruses (see Description (11)).
Despite these measures, such products may still potentially transmit disease and there is also the possibility that unknown infectious agents may be present in such products. However, since implementation of these measures, no case reports on suspected transmission of viruses have demonstrated a causal relationship to the administration of BERINERT.
All infections thought by a physician possibly to have been transmitted by BERINERT should be reported by lot number, by the physician, or other healthcare provider to the CSL Behring Pharmacovigilance Department at 1-866-915-6958.

5.4 Laryngeal HAE Attacks
Given the potential for airway obstruction during acute laryngeal HAE attacks, patients self-administering BERINERT should be advised to immediately seek medical attention in an appropriate healthcare facility after treatment with BERINERT.

6 ADVERSE REACTIONS
The most serious adverse reaction reported in subjects enrolled in clinical studies who received BERINERT was an increase in the severity of pain associated with HAE attacks. After initial infusion or rescue Medication treatment with BERINERT versus placebo, in the intent-to-treat population only one adverse reaction was reported in greater than one subject in either treatment group, at a frequency higher than placebo: dysgeusia was reported within 4 hours of infusion of BERINERT versus placebo (2/43, 4.7% vs. 0/42, 0%) and up to 72 hours (2/43, 4.7% vs. 1/42, 2.4%). Because more subjects in the placebo group than in the BERINERT group received rescue treatment, the median observation period in this analysis for subjects randomized to placebo was slightly longer than for subjects randomized to receive BERINERT.
Subjects were tested at baseline and after 3 months for possible exposure to Parvovirus B19, hepatitis B, hepatitis C, and HIV-1 and HIV-2. No subject who underwent testing evidenced seroconversion or treatment-emergent positive polymerase chain reaction testing for these pathogens.

Open-Label Extension Study
In the safety analysis of the open-label extension study, 57 subjects with 1085 acute moderate to severe abdominal, facial, peripheral, and laryngeal HAE attacks received a 20 IU/kg body weight dose of BERINERT (see Clinical Studies (14)). This study provides additional safety data in subjects who received multiple infusions of the product for sequential HAE attacks (one infusion per attack).
Table 1 lists the adverse reactions that occurred in the safety analysis of the open-label extension study in ≥2 subjects or associated with ≥5 HAE attacks Overall by Preferred Term (Safety Subject and HAE Attack Populations) - Open-Label Extension Study

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Number (%) of Subjects (n=57)</th>
<th>ARS within 24 hours</th>
<th>ARS within 72 hours</th>
<th>ARS within 24 hours</th>
<th>ARS within 72 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any preferred term</td>
<td>13 (22.8%)</td>
<td>20 (35.1%)</td>
<td>27 (25.7%)</td>
<td>41 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.5%)</td>
<td>4 (7.0%)</td>
<td>3 (0.3%)</td>
<td>6 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (1.8%)</td>
<td>2 (3.5%)</td>
<td>1 (&lt;0.1%)</td>
<td>2 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain or discomfort</td>
<td>1 (1.8%)</td>
<td>3 (5.3%)</td>
<td>2 (0.2%)</td>
<td>6 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0 (0)</td>
<td>1 (1.8%)</td>
<td>0 (0)</td>
<td>1 (&lt;0.1%)</td>
<td></td>
</tr>
<tr>
<td>Hereditary angioedema attack†</td>
<td>1 (1.8%)</td>
<td>1 (1.8%)</td>
<td>1 (&lt;0.1%)</td>
<td>1 (&lt;0.1%)</td>
<td></td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>1 (1.8%)</td>
<td>2 (3.5%)</td>
<td>1 (&lt;0.1%)</td>
<td>2 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2 (3.5%)</td>
<td>2 (3.5%)</td>
<td>2 (0.2%)</td>
<td>2 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal mycotic infection</td>
<td>0 (0)</td>
<td>2 (3.5%)</td>
<td>0 (0)</td>
<td>2 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1.8%)</td>
<td>1 (1.8%)</td>
<td>4 (0.4%)</td>
<td>5 (0.5%)</td>
<td></td>
</tr>
</tbody>
</table>

n = total number of subjects/ HAE attacks

† Data are sorted by decreasing frequency by number of subjects.
† Hereditary angioedema attacks were only to be reported as adverse reaction if it was a worsening of symptoms during a treated HAE attack. New HAE attacks were not to be reported as adverse reactions. Although the adverse reaction of hereditary angioedema in subject 22301 was a new HAE attack that started after the previous HAE attack had completely resolved, this HAE attack was reported as an adverse reaction, because the HAE attack was not included in the study and treated outside study site with medication other than the study medication.

The incidence and type of adverse reactions with BERINERT when administered for treatment of multiple consecutive acute HAE attacks of any type was similar to those previously observed. As in the placebo-controlled study, no proven cases of infections due to HIV-1/2, HAV, HBV, HCV or Parvovirus B19 were observed during the study.

