AUSTRALIAN PRODUCT INFORMATION

BERINERT® IV

(Human C1 esterase inhibitor)

1 NAME OF THE MEDICINE

Human C1 esterase inhibitor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Berinert® IV is a highly purified, freeze-dried C1 esterase inhibitor concentrate derived from human plasma.

Berinert® IV is available in two presentations with different concentrations (strengths) as detailed in **Table 1**. When reconstituted, the 500 IU presentation contains 500 IU of C1 esterase inhibitor per vial at 50 IU/mL and the 1500 IU presentation contains 1500 IU of C1 esterase inhibitor per vial at 500 IU/mL.

Table 1: Berinert® IV presentations[a]

Presentation	**500 IU**	**1500 IU**
Active ingredients (IU/vial)		
C1 esterase inhibitor	500	1500
Reconstitution volume (mL)	10	3
Concentration	50 IU/mL	500 IU/mL
Total protein content (mg/mL)	6.5	65

[a] Nominal values

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

Berinert® IV contains up to 486 mg sodium per 100 mL of solution. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Berinert® IV is produced as a sterile, pyrogen-free, freeze-dried white powder for intravenous injection and supplied with Water for Injections (clear, colourless) for reconstitution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Berinert® IV is indicated for the treatment of acute attacks in patients with hereditary angioedema (HAE).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

It is recommended that prescribed doses of Berinert® IV should be expressed as International Units written in full.

Berinert® IV is administered intravenously by a doctor or nurse. If self administration and home treatment is considered appropriate, refer to the ***Self administration and home treatment*** section under **Administration**.

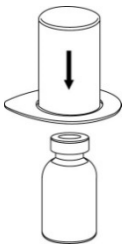
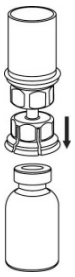
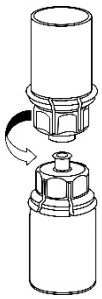
Dosage

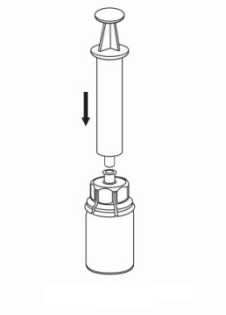
The recommended dose is 20 IU per kg body weight for adult and paediatric patients.

Reconstitution

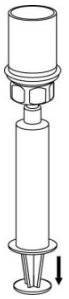
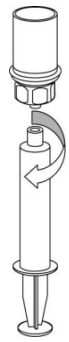
Reconstitution and withdrawal must be carried out under aseptic conditions. Use the syringe provided with the product or a silicone-free syringe. Bring the diluent to room temperature. Ensure product and diluent vial flip caps are removed and the stoppers are treated with a disinfectant and allowed to dry prior to opening the Mix2Vial™ package.

Open the carton and remove the Mix2Vial™ filter transfer set. The Mix2Vial™ filter transfer set is intended to filter the contents of a single vial of Berinert® IV only.

 1	1. Open the Mix2Vial™ package by peeling off the lid. Do **not** remove the Mix2Vial™ from the blister package!
 2	2. Place the diluent 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 diluent 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 diluent vial with the Mix2Vial™ set attached and push the spike of the transparent adapter end **straight down** through the product vial stopper. The diluent 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 diluents side and unscrew the set carefully into two pieces. Discard the diluent 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. 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 concentrate into the syringe by pulling the plunger back slowly.
 9	9. Now that the concentrate 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.

Note: The Mix2Vial™ is intended to filter the contents of a single vial of Berinert® IV only. If multiple vials of Berinert® IV are to be administered, a separate Mix2Vial™ must be used for each vial.

The Berinert® IV 500 IU solution should be colourless and clear. The Berinert® IV 1500 IU solution should be colourless and clear to slightly opalescent. After filtering/withdrawal the

reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that are cloudy or contain flakes or particles.

Administration

CAUTION: The product does not contain an antimicrobial preservative. The reconstituted product should only be stored in the vial. Any unused solution must be discarded appropriately. Use in one patient on one occasion only.

Berinert® IV should not be mixed with other medicinal products and diluents.

