

**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 or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients (1).

The safety and efficacy of Berinert for prophylactic therapy has not been established (1).

**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 (2).
- Administer 20 units per kg body weight (2).
- Reconstitute Berinert prior to use (2.1).
- Administer at room temperature within 8 hours of reconstitution (2.1).
- Inject at a rate of approximately 4 mL per minute (2.2).
- Do not mix Berinert with other medicinal products or solutions (2.2).

**DOSAGE FORMS AND STRENGTHS**

500 units lyophilized concentrate in a single-use vial for reconstitution with 10 mL of diluent (sterile water) (3).

**CONTRAINDICATIONS**

- Do not use in patients with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis to C1 esterase inhibitor preparations (4).

**WARNINGS AND PRECAUTIONS**

- Hypersensitivity reactions may occur. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions following discontinuation of administration (5.1).
- Thrombotic events have occurred in patients receiving off-label high doses of Berinert. Monitor patients with known risk factors for thrombotic events (5.2).
- Berinert is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.3).

**ADVERSE REACTIONS**

- The most serious adverse reaction reported in subjects who received Berinert was an increase in the severity of pain associated with HAE (6.1).
- The most common adverse reactions observed by ≥4% of subjects after Berinert treatment were subsequent HAE attack, headache, abdominal pain, nausea, muscle spasms, pain, diarrhea and vomiting (6.1).

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

**DRUG INTERACTIONS**

No drug interaction studies have been conducted (7).

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: No animal data. Limited human data. Use only if clearly needed (8.1).
- Children: Safety and effectiveness in children ages 0 through 12 have not been established. Berinert was evaluated in 5 children (ages 3 through 12) and in 8 adolescent subjects (ages 13 through 16). Compared to adults, the half-life of Berinert was shorter and clearance was faster in children. The clinical implication of this difference is not known (8.4).

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

Issued: October 2009

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\*Sections or subsections omitted from the full prescribing information are not listed.

1  
2 **FULL PRESCRIBING INFORMATION**

3  
4 **Berinert® [C1 Esterase Inhibitor (Human)]**  
5 **Freeze-dried powder**

6  
7  
8 **1 INDICATIONS AND USAGE**

9  
10 Berinert is a plasma derived concentrate of C1 Esterase Inhibitor (Human) indicated for the  
11 treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and  
12 adolescent patients.

13  
14 The safety and efficacy of Berinert for prophylactic therapy has not been established.

15  
16  
17 **2 DOSAGE AND ADMINISTRATION**

18  
19 **For Intravenous Use Only.**

20  
21 Administer Berinert at a dose of 20 units per kg body weight by intravenous injection.

22  
23 Freeze-dried powder for reconstitution. Store the vial in the original carton in order to  
24 protect from light. Do not freeze.

25  
26 **2.1 Preparation and Handling**

- 27
- 28 • Check the expiration date on the product vial label. Do not use beyond the  
29 expiration date.
  - 30 • Use aseptic technique when preparing and administering Berinert (*see*  
31 *Reconstitution and Administration [2.2]*).
  - 32 • After reconstitution, inspect Berinert visually for particulate matter and  
33 discoloration prior to administration. The reconstituted solution should be  
34 colorless, clear, and free from visible particles. Do not use if the solution is cloudy,  
35 discolored, or contains particulates.
  - 36 • The Berinert vial is for single use only. Berinert contains no preservative. Any  
37 product that has been reconstituted should be used promptly. The reconstituted  
38 solution must be used within 8 hours. Discard partially used vials.
  - Do not freeze the reconstituted solution.

39

40 **2.2 Reconstitution and Administration**

41 Each Berinert kit consists of one carton containing one single-use vial of Berinert, one 10 mL  
 42 vial of diluent (sterile water), one Mix2Vial™ transfer set, and one alcohol swab.

43

44 Use either the Mix2Vial transfer set provided with Berinert (*see How Supplied [16.1]*) or a  
 45 commercially available double-ended needle and vented filter spike.





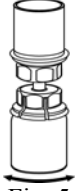
46




47 Reconstitution

48

49 The procedures below are provided as general guidelines for the reconstitution and  
 50 administration of Berinert.

51

<p>1. Ensure that the Berinert vial and diluent vial are at room temperature. Use aseptic technique during the reconstitution procedure.</p>	
<p>2. Place the Berinert vial, diluent vial and Mix2Vial transfer set on a flat surface.</p>	
<p>3. Remove the flip caps from the Berinert and diluent vials. Treat the vial stoppers with the alcohol swab provided and allow to dry prior to opening the Mix2Vial transfer set package.</p>	
<p>4. Open the Mix2Vial transfer set package by peeling away the lid (Fig. 1). Leave the Mix2Vial transfer set in the clear package.</p>	 <p>Fig. 1</p>
<p>5. Place the diluent vial on a flat surface and hold the vial tight. Grip the Mix2Vial transfer set together with the clear package and snap the blue end of the Mix2Vial transfer set onto the diluent vial stopper at a 90° angle (Fig. 2).</p>	 <p>Fig. 2</p>
<p>6. Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you only pull up the clear package and not the Mix2Vial transfer set (Fig. 3).</p>	 <p>Fig. 3</p>
<p>7. With the Berinert vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and snap the transparent adapter onto the Berinert vial stopper at a 90° angle (Fig. 4). The diluent will automatically transfer into the Berinert vial.</p>	 <p>Fig. 4</p>
<p>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 (Fig. 5). Do not shake the vial.</p>	 <p>Fig. 5</p>

<p>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. (Fig. 6).</p>	 <p>Fig. 6</p>
<p>10. Draw air into an empty, sterile 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. (Fig. 7).</p>	 <p>Fig. 7</p>
<p>11. 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 (Fig. 8). Attach the syringe to a suitable intravenous (IV) administration set.</p>	 <p>Fig. 8</p>
<p>12. If the same patient is to receive more than one vial, the contents of multiple vials may be pooled in a single administration device (e.g. syringe). A new unused Mix2Vial transfer set should be used for each Berinert vial.</p>	
<p>13. 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 25°C (77°F). Do not refrigerate or freeze the reconstituted solution.</p>	

52

53 Administration

54

55 Do not mix Berinert with other medicinal products and administer by a separate infusion line.

56

57 Use aseptic technique when administering Berinert.

58

59 Administer Berinert by slow intravenous injection at a rate of approximately 4 mL per  
60 minute.

61

62

63 **3 DOSAGE FORMS AND STRENGTHS**

64

65 • Berinert is a lyophilized concentrate available in a single-use vial that contains 500  
66 units.