6.2 Immunogenicity
In a post-marketing study forty-six subjects with Type I or Type II HAE were monitored for inhibitory or non-inhibitory antibodies to C1-INH. Blood samples for antibody assessment were taken at Day 1 (first HAE attack requiring administration of a dose of
20 IU/kg (IV baseline value), and at 3, 6, and 9 months. No subjects developed inhibitory antibodies to C1-INH at any of the time points following infusion of BERINERT. Thirteen subjects (28.2%) however, had detectable levels of non-inhibitory Abs at some point during the study, including 9 subjects (19.6%) who had detectable non-inhibitory Abs at baseline. The presence of non-inhibitory anti-C1-INH Abs did not induce apparent immunologically-associated clinical events. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, it may be misleading to compare the incidence of antibodies to BERINERT in the studies described above with the incidence of antibodies in other studies or to other products.

6.3 Postmarketing Experience
Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure. Adverse reactions reported in Europe since 1979 in patients receiving BERINERT for treatment of HAE include hypersensitivity/anaphylactic reactions, injection-site pain, injection-site redness, chills, and fever. TE Events Associated with HAE Treatment
TE events including basilar artery thrombosis, multiple pulmonary microemboli, and thrombosis have been reported with the use of BERINERT at the recommended dose following treatment of HAE.

6.4 Pediatric Use
The development of thrombosis has been reported after doses exceeding 20 IU/kg body weight of BERINERT when used for unapproved indications in newborns and young children with congenital heart anomalies during or after cardiac surgery under extracorporeal circulation.1

The maximum dose administered in clinical studies in hereditary angioedema was 20 IU/kg body weight.

11 DESCRIPTION
BERINERT is a human plasma-derived, purified, pasteurized, lyophilized concentrate of C1 esterase inhibitor to be reconstituted for intravenous administration. BERINERT is prepared from large pools of human plasma from US donors. The potency of C1 esterase inhibitor is expressed in International Units (IU), which is related to the current WHO Standard for C1 esterase inhibitor products.

C1 esterase inhibitor is a soluble, single-chain glycoprotein containing 478 amino acid residues organized into three beta-sheets and eight alpha-helices.4 The heavily glycosylated molecule has an apparent molecular weight of 105 kD, of which the carbohydrate chains comprise 26% to 35%.6

Each 500 IU vial of reconstituted BERINERT contains 400-625 IU C1 esterase inhibitor, 50 to 80 mg total protein, 85 to 115 mg glycine, 70 to 100 mg sodium chloride, and 25 to 35 mg sodium citrate.

All plasma used in the manufacture of BERINERT is obtained from US donors and tested using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV. Additionally, the plasma is tested with Nucleic Acid Testing (NAT) for HBV, HCV, HIV-1 and HAV and found to be non-reactive (negative). In addition, the plasma is also tested by NAT for Human Parvovirus B19. Only plasma that has passed virus screening is used for production, and the limit for Parvovirus B19 in the fractionation pool is set not to exceed 10 IU of Parvovirus B19 DNA per mL.

The manufacturing process for BERINERT includes multiple steps that reduce the risk of virus transmission. The virus inactivation/reduction capacity consists of three steps:
- Pasteurization in aqueous solution at 60°C for 10 hours
- Hydrophobic interaction chromatography
- Virus filtration (also called nanofiltration) by two filters, 20 nm and 15 nm, in series

This was evaluated in a series of in vitro spike experiments. The total mean cumulative virus inactivation/reduction is shown in Table 2.

### Table 2. Mean Virus Inactivaiton/Reductions in BERINERT

<table>
<thead>
<tr>
<th>Virus Studied</th>
<th>Mean Virus Inactivation</th>
<th>Hydrophobic Interaction</th>
<th>Virus Filtration</th>
<th>Total Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>log₁₀ IU/mL</td>
<td>log₁₀ IU/mL</td>
<td>log₁₀ IU/mL</td>
<td>log₁₀ IU/mL</td>
</tr>
<tr>
<td>HIV-1</td>
<td>≥6.6</td>
<td>≥4.5</td>
<td>≥5.1</td>
<td>≥16.2</td>
</tr>
<tr>
<td>BVDV</td>
<td>≥9.2</td>
<td>≥4.7</td>
<td>≥3.5</td>
<td>≥19.2</td>
</tr>
<tr>
<td>PRV</td>
<td>6.3</td>
<td>≥6.5</td>
<td>≥7.1</td>
<td>≥19.9</td>
</tr>
<tr>
<td>WNV</td>
<td>≥7.0</td>
<td>ND</td>
<td>≥8.0</td>
<td>≥15.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Envelope Virus</th>
<th>Mean Virus Inactivation</th>
<th>Hydrophobic Interaction</th>
<th>Virus Filtration</th>
<th>Total Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>≥6.4</td>
<td>2.8</td>
<td>≥5.3</td>
<td>≥14.5</td>
</tr>
<tr>
<td>CPV</td>
<td>1.4</td>
<td>6.4</td>
<td>≥7.2</td>
<td>≥15.0</td>
</tr>
<tr>
<td>B19V</td>
<td>3.9</td>
<td>ND</td>
<td>ND</td>
<td>NA</td>
</tr>
</tbody>
</table>

HIV-1: Human immunodeficiency virus type 1, a model for HIV-1 and HIV-2
BVDV: Bovine viral diarrhea virus, a model for HIV-3
PRV: Pseudorabies virus, a model for large enveloped DNA viruses
WNV: West Nile virus
HAV: Hepatitis A virus
CPV: Canine parvovirus
B19V: Human Parvovirus B19
ND: Not determined
NA: Not applicable

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, alpha1-antitrypsin, alpha1-antitrypsin, and heparin cofactor II. As with the other inhibitors in this group, C1 esterase inhibitor has an important inhibiting potential on several of the major coagulation systems of the human body, including the complement system, the intrinsic coagulation (contact) system, the fibrinolytic system, and the coagulation cascade. Regulation of these systems is performed through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation of both and consumption of the C1 esterase inhibitor.

