Public Assessment Report

Berinert

C1-Esterase-Inhibitor, human

DE/H/0481/001/MR

Applicant: CSL Behring GmbH

Date of Report: 02.02.2009

This module reflects the scientific discussion for the approval of Berinert. The procedure has been finalised at 2008-12-11. For information on changes after this date please refer to the module ‘Update’.
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1. INFORMATION OF THE INITIAL PROCEDURE

1. **Type of application**
   Full application according article 8.3 (i) Directive 2001/83/EC

2. **Active substance**
   C1-Esterase-Inhibitor, human

3. **Form**
   Powder and solvent for solution for injection/infusion

4. **Strength**
   500 units/vial

5. **Marketing Authorisation Holder**
   CSL Behring GmbH
   Emil-von-Behring-Straße 76
   35041 Marburg
   Germany

6. **Reference Member State**
   Paul-Ehrlich-Institut
   Germany

7. **Concerned Member States**
   AT, BE, BG, CY, CZ, DK, FI, FR, EL, HU, IT, LU, NL, NO, PL, PT, RO, SE, SK, SI, ES, UK

8. **Procedure-number**
   DE/H/0481/001/MR

9. **Timetable**
   submission of application: 2008-08-29
   start of procedure: 2008-09-12
   termination of procedure: 2008-12-11
I. EXECUTIVE SUMMARY

Berinert is a highly purified, pasteurised, lyophilised C1-esterase inhibitor (C1-INH) concentrate which is manufactured by CSL Behring GmbH, Marburg, Germany. The medicinal product has been marketed since 1979. C1-INH belongs to the group of serine protease inhibitors which is mainly synthesized in the liver and is obtained from human plasma pools.

The finished product comprises one vial of lyophilised powder and one vial containing water for injections for reconstitution. Berinert is to be administered by the intravenous route. A needleless medical device is enclosed in a separate carton to transfer the solvent into the vial containing the lyophilised powder. In addition, devices for intravenous application of the product are included.

Berinert is supplied in one presentation, containing 500 Units of the active ingredient per vial.

Berinert is indicated for the treatment of acute episodes of hereditary angioedema (HAE). The recommended dose is 20 units per kg body weight at an infusion rate of 4 mL per minute.

I.1 General comments on the submitted dossier

Berinert is a stand alone application according Art. 8(3) of Directive 2001/83 EC.

I.2 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for the manufacture and assembly of Berinert.

The pharmacodynamic and pharmacokinetic profile of Berinert was investigated in non-GLP-compliant studies (GLP=Good Laboratory Practice). However, the safety pharmacology investigation and toxicology studies were GLP conform.

The pivotal clinical data base resulted from studies conducted in compliance with Good Clinical Practice (GCP). The studies also met the requirements of the Declaration of Helsinki. Some of the supportive clinical studies were performed prior to the introduction of the ICH E6 Guideline for GCP. However, all these studies did strictly adhere to the Declaration of Helsinki and other national laws and regulations applicable at that time.

I.3 Assessment of Similarity

On 11 July 2008 an orphan designated product Firazyr was authorised by the European Commission with the procedure No: EU/3/03/133.

Firazyr is indicated for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase-inhibitor deficiency.

Active ingredient of Firazyr is Icatebant acetate, a peptide which acts as a bradykinin-B2-receptor antagonist whilst the active substance of Berinert is C1-esterase-inhibitor which plays a role in the control of the complement system and the contact activation pathway. Therefore, neither the same molecular structure nor the same mechanism of action is considered similar as described in the criteria of Regulation No. 141/2000/EC.
Thus, following the criteria laid down in Regulation No. 847/2000/EC, Berinert is regarded to be not similar to Firazyr.

II. SCIENTIFIC OVERVIEW

Quality
Berinert is a highly purified, pasteurised, lyophilised C1-esterase inhibitor (C1-INH) concentrate. C1-INH is a soluble, single-chain glycoprotein containing 478 amino acid residues organised into three beta-sheets and eight or nine alpha-helices. C1-INH belongs to the group of serine protease inhibitors which is mainly synthesized in the liver and is obtained from human plasma pools.