67 • Each vial must be reconstituted with 10 mL of diluent (sterile water) provided.

68

69

70 **4 CONTRAINDICATIONS**

71

72 Berinert is contraindicated in individuals who have had life-threatening hypersensitivity  
73 reactions, including anaphylaxis, to C1 esterase inhibitor preparations.

74

75

76 **5 WARNINGS AND PRECAUTIONS**

77

78 **5.1 Hypersensitivity**

79 Severe hypersensitivity reactions may occur. Epinephrine should be immediately available  
80 for treatment of acute severe hypersensitivity reaction (*see Patient Counseling Information*  
81 *[17.1]*). The signs and symptoms of hypersensitivity reactions may include hives,  
82 generalized urticaria, tightness of the chest, wheezing, hypotension, and/or anaphylaxis  
83 during or after injection of Berinert.

84

85 Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment  
86 methods should be carefully considered. In case of suspected hypersensitivity, immediately  
87 discontinue administration of Berinert and institute appropriate treatment.

88

89 **5.2 Thrombotic Events**

90 Thrombotic events have been reported in association with Berinert when used off-label and  
91 at higher than labeled doses.<sup>1</sup> Animal studies have confirmed the risk of thrombosis from  
92 intravenous administration of C1 esterase inhibitor products<sup>2</sup> (*see Overdosage [10] and*  
93 *Animal Toxicology and/or Pharmacology [13.2]*).

94

95 **5.3 Transmission of Infectious Agents**

96 Because Berinert is made from human blood, it may contain infectious agents (e.g., viruses  
97 and theoretically the Creutzfeldt-Jakob disease agent [CJD]) that can cause disease. The risk  
98 that such products will transmit an infectious agent has been reduced by screening plasma  
99 donors for prior exposure to certain viruses, by testing for the presence of certain current  
100 virus infections, and by processes demonstrated to inactivate and/or remove certain viruses  
101 during manufacturing (*see Description [11] and Patient Counseling Information [17.1]*).

102

103 Despite these measures, such products may still potentially transmit disease. There is also  
104 the possibility that unknown infectious agents may be present in such products.

105

106 Since 1979, a few suspected cases of viral transmission have been reported with the use of  
107 Berinert outside the US, including cases of acute hepatitis C. From the incomplete  
108 information available from these cases, it was not possible to determine with certainty if the  
109 infections were or were not related to prior administration of Berinert.

110

111 The physician should discuss the risks and benefits of this product with the patient before  
112 prescribing or administering it to the patient. (*See Patient Counseling Information [17.1]*).

113

114 All infections thought by a physician possibly to have been transmitted by Berinert should be  
115 reported by lot number, by the physician, or other healthcare provider to CSL Behring  
116 Pharmacovigilance Department at 1-866-915-6958.

117

118

## 119 6 ADVERSE REACTIONS

120

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

123

124 The most common adverse reactions that have been reported in greater than 4% of the  
125 subjects who received Berinert in clinical studies were subsequent HAE attack, headache,  
126 abdominal pain, nausea, muscle spasms, pain, diarrhea and vomiting.

127

### 128 6.1 Clinical Trials Experience

129 *Because clinical studies are conducted under widely varying conditions, adverse reaction*  
130 *rates observed in the clinical trials of a drug cannot be directly compared to rates in the*  
131 *clinical trials of another drug and may not reflect the rates observed in practice.*

132

#### 133 Placebo-controlled Clinical Study

134 In the placebo-controlled clinical study, referred to as the randomized clinical trial (RCT) (*see*  
135 *Clinical Studies [14]*), 124 subjects experiencing an acute moderate to severe abdominal or  
136 facial HAE attack were treated with Berinert (either a 10 unit per kg body weight or a 20 unit  
137 per kg body weight dose), or placebo (physiological saline solution).

138

139 The treatment-emergent serious adverse reactions/events that occurred in 5 subjects in the  
140 RCT were laryngeal edema, facial attack with laryngeal edema, swelling (shoulder and  
141 chest), exacerbation of hereditary angioedema, and laryngospasm.

142

143 **Table 1: Adverse Reactions\* Occurring up to 4 hours after Initial Infusion in More**  
144 **than 4% of Subjects, Irrespective of Causality†**

145

Adverse Reactions	Number (%) of Subjects Reporting Adverse Reactions Berinert 20 units/kg (n = 43)	Number (%) of Subjects Reporting Adverse Reactions [Placebo] (n = 42)
Nausea†	3 (7%)	5 (11.9%)
Dysgeusia	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%)

146

147

148

149

\* The study protocol specified that adverse events which began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (i.e. adverse reactions).

† The following abdominal symptoms were identified in the protocol as associated with HAE abdominal attacks: abdominal pain, bloating, cramps, nausea, vomiting, and diarrhea.

150 **Table 2: Adverse Reactions\* Occurring in More than 4% of Subjects up to 72 hours**  
 151 **after Infusion of Initial or Rescue Medication† by Intent-to-Treat,**  
 152 **Irrespective of Causality**  
 153

Adverse Reactions	Number (%) of Subjects Reporting Adverse Reactions <sup>‡</sup> Berinert 20 units/kg (n = 43)	Number (%) of Subjects Reporting Adverse Reactions <sup>‡</sup> [Placebo] (n = 42)
Nausea	3 (7%)	11 (26.2%)
Headache	3 (7%)	5 (11.9%)
Abdominal Pain	3 (7%)	5 (11.9%)
Dysgeusia	2 (4.7%)	1 (2.4%)
Vomiting	1 (2.3%)	7 (16.7%)
Pain	1 (2.3%)	4 (9.5%)
Muscle spasms	1 (2.3%)	4 (9.5%)
Diarrhea	0 (0)	8 (19%)
Back pain	0 (0)	2 (4.8%)
Facial pain	0 (0)	2 (4.8%)

154 \* The study protocol specified that adverse events which began within 72 hours of blinded study medication administration  
 155 were to be classified as at least possibly related to study medication (i.e. adverse reactions).