C1 esterase inhibitor, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1 esterase inhibitor is the only known inhibitor for the subcomponent of the complement component 1 (C1), complement factor B, and complement factor H. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation factor Xa of the intrinsic coagulation cascade.

HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it has been postulated that increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin.5
Administration of BERINERT to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients. The plasma concentration of C1 esterase inhibitor in healthy volunteers is approximately 270 mg/L.¹

12.3 Pharmacokinetics

The pharmacokinetics of BERINERT were evaluated in an open-label, uncontrolled, single-center study in 40 subjects (35 adults and 5 children under 16 years of age) with either mild or severe HAE. All subjects received a single intravenous injection of BERINERT ranging from 500 IU to 1500 IU. Blood samples were taken during an HAE attack-free period at baseline and for up to 72 hours after drug administration. Pharmacokinetic parameters were estimated using non-compartmental analysis (with or without baseline adjustment). Table 3 summarizes the pharmacokinetic parameters in 35 adult subjects with HAE.

Table 3. Pharmacokinetic Parameters of BERINERT in Adult Subjects with HAE by Non-compartmental Analysis (n=35)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unadjusted for baseline</th>
<th>Adjusted for baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC∞ (hr x IU/mL)*</td>
<td>27.5 ± 8.5 (15.7-44.7)</td>
<td>12.8 ± 6.7 (8.9-34.7)</td>
</tr>
<tr>
<td>CL (ml/hr/kg)</td>
<td>0.60 ± 0.17 (0.34-0.96)</td>
<td>1.44 ± 0.67 (0.43-3.85)</td>
</tr>
<tr>
<td>Vc (ml/kg)</td>
<td>18.6 ± 4.9 (11.1-27.6)</td>
<td>35.4 ± 10.5 (14.1-56.1)</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>21.9 ± 1.7 (16.5-24.4)</td>
<td>18.4 ± 3.5 (7.4-22.8)</td>
</tr>
<tr>
<td>MRT (hrs)</td>
<td>31.5 ± 2.4 (23.7-35.2)</td>
<td>26.4 ± 5.0 (10.7-33.0)</td>
</tr>
</tbody>
</table>

AUC: Area under the curve
CL: Clearance
Vc: Volume steady state
MRT: Mean residence time
*Based on a 15 IU/kg dose. Numbers in parentheses are the range.

Table 4 summarizes the pharmacokinetic parameters in 5 pediatric subjects (ages 6 through 13) with HAE. When adjusted for baseline, compared to adults, the half-life of BERINERT was shorter and clearance (on per kg basis) was faster in this limited cohort of children. However, the clinical implication of this difference is not known.

Table 4. Pharmacokinetic Parameters of BERINERT in Pediatric subjects (n=5)* with HAE by Non-compartmental Analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unadjusted for baseline</th>
<th>Adjusted for baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC∞ (hr x IU/mL)*</td>
<td>25.45 ± 5.8 (16.8-31.7)</td>
<td>9.78 ± 4.37 (4.1-15.2)</td>
</tr>
<tr>
<td>CL (ml/hr/kg)</td>
<td>0.62 ± 0.17 (0.47-0.89)</td>
<td>1.9 ± 1.1 (0.98-3.69)</td>
</tr>
<tr>
<td>Vc (ml/kg)</td>
<td>19.8 ± 4.0 (16.7-26.1)</td>
<td>38.8 ± 8.9 (31.9-54.0)</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>22.4 ± 1.6 (20.3-24.4)</td>
<td>16.7 ± 5.8 (7.4-22.5)</td>
</tr>
<tr>
<td>MRT (hrs)</td>
<td>32.3 ± 2.3 (29.3-35.2)</td>
<td>24.0 ± 8.3 (10.7-32.4)</td>
</tr>
</tbody>
</table>

AUC: Area under the curve
CL: Clearance
Vc: Volume steady state
MRT: Mean residence time
*Age Range: 6-13 years

Studies have not been conducted to evaluate the pharmacokinetics of BERINERT in special patient populations identified by gender, race, geriatric age, or the presence of renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been completed to evaluate the effects of BERINERT on carcinogenesis, mutagenesis, and impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

Acute intravenous toxicity of BERINERT was performed in mice at 1500, 3000, and 6000 IU/kg and in rats at 1000, 2000, and 3000 IU/kg. BERINERT was well tolerated and no signs of toxicity were observed up to the highest dose administered. Repeat intravenous dose toxicity was studied in a 14-day repeat dose study in rats at doses of 20, 60, and 200 IU/kg/day. BERINERT was well tolerated and no toxicity was observed up to the highest dose administered. No antibody response against BERINERT was observed up to the highest dose administered. No toxicity was observed in rat and mouse studies after intravenous injection of a single dose of up to 3500 IU/kg.