Berinert is a sterile, preservative free concentrate in a 17 mL glass vial for reconstitution and intravenous administration. Each Berinert vial contains: 500 U of C1-INH, 50 to 80 mg total protein, 85 to 115 mg glycine, 25 to 35 mg sodium citrate and 70 to 100 mg sodium chloride.

Berinert is derived from human plasma which properties are described in an EU-certified Plasma Master File.

The final bulk is an intermediate product in the manufacturing process of the drug product, which is regarded as the drug substance only for formal reasons. In the continuous manufacturing process, the final bulk represents the last stage of the active ingredient in dissolved form prior to filling into final containers and lyophilisation.

The data submitted demonstrate that the manufacturing process of Berinert fulfils the current state of the art criteria. All predefined acceptance criteria from different process validation studies were met and it is considered that the Berinert drug product manufacturing process has been successfully validated.

Adventitious Agents
Berinert is produced from human plasma. The overall viral safety strategy includes selection of qualified donors and testing of plasma donations. Plasma is collected in Austria, Germany and the USA. The donor selection and plasma donation testing strategy for viral markers is considered adequate.

The drug substance is purified by several chromatographic and precipitation steps. Of these, hydrophobic interaction chromatography has been shown to be an effective step to reduce both enveloped and non-enveloped viruses. Virus inactivation/removal is also achieved by pasteurisation. Significant inactivation of enveloped viruses as well as of non-enveloped viruses such as HAV and B19V (although more limited, particularly when the far more heat resistant CPV model virus is studied) has been shown and robustness of virus inactivation has been demonstrated. In summary, compliance with the requirements on virus safety as outlined in Guideline CPMP/BWP/269/95 has been demonstrated.

Non-clinical aspects
The non-clinical testing program for Berinert comprises pharmacology and toxicology studies. The pharmacodynamic efficacy of Berinert was investigated in-vitro and in-vivo in different animal models. The in-vitro study evaluating the influence of C1-INH on complement activity in human or rat plasma demonstrated that Berinert effectively inhibited the classical complement pathway. The in-vivo studies showed Berinert to be efficacious in animal models of edema, capillary leakage, reperfusion...
injury, sepsis and stroke. A safety pharmacology study has been performed in dogs and revealed no significant effects to be expected within the intended clinical use. The pharmacokinetics of Berinert was investigated in rats and rabbits after single intravenous administration. Concerning toxicology studies on acute and repeat-dose toxicity, on local tolerance and on the immunogenic potential have been performed.

In summary, the non-clinical data provide evidence that Berinert has a convincing pharmacodynamic efficacy and a non-clinical safety profile which does not raise concerns.

Clinical aspects
Berinert is indicated for the treatment of acute episodes of hereditary angioedema (HAE). HAE is a rare disorder causing quantitative or functional impairment of C1-esterase inhibitor. Affected patients suffer from deranged vascular permeability presenting with subcutaneous swellings of the skin, submucous tissue of abdominal organs or potentially life-threatening laryngeal swellings. Berinert has been marketed for more than 20 years with clinically proven efficacy and without safety concerns. Additionally, clinical evaluation has been amended by recently completed clinical trials together with an analysis of “historical” data and a retrospective case collection. One follow-up study is ongoing and an Interim Report has been compiled.

In conclusion, on the basis of submitted data it has been considered that Berinert demonstrates adequate evidence of efficacy for the approved indications.
III. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Berinert has been granted in the indication of hereditary angioedema, which is a rare disorder causing quantitative or functional impairment of C1-INH. Affected patients suffer from deranged vascular permeability presenting with subcutaneous swellings of the skin, submucous tissue of abdominal organs or potentially life-threatening laryngeal swellings. The manufacturing process of Berinert fulfils the current state of the art criteria. The overall viral safety strategy includes selection of qualified donors and testing of plasma donations and is considered to be in compliance with the current requirements on virus safety. The non-clinical data demonstrated a convincing pharmacodynamic efficacy and a non-clinical safety profile which does not raise concerns for human use. Efficacy and safety of Berinert in patients with hereditary angioedema type I and type II have been followed since introduction on the market in 1985 and of the predecessor product in 1979. Treatment of acute attacks has consistently been reported to be efficient and safe. Progression in clinical/scientific knowledge included administration of high doses in other indications e.g. postoperative management of capillary leakage syndrome. Associated risk of thrombosis following administration of extremely high dosages of C1-INH was intensively discussed and corresponding statements have been included into the SPC. Clinical experience with Berinert in the approved indication has been completed by recent clinical studies representing high scientific standard and supporting the dosage, efficacy and safety profile of more than 20 years experience on the market. Use in children has been documented within those studies.

