Biotherapies for Life® CSL Behring

Berinert® Resource Guide for Healthcare Professionals

Contents

Important safety information for Berinert®

Berinert® is a plasma-derived concentrate of C1 Esterase Inhibitor (Human), indicated for the treatment of acute abdominal, facial or laryngeal attacks of hereditary angioedema (HAE) of moderate to severe intensity* in pediatric and adult patients. The safety and efficacy of Berinert® for prophylactic therapy have not been established.

Berinert® is contraindicated in individuals who have a known hypersensitivity or have had an anaphylactic or severe systemic reaction to C1 esterase inhibitor preparations or to any ingredient in the formulation or component of the container.

Thrombotic events have been reported at the recommended dose of C1 Esterase Inhibitor (Human) products, including Berinert®, following treatment of HAE attacks. Thrombotic events also have been reported when used off-label and at higher than labeled doses. Patients with known risk factors for thrombotic events should be monitored closely.

Berinert® is made from human plasma and may contain pathogens such as viruses and, theoretically, the agent responsible for the Creutzfeldt-Jakob disease (CJD). The risk that such products will transmit an infectious agent has been reduced by implementing stringent measures to reduce the risk of contamination by pathogens.

*An HAE attack of moderate intensity is characterized by a degree of discomfort caused by clinical HAE symptoms that results in some interference with daily activities. An HAE attack of severe intensity is characterized by a degree of discomfort caused by clinical HAE symptoms that makes it impossible to perform daily activities.

The most serious adverse reaction reported in subjects in clinical studies who received Berinert® was an increase in the severity of pain associated with HAE.

The most common adverse reactions that have been reported in greater than 4% of the subjects who received Berinert® are HAE, headache, dysgeusia, abdominal pain, nausea, muscle spasms, pain, diarrhea, and vomiting.

Pregnant women Animal reproduction studies have not been conducted with Berinert®. In a retrospective case collection study, 20 pregnant women ranging in age from 20 to 35 years who received Berinert® with repeated doses, up to 3,500 IU per attack, reported no complications during delivery and no harmful effects on their 34 neonates. In pregnant women, the benefits of treatment should be weighed against the potential risks.

Nursing mothers Berinert® has not been evaluated in nursing mothers with HAE. Berinert® should be given to nursing mothers only if clearly needed.

Pediatric population The safety and efficacy of Berinert® have been evaluated in 12 pediatric patients with HAE (age range 10 to 16 years) in the placebo-controlled pivotal study and open-label extension study. Berinert® was also evaluated in 18 pediatric patients with HAE (age range 5 to 11 years) in a Registry Study conducted in the US and Europe. The safety profile observed in the pediatric population was similar to that observed in adults.

Geriatric population The safety and efficacy of Berinert® in the geriatric population have not been evaluated in controlled clinical studies. Berinert® was evaluated in 27 geriatric subjects (age range 65 to 83 years) with HAE in a Registry Study conducted in the US and Europe. The safety profile observed in the geriatric population was similar to that observed in the younger populations studied.

Understanding HAE

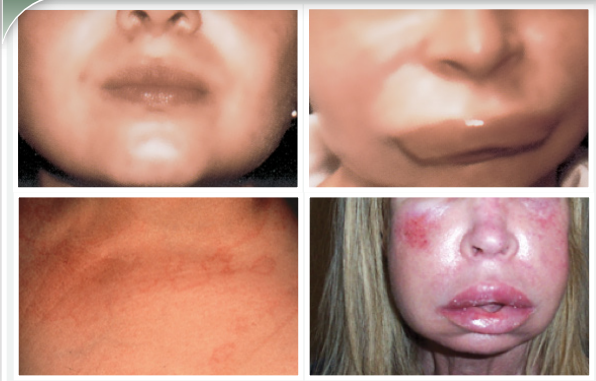
What is Hereditary Angioedema (HAE)?