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

Berinert® IV 500 IU

It is recommended that Berinert® IV 500 IU be administered by slow intravenous injection at a rate of 4 mL/minute.

If not administered immediately, it must be stored at 2–8°C and used within 24 hours of reconstitution. Allow solution to reach room temperature before administration.

Berinert® IV 1500 IU

It is recommended that Berinert® IV 1500 IU be administered as a bolus intravenous injection.

If not administered immediately, it must be stored at 2–8°C and used within 8 hours of reconstitution. Allow solution to reach room temperature before administration.

Self administration and home treatment

If deemed appropriate by the treating physician, Berinert® IV may be self-administered by the patient (or carer) following adequate training. This includes its administration in the home or other appropriate setting.

If self administration/home treatment is deemed appropriate, ensure that the patient/carer receives clear instructions, adequate training on intravenous administration and has demonstrated the ability to perform intravenous infusions.

- Ensure the patients/carers understand the importance of not starting treatment if the attack (regardless of type) has progressed to a point that the patients/carers would be unable to successfully prepare and administer Berinert® IV.

- Given the potential for airway obstruction during acute laryngeal HAE attacks, patients should be advised to immediately call an ambulance or seek urgent hospital treatment in addition to treatment with Berinert® IV.
- To help exclude the possibility that another potentially serious medical cause may be responsible for their symptoms, advise patients to contact their physician after treating suspected abdominal HAE attacks.
- Instruct patients that Berinert® IV is made from human blood and therefore it may carry a risk of transmitting infectious agents, e.g. viruses such as HIV, hepatitis B and C (see Section 4.4 Special warnings and precautions for use – Pathogen safety). Inform patients of the risks and benefits of Berinert® IV before prescribing or administering it to the patient.
- Advise female patients to notify their physician if they become pregnant or intend to become pregnant or if they are breastfeeding or plan to breastfeed during the treatment of HAE attacks with Berinert® IV.
- The Australian Product Information (PI) and Consumer Medicine Information (CMI) document for Berinert® IV are provided as a package insert and contain useful instructions for patients/carers who will be administering Berinert® IV. These documents are also available through https://www.ebs.tga.gov.au/ .

4.3 CONTRAINDICATIONS

Berinert® IV is contraindicated in individuals with a known hypersensitivity to any of the components of the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Antihistamines and corticosteroids should be administered prophylactically in patients with a known tendency towards allergies.

If allergic or anaphylactic-type reactions occur, the administration of Berinert® IV should stop immediately (e.g. discontinue injection/infusion) and an appropriate treatment 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.

Treatment of Capillary Leak Syndrome with Berinert® IV is not advised (see Section 4.8 Adverse effects (undesirable effects)).

Berinert® IV contains up to 486 mg sodium per 100 mL of solution. This is to be taken into consideration for patients on a controlled sodium diet.

Home treatment and self-administration

There are limited data on the use of this medicinal product in home treatment or self administration. 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 is reviewed at intervals to ensure the continued appropriate administration.

Patients with laryngeal oedema require particularly careful monitoring. Given the potential for airway obstruction during acute laryngeal HAE attacks, patients self-administering Berinert® IV should be advised to immediately seek medical attention.

Refer to Section 4.2 Dose and method of administration for further precautions regarding administration of Berinert® IV.

Pathogen safety

This product is made from human plasma. Products made from human plasma may contain infectious agents such as viruses that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain viral markers.

In addition, the Berinert® IV manufacturing process includes pasteurisation (at 60°C for 10 hours), hydrophobic interaction chromatography and virus filtration (also called nanofiltration) by two filters, 20 nm and 15 nm, in series, as dedicated virus inactivation and removal steps to reduce the potential for pathogen transmission.

The current procedures applied in the manufacture of this product are effective against enveloped viruses such as HIV (human immunodeficiency virus), hepatitis B and hepatitis C viruses and for the non-enveloped viruses hepatitis A and parvovirus B19.

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

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

Use in the elderly

Safety and efficacy of Berinert® IV in the elderly population has not been established.

