SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Berinert®

500 IU
Powder and solvent for solution for injection / infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: human C1-esterase inhibitor (from human plasma).

Berinert contains 500 IU per injection vial.

The potency of human C1-esterase inhibitor is expressed in International Units (IU), which are related to the current WHO Standard for C1-esterase inhibitor products.

Berinert 500 contains 50 IU/ml human C1-esterase inhibitor after reconstitution with 10 ml water for injections.

The total protein content of the reconstituted 500 IU solution is 6.5 mg/ml.

Excipients with known effect:
Sodium up to 486 mg (approximately 21 mmol) per 100 ml solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection / infusion.
White Powder.
Clear, colourless solvent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hereditary angioedema type I and II (HAE)
Treatment and pre-procedure (prior to oral, dental, and upper respiratory tract procedures) prevention of acute episodes.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of C1-esterase inhibitor deficiency.

Posology

Adults
Treatment of acute angioedema attacks:
20 IU per kilogram body weight (20 IU/kg b.w.)

Pre-procedure prevention of angioedema attacks:
1000 IU less than 6 hours prior to oral, dental, and upper respiratory tract procedures.

Paediatric Population
Treatment of acute angioedema attacks:
20 IU per kilogram body weight (20 IU/kg b.w.).

Pre-procedure prevention of angioedema attacks:
15 to 30 IU per kilogram body weight (15-30 IU/kg b.w.) less than 6 hours prior to oral, dental, and upper respiratory tract procedures. Dose should be selected taking into account clinical circumstances (e.g. type of procedure and disease severity).

Method of administration
Berinert is to be reconstituted according to section 6.6. The reconstituted solution should be colourless and clear. The solution is to be administered by slow i.v. injection or infusion (4 ml/minute).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In patients with known tendency towards allergies, antihistamines and corticosteroids should be administered prophylactically.

If allergic or anaphylactic-type reactions occur, the administration of Berinert has to be stopped immediately (e.g. discontinue injection/infusion) and an appropriate treatment has to be initiated. Therapeutic measures depend on the kind and severity of the undesirable effect. The current medical standards for shock treatment are to be observed.

Patients with laryngeal oedema require particularly careful monitoring with emergency treatment in stand-by.

Unlicensed use or treatment of Capillary Leak Syndrome (CLS) with Berinert (see also section “4.8 Undesirable effects”) is not advised.

Berinert 500 IU contains up to 49 mg sodium per vial, equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Home-treatment and self-administration
There are limited data on the use of this medicinal product in home- or self-administration, which is defined as patient-self administration or an administration by a relative or another caregiver (i.e. visiting nurse) in a home setting. Patients should only be considered for self-administration if they have been trained by a healthcare professional and have demonstrated their proficiency by a series of uneventful and witnessed successful injections. Potential risks associated with home-treatment are related to the administration itself as well as the handling of adverse drug reactions, particularly hypersensitivity. The decision on the use of home-treatment for an individual patient should be made by the treating physician, who should ensure that appropriate training is provided and the use reviewed at intervals.

Virus safety
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/ removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, HCV and for the non-enveloped viruses HAV and parvovirus B19.

Appropriate vaccination (hepatitis A and B) should be generally considered for patients in regular/repeated receipt of human plasma-derived products.

It is strongly recommended that every time Berinert is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interactions with other medicinal products and other forms of interactions

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited amount of data that indicate no increased risk from the use of Berinert in pregnant women. Berinert is a physiological component of human plasma. Therefore, no studies on reproduction and developmental toxicity have been performed in animals and no adverse effects on fertility, pre- and postnatal development are expected in humans. Therefore, Berinert should be given to a pregnant woman only if clearly needed.

Breastfeeding
It is unknown whether Berinert is excreted in human milk, but due to its high molecular weight, the transfer of Berinert into breast milk seems unlikely. However, breastfeeding is questionable in women suffering from hereditary angioedema. A decision must be made whether to discontinue breastfeeding or to discontinue the Berinert therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
Berinert is a physiological component of human plasma. Therefore, no studies on reproduction and developmental toxicity have been performed in animals and no adverse effects on fertility, pre- and postnatal development are expected in humans.