156 † If a subject experienced no relief or insufficient relief of symptoms within 4 hours after infusion, investigators had the  
 157 option to administer a blinded second infusion (“rescue” treatment) of Berinert (20 units/kg for the placebo group, 10  
 158 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group).

159 ‡ Adverse reactions following either initial treatment and/or blinded “rescue” treatment. Because more subjects in the  
 160 placebo randomization group than in the Berinert randomization group received rescue treatment, the median observation  
 161 period in this analysis for subjects randomized to placebo was slightly longer than for subjects randomized to receive  
 162 Berinert.

163  
 164 Table 3 lists the Adverse Events that occurred in more than 4% of the subjects 7 to 9 days  
 165 after the end of a Berinert infusion, *irrespective of causality*.

166  
 167 **Table 3: Adverse Events Occurring in More than 4% of Subjects\* Receiving Berinert**  
 168 **at either 10 units/kg or 20 units/kg 7 to 9 Days after Infusion, Irrespective of**  
 169 **Causality**  
 170

Adverse Event	Number of Subjects Reporting Adverse Event (n=108)	Percent
Hereditary angioedema	12	11.1
Headache	12	11.1
Abdominal pain <sup>†</sup>	7	6.5
Nausea <sup>†</sup>	7	6.5
Muscle spasms	6	5.6
Pain	6	5.6
Diarrhea <sup>†</sup>	5	4.6
Vomiting <sup>†</sup>	5	4.6

171 \* Includes subjects in the placebo group who received Berinert 20 units/kg as rescue study medication.

172 † These symptoms were identified in the protocol as related to the underlying disease. Any increase in intensity or new  
 173 occurrence of these symptoms after study medication administration was considered to be an adverse event.

174

175 Subjects were tested at baseline and after 3 months for exposure to Parvovirus B19, hepatitis  
176 B, hepatitis C, and HIV-1 and HIV-2. No subject who underwent testing evidenced  
177 seroconversion or treatment-emergent positive polymerase chain reaction testing for the  
178 above pathogens.

179

### 180 Extension Study

181 In an interim safety analysis, of the ongoing open-label extension study, 56 subjects with 559  
182 acute moderate to severe abdominal or facial attacks received a 20 unit/kg body weight dose  
183 of Berinert (*see Clinical Studies [14]*). This study provides additional safety data in subjects  
184 who received multiple infusions of the product for sequential HAE attacks (one infusion per  
185 attack).

186

187 Table 4 lists the adverse events that occurred in this interim safety analysis of the ongoing  
188 open-label extension study in more than 4% of subjects up to 72 hours or 9 days after the end  
189 of a Berinert infusion, *irrespective of causality*.

190

191 **Table 4: Incidence of Adverse Events by Descending Frequency Occurring in More**  
192 **than 4% of Subjects Receiving Berinert up to 72 Hours or 9 Days after**  
193 **Infusion, Irrespective of Causality**

194

Adverse Event	Number (%) of Subjects Reporting Adverse Event up to 72 hours (n=56)	Number (%) of Subjects Reporting Adverse Event up to 9 Days (n=56)
Headache	3 (5.4%)	4 (7.1%)
Abdominal pain	3 (5.4%)	3 (5.4%)
Hereditary angioedema	2 (3.6%)	4 (7.1%)
Nasopharyngitis	2 (3.6%)	3 (5.4%)

195

## 196 **6.2 Postmarketing Experience**

197 *Because postmarketing reporting of adverse reactions is voluntary and from a population of*  
198 *uncertain size, it is not always possible to reliably estimate the frequency of these reactions*  
199 *or establish a causal relationship to product exposure.*

200

201 Adverse reactions reported in Europe since 1979 in patients receiving Berinert for treatment  
202 of HAE include hypersensitivity/anaphylactic reactions, a few suspected cases of viral  
203 transmission, including cases of acute hepatitis C, injection-site pain, injection-site redness,  
204 chills, and fever.

205

206 The following adverse reactions, identified by system organ class, have been attributed to  
207 Berinert during post approval use outside the US.

208

- 209 • *Immune System Disorder: Hypersensitivity/anaphylactic reactions, and shock*
- 210 • *General/Body as a Whole: Pain on injection, redness at injection site, chills, and fever*

211

212

## 213 **7 DRUG INTERACTIONS**

214 No drug interaction studies have been conducted.

215

216

## 217 **8 USE IN SPECIFIC POPULATIONS**

218

### 219 **8.1 Pregnancy**

220 Pregnancy Category C. Animal reproduction studies have not been conducted with Berinert.  
221 It is not known whether Berinert can cause fetal harm when administered to a pregnant  
222 woman or can affect reproduction capacity. Berinert should be given to a pregnant woman  
223 only if clearly needed. In a retrospective case collection study, 20 pregnant women ranging  
224 in age from 20 to 35 years who received Berinert with repeated doses up to 3,500 units per  
225 attack reported no complications during delivery and no harmful effects on their 34 neonates.

226

### 227 **8.2 Labor and Delivery**

228 The safety and effectiveness of Berinert administration prior to or during labor and delivery  
229 have not been established. Use only if clearly needed.

230

### 231 **8.3 Nursing Mothers**

232 It is not known whether Berinert is excreted in human milk. Because many drugs are  
233 excreted in human milk, use only if clearly needed when treating a nursing woman.

234

### 235 **8.4 Pediatric Use**

236 Safety and efficacy of Berinert in children (ages 0 through 12) have not been established.  
237 There was an insufficient number of subjects in this age group to determine whether they  
238 respond differently from older subjects. The safety and efficacy of Berinert were evaluated  
239 in 5 children (ages 3 through 12) and in 8 adolescent subjects (ages 13 through 16) (*see*  
240 *Pharmacokinetics [12.3]*).

241

### 242 **8.5 Geriatric Use**

243 Safety and efficacy of Berinert in the geriatric population have not been established. Clinical  
244 studies with Berinert included four subjects greater than 65 years old. There was an  
245 insufficient number of subjects in this age group to determine whether they respond  
246 differently from younger subjects.