Paediatric use

The safety and efficacy of Berinert® IV was not systematically evaluated in children. There were no apparent differences in the safety and efficacy profiles as compared to adult subjects.

Effects on laboratory tests

C1 esterase inhibitor is an endogenous plasma protein so no specific effects on laboratory tests are anticipated.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The interaction of Berinert® IV with other medicines has not been established in appropriate studies.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies examining the effect of Berinert® IV on fertility have been conducted.

Use in pregnancy

The safety of Berinert® IV for use in human pregnancy has not been established in controlled clinical trials. Experiences on the treatment of women during pregnancy have shown good tolerance and no negative impact on the mother and child during the observation period until directly after birth. Berinert® IV should be used during pregnancy only if clearly needed.

Animal reproductive toxicity studies have not been conducted with Berinert® IV.

Use in lactation

The safety of Berinert® IV for use during lactation has not been established in controlled clinical trials. Berinert® IV should be used during lactation only if clearly indicated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Undesired reactions with Berinert® IV are rare.

Clinical studies experience

The following safety data were obtained from clinical trials conducted using the Berinert® IV 500 IU presentation (see Section 5.1 Pharmacodynamic properties – Clinical trial**)**. Berinert® IV 500 IU and 1500 IU had favourable and comparable safety and tolerability profiles when administered intravenously in a phase I study in healthy volunteers.

Pivotal study

The most common adverse events (AEs) reported in subjects up to 4 hours after receiving 20 IU/kg body weight Berinert® IV in the pivotal phase III study were nausea, dysgeusia, abdominal pain and vomiting.

Open-label extension study

The most common AEs reported in subjects within 24 hours after receiving 20 IU/kg body weight Berinert® IV in the open-label extension study were headache and rash.

The incidence and type of adverse reactions with Berinert® IV when administered for treatment of HAE attacks was consistent across studies.

The most common AEs reported in subjects up to 9 days after infusion with 20 IU/kg body weight Berinert® IV in the clinical studies were headache, HAE, abdominal pain, nausea, muscle spasms, pain, diarrhoea and vomiting. Of these, an increase in the severity of pain associated with HAE was considered the most serious.

Table 2 provides a summary of AEs in >1 subject overall by preferred term and system organ class.

Table 2: Summary of AEs in >1 subject overall by preferred term and system organ class (4-hour safety population)

System organ class **Preferred term (MedDRA)**	**Placebo** **(N = 41)**	**Berinert®** IV **20 IU/kg body weight** **(N = 46)**
Number of subjects with at least 1 AE	**18 (43.9)**	**9 (19.6)**
Gastrointestinal disorders	13 (31.7)	5 (10.9)
Nausea	5 (12.2)	3 (6.5)
Abdominal pain	3 (7.3)	2 (4.3)
Diarrhoea	4 (9.8)	0
Vomiting	3 (7.3)	1 (2.2)
Lip swelling	1 (2.4)	0
General disorders and administration site conditions	3 (7.3)	2 (4.3)
Pain	1 (2.4)	1 (2.2)
Edema peripheral	0	1 (2.2)
Face edema	1 (2.4)	0
Musculoskeletal and connective tissue disorders	4 (9.8)	1 (2.2)
Muscle spasms	2 (4.9)	1 (2.2)
Nervous system disorders	2 (4.9)	2 (4.3)
Dysgeusia	0	2 (4.3)
Headache	2 (4.9)	0

Table 3 provides a summary of AEs in >1 subject overall by preferred term and system organ class (after 4-hour safety populations).

Table 3: Summary of AEs in >1 subject overall by preferred term and system organ class (after 4-hour safety populations)