- HAE is a rare, inherited disease that results in a quantitative and/or qualitative deficiency in C1 esterase inhibitor (C1-INH), a key regulator of inflammation that is integral in bradykinin-mediated angioedema[1]
- As a result of C1-INH deficiency, people born with HAE develop, recurring episodes of edema, which may occur in areas including, (but not limited to): the abdomen, face, and throat[2]
- This condition affects approximately 1:10,000 to 1:50,000 individuals[3]
- HAE is characterized by acute, recurrent attacks of localized edema in (but not limited to) the skin, upper respiratory tract, or gastrointestinal tract[1]
- Laryngeal (in the throat) HAE attacks can be fatal (due to asphyxia) if not properly diagnosed and treated[4,5]

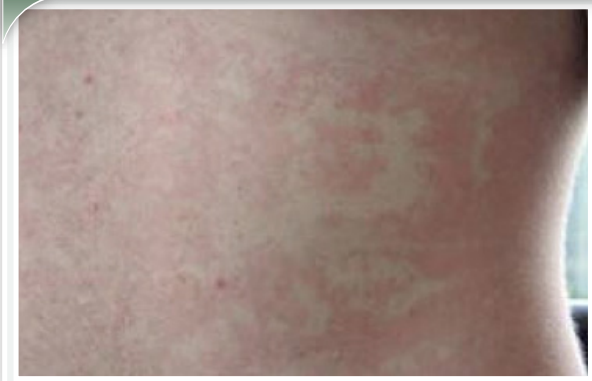
Signs and Symptoms

- HAE can produce episodes of nonpitting, nonerythematous swelling areas including (but not limited to): the abdomen, face, and throat[6,7]
- Unlike allergic reactions, there is no itching with HAE[8]
- About 1/3 of patients develop erythema marginatum, a serpentine rash that is not itchy or raised at the start of an attack[2,8]
- The swelling associated with an attack often gets worse over a period of 12-24 hours, then typically resolves within 72 hours. However, symptoms can last up to five days[2,6]

Edema



Erythema marginatum



Signs and Symptoms (continued)

- The number of episodes an individual may experience can be unpredictable. Some people experience weekly attacks, while others may go years between attacks[6]
- Abdominal attacks can cause severe abdominal pain, nausea, vomiting, and diarrhea[2,6]
  – These can mimic symptoms of a surgical emergency, resulting in unnecessary surgery for about 1/3 of patients with undiagnosed HAE[9]

⚠ Laryngeal edema poses the greatest risk for patients with HAE, due to the chance of asphyxiation, and should be treated as a medical emergency, requiring prompt treatment as soon as throat involvement is suspected[6]

Learning to Recognize Symptoms and Triggers[10]

- HAE attacks can be unpredictable and vary in terms of frequency and severity
- Some common triggers that could cause an acute HAE attack are:
  - Mental stress
  - Dental procedures
  - Menstruation
  - Mechanical trauma
  - Infection
  - Use of estrogen-containing oral contraceptives
- Many patients develop symptoms that signal the onset of an acute HAE attack, including:[4]
  - Tingling
  - Paresthesias
  - Erythematous rash
  - Fatigue
  - Malaise
  - Nausea
  - Vomiting
  - Abdominal Pain
- Teach patients to recognize symptoms such as these, so they can learn to recognize the early signs of an attack, and treat promptly[11]
- Having a fast and reliable on-demand treatment plan can help put them in control of their HAE and increase their independence[11]

About Berinert®

What is Berinert®?

- Berinert® is an C1esterase inhibitor (C1-INH) approved for treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in pediatric and adult patients.[12]
- Approved for use in Canada in 2010
- The safety and efficacy of Berinert® for prophylactic therapy have not been established
- Self-administered Berinert® treats HAE at the first sign of an acute attack
- Berinert® is available as a single-use vial of 500 IU of lyophilized powder. Each vial must be reconstituted with 10 mL of Sterile Water for Injection
- Berinert® is also available in a 1500 IU format that must be reconstituted with 3 mL of Sterile Water for Injection
- Berinert® is approved for patient self-administration (after proper training by a healthcare professional) during an acute attack. The safety and efficacy of Berinert® for prophylactic therapy have not been established[12]
- Individualized weight-based dosing provides an optimized dose during an attack

Contraindication

Berinert® is contraindicated in individuals who have a known hypersensitivity or have had an anaphylactic or severe systemic reactions to C1 esterase inhibitor preparations or to any ingredient in the formulation or component of the container