247

248

249 **10 OVERDOSAGE**

250

251 The development of thrombosis has been reported after doses exceeding 20 units/kg body  
252 weight of Berinert in newborns and young children with congenital heart anomalies during or  
253 after cardiac surgery under extracorporeal circulation when used off-label.<sup>1</sup>

254

255 The maximum dose administered in clinical studies in hereditary angioedema was 20  
256 units/kg body weight. Overdosage did not occur in connection with treatment of HAE.

257

258

259 **11 DESCRIPTION**

260

261 Berinert is a human plasma derived, purified, pasteurized, lyophilized concentrate of C1  
262 esterase inhibitor to be reconstituted for intravenous administration. Berinert is prepared  
263 from large pools of human plasma from US donors. One standard unit of C1 esterase  
264 inhibitor concentrate is equal to the amount of C1 esterase inhibitor in 1 mL of fresh citrated  
265 human plasma, which is equivalent to 270 mg/L or 2.5 µM/L. There exists no international  
266 laboratory standard for quantifying C1 esterase inhibitor. An in-house standard is used to  
267 assure lot-to-lot consistency in product potency.

268

269 C1 esterase inhibitor is a soluble, single-chain glycoprotein containing 478 amino acid  
270 residues organized into three beta-sheets and eight or nine alpha-helices.<sup>3</sup> The heavily  
271 glycosylated molecule has an apparent molecular weight of 105 kD, of which the  
272 carbohydrate chains comprise 26% to 35%.<sup>4</sup>

273

274 Each vial of Berinert contains 500 units C1 esterase inhibitor, 50 to 80 mg total protein, 85 to  
275 115 mg glycine, 70 to 100 mg sodium chloride, and 25 to 35 mg sodium citrate.

276

277 All plasma used in the manufacture of Berinert is obtained from US donors and is tested  
278 using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV.  
279 Additionally, the plasma is tested with Nucleic Acid Testing (NAT) for HCV and HIV-1 and  
280 found to be non-reactive (negative). In addition, the plasma has been tested by NAT for  
281 HAV and Human Parvovirus B19. Only plasma that passed virus screening is used for  
282 production, and the limit for Parvovirus B19 in the fractionation pool is set not to exceed  
283 10<sup>4</sup> IU of Parvovirus B19 DNA per mL.

284

285 The manufacturing process for Berinert includes multiple steps that reduce the risk of virus  
286 transmission. The virus inactivation/reduction capacity of three steps (pasteurization in  
287 aqueous solution at 60°C for 10 hours, hydrophobic interaction chromatography, and the  
288 combination of ion exchange chromatographies and ammonium sulphate precipitation) was  
289 evaluated in a series of *in vitro* spiking experiments. The total mean cumulative virus  
290 inactivation/reduction is shown in Table 5.

291

292

293

**Table 5: Mean Virus Inactivation/Reductions in Berinert**

Virus Studied	Pasteurization [log <sub>10</sub> ]	Hydrophobic Interaction Chromatography [log <sub>10</sub> ]	DEAE-Sephadex A50 Chromatography QAE-Sephadex Chromatography and Ammonium Sulphate Precipitation [log <sub>10</sub> ]	Total Cumulative [log <sub>10</sub> ]
<b>Enveloped Viruses</b>				
HIV-1	≥6.6	≥4.5	4.3	≥15.4
BVDV	≥9.2	≥4.6	NA	≥13.8
PRV	6.3	≥6.5	≥7.7	≥20.5
WNV	≥7.0	ND	NA	NA
<b>Non-Enveloped Viruses</b>				
HAV	≥6.4	4.5	NA	≥10.9
CPV	1.4	6.1	NA	7.5
B19V	3.9	ND	NA	NA

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HIV-1, Human immunodeficiency virus type 1, a model for HIV-1 and HIV-2

BVDV, Bovine viral diarrhea virus, a model for HCV

PRV, Pseudorabies virus, a model for large enveloped DNA viruses (e.g., herpes virus)

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, alpha<sub>1</sub>-protease inhibitor, alpha<sub>2</sub>-antiplasmin, 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 cascade 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 (C1r), C1s, coagulation factor XIIa, and kallikrein. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade.

324 HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although  
 325 the events that induce attacks of angioedema in HAE patients are not well defined, it has  
 326 been postulated that increased vascular permeability and the clinical manifestation of HAE  
 327 attacks may be primarily mediated through contact system activation. Suppression of contact  
 328 system activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and  
 329 factor XIIa is thought to modulate this vascular permeability by preventing the generation of  
 330 bradykinin.<sup>5</sup>

331

332 Administration of Berinert to patients with C1 esterase inhibitor deficiency replaces the  
 333 missing or malfunctioning protein in patients. The plasma concentration of C1 Esterase  
 334 Inhibitor in healthy volunteers is approximately 270 mg/L.<sup>6</sup>

335

336

### 337 12.3 Pharmacokinetics

338 The pharmacokinetics (PK) of Berinert were evaluated in an open-label, uncontrolled, single-  
 339 center study in 40 subjects (35 adults and 5 children under 16 years of age) with either mild  
 340 or severe HAE. All subjects received a single intravenous injection of Berinert ranging from  
 341 500 units to 1500 units. Blood samples were taken during an attack-free period at baseline  
 342 and for up to 72 hours after drug administration. Pharmacokinetic parameters were estimated  
 343 using non-compartmental analysis (with or without baseline adjustment). Table 6  
 344 summarizes the pharmacokinetic parameters in 35 adult subjects with HAE.