In conclusion, based on data on quality, non-clinical and clinical aspects it has been considered that Berinert demonstrates adequate evidence of efficacy and safety for the approved indication as well as a favourable risk/benefit profile.
IV. PRODUCT INFORMATION

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

   Berinert P
   500 units
   Powder and solvent for solution for injection / infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

   Active substance: C1-esterase inhibitor, human

   Berinert P contains 500 units C1-esterase inhibitor per injection vial. 1 U is equivalent
to the C1-esterase inhibitor activity in 1 ml of fresh citrated plasma of healthy donors, 1
U is equivalent to 6 Levy-Lepow units.

   The product contains 50 U/ml C1-esterase inhibitor after reconstitution with 10 ml
water for injections.

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

   Excipients recognized to have a known effect:
Sodium up to 486 mg (approximately 21 mmol) per 100 ml solution.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

   Powder (white lyophilisate) and solvent for solution for injection / infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

   Hereditary angioedema type I and II (HAE)

   Treatment 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
   20 units per kilogram body weight (20 U/kg b.w.)

   Dosage for neonates, infants and children
The dose for children is 20 units per kilogram body weight (20 U/kg b.w.).

Method of administration
Berinert P is to be reconstituted according to section 6.6. The reconstituted solution is to be administered by slow i.v. injection or infusion.

4.3 Contraindications

Known hypersensitivity to any of the components of the product.

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 P 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 P (see also section "4.8 Undesirable effects") is not advised.

Berinert P contains up to 486 mg sodium (approximately 21 mmol) per 100 ml solution. To be taken into consideration by patients on a controlled sodium diet.

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 and HCV and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

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 Pregnancy and lactation

**Pregnancy**

There are limited amount of data that indicate no increased risk from the use of Berinert P in pregnant women. Berinert P 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 P should be given to a pregnant woman only if clearly needed.

**Lactation**

It is unknown whether Berinert P is excreted in human milk, but due to its high molecular weight, the transfer of Berinert P 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 P therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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:** $\geq 1/10$
- **Common:** $1/100$ and $< 1/10$
- **Uncommon:** $1/1,000$ and $< 1/100$
- **Rare:** $1/10,000$ and $< 1/1,000$
- **Very rare:** $< 1/10,000$ (including reported single cases)

Undesired reactions with Berinert P are rare.
<table>
<thead>
<tr>
<th>Organ class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td>Development of thrombosis*</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td>Rise in temperature, reactions at the injection side</td>
<td></td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td>Allergic or anaphylactic-type reactions (e.g. tachycardia, hyper- or hypotension, flushing, hives, dyspnoea, headache, dizziness, nausea)</td>
<td>Shock</td>
</tr>
</tbody>
</table>

* In treatment attempts with high doses of Berinert P 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.

### 4.9 Overdose

No case of overdose has been reported.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: C1-inhibitor  
ATC code: B02A B03

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 P 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.

Pharmacokinetic properties have been investigated in 40 patients (6 patients < 18 years) with hereditary angioedema. 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%/U/kg b.w. (range: 1.4 – 6.9 %/U/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 %/U/kg b.w.).

The maximum concentration of C1-esterase inhibitor activity in plasma was reached within 0.8 hours after administration of Berinert P 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 P contains as active ingredient C1-esterase inhibitor. It is derived from human plasma and acts like an endogenous constituent of plasma. Single-dose application of Berinert P 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 P following pasteurization.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

*Powder:*
- Glycine
- Sodium chloride
- Sodium citrate

*Solvent:*
- Water for injections

6.2 **Incompatibilities**

Berinert P should not be mixed with other medicinal products and diluents in the syringe/infusion set.