Efficacy for Abdominal and Facial Attacks[12]

- Overall median time to onset of abdominal and facial attack symptom relief was 30 minutes vs. 90 minutes in the placebo group

Median time to onset of symptom relief*

Attack type	Berinert® 20 IU/kg body weight (n=43)	Placebo group (n=42)
Overall	30 minutes†	90 minutes
Abdominal	30 minutes	75 minutes
Facial	55 minutes	24 hours

*Results from a phase III prospective, multinational, randomized, parallel-group, placebo-controlled, dose-finding, three-arm, double-blind clinical study assessing the efficacy and safety of Berinert® in 124 adult and pediatric subjects with C1 esterase inhibitor (C1-INH) deficiency who were experiencing an acute moderate to severe attack of abdominal or facial HAE

†Statistically significant reduction (p=0.0025) compared to placebo

Efficacy for Laryngeal Attacks[12]

- In I.M.P.A.C.T.† (International Multi-centre Prospective Angioedema C1-Inhibitor Trial) 2, median time to onset of laryngeal attack symptom relief was **15** minutes

Time to initial onset of symptom relief and time to complete resolution of HAE symptoms for laryngeal attacks

Statistic	Laryngeal (n=48)
Time to initial onset of symptom relief [hours] Median (range) 95% CI for median	0.25 (0.10 – 1.25) [0.23; 0.42]
Time to complete resolution of HAE symptoms [hours] Median (range) 95% CI for median	8.38 (0.63 – 61.83*) [6.22; 21.50]

* The maximum time to complete resolution of 61.8 hours was an imputed value. Subject 29301 had 2 laryngeal attacks with missing times to complete resolution of HAE symptoms, which were imputed with the maximum time to complete resolution of HAE symptoms observed for an attack in this subject.

CI = confidence interval

HAE = hereditary angioedema

N = number of attacks

† I.M.P.A.C.T: a prospective, open-label, uncontrolled, multicenter extension study conducted with 57 subjects having previously participated in the pivotal phase III study and having experienced any type of subsequent HAE attack. Berinert® 20IU/kg was provided to all enrolled patients and each HAE attack was treated and evaluated individually. All patients were monitored for changes in vital signs, and for the occurrence of any AEs. Time to onset of symptom relief and time to complete resolution of HAE symptoms were assessed every 15 minutes for the first 2 hours, every 30 minutes for the subsequent 2 hours, and at 5, 6, 7, 8, 12, 16, 20, and 24 hours after administration of the study medication. Each attack was followed up until complete resolution of all HAE symptoms.

Safety[12]

- Berinert® (20 IU/Kg) demonstrated a safety profile, with a low number of adverse reactions compared to placebo (p=0.0025)
- The most serious adverse reaction reported in subjects in clinical studies who received Berinert® is an increase in the severity of pain associated with HAE
- The most common adverse reactions that have been reported in greater than 4% of the subjects who received Berinert® are HAE, headache, dysgeusia, abdominal pain, nausea, muscle spasms, pain, diarrhea, and vomiting

Adverse reactions* occurring up to 4 hours after initial infusion in more than 4% of subjects, irrespective of causality

Adverse reactions	Number (%) of subjects reporting adverse reactions Berinert® 20 IU/kg (n=43)	Number (%) of subjects reporting adverse reactions Placebo group (n=42)
Nausea†	3 (7%)	5 (11.9%)
Dysgeusia (distortion of the sense of taste)	2 (4.7%)	0 (0)
Abdominal pain†	2 (4.7%)	3 (7.1%)
Vomiting†	1 (2.3%)	3 (7.1%)
Diarrhea†	0 (0)	4 (9.5%)
Headache	0 (0)	2 (4.8%)

*Comprises adverse events that began within 4 hours of infusion; these events were considered adverse reactions irrespective of reported causality.
†The following abdominal symptoms were identified in the protocol as associated with HAE abdominal attacks: abdominal pain, bloating, cramps, nausea, vomiting, and diarrhea.