345

346 **Table 6: Pharmacokinetic Parameters of Berinert in Adult Subjects with HAE by**  
 347 **Non-compartmental Analysis (n=35)**

348

Parameters	Unadjusted for baseline	Adjusted for baseline
AUC <sub>(0-t)</sub> (hr x IU/mL)*	27.5 ± 8.5 (15.7-44.7)	12.8 ± 6.7 (3.9-34.7)
CL (mL/hr/kg)	0.60 ± 0.17 (0.34-0.96)	1.44 ± 0.67 (0.43-3.85)
V <sub>ss</sub> (mL/kg)	18.6 ± 4.9 (11.1-27.6)	35.4 ± 10.5 (14.1-56.1)
Half-life (hrs)	21.9 ± 1.7 (16.5-24.4)	18.4 ± 3.5 (7.4-22.8)
MRT (hrs)	31.5 ± 2.4 (23.7-35.2)	26.4 ± 5.0 (10.7-33.0)

349

AUC: Area under the curve

350

CL: Clearance

351

V<sub>ss</sub>: Volume steady state

352

MRT: Mean residence time

353

\*Based on a 15 unit/kg dose. Numbers in parenthesis are range

354

355 Table 7 summarizes the pharmacokinetic parameters in 5 pediatric subjects (ages 6 through  
356 13) with HAE. Based on adjusted baseline, compared to adults, the half-life of Berinert was  
357 shorter and clearance was faster in this limited cohort of children. However, the clinical  
358 implication of these differences is not known.

359

360 **Table 7: Pharmacokinetic Parameters of Berinert in Pediatric Subjects with HAE by**  
361 **Non-compartmental Analysis (n=5)**

362

Parameters	Unadjusted for baseline	Adjusted for baseline
AUC <sub>(0-t)</sub> (hr x IU/mL)*	25.45 ± 5.8 (16.8-31.7)	9.78 ± 4.37 (4.1-15.2)
CL (mL/hr/kg)	0.62 ± 0.17 (0.47-0.89)	1.9 ± 1.1 (0.98-3.69)
V <sub>ss</sub> (mL/kg)	19.8 ± 4.0 (16.7-26.1)	38.8 ± 8.9 (31.9-54.0)
Half-life (hrs)	22.4 ± 1.6 (20.3-24.4)	16.7 ± 5.8 (7.4-22.5)
MRT (hrs)	32.3 ± 2.3 (29.3-35.2)	24.0 ± 8.3 (10.7-32.4)

363

AUC: Area under the curve

364

CL: Clearance

365

V<sub>ss</sub>: Volume steady state

366

MRT: Mean residence time

367

\*Based on a 15 unit/kg dose. Numbers in parenthesis are range

368

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

371

372

### 373 13 NONCLINICAL TOXICOLOGY

374

#### 375 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

378

#### 379 13.2 Animal Toxicology and/or Pharmacology

380 Acute toxicity (i.v.) of Berinert was performed in mice at 1500, 3000, and 6000 units/kg and  
381 in rats at 1000, 2000, and 3000 units/kg. Berinert was well tolerated and no signs of toxicity  
382 were observed up to the highest dose administered.

383

384 Repeat dose toxicity (i.v.) was studied in a 14-day repeat dose study in rats at doses of 20, 60,  
385 and 200 units/kg/day. Berinert was well tolerated and no toxicity was observed up to the  
386 highest dose administered. No antibody response against C1-esterase inhibitor could be  
387 demonstrated in this study after multiple dosing with Berinert.

388

389 In a safety pharmacology study, Berinert was administered to beagle dogs i.v. at a cumulative  
390 dose of 3500 units/kg. No adverse effects were seen on the cardiovascular and respiratory  
391 system. There was a drop in body temperature, reduced coagulation time, and a decrease in  
392 thrombocyte aggregation.

393

394 Local tolerance (i.v.) of Berinert was evaluated in rabbits at 1500 units. No pathological  
395 changes at the time of injection or during the following 24 hours. No pathological signs were  
396 noted during necropsy.

397

398 Thrombotic events have been reported in association with C1 esterase inhibitor products  
399 when used off-label and at higher than labeled doses<sup>1</sup> (see *Overdosage [10]*). Animal studies  
400 have confirmed the risk of thrombosis from intravenous administration of C1 esterase  
401 inhibitor products<sup>2</sup>.

402

403

#### 404 **14 CLINICAL STUDIES**

405

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

414

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

421

422 Subjects were randomized to receive a single 10 unit/kg body weight dose of Berinert (39  
423 subjects), a single 20 unit/kg dose of Berinert (43 subjects), or a single dose of placebo (42  
424 subjects) by slow intravenous infusion (recommended to be given at a rate of approximately  
425 4 mL per minute) within 5 hours of an attack. At least 70% of the subjects in each treatment  
426 group were required to be experiencing an abdominal attack.

427

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

434

435 In the rare case that a subject developed life-threatening laryngeal edema after inclusion into  
436 the study, immediate start of open-label treatment with a 20 unit/kg body weight dose of  
437 Berinert was allowed.

438 All subjects who received confounding medication (rescue medication) before symptom  
439 relief were regarded as “non-responders”. Therefore, time to onset of symptom relief was set  
440 at 24 hours if a subject received any rescue medication (i.e. rescue study medication, narcotic  
441 analgesics, non-narcotic analgesics, anti-emetics, open-label C1Esterase Inhibitor, or fresh  
442 frozen plasma) between 5 hours before administration of blinded study medication until time  
443 to onset of relief.

444

445 For the trial to be considered successful, the study protocol specified the following criteria  
446 for the differences between the Berinert 20 units/kg and the placebo group:

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

454

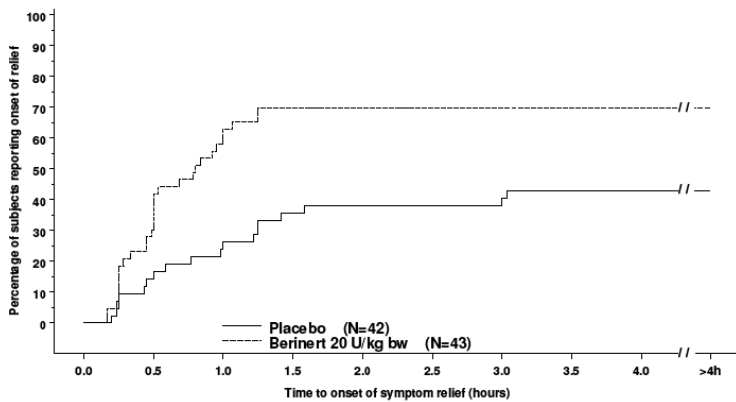
455 Subjects treated with 20 units/kg body weight of Berinert experienced a significant reduction  
456 ( $p=0.0016$ ) in time to onset of relief from symptoms of an HAE attack as compared to  
457 placebo (median of 50 minutes for Berinert 20 units/kg body weight, as compared to >4  
458 hours for placebo). The time to onset of relief from symptoms of an HAE attack for subjects  
459 in the 10 unit/kg dose of Berinert was not statistically significantly different from that of  
460 subjects in the placebo group.