6.3 **Shelf life**

30 months

After reconstitution, from a microbiological point of view and as Berinert P contains no preservative, the reconstituted product should be used immediately. The physico-chemical stability has been demonstrated for 48 hours at room temperature (max. 25°C). However, if it is not administered immediately, storage shall not exceed 8 hours at room temperature.
6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Powder: Injection vial of colourless glass Type II, sealed with bromobutyl rubber infusion stopper Type I, aluminium seal and plastic flip-off cap.
Solvent: 10 ml water for injections in an injection vial of colourless glass Type I, sealed with chlorobutyl rubber infusion stopper Type I, aluminium seal and plastic flip-off cap.
Administration set: 1 filter transfer device 20/20, 1 disposable 10 ml syringe, 1 venipuncture set, 2 alcohol swabs, 1 plaster

6.6 Special precautions for disposal and other handling

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

Method of administration

General instructions
- The solution should be clear or slightly opalescent. 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.

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

1. Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!

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. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling \textit{vertically} upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.

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 \textit{straight down} through the product vial stopper. The solvent will automatically flow into the product vial.

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 into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.

6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting. Inject air into the product vial.

8. While keeping the syringe plunger pressed, invert the system upside down and draw the solution into the syringe by pulling the plunger back slowly.

Withdrawal and application
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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

- country specific -

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- country specific -

10. DATE OF REVISION OF THE TEXT

December 2008
Berinert P
500 units
Powder and solvent for solution for injection / infusion.
C1-esterase inhibitor, human

Read all of this leaflet carefully before you start using this medicine.
• Keep this leaflet. You may need to read it again.
• If you have further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Berinert P is and what it is used for
2. Before you use Berinert P
3. How to use Berinert P
4. Possible side effects
5. How to store Berinert P
6. Further information

1. WHAT BERINERT P IS AND WHAT IT IS USED FOR

What is Berinert P?
Berinert P is presented as powder and solvent. The made up solution is to be given by injection or infusion into a vein.

Berinert P is made from human plasma (this is the liquid part of the blood). It contains the human protein C1-esterase inhibitor as active ingredient.

What is Berinert P used for?
Berinert P is used for the treatment of the hereditary angioedema type I and II (HAE, oedema = swelling). HAE is a congenital disease of the vascular system. It is a non-allergic disease. HAE is caused by deficiency, absence or defective synthesis of C1-esterase inhibitor, an important protein. The illness is characterised by the following symptoms:
- swelling of the hands and feet that occurs suddenly,
- facial swelling with tension sensation that occurs suddenly
- eyelid swelling, lip swelling, possibly laryngeal (voice-box) swelling with difficulty in breathing,
- tongue swelling,
- colic pain in abdominal region
Generally, all parts of the body can be affected.
2. BEFORE YOU USE BERINERT P

The following sections contain information that your doctor should consider before you are given Berinert P.

Do NOT use Berinert P:
• if you are hypersensitive (allergic) to the protein C1-esterase inhibitor or any other ingredients of Berinert P (see section 6. "Further Information").
  Please inform your doctor or pharmacist if you are allergic to any medicine or food.

Take special care with Berinert P:
• if you have experienced allergic reactions on Berinert P in the past. You should take antihistamines and corticosteroids prophylactically if advised by your doctor.
• when allergic or anaphylactic-type reactions occur (a serious allergic reaction that causes severe difficulty in breathing or dizziness). The administration of Berinert P should then be stopped immediately (e.g. discontinue infusion).
• if you suffer from laryngeal swelling (laryngeal oedema). You should be carefully monitored with emergency treatment in stand-by.
• during unlicensed use beyond the approved indications and posology (e.g. Capillary Leak Syndrome, CLS). See section 4. "Possible side effects".

Your doctor will consider carefully the benefit of treatment with Berinert P compared with the risk of these complications.

Virus safety
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:
• careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and
• the testing of each donation and pools of plasma for signs of virus/infections.

Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV, the AIDS virus), hepatitis B virus and hepatitis C virus (inflammation of the liver) and for the non-enveloped virus hepatitis A (inflammation of the liver).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious
• for pregnant women (infection of the unborn child) and
• for individuals with a depressed immune system or with an increased production of red blood cells due to certain types of anaemia (e.g. sickle cell anaemia or haemolytic anaemia).
Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived products.

It is strongly recommended that every time that Berinert P is given, the date of administration, the batch number and the injected volume should be recorded.

**Taking other medicines**
- Please tell your doctor or pharmacist if you are taking or have recently taken any medicines, including medicines obtained without a prescription.
- Berinert P should not be mixed with other medicinal products and diluents in the syringe/infusion set.