Product handling

How to Store Berinert®[12]

- Store in the refrigerator or at room temperature (at +2°C to 30°C). Do not freeze. Protect from light
- This means that Berinert® does not need to be refrigerated. Patients can carry it with them to use at the first sign of an attack
- Keep the product at a stable temperature. Avoid extreme heat or cold

Traveling with Berinert®

- Patients should bring enough Berinert® (and accompanying supplies) for their entire travel period
- Patients should bring copies of their prescription, along with any other necessary documentation (e.g. Emergency Info Card, Letter from Physician)

Elements for successful training

The Nurse as an Essential Element in HAE Patient Care[14]

- Educates, advocates, manages patients and healthcare team
- Encourages patients to take ownership of therapy
- Empowers patients to take control of their lives

Setting Expectations to Ensure Greater Commitment to Therapy

- Explain benefits and risks of on-demand C1 esterase inhibitor (C1-INH) therapy/reasons for choice
- Set expectations:
  - How long administration takes
  - Necessary equipment
  - Transition/adjustment period to therapy

Strategies for Effective Patient Teaching

- Use helpful learning tools for Berinert®:
  - Self-Administration Videos (Reconstitution & Administration)
  - Available on the Berinert® YouTube channel and through the DVD
  - Flip Chart (Step-by-step process)
  - Patient Journal
- Assess patient proficiency by watching demonstration of self-administration
  - Ensure patient comfort level
  - Multiple patient visits when necessary
  - Include "patient engagement" in assessment of independence

Basic Patient Training: Checklist

- ✓ Aseptic technique and infection control
- ✓ Reconstitution
- ✓ Site selection
- ✓ Intravenous insertion
- ✓ Expected benefits and risks of on-demand C1 esterase inhibitor (C1-INH) therapy
- ✓ Proper storage and handling
- ✓ Expected adverse reactions and management
- ✓ Documentation in journal

Helping patients self-administer Berinert®

Berinert® Self-Administration Training Kit

Berinert® Patient Welcome Kit with important patient information and support offerings

Infusion practice mat with training needles, infusion sets and tourniquets

Getting started

Gather your supplies

Generally, you will need:

- Berinert® vial
- Diluent (Sterile Water for Injection) vial
- Mix2Vial®*
- Disposable syringe(s)
- Butterfly infusion set(s)
- Tourniquet
- Antiseptics (alcohol wipes, disinfection swabs such as alcohol swabs)
- Sterile gauze pads
- Surgical / paper tape (if required)
- 1 bandage (if required)
- Sharps/Biohazard container
- HAE patient diary/log sheets

* Mix2Vial® is a registered trademark of West Pharma. Services IL, Ltd., of West Pharmaceuticals Services, Inc.

Reconstitution

Inspect both vials

- Make sure Berinert® and water vials are at room temperature
- **Do not use the vials if:**
  - Their protective caps are missing
  - Their expiration dates (see labels) have passed
- **Problem with self-administration**
  - If a patient has any problem with self-administration, he or she should contact a healthcare professional immediately

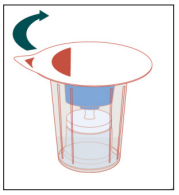
Wash your hands and clean surface

- **Thoroughly wash and dry your hands**
  - Put on the gloves if you've been told to wear them while preparing your infusion
- **Thoroughly clean your mat or other flat surface**
  - Use one or more of the antiseptic wipes

Step 1: **Clean water and Berinert® vial stoppers**

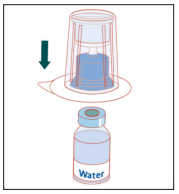
- Remove the flip caps from both vials (Water and Berinert®)
  - Wipe the rubber stoppers with an antiseptic
  - Allow the stopper to dry for 30 seconds before puncturing

Step 2: **Open the Mix2Vial® transfer set**



- Peel away the blister lid from the Mix2Vial® transfer set
- To maintain sterility, leave Mix2Vial® set in its clear outer package

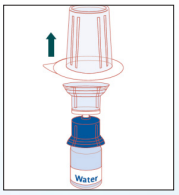
Step 3: **Prepare diluent vial**



- Place the water vial on a flat, hard surface and hold the vial tightly
  - Grip the Mix2Vial® transfer set while keeping it in the package
  - Push the plastic spike of the blue end of the Mix2Vial® set firmly, through the center of the water vial stopper