461

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

467

468 **Figure 9: Time to Onset of Symptom Relief with Imputation to > 4 Hours for Subjects**  
469 **Who Received any Rescue Medication\* or Non-narcotic Analgesics Before**  
470 **Start of Relief**



471

472 \* Rescue study medication with C1-INH, narcotic analgesics, anti-emetics, open-label C1-INH,  
473 androgens at increased dose, or fresh frozen plasma. Anti-emetics included antidopaminergics,  
474 benzodiazepines, antihistamines, serotonin 5-HT<sub>3</sub> receptor antagonists, corticosteroids, and  
475 other drugs with anti-emetic properties. Analgesics included narcotic and non-narcotic  
476 medications.

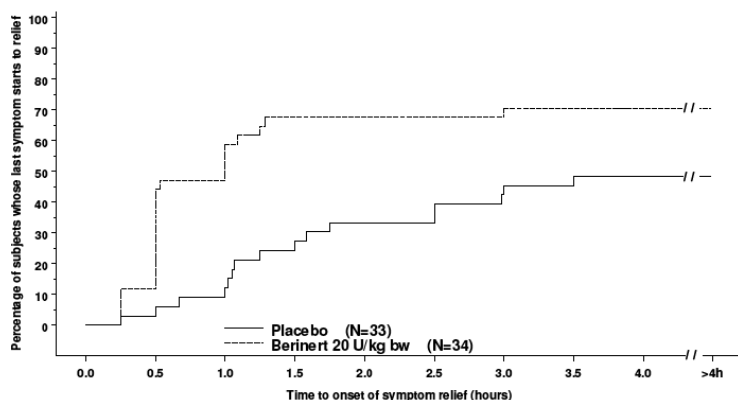
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478 In addition, the efficacy of Beriner 20 units/kg body weight could be confirmed by  
479 observing a reduction in the intensity of single HAE symptoms at an earlier time compared to  
480 placebo. For abdominal attacks Figure 10a shows the time to start of relief of *last* symptom  
481 to improve that was already present at baseline. Pre-defined abdominal HAE symptoms  
482 included pain, nausea, vomiting, cramps and diarrhea. Figure 10b shows the respective time  
483 to start of relief of *first* symptom to improve that was already present at baseline.

484

485 **Figure 10a: Time to Start of Relief of Last Symptom (Abdominal Attacks) with**  
486 **Imputation to > 4 Hours for Subjects Who Received any Rescue**  
487 **Medication\*before Start of Relief**

488

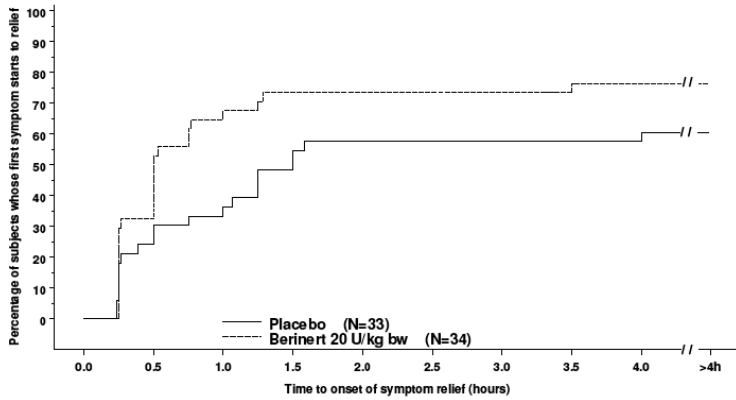


489

490 \* Rescue study medication with C1-INH, narcotic analgesics, anti-emetics, open-label C1INH,  
491 androgens at increased dose, or fresh frozen plasma. Anti-emetics included antidopaminergics,  
492 benzodiazepines, antihistamines, serotonin 5-HT<sub>3</sub> receptor antagonists, corticosteroids, and  
493 other medications with anti-emetic properties.

494  
 495  
 496  
 497  
 498

**Figure 10b: Time to Start of Relief of First Symptom (Abdominal Attacks) with Imputation to > 4 Hours for Subjects Who Received any Rescue Medication\* Before Start of Relief**



499  
 500  
 501  
 502  
 503

\* Rescue study medication with C1-INH, narcotic analgesics, anti-emetics, open-label C1INH or fresh frozen plasma. Anti-emetics included antidopaminergics, benzodiazepines, corticosteroids, antihistamines, serotonin 5-HT<sub>3</sub> receptor antagonists, and other medications with anti-emetic properties.

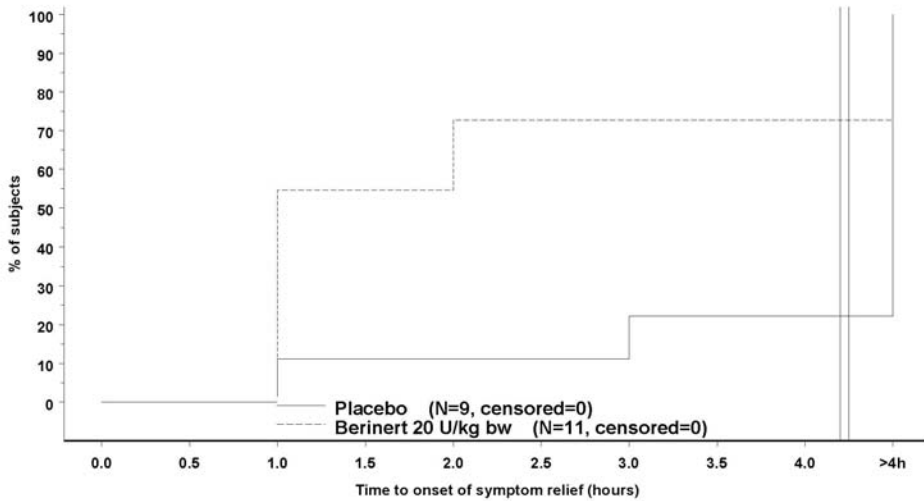
504

505 For facial attacks, single HAE symptoms were recorded. In addition, photos were taken at  
506 pre-determined time points and assessed by the members of an independent Data Safety  
507 Monitoring Board (DSMB), who were blinded as to treatment, center and other outcome  
508 measures. The change in the severity of the edema when compared to baseline was assessed  
509 on a scale with outcomes "no change", "better", "worse" and "resolved". Figure 11 shows the  
510 time to start of relief from serial facial photographs by DSMB assessment.