In a safety pharmacology study, BERINERT was administered to beagle dogs intravenously at a cumulative dose of 3500 IU/kg. No adverse effects were seen on the cardiovascular and respiratory system. There was a drop in body temperature, reduced coagulation time, and a decrease in thrombocyte aggregation.

In a study in pigs investigating cardioprotective effects of C1 esterase inhibitor suggests a risk of thrombosis from intravenous administration of C1 esterase inhibitor products at doses of 200 IU/kg; however, in this model, cardioprotective effects were observed at a dose of 40 IU/kg.²

14 CLINICAL STUDIES

The safety and efficacy of BERINERT in the treatment of acute abdominal or facial HAE attacks in subjects with hereditary angioedema were demonstrated in a placebo-controlled, double-blind, prospective, multinational, randomized, parallel-group, dose-finding, three-arm, clinical study, referred to as the randomized clinical trial (RCT). The RCT assessed the efficacy and safety of BERINERT in 124 adult and pediatric subjects with C1 esterase inhibitor deficiency who were experiencing an acute moderate to severe attack of abdominal or facial HAE. Subjects ranged in age from six to 72 years of age; 67.7% were female and 32.3% were male; and approximately 90% were Caucasian.

The study objectives were to evaluate whether BERINERT shortens the time to onset of relief of symptoms of an abdominal or facial HAE attack compared to placebo and to compare the efficacy of two different doses of BERINERT. The time to onset of relief of symptoms was determined by the subject's response to a standard question posed at appropriate time intervals for as long as 24 hours after start of treatment, taking into account all single HAE symptoms. In addition the severity of individual HAE symptoms was assessed over time.

Subjects were randomized to receive a single 10 IU/kg body weight dose of BERINERT (39 subjects), a single 20 IU/kg dose of BERINERT (43 subjects), or a single dose of placebo (42 subjects) by slow intravenous infusion (recommended to be given at a rate of approximately 4 mL per minute) within 5 hours of an HAE attack. At least 70% of the subjects in each treatment group were required to be experiencing an abdominal HAE attack.

If a subject experienced no relief or insufficient relief of symptoms by 4 hours after infusion, investigators had the option to administer a second infusion of BERINERT (20 IU/kg for the placebo group, 10 IU/kg for the 10 IU/kg group, or placebo for the 20 IU/kg group). This masked (blinded) “rescue study medication” was administered to subjects and they were then followed until complete resolution of symptoms was achieved. Adverse events were collected for up to 7 to 9 days following the initial administration of BERINERT or placebo.

In the recent study a subject developed life-threatening laryngeal edema after inclusion into the study, immediate start of open-label treatment with a 20 IU/kg body weight dose of BERINERT was allowed.

All subjects who received confounding medication (rescue medication) before symptom relief were regarded as “non-responders.” Therefore, time to onset of symptom relief was set at 24 hours if a subject received any rescue medication (ie, rescue study medication, narcotic analgesics, non-narcotic analgesics, anti-emetics, open-label C1 inhibitor, androgens at increased dose, or fresh frozen plasma) between 5 hours before administration of blinded study medication until time to onset of relief.

For the trial to be considered successful, the study protocol specified the following criteria for the differences between the BERINERT 20 IU/kg and the placebo group:

- The time to onset of relief of symptoms of the HAE attack had to achieve a one-sided p-value of less than 0.0249 for the final analysis, and at least one of the following criteria had to demonstrate a trend in favor of BERINERT with a one-sided p-value of less than 0.1:
  - The proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment with study medication compared to baseline, or
  - The number of vomiting episodes within 4 hours after start of study treatment.

Subjects treated with 20 IU/kg body weight of BERINERT experienced a significant reduction (p=0.0016; “Wilcoxon Rank Sum test”) in time to onset of relief of symptoms of an HAE attack as compared to placebo (median of 48 minutes for BERINERT 20 IU/kg body weight as, compared to a median of >4 hours for placebo). The time to onset of relief from symptoms of an HAE attack for subjects in the 10 IU/kg dose of BERINERT was not statistically significantly different from that of subjects in the placebo group.

Figure 9 is a Kaplan-Meier curve showing the percentage of subjects reporting onset of relief of HAE attack symptoms as a function of time. Individual time points beyond 4 hours are not presented on the graph because the protocol permitted blinded rescue medication, analgesics, and/or anti-emetics to be administered starting 4 hours after randomization blinded study medication had been administered.

Figure 9. Time to Onset of Symptom Relief With Imputation to ≥4 Hours for Subjects Who Received any Rescue Medication* or Non-narcotic Analgesics Before Start of Relief

* Included rescue study medication (as blinded C1 inhibitor or placebo given as rescue medication), open-label C1 inhibitor, narcotic and non-narcotic analgesics, anti-emetics, androgens at increased dose, or fresh frozen plasma.
In addition, the efficacy of BERINERT 20 IU/kg body weight could be confirmed by observing a reduction in the intensity of single HAE symptoms at an earlier time compared to placebo. For abdominal attacks Figure 10 shows the time to start of relief of the last symptom to improve that was already present at baseline. Pre-defined abdominal HAE symptoms included pain, nausea, vomiting, cramps and diarrhea. Figure 11 shows the respective time to start of relief of the first symptom to improve that was already present at baseline.