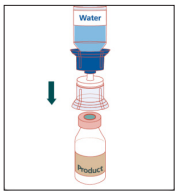
Hint: *The blue end locks onto the water vial*

Step 4: **Remove the Mix2Vial® clear packaging**



- While holding the water vial, 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

Step 5: **Transfer Diluent into Berinert® Vial**



- With the Berinert® vial placed firmly **(hold the vial tight)** on a hard, even, flat surface, invert the water vial with the Mix2Vial® transfer set attached
  - Push the plastic spike on the clear end of Mix2Vial® straight down onto the Berinert® vial stopper

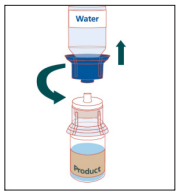
  - The diluent will transfer into the Berinert® vial automatically

Step 6: **Dissolve Berinert® powder**

- With the Berinert® vial still attached to the Mix2Vial® transfer set, gently swirl the Berinert® vial to ensure that the Berinert® is fully dissolved
  - Do not shake the vial
  - Make sure that the powder dissolves completely

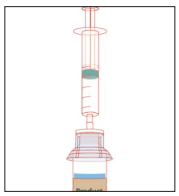
Note: *Berinert® 1500 may take longer than Berinert® 500 to dissolve*

Step 7: **Disconnect the vials**



- Separate the set
  - Unscrew empty diluent (blue) vial: with one hand grip the clear end of the Mix2Vial® set, and with the other hand grip the blue end of the Mix2Vial® set and unscrew the set into 2 pieces

Step 8: **Inspect the solution and draw it into a syringe**



- The reconstituted solution for Berinert® 500 IU should be colourless and clear. The reconstituted solution for Berinert® 1500 IU should be colourless, clear to slightly opalescent. Inspect Berinert® visually for particulate matter and discolouration prior to administration

- Draw the solution into a syringe.
  - Draw air into an empty, sterile syringe
  - Use the syringe provided with the product
  - With the Berinert® vial upright, screw the syringe to the Mix2Vial® transfer set
  - Inject air into the Berinert® vial
  - While keeping the syringe pressed, invert the Berinert® vial and draw the liquid into the syringe by pulling the plunger back slowly

Step 9: **Prepare the syringe for self-administration**

- Once the solution has been transferred into the syringe, firmly grip the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial® transfer set
  - Attach the syringe to an infusion set or another suitable administration set

Administer Berinert® using aseptic technique:

- Thoroughly wash and dry hands
- Locate vein
- Clean the injection site(s) using an antiseptic skin preparation Allow each site to dry before proceeding
- Insert the needle into the vein
- Check for proper placement of the needle
- Inject Berinert® 500 IU into the vein using a slow intravenous injection (4 mL/minute). Inject Berinert® 1500 IU into the vein using a slow intravenous injection

Repeat if necessary

- If your dose of Berinert® requires additional vials, repeat steps 3 to 8 for each additional vial of Berinert®
  - Use a new, unused Mix2Vial® transfer set for each vial of Berinert®
- Do not refrigerate after reconstitution

Vacuum Loss

- The Vacuum in the Berinert vial will allow for the diluent to transfer automatically into the Berinert powder. Vacuum loss may occur if the spike is not inserted at a 90 degree angle through the center of the
rubber stopper

- If the fluid does not transfer automatically, instruct the patient to contact the training nurse for further instructions

- Instruct the patient to use new vials of Berinert® and diluent if the diluent does not transfer into the Berinert® powder

Self-Administration

Step 1: **Gather Supplies for Administration**

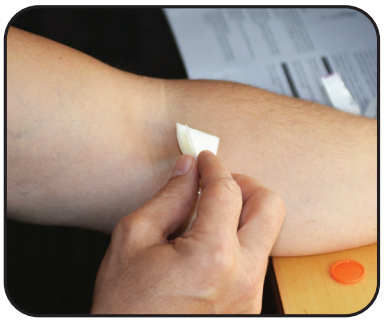
- Reconstituted Berinert® vial(s) in silicone-free sterile syringe
- Butterfly catheter infusion set
- Tourniquet
- Sterile gauze and tape, or transparent dressing
- Bandage (adhesive dressing)
- Alcohol wipes
- Gloves (if recommended by your doctor)
- Sharps container
- Berinert® Treatment/Therapy Journal