511

512 **Figure 11: Time to Start of Relief from Serial Facial Photographs\***

513



514

515 \* Includes abdominal attacks with concomitant facial attacks.

516 Table 8 compares additional endpoints, including changes in HAE symptoms and use of  
517 rescue medication in subjects receiving Berinert at 20 units/kg body weight and placebo.

518

519 **Table 8: Changes in HAE Symptoms and Use of Rescue Medication in Subjects**  
520 **Receiving Berinert 20 units/kg Body Weight vs. Placebo**

521

Additional Endpoints	Number (%) of Subjects Berinert 20 units/kg Body Weight Group (n=43)	Number (%) of Subjects Placebo Group (n=42)
Onset of symptom relief within 60 minutes after administration of study medication ( <i>post-hoc</i> )	25 (58.1%)	11 (26.2%)
Onset of symptom relief within 4 hours after administration of study medication	28 (65.1%)	18 (42.9%)
Number of vomiting episodes within 4 hours after start of study treatment*	6 episodes	35 episodes
Worsened intensity of clinical HAE symptoms between 2 and 4 hours after administration of study medication compared to baseline†	0 (0%)	12 (28.6%)
Number (percent) of combined abdominal and facial attack subjects receiving rescue study medication, analgesics, or anti-emetics at any time prior to complete relief of symptoms	13 (30.2%)	23 (56.1%)
At least one new HAE symptom not present at baseline and starting within 4 hours after administration of study medication	2 (4.6%)	6 (14.3%)

522

\* p-value = 0.033

523

† p-value = 0.00008

524

525 Both the proportion of subjects with increased intensity of clinical HAE symptoms between 2  
526 and 4 hours after start of treatment compared to baseline, and the number of vomiting  
527 episodes within 4 hours after start of study treatment demonstrated trends in favor of Berinert  
528 in comparison to placebo (p values < 0.1). Tables 9 through 12 present additional  
529 information regarding responses to treatment.

530

531 **Table 9: Proportion of Subjects Experiencing Start of Self-Reported Relief of**  
532 **Symptoms by 4 hours by Attack Type**

533

Attack Type	Berinert 20 units/kg Body Weight (Abdominal Subjects =34) (Facial Subjects = 9) (Other subjects = 0)	Placebo (Abdominal Subjects = 33) (Facial Subjects = 8) (Other subjects = 1)*
Abdominal	24 (70.6%)	15 (45.5%)
Facial	6 (66.7%)	3 (37.5%)

534

\* Laryngeal edema initially classified as facial edema.

535

536 **Table 10: Proportion of Subjects Experiencing Reduction in Severity of at Least One**  
537 **Individual HAE Attack Symptom by 4 hours**

538

Attack Type	Berinert 20 units/kg Body Weight (Abdominal Subjects = 34) (Facial Subjects = 9)	Placebo (Abdominal Subjects = 33) (Facial Subjects = 8)
Abdominal	33 (97.1%)	30 (90.9%)
Facial	6 (66.7%)	4 (50%)

539

540 **Table 11: Proportion of Subjects with Facial Attacks Demonstrating Improvement in**  
541 **Serial Facial Photographs by 4 hours\*\***

542

Attack Type	Berinert 20 units/kg Body Weight (Subjects = 9)	Placebo (Subjects = 8)
Facial	7 (77.8%)	2 (25%)

543

\*\* Based on masked (blinded) evaluation by data safety monitoring board.

544

545 **Table 12: Proportion of Subjects with Abdominal and Facial Attack Receiving Rescue**  
 546 **Study Medication or Other Confounding Medications (Narcotic Analgesics,**  
 547 **Non-Narcotic Analgesics, Open-Label C1 Esterase Inhibitor, Androgens at**  
 548 **Increased Dose, or Anti-emetics) at any Time Prior to Complete Relief of**  
 549 **Symptoms**

550

Attack Type	Berinert 20 U/kg Body Weight (Abdominal Subjects = 31) (Facial Subjects = 4)		Placebo (Abdominal Subjects = 23) (Facial Subjects = 4)	
	Rescue Medication	Other Potentially Confounding Concomitant Medication	Rescue Medication	Other Potentially Confounding Concomitant Medication
Abdominal	4 (12.9%)	6 (19.4%)	12 (52.2%)	7 (30.4%)
Facial	2 (50%)	1 (25%)	3 (75%)	1 (25%)

551

552 No subjects treated with Berinert at 20 units/kg body weight reported worsening of symptoms  
 553 at 4 hours after administration of study medication compared to baseline.

554

555 The study demonstrated that the Berinert 20 unit/kg body weight dose was significantly more  
 556 efficacious than the Berinert 10 unit/kg body weight dose or placebo.

557

#### 558 Open-Label Extension Study

559 Berinert was evaluated in a prospective, open-label, uncontrolled, multicenter extension  
 560 study conducted at 10 centers in the US and Canada in subjects who had participated in the  
 561 RCT study for the treatment of acute abdominal or facial attacks in subjects with hereditary  
 562 angioedema.

563

564 The purpose of this ongoing extension study is to provide Berinert to subjects who had  
 565 participated in the RCT study and who experienced any type of subsequent HAE attack (i.e.,  
 566 abdominal, facial, peripheral, or laryngeal).

567

568 In a non-pre-specified interim safety analysis of the ongoing open-label extension study, a  
 569 total of 56 subjects (19 males and 37 females, age range: 10 to 53 years) with 559 HAE  
 570 attacks treated with 20 unit/kg body weight dose of Berinert per attack, were observed at the  
 571 study site until onset of relief of HAE symptoms, and were followed up for adverse events  
 572 for 7 to 9 days following treatment of each HAE attack (see *Adverse Reactions, Clinical*  
 573 *Trials Experience [6.1]*). There were 49 subjects with abdominal attacks, 11 subjects with  
 574 facial attacks, 28 subjects with peripheral attacks, and 12 subjects with laryngeal attacks.