**Pregnancy and breast-feeding**
- If you are pregnant or breast-feeding, please ask your doctor or pharmacist for advice before taking any medicine.
- During pregnancy and breast-feeding Berinert P should be given only if it is clearly needed.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed.

**Important information about some of the ingredients of Berinert P**
Berinert P contains up to 486 mg sodium (approximately 21 mmol) per 100 ml solution. Please take this into account if you are on a controlled sodium diet.

### 3. HOW TO USE BERINERT P

Treatment should be started and supervised by a doctor who is experienced in the treatment of C1-esterase inhibitor deficiency.

**Dosage**
20 units per kilogram body weight (20 U/kg b.w.).

**Dosage for neonates, infants and children**
Children are to receive 20 units per kilogram body weight (20 U/kg b.w.).
**Overdose**
No case of overdose has been reported.

**Method of administration**
If you have any further questions on the use of this product, ask your doctor or pharmacist (see section “The following information is intended for medical or healthcare professionals only”).

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Berinert P can cause side effects, although not everybody gets them.

Please contact your doctor immediately
- if any of the side effects occur, or
- if you notice any side effects not listed in this leaflet.

Undesired reactions with Berinert P are rare.

The following side effects have been observed rarely (at 1 or more than 1 of 10,000 and less than 1 of 1,000 patients):
- There is a risk of increased formation of blood clots in treatment attempts for prophylaxis or therapy of Capillary Leak Syndrome (outflow of fluid from the small blood vessels into the tissue) e.g. during or after cardiac surgery under extracorporal circulation. See section 2. "Take special care with Berinert P".
- Increase in body temperature as well as burning and stinging where the injection was given.
- Hypersensitive or allergic reactions (such as irregular heart beat, faster heart beat, fall in blood pressure, reddening of the skin, rash, difficulty in breathing, headache, dizziness, sickness).

In very rare cases (less than 1 of 10,000 patients or in single cases) hypersensitive reactions might progress as far as shock.

5. **HOW TO STORE BERINERT P**

- **Keep out of the reach and sight of children.**
- Do not use Berinert P after the expiry date, which is stated on the label and carton.
- Do not store above 25°C.
- Do not freeze.
- Keep the vial in the outer carton, in order to protect from light.
- Berinert P does not contain a preservative so the made-up solution should preferably be used immediately.
- If the made-up solution is not administered immediately it must be used within 8 hours.

6. **FURTHER INFORMATION**
What Berinert P contains

The active substance is:
C1-esterase inhibitor, human (500 U/vial; after reconstitution 50 U/ml)
See section “The following information is intended for medical or healthcare professionals only” for further information.

The other ingredients are:
Glycine, sodium chloride, sodium citrate
See last paragraph of section 2. "Important information about some of the ingredients of Berinert P”.
Solvent: Water for injections

What Berinert P looks like and contents of the pack
Berinert P is presented as a white powder and is supplied with water for injections as solvent. The made-up solution should be clear or slightly opalescent, i.e. it might sparkle when held up to the light but must not contain any obvious particles.

Presentation
One pack with 500 U contains:
1 vial with powder (500 U)
1 vial with 10 ml water for injections
One device pack contains:
1 filter transfer device 20/20
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 plaster

Marketing Authorisation Holder and Manufacturer
CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:
Berinert P __________________________ Germany, Hungary
Berinert P 500E Pulver und Lösungsmittel zur Herstellung einer Injektions- oder Infusionslösung ______ Austria
T.b.d. nationally ______________________ Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Greece, Italy,
Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK

This leaflet was last approved in December 2008

The following information is intended for medical or healthcare professionals only
QUALITATIVE AND QUANTITATIVE COMPOSITION

1 U is equivalent to the C1-esterase inhibitor activity in 1 ml of fresh citrated plasma of healthy donors, 1 U is equivalent to 6 Levy-Lepow units.

METHOD OF ADMINISTRATION

General instructions
- The powder must be dissolved and withdrawn from the vial under aseptic conditions.
- The made up solution should be clear or slightly opalescent, i.e. it might be sparkling when held up to the light but must not contain any obvious particles. After filtering or withdrawal (see below) the solution should be checked by eye for small particles and discoloration, before it is administered.
- Do not use the solution if it is visibly cloudy or if it contains flakes or particles.
- Any unused product or waste material should be disposed of in accordance with local requirements and as instructed by your doctor.