Step 2: **Clean surface**

- Thoroughly clean your mat or other flat surface
  – Use one or more of the antiseptic wipes

Self-Administration (continued)

Step 3: Prepare the infusion site

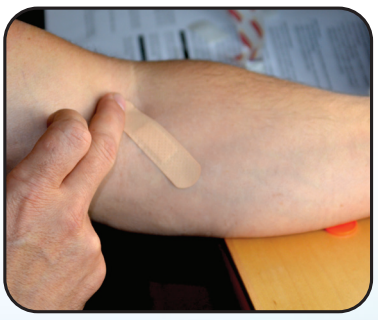


- Apply a tourniquet on the arm above the site of the injection
  - Prepare the injection site by wiping the skin well with an alcohol swab

Step 4: Infusion

- Remove the air from the tubing
- Insert the butterfly needle of the infusion set into your vein
- Remove the tourniquet
- If necessary, use sterile gauze and tape or transparent dressing to hold the needle in place
- Inject the Berinert® 500 solution slowly at a rate of approximately 4 mL per minute or inject the Berinert® 1500 solution as a slow intravenous injection

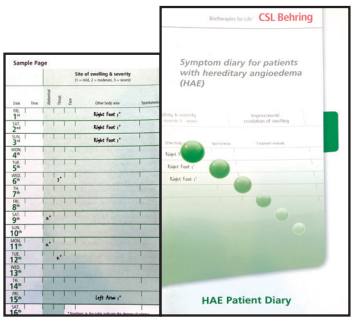
Step 5: Clean up



- After infusing Berinert®, remove the infusion set and cover the infusion site with a bandage
  - Dispose of all unused solution, the empty vials, and the used needles and syringe in an appropriate container

Step 6: **Record infusion details**

- Record the lot number from the Berinert® vial label in your treatment diary/log book with all other pertinent information instructed by your healthcare provider



Patients should be sure to tell their doctor about any problems they may have during infusions. The doctor may also ask to see the Berinert® Treatment/Therapy Journal, so instruct them to take it to each visit to the doctor's office.

Troubleshooting for Needle Injection

For any of the following situations, continue the injection in another vein with a new butterfly:

– Clear bubble on the skin (you are not in the vein)
– The needle is inserted at an angle of less than 30 degrees[13]
  The bevel scrapes the outer surface of the vein wall, failing to puncture it
– Coloured bubble on the skin (you have gone through the vein)
– The needle is inserted at an angle greater than 30 degrees
  It punctures through both sides of the vein
– Pain or swelling occur during the injection

Emergency procedures

- Know the common potential side effects of Berinert®, including:
  - HAE
  - Headache
  - Dysgeusia
  - Abdominal pain
  - Nausea
  - Muscle spasms
  - Pain
  - Diarrhea
  - Vomiting
- Seek emergency treatment immediately for any of the following:
  - Wheezing
  - Difficulty breathing
  - Chest tightness
  - Fast heartbeat
  - Faintness
  - Swelling of the face
  - Turning blue (look at lips and gums)
  - Rash
  - Hives
- Patients should carry emergency information cards
- Remind patients that if they self-administer to treat a laryngeal attack, they should immediately seek medical attention afterwards

Additional resources

Online Resources

Online resources	
AllAboutHAE.ca	all about HAE

Patient Support

Patient Support: HAE	
Canadian Hereditary Angioedema Network (CHAEN), a not-for-profit organization of physicians who treat and/or are interested in HAE.	RC CHAEN H
Hereditary Angioedema Canada, a group of dedicated volunteers from all across the country who are working to change the lives of hereditary angioedema patients in Canada.	HAE AOH CANADA

Conclusion

- Information about hereditary angioedema, what Berinert® is and how it should be handled
- Strategies for successfully teaching patients how to self-administer Berinert®
- Aseptic technique, reconstitution, site selection, intravenous needle insertion, possible infusion reactions, storage and handling, and documentation
- Reminders about emergency procedures, as well as additional resources that you and your patients may find helpful

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Thank you for completing Berinert® RN Compass Nurse Training!