575

576

577

**15 REFERENCES**

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592

593

594

**16 HOW SUPPLIED/STORAGE AND HANDLING**

595

596

**16.1 How Supplied**

597

Berinert is supplied in a single-use vial containing 500 units of lyophilized concentrate for reconstitution with 10 mL of diluent containing sterile water (meets USP chemistry requirements except for pH; pH 4.5-8.5). The components used in the packaging for Berinert are latex-free.

598

599

600

601

602

Each product package consists of the following:

603

NDC Number	Component
63833-825-02	Carton (kit) containing one 500 unit vial of Berinert [NDC 63833-835-01], one 10 mL vial of diluent (sterile water) [NDC 63833-765-15], one Mix2Vial filter transfer set, and one alcohol swab.

604

605

**16.2 Storage and Handling**

606

When stored at temperatures of 2-25°C (36-77°F), Berinert is stable for the period indicated by the expiration date on the carton and vial label (up to 30 months). Keep Berinert in its original carton until ready to use. Do not freeze. Protect from light.

607

608

609

610 **17 PATIENT COUNSELING INFORMATION**611 **Inform patients to immediately report the following to their physician:**

- 612 • Signs and symptoms of allergic hypersensitivity reactions, such as hives, urticaria,  
613 tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during  
614 or after injection of Berinert (*see WARNINGS AND PRECAUTIONS/Hypersensitivity*  
615 *[5.1]*).
- 616 • Signs and symptoms of thrombosis, such as new onset swelling and pain in the limbs  
617 or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor  
618 power, or altered consciousness or speech (*see WARNINGS AND*  
619 *PRECAUTIONS/Thrombotic Events [5.2]*).
- 620 • Advise female patients to notify their physician if they become pregnant or intend to  
621 become pregnant during the treatment of acute abdominal or facial attacks of HAE  
622 with Berinert.
- 623 • Advise patients to notify their physician if they are breastfeeding or plan to  
624 breastfeed.
- 625 • Advise patients to consult with their healthcare professional prior to travel.
- 626 • Advise patients that, because Berinert is made from human blood, it may carry a risk  
627 of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-  
628 Jakob (CJD) agent (*see WARNINGS AND PRECAUTIONS/Transmission of Infectious*  
629 *Agents [5.3] and Description [11]*). Inform patients of the risks and benefits of  
630 Berinert before prescribing or administering it to the patient.

631

632 **17.1 FDA-Approved Patient Labeling – Patient Product Information (PPI)**

633

634

635

636

637

**Berinert (BEAR-ĭ-nerť)**  
**C1 Esterase Inhibitor (Human)**  
**Freeze-Dried Powder for Reconstitution**

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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. 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.

**What is BERINERT?**

BERINERT is an injectable medicine used to treat swelling and /or painful attacks in adults and adolescents with Hereditary Angioedema (HAE). HAE is caused by the poor functioning 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.

651

652 **Who should not use BERINERT?**

653

654 You should not use BERINERT if you have had life-threatening immediate hypersensitivity  
655 reactions, including anaphylaxis to the product.

656

657 **What should I tell my healthcare provider before using BERINERT?**

658

659 Tell your healthcare provider about all of your medical conditions, including if you:

660

661 • are pregnant or planning to become pregnant. It is not known if BERINERT can harm  
662 your unborn baby.

663

664 • are breastfeeding or plan to breastfeed. It is not known if BERINERT passes into your  
665 milk and if it can harm your baby.

666

667 • have a history of blood clotting problems. Blood clots (thrombosis) have occurred in  
668 patients receiving large amounts of Berinert. Very high doses of C1 esterase inhibitor  
669 could increase the risk of blood clots.

670

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

674

675 **How is BERINERT given?**

676

677 Your healthcare provider will infuse BERINERT into your vein (intravenous injection).  
678 Before infusing, he or she must dissolve the BERINERT powder using the sterile water  
679 provided. Your healthcare provider will prescribe the dose that you should be given.

680

681 **What are the possible side effects of BERINERT?**

682

683 **Allergic reactions may occur with BERINERT. Call your healthcare provider or the**  
684 **emergency department right away if you have any of the following symptoms after**  
685 **using BERINERT:**

686

- **wheezing**

687

- **difficulty breathing**

688

- **chest tightness**

689

- **turning blue (look at lips and gums)**

690

- **fast heartbeat**

691

- **swelling of the face**

692

- **faintness**

693

- **rash**

694

- **hives**

695

696 Signs of a blood clot include:

- 697 • new onset of swelling and pain in the limbs or abdomen
- 698 • new onset chest pain
- 699 • shortness of breath
- 700 • loss of sensation or control of muscles/muscle weakness on one side of the body
- 701 • altered consciousness, vision, or speech.

702

703 In clinical studies, the most severe side effect reported in subjects who received BERINERT  
704 was an increase in the severity of pain associated with HAE.

705

706 Other side effects patients experienced during clinical research studies include:

- 707 • subsequent HAE attack
- 708 • headache
- 709 • abdominal pain
- 710 • nausea
- 711 • muscle spasms
- 712 • pain
- 713 • diarrhea
- 714 • vomiting

715

716 Because BERINERT is made from human blood, it may carry a risk of transmitting  
717 infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent.

718

719 These are not all the possible side effects of BERINERT.

720

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

723

**724 What else should I know about BERINERT?**

725

726 Medicines are sometimes prescribed for purposes other than those listed here. Do not use  
727 BERINERT for a condition for which it is not prescribed. Do not share BERINERT with  
728 other people, even if they have the same symptoms that you have.

729

730 This leaflet summarizes the most important information about BERINERT. If you would  
731 like more information, talk to your healthcare provider. You can ask your healthcare  
732 provider or pharmacist for information about BERINERT that was written for healthcare  
733 professionals.

734

735 Talk to your healthcare provider before traveling.

736

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

739

740 Manufactured by:

741 **CSL Behring GmbH**

742 35041 Marburg, Germany

743 US License No. 1765

744

745 Distributed by:

746 **CSL Behring LLC**

747 Kankakee, IL 60901 USA

748

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