**Figure 10. Time to Start of Relief of the Last Symptom to Improve (Abdominal HAE Attacks) with Imputation to >4 Hours for Subjects Who Received Any Rescue Medication**

<table>
<thead>
<tr>
<th>Time to Start of Relief (hours)</th>
<th>BERINERT 20 IU/kg Body Weight</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>27 (62.8%)</td>
<td>11 (26.2%)</td>
</tr>
<tr>
<td>1.0</td>
<td>30 (69.8%)</td>
<td>18 (42.9%)</td>
</tr>
<tr>
<td>2.0</td>
<td>6 episodes</td>
<td>35 episodes</td>
</tr>
<tr>
<td>4.0</td>
<td>0 (0%)</td>
<td>12 (28.6%)</td>
</tr>
</tbody>
</table>

Additional Endpoints

<table>
<thead>
<tr>
<th>Onset of symptom relief within 60 minutes after administration of study medication (post-hoc)</th>
<th>BERINERT 20 IU/kg Body Weight (n=43)</th>
<th>Placebo Group (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of combined abdominal and facial HAE attack subjects receiving rescue study medication, analgesics, or anti-emetics at any time prior to initial relief of symptoms</td>
<td>13 (30.2%)</td>
<td>23 (54.8%)</td>
</tr>
<tr>
<td>At least one new HAE symptom not present at baseline and starting within 4 hours after administration of study medication</td>
<td>2 (4.6%)</td>
<td>6 (14.3%)</td>
</tr>
</tbody>
</table>

Both the proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment compared to baseline, and the number of vomiting episodes within 4 hours after start of study treatment demonstrated trends in favor of BERINERT in comparison to placebo (p-values <0.1). Tables 6 through 9 present additional information regarding responses to treatment.

**Table 5. Changes in HAE Symptoms and Use of Rescue Medication in Subjects Receiving BERINERT 20 IU/kg Body Weight vs. Placebo**

<table>
<thead>
<tr>
<th>Additional Endpoints</th>
<th>BERINERT 20 IU/kg Body Weight</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptom relief within 60 minutes after administration of study medication</td>
<td>27 (62.8%)</td>
<td>11 (26.2%)</td>
</tr>
<tr>
<td>Onset of symptom relief within 4 hours after administration of study medication</td>
<td>30 (69.8%)</td>
<td>18 (42.9%)</td>
</tr>
<tr>
<td>Number of vomiting episodes within 4 hours after start of study treatment</td>
<td>6 episodes</td>
<td>35 episodes</td>
</tr>
<tr>
<td>Worsened intensity of clinical HAE symptoms between 2 and 4 hours after administration of study medication compared to baseline</td>
<td>0 (0%)</td>
<td>12 (28.6%)</td>
</tr>
</tbody>
</table>

Table 6. Proportion of Subjects Experiencing Start of Self-Reported Relief of Symptoms by 4 Hours by HAE Attack Type

<table>
<thead>
<tr>
<th>HAE Attack Type</th>
<th>BERINERT 20 IU/kg Body Weight (Abdominal Subjects = 34) (Facial Subjects = 9)</th>
<th>Placebo Group (Abdominal Subjects = 33) (Facial Subjects = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>24 (70.6%)</td>
<td>15 (45.5%)</td>
</tr>
<tr>
<td>Facial</td>
<td>6 (66.7%)</td>
<td>3 (37.5%)</td>
</tr>
</tbody>
</table>

Table 7. Proportion of Subjects Experiencing Reduction in Severity of at Least One Individual HAE Attack Symptom by 4 Hours

<table>
<thead>
<tr>
<th>HAE Attack Type</th>
<th>BERINERT 20 IU/kg Body Weight (Abdominal Subjects = 34) (Facial Subjects = 9)</th>
<th>Placebo Group (Abdominal Subjects = 33) (Facial Subjects = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>33 (97.1%)</td>
<td>29 (87.9%)</td>
</tr>
<tr>
<td>Facial</td>
<td>6 (66.7%)</td>
<td>4 (50%)</td>
</tr>
</tbody>
</table>

Table 8. Proportion of Subjects with Facial HAE Attacks Demonstrating Improvement in Serial Facial Photographs by 4 Hours

<table>
<thead>
<tr>
<th>Attack Type</th>
<th>BERINERT 20 IU/kg Body Weight (Subjects = 9)</th>
<th>Placebo Group (Subjects = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial</td>
<td>7 (77.8%)</td>
<td>2 (25%)</td>
</tr>
</tbody>
</table>
No subjects treated with BERINERT at 20 IU/kg body weight reported worsening of symptoms at 4 hours after administration of study medication compared to baseline. The study demonstrated that the BERINERT 20 IU/kg body weight dose was significantly more efficacious than the BERINERT 10 IU/kg body weight dose or placebo.

Open-Label Extension Study

BERINERT was evaluated in a prospective, open-label, uncontrolled, multicenter extension study conducted at 15 centers in the US and Canada in subjects who had participated in the RCT study for the treatment of acute abdominal or facial HAE attacks in subjects with hereditary angioedema.

The purpose of this extension study was to provide BERINERT to subjects who had participated in the RCT study and who experienced any type of subsequent HAE attack (ie, abdominal, facial, peripheral, or laryngeal).