4.7 Effects on ability to drive and use machines

Berinert has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following adverse reactions are based on post marketing experience as well as scientific literature. The following standard categories of frequency are used:

Very common:	≥	1/10
Common:	≥	1/100 to < 1/10
Uncommon:	≥	1/1,000 to < 1/100
Rare:	≥	1/10,000 to < 1/1,000
Very rare:	<	1/10,000 (including reported single cases)

Undesired reactions with Berinert are rare.

Organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**
Vascular disorders				Development of thrombosis*	
General disorders and administration site conditions				Rise in temperature, reactions at the injection site	
Immune system disorders				Allergic or anaphylactic-type reactions (e.g. tachycardia, hyper- or hypotension, flushing, hives,	Shock

				dyspnoea, headache, dizziness, nausea)	

* In treatment attempts with high doses of Berinert for prophylaxis or therapy of Capillary Leak Syndrome (CLS) before, during or after cardiac surgery under extracorporal circulation (unlicensed indication and dose), in single cases with fatal outcome.

For safety with respect to transmissible agents, see section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

and emailed to the Registration Holder's Patient Safety Unit at: PV-IL@cslbehring.com

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: C1-inhibitor, plasma derived
ATC code: B06AC01

C1-esterase inhibitor is a plasma glycoprotein with a molecular weight of 105 kD and a carbohydrate moiety of 40 %. Its concentration in human plasma ranges around 240 mg/l. Besides its occurrence in human plasma, also the placenta, the liver cells, monocytes and platelets contain C1-esterase inhibitor.

C1-esterase inhibitor belongs to the serine-protease-inhibitor-(serpin)-system of human plasma as do also other proteins like antithrombin III, alpha-2-antiplasmin, alpha-1-antitrypsin and others.

Under physiological conditions C1-esterase inhibitor blocks the classical pathway of the complement system by inactivating the enzymatic active components C1s and C1r. The active enzyme forms a complex with the inhibitor in a stoichiometry of 1 : 1.

Furthermore, C1-esterase inhibitor represents the most important inhibitor of the contact activation of coagulation by inhibiting factor XIIa and its fragments. In addition, it serves, besides alpha-2-macroglobulin, as the main inhibitor of plasma kallikrein.

The therapeutic effect of Berinert in hereditary angioedema is induced by the substitution of the deficient C1-esterase inhibitor activity.

5.2 Pharmacokinetic properties

The product is to be administered intravenously and is immediately available in the plasma with a plasma concentration corresponding to the administered dose.

The pharmacokinetic properties of Berinert have been investigated in two studies.

A phase I study conducted in 15 healthy, adult subjects provided PK data that was used to assess the relative bioavailability of Berinert 1500 and Berinert 500. Comparable bioavailability of the two presentations of Berinert was demonstrated. For C1-INH antigen concentrations the C_{max} and $AUC_{0\text{-last}}$ geometric mean ratios (90% CIs) were 1.02 (0.99, 1.04) and 1.02 (0.99, 1.05) respectively. Half-life was estimated in a subset of subjects using non-compartmental PK analyses. The mean half-life of Berinert 1500 and Berinert 500 was 87.7 hours and 91.4 hours, respectively.

Pharmacokinetic properties have been investigated in patients with hereditary angioedema (34 patients > 18 years, 6 patients < 18 years). These included 15 patients under prophylactic treatment (with frequent/severe attacks), as well as 25 patients with less frequent/mild attacks and "on demand" treatment. The data were generated in an attack-free interval.

The median *in vivo* recovery (IVR) was 86.7 % (range: 54.0 – 254.1 %). The IVR for children was slightly higher (98.2 %, range: 69.2 – 106.8 %) than for adults (82.5 %, range: 54.0 – 254.1 %). Patients with severe attacks had a higher IVR (101.4 %) compared to patients with mild attacks (75.8 %, range: 57.2 – 195.9 %).