Reconstitution
Without opening either vial, warm the Berinert P powder and the solvent to room temperature. This can be done either by leaving the vials at room temperature for about an hour, or by holding them in your hands for a few minutes. DO NOT expose the vials to direct heat. The vials must not be heated above body temperature (37°C). Carefully remove the protective caps from the solvent vial and the product vial. Clean the exposed rubber stoppers of both vials with one alcohol swab each and allow them to dry. The solvent can now be transferred to the powder with the administration set (Mix2Vial) attached. Please follow the instructions given below.

<table>
<thead>
<tr>
<th>Step</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!</td>
</tr>
<tr>
<td>2</td>
<td>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.</td>
</tr>
<tr>
<td>3</td>
<td>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.</td>
</tr>
</tbody>
</table>
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. 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 into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.

6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting. Inject air into the product vial.

**Withdrawal and application**

8. While keeping the syringe plunger pressed, invert the system upside down and draw the solution into the syringe by pulling the plunger back slowly.

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.
**Administration**
The solution is to be administered by slow intravenous (i.v.) injection or infusion.
V.  Labelling

Particulars to appear on the outer packaging (carton substance and water for injections)

1.  NAME OF THE MEDICINAL PRODUCT

Berinert P
500 units
Powder and solvent for solution for injection / infusion.

2.  STATEMENT OF THE ACTIVE SUBSTANCE(S)

Berinert P contains the following active substance per vial:

C1-esterase inhibitor, human  500 U
Total protein  65 mg

3.  LIST OF EXCIPIENTS

Other ingredients per vial:
Glycine, *sodium chloride, *sodium citrate, water for injections

4.  PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection / infusion.
The pack contains:
1 vial with 250 mg dried substance
1 vial with 10 ml water for injections

5.  METHOD AND ROUTE(S) OF ADMINISTRATION

*Read the package leaflet before use.

6.  SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7.  OTHER SPECIAL WARNING(S), IF NECESSARY

- not applicable -
8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Do not freeze.
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

MA No.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

- not applicable -

16. INFORMATION IN BRAILLE

- not applicable -
## Minimum particulars to appear on small immediate packaging units (substance label)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Berinert P</strong></td>
<td>Powder for intravenous administration after reconstitution.</td>
</tr>
<tr>
<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
<td>Lot</td>
</tr>
</tbody>
</table>
| **5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT** | 500 U C1-esterase inhibitor, human  
(50 U/ml reconstituted solution) |
| **6. OTHER** | CSL Behring GmbH, 35041 Marburg, Germany |
Minimum particulars to appear on small immediate packaging units (diluent label)

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water for injections</td>
</tr>
</tbody>
</table>

2. METHOD OF ADMINISTRATION

- not applicable -

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

Do not freeze.

Keep out of the reach and sight of children!

CSL Behring GmbH, 35041 Marburg, Germany
### Particulars to appear on the outer packaging (Administration set)

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
</tr>
</thead>
</table>
| **1. NAME OF THE MEDICINAL PRODUCT** | Administration Set  
Sterile and non-pyrogenic. |
| **2. STATEMENT OF THE ACTIVE SUBSTANCE(S)** | - not applicable - |
| **3. LIST OF EXCIPIENTS** | - not applicable - |
| **4. PHARMACEUTICAL FORM AND CONTENTS** | Contents:  
1 filter transfer device 20/20  
1 disposable 10 ml syringe  
1 venipuncture set  
2 alcohol swabs  
1 non-sterile plaster |
| **5. METHOD AND ROUTE(S) OF ADMINISTRATION** | - not applicable - |
| **6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN** | - not applicable – |
| **7. OTHER SPECIAL WARNING(S), IF NECESSARY** | Do not use if package is opened or damaged. |
| **8. EXPIRY DATE** | EXP: |
9. SPECIAL STORAGE CONDITIONS

- not applicable -

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

- not applicable -

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

- not applicable -

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

- not applicable -

15. INSTRUCTIONS ON USE

For single use

16. INFORMATION IN BRAILLE

- not applicable -