The safety analysis of the open-label extension study included a total of 57 subjects (19 males and 38 females, age range: 10 to 53 years) with 1085 HAE attacks treated with 20 IU/kg body weight dose of BERINERT per attack, who were observed at the study site until onset of relief of HAE symptoms, and were followed up for adverse reactions for 7 to 9 days following treatment of each HAE attack [see Adverse Reactions (6.1)]. During the extension study, 51 subjects experienced 747 abdominal attacks, 21 subjects experienced 51 facial attacks, 30 subjects experienced 235 peripheral HAE attacks, and 16 subjects experienced 48 laryngeal HAE attacks. Some study subjects may have experienced HAE attacks in more than one location.

An analysis of laryngeal HAE attacks showed that the median time to initial onset of symptom relief and median time to complete resolution in the per-attack analysis were 0.25 hours and 8.4 hours, respectively (Table 10), which were the shortest times among the various HAE attack locations.

### Table 9. Proportion of Subjects with Abdominal and Facial HAE Attacks Receiving Rescue Study Medication at any Time Prior to Complete Relief of Symptoms

<table>
<thead>
<tr>
<th>HAE Attack Type</th>
<th>BERINERT 20 IU/kg Body Weight (Abdominal Subjects = 34)</th>
<th>Placebo Group (Abdominal Subjects = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>7 (20.6%)</td>
<td>17 (51.5%)</td>
</tr>
<tr>
<td>Facial</td>
<td>1 (11.1%)</td>
<td>6 (15%)</td>
</tr>
</tbody>
</table>

No subjects treated with BERINERT at 20 IU/kg body weight reported worsening of symptoms at 4 hours after administration of study medication compared to baseline. The study demonstrated that the BERINERT 20 IU/kg body weight dose was significantly more efficacious than the BERINERT 10 IU/kg body weight dose or placebo.

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An analysis of laryngeal HAE attacks showed that the median time to initial onset of symptom relief and median time to complete resolution in the per-attack analysis were 0.25 hours and 8.4 hours, respectively (Table 10), which were the shortest times among the various HAE attack locations.

### Table 10. Time to Initial Onset of Symptom Relief and Time to Complete Resolution of HAE Symptoms for Laryngeal HAE Attacks

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Laryngeal (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to initial onset of symptom relief [hours]</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.25 (0.10 - 1.25)</td>
</tr>
<tr>
<td>95% CI for median</td>
<td>[0.23; 0.42]</td>
</tr>
<tr>
<td><strong>Time to complete resolution of HAE symptoms [hours]</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>8.4 (0.6 - 61.8)</td>
</tr>
<tr>
<td>95% CI for median</td>
<td>[6.2; 21.5]</td>
</tr>
</tbody>
</table>

### Storage and Handling

When stored at temperatures of 2-8°C (36-86°F), BERINERT is stable for the period indicated by the expiration date on the carton and vial label.

- Keep BERINERT in its original carton until ready to use.
- Do not freeze.
- Protect from light.

### 17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Patient Information).

Inform patients to immediately report the following to their physician:

- Signs and symptoms of allergic hypersensitivity reactions, such as hives, urticaria, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of BERINERT [see Warnings and Precautions (5.1)].
- Signs and symptoms of a thromboembolic event including pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body. Advise patients with known risk factors for thromboembolic events that they are at an increased risk for these events [see Warnings and Precautions (5.2)].
- Advise female patients to notify their physician if they become pregnant or intend to become pregnant during the treatment of acute abdominal or facial HAE attacks with BERINERT [see Use in Specific Populations (8.1)].
- Advise patients to notify their physician if they are breastfeeding or plan to breastfeed [see Use in Specific Populations (8.2)].
- Advise patients to consult with their healthcare professional prior to travel.
- Advise patients/caregivers to bring an adequate supply of BERINERT when traveling.
- Advise patients to bring BERINERT with them when they visit a healthcare provider for an acute HAE attack.
- Advise patients that, because BERINERT is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob (CJD) agent [see Warnings and Precautions (5.3) and Description (11)]. Inform patients of the risks and benefits of BERINERT before prescribing or administering it to the patient.

Self-administration — Ensure that the patient (or caregiver) is an appropriate candidate for self-administration, this includes, but not limited to a determination that:

- The patient (or caregiver) is reliably able to recognize the signs and symptoms of their HAE attacks.
- The patient (or caregiver) has the necessary dexterity and comprehension to be trained to self-administer.

If self-administration is deemed appropriate, ensure that the patient/caregiver receives clear instructions and training on intravenous administration in the home or other appropriate setting and has demonstrated the ability to perform intravenous infusions.

- Ensure the patients/caregivers understand the importance of not starting self-administration if the HAE attack (regardless of type) has progressed to a point that the patient/caregiver would be unable to successfully prepare or administer BERINERT.
- Given the potential for airway obstruction during acute laryngeal HAE attacks, patients self-administering BERINERT should be advised to immediately seek medical attention in an appropriate healthcare facility in addition to treatment with BERINERT.
To help exclude the possibility that another potentially serious medical cause may be responsible for their symptoms, advise patients self-administering BERINERT to contact their healthcare provider after treating suspected abdominal HAE attacks.

Instruct patients/caregivers to record the lot number from the BERINERT vial label every time they use BERINERT.