The median increase in activity was 2.3%/IU/kg b.w. (range: 1.4 – 6.9 %/IU/kg b.w.). No significant differences were seen between adults and children. Patients with severe attacks showed a slightly higher increase in activity than patients with mild attacks (2.9, range: 1.4 – 6.9 vs. 2.1, range: 1.5 – 5.1 %/IU/kg b.w.).

The maximum concentration of human C1-esterase inhibitor activity in plasma was reached within 0.8 hours after administration of Berinert without significant differences between the patient groups.

The median half-life was 36.1 hours. It was slightly shorter in children than in adults (32.9 vs. 36.1 hours) and in patients with severe attacks than in patients with mild attacks (30.9 vs. 37.0).

5.3 Preclinical safety data

Berinert contains as active ingredient human C1-esterase inhibitor. It is derived from human plasma and acts like an endogenous constituent of plasma. Single-dose application of Berinert in rats and mice and repeated-dose application in rats did not show any evidence of toxicity.

Preclinical studies with repeated-dose application to investigate carcinogenicity and reproductive toxicity have not been conducted because they cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

The *in vitro* Ouchterlony test and the *in vivo* PCA model in guinea pigs did not show any evidence of newly arising antigenic determinants in Berinert following pasteurization.

In-vivo thrombogenicity tests in rabbits were performed with doses up to 800 IU/kg of Berinert. There was no pro-thrombotic risk associated with the i.v. administration of Berinert up to 800 IU/kg.

Local tolerance studies in rabbits demonstrated that Berinert was clinically, locally and histologically well-tolerated after intravenous, subcutaneous, intra-arterial and intramuscular application.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Glycine
Sodium chloride
Sodium citrate

Solvent:
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products and diluents in the syringe/infusion set.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After reconstitution, the physico-chemical stability of Berinert has been demonstrated for 48 hours at maximum 30 °C.

From a microbiological point of view and as Berinert contains no preservative, the reconstituted product should be used immediately.
If it is not administered immediately, storage shall not exceed 8 hours when stored below +30 ^{0}C. The reconstituted product should only be stored in the **vial**.

6.4 Special precautions for storage

Do not store above 30 °C.
Do not freeze.
Keep the vial in the outer carton, in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Immediate containers :
Powder (500 IU) in a vial (Type II glass) with a stopper (bromobutyl rubber), old gold seal (aluminium) and lime flip-off cap (plastic).
10 ml of solvent in a vial (Type I glass) with a stopper (chlorobutyl rubber), blue seal (aluminium) and blue flip-off cap (plastic).

Presentation
Box containing:
1 vial with powder
1 solvent vial (10 ml)
1 filter transfer device 20/20 (Mix2Vial)

Administration set (inner box):
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 plaster

Pack size of 1.

6.6 Special precautions for disposal

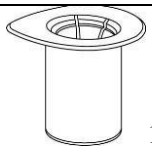
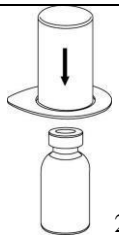
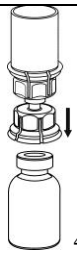
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

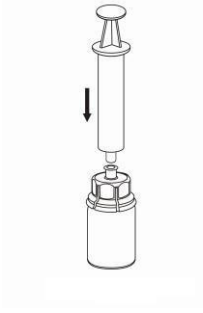
Method of administration

General instructions
- The solution should be colourless and clear.
- After filtering/withdrawal (see below) reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Do not use solutions that are cloudy or have deposits.

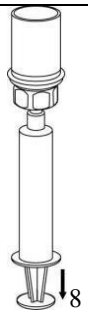
- Reconstitution and withdrawal must be carried out under aseptic conditions. Use the syringe provided with the product or a silicone-free syringe.

Reconstitution
Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

 1	1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	2. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end **straight down** through the solvent vial stopper.
 3	3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
 4	4. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
 5	5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counterclockwise into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

 7	7. Draw air into an empty, sterile syringe. Use the syringe provided with the product or a silicone-free syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and application

 8	8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
 9	9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise.

7. MANUFACTURER

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

8. LICENSE NUMBER

145 06 33056

9. REGISTRATION HOLDER

CSL BEHRING LTD.,
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Revised in September 2023 according to MoH guidelines.

CSL Behring