The attached BERINERT “Patient Product Information (PPI)” contains more detailed instructions for patients/caregivers who will be self-administering BERINERT.

FDA-Approved Patient Labeling – Patient Product Information (PPI)

BERINERT (BEAR-ing)
C1 Esterase Inhibitor (Human)
Freeze-Dried Powder for Reconstitution

This leaflet summarizes important information about BERINERT. Please read it carefully before using BERINERT and each time you get a refill. There may be new information provided. This information does not take the place of talking with your healthcare provider and it does not include all of the important information about BERINERT. If you have any questions after reading this, ask your healthcare provider.

Do not attempt to self-administer unless you have been taught how by your healthcare provider.

What is BERINERT?
BERINERT is an injectable medicine used to treat swelling and/or painful HAE attacks in adults and children with Hereditary Angioedema (HAE). HAE is caused by the poor functioning or lack of a protein called C1 that is present in your blood and helps control inflammation (swelling) and parts of the immune system. BERINERT contains C1 esterase inhibitor, a protein that helps control C1.

Who should not use BERINERT?
You should not use BERINERT if you have experienced life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product.

What should I tell my healthcare provider before using BERINERT?
Tell your healthcare provider about all of your medical conditions, including if you:
- Are pregnant or planning to become pregnant. It is not known if BERINERT can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if BERINERT passes into your milk and if it can harm your baby.
- Have a history of blood clotting problems. Blood clots have occurred in patients receiving BERINERT. Very high doses of C1 esterase inhibitor could increase the risk of blood clots. Tell your healthcare provider if you have a history of heart or blood vessel disease, stroke, blood clots, or have thick blood, an indwelling catheter/access device in one of your veins, or have been immobile for some time. These things may increase your risk of having a blood clot after using BERINERT. Also, tell your healthcare provider what drugs you are using, as some drugs, such as birth control pills or certain androgens, may increase your risk of developing a blood clot.

Tell your healthcare provider and pharmacist about all of the medicines you take, including all prescription and non-prescription medicines such as over-the-counter medicines, supplements, or herbal remedies.

What are the possible side effects of BERINERT?
Allergic reactions may occur with BERINERT. Call your healthcare provider or seek emergency support services right away if you have any of the following symptoms after using BERINERT:
- wheezing
- difficulty breathing
- chest tightness
- turning blue (look at lips and gums)
- fast heartbeat
- swelling of the face
- faintness
- rash
- hives

Signs of a blood clot include:
- pain and/or swelling of an arm or leg with warmth over the affected area
- discoloration of an arm or leg
- unexplained shortness of breath
- chest pain or discomfort that worsens on deep breathing
- unexplained rapid pulse
- numbness or weakness on one side of the body

In clinical studies, the most serious adverse reaction reported in subjects who received BERINERT was an increase in the severity of pain associated with HAE.

In clinical studies, the most common adverse reaction reported among subjects who received BERINERT in the placebo-controlled clinical trial was dysgeusia (bad taste in mouth).

Because BERINERT is made from human blood, it may carry a risk of transmitting infectious agents, such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob (CJD) agent.

These are not all the possible side effects of BERINERT.

Tell your healthcare provider about any side effect that bothers you or that does not go away. You can also report side effects to the FDA at 1-800-FDA-1088.

How should I store BERINERT?
- Keep BERINERT in its original carton to protect from light until ready to use.
- When stored at temperatures of 2-30°C (36-86°F), BERINERT is stable for the period indicated by the expiration date on the carton and vial label.
- Do not freeze.

What else should I know about BERINERT?
Medicines are sometimes prescribed for purposes other than those listed here. Do not use BERINERT for a condition for which it is not prescribed. Do not share BERINERT with other people, even if they have the same symptoms that you have.

This leaflet summarizes the most important information about BERINERT. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about BERINERT that was written for healthcare professionals. For more information, go to www.BERINERT.com or call 1-877-236-4423.

What are the symptoms of a facial, abdominal or laryngeal Hereditary Angioedema (HAE) attack?
Early HAE symptoms appear anywhere from minutes to one to two days before the attack worsens. HAE attacks can last hours to several days, and range in severity. Itching is not a typical feature of HAE attacks.

Facial attacks — These HAE attacks can occur in areas around the eyes and mouth, and result from local edema of tissue beneath the skin (subcutaneous).

Abdominal attacks — These HAE attacks appear as pain (colic), nausea, vomiting, and/or diarrhea. These symptoms result from the swelling of walls of the gastrointestinal tract.

Laryngeal HAE attacks — Laryngeal edema (swelling of the voice box, difficulty breathing, loss of voice, and noisy breathing on inspiration), can occur by itself, or with swelling of the lips, tongue, uvula (the piece of mouth tissue that hangs down from the top of the mouth over the back of the tongue), and soft palate (the soft tissue at the back of the mouth). Removing a tooth and oral surgery can trigger a laryngeal attack. Laryngeal swelling can develop in minutes or hours.

Many HAE attacks involve only one location of the body at a time, although combination attacks, such as cutaneous attacks that spread to involve the larynx (the voice box), can occur.

What other diseases or symptoms could resemble a HAE attack?
Some abdominal-related causes that can appear as an HAE attack include:
- Appendix
- Heartburn
- Gall bladder attack
- Diverticulitis
- Pancreatitis
- Stomach ulcer
- General abdominal distress
Reconstitution and Administration
Each BERINERT vial contains 500 IU of C1 esterase inhibitor as a lyophilized concentrate for reconstitution with 10 mL of Sterile Water for Injection, USP provided.

Check the expiration date on the product vial label. Do not use beyond the expiration date.

Use either the Mix2Vial transfer set provided with BERINERT or a commercially available double-ended needle and vented filter spike.

Prepare and administer using aseptic techniques.

After reconstitution and prior to administration inspect BERINERT. The reconstituted solution should be colorless, clear, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.

Reconstitution
The procedures below are provided as general guidelines for the reconstitution of BERINERT.

1. Ensure that the BERINERT vial and diluent vial are at room temperature.

2. Place the BERINERT vial, diluent vial and Mix2Vial transfer set on a flat surface.

3. Remove the flip caps from the BERINERT and diluent vials. Wipe the vial stoppers with the alcohol swab provided. Allow to dry prior to opening the Mix2Vial transfer set package.

4. Open the Mix2Vial transfer set package by peeling away the lid (Figure 1). Leave the Mix2Vial transfer set in the clear package.

5. Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial (Figure 2).

6. Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package, and not the Mix2Vial transfer set (Figure 3).

7. With the BERINERT vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the BERINERT vial (Figure 4). The diluent will automatically transfer into the BERINERT vial.

8. With the diluent and BERINERT vial still attached to the Mix2Vial transfer set, gently swirl the BERINERT vial to ensure that the BERINERT is fully dissolved (Figure 5). Do not shake the vial.

9. With one hand, grasp the BERINERT-side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set and unscrew the set into two pieces (Figure 6).

10. Carefully look at reconstituted solution in each vial of BERINERT. It should be colorless, clear, and free from visible particles. Do not use the vial if the liquid looks cloudy, contains particles, or has changed color. Do not use if the expiration date on the label has expired.

11. Draw air into an empty, sterile syringe. Use a silicone-free syringe. While the BERINERT vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the BERINERT vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Figure 7).

12. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial transfer set (Figure 8). Attach the syringe to a suitable intravenous administration set.

13. If patient is to receive more than one vial, pool the contents of multiple vials into one syringe. A new unused Mix2Vial transfer set should be used for each BERINERT vial.
Do not refrigerate after reconstitution. When reconstitution is carried out using aseptic technique, administration may begin within 8 hours, provided the solution has been stored at up to 30°C (86°F). Do not refrigerate or freeze the reconstituted solution. Only store the reconstituted product in the vial.

**SELF-ADMINISTRATION (Intravenous Infusion)**

Your healthcare provider will teach you how to safely administer BERINERT. It is important that BERINERT is injected directly into a visible vein. Do not inject into surrounding tissues or into an artery. Once you learn how to self-administer, follow the instructions provided below.

**Step 1: Assemble supplies**

Gather the BERINERT syringe, the following disposable supplies (not provided with BERINERT), and other items (sharps or other container, treatment diary or log book):

- Standard butterfly catheter infusion set (IV administration set with winged adapter and needle)
- Sterile syringe (Use a silicone-free syringe.)
- Tourniquet
- Sterile gauze and tape, or transparent dressing
- Bandage (adhesive dressing)
- Gloves (if recommended by your healthcare provider)
- Alcohol wipe for cleaning the skin

**Step 2: Wash hands**

- Thoroughly wash and dry your hands.
- If you have been told to wear gloves when preparing your infusion, put the gloves on.

**Step 3: Clean surface**

Thoroughly clean a table or other flat surface using one or more of the alcohol wipes.

**Step 4: Prime the infusion set**

As instructed by your healthcare provider:

- To prime (fill) the infusion tubing, connect the syringe filled with BERINERT to the infusion set tubing and gently push on the syringe plunger to fill the tubing with BERINERT (Figure 9).

**Step 5: Prepare the infusion site**

- Apply a tourniquet above the site of the infusion.
- Prepare the infusion site by wiping the skin well with an alcohol swab and allow it to dry (Figure 10).

**Step 6: Infusion**

As instructed by your healthcare provider:

- Insert the butterfly needle of the infusion set tubing into your vein (Figure 11).
- If necessary, use sterile gauze and tape or transparent dressing to hold the needle in place.
- To make sure that the needle is in a vein, gently pull back on the syringe plunger and check to see if blood is in the tubing (Figure 12). If there is blood present, then the needle is in a vein. If there is no blood present, remove the needle and repeat this step using a new needle, new administration tubing, and a different injection site.
- Remove the tourniquet.
- Inject the BERINERT solution slowly at a rate of approximately 4 mL per minute (Figure 13).

**Step 7: Clean up**

- After infusing the entire amount of BERINERT, remove the infusion set (Figure 14) and cover the infusion site with a bandage (Figure 15), holding pressure on the site for a few minutes.
- Dispose of all unused solution, the empty vials, and the used needles and syringe in an appropriate container used for throwing away waste that might hurt others if not handled properly.

**Step 8: Record treatment**

- Record the lot number from the BERINERT vial label in your treatment diary or log book with the date and time of infusion every time you use BERINERT.

This Patient Package Insert has been approved by the US Food and Drug Administration.

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