System organ class Preferred term (MedDRA)	Without rescue study medication		With rescue study medication	
	Placebo	Berinert® IV 20 IU/kg body weight	Placebo + Berinert® IV 20 IU/kg body weight	Berinert® IV 20 IU/kg body weight + Placebo
	(N = 18)	(N = 38)	(N = 23)	(N = 8)
Number of subjects with at least 1 AE	**9 (50.0)**	**11 (28.9)**	**14 (60.9)**	**5 (62.5)**
Congenital, familial and genetic disorders	0	5 (13.2)	3 (13.0)	1 (12.5)
Hereditary angioedema	0	5 (13.2)	3 (13.0)	1 (12.5)
Nervous system disorders	0	3 (7.9)	4 (17.4)	3 (37.5)
Headache	0	3 (7.9)	4 (17.4)	3 (37.5)
Dysgeusia	0	0	1 (4.3)	1 (12.5)
Gastrointestinal disorders	5 (27.8)	2 (5.3)	8 (34.8)	1 (12.5)
Abdominal pain	1 (5.6)	1 (2.6)	1 (4.3)	0
Diarrhoea	2 (11.1)	1 (2.6)	3 (13.0)	0
Nausea	2 (11.1)	0	4 (17.4)	0
Vomiting	0	0	4 (17.4)	0
Abdominal distension	0	0	0	1 (12.5)
Infections and infestations	1 (5.6)	2 (5.3)	1 (4.3)	0
Upper respiratory tract infection	0	1 (2.6)	0	0
General disorders and administration site conditions	3 (16.7)	0	5 (21.7)	0
Pain	1 (5.6)	0	2 (8.7)	0
Musculoskeletal and connective tissue disorders	1 (5.6)	1 (2.6)	5 (21.7)	1 (12.5)
Back pain	0	0	3 (13.0)	1 (12.5)
Muscle spasms	0	0	2 (8.7)	0

This table includes only SOCs with individual preferred terms that occurred in >1 subject overall. Data are sorted by frequency of AEs in the group without rescue medication.

N = Total number of subjects.

Post-marketing surveillance

Post-market reporting of adverse reactions is voluntary and from a population of uncertain size and consequently it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Adverse reactions reported in patients receiving Berinert® IV for treatment of HAE include allergic/anaphylactic reactions, injection site pain, injection site redness, chills and fever.

In treatment attempts with high doses (>90 IU/kg body weight) of Berinert® IV for prophylaxis or therapy of Capillary Leak Syndrome before, during or after cardiac surgery under extracorporeal circulation (unlicensed indication and dose) the development of thrombosis was reported, including cases with fatal outcome.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No case of overdose has been reported in connection with treatment of HAE.

The development of thrombosis has been reported after high doses (greater than 90 IU/kg body weight) of Berinert® IV in newborns and young children with congenital heart anomalies during or after cardiac surgery under extracorporeal circulation.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

C1 esterase inhibitor belongs to the group of serine protease inhibitors that includes antithrombin III, alpha$_1$-protease inhibitor, alpha$_2$-antiplasmin and heparin cofactor II. It is a major inhibitor of the activated serine proteinases C1r and C1s, kallikrein and coagulation factors XIIa and XIa.

C1 esterase inhibitor has an important inhibiting potential on several of the major cascade systems of the human body including the complement system, the contact system, the

fibrinolytic system and the coagulation cascade. A major function of C1 esterase inhibitor is the inhibition of the complement system to prevent spontaneous activation.

Berinert® has been shown to inhibit the classical complement activity in both human (IC_{50} = 1.05 IU/mL) and rat (IC_{50} = 1.01 IU/mL) plasma *in vitro*. In animal disease models, it has been shown to block oedema formation, capillary leakage, sepsis and stroke where the complement and kallikrein/kinin systems are also implicated.

Administration of Berinert® IV to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients to relieve symptoms of hereditary angioedema (HAE). The product is to be administered intravenously and is immediately available in the plasma with a plasma concentration corresponding to the administered dose.

Clinical trials

The following clinical trial data were obtained from clinical trials conducted using the Berinert® IV 500 IU presentation. Bioequivalence of the 500 IU and 1500 IU presentations has been established in a separate clinical trial in healthy volunteers (see Section 5.2 Pharmacokinetic properties**)**.

A pivotal Phase III prospective, multinational, randomised, parallel-group, placebo-controlled, dose-finding, three-arm, double-blind clinical study assessed the efficacy and safety of Berinert® IV in 124 adult and paediatric subjects with C1 esterase inhibitor deficiency who were experiencing an acute moderate to severe attack of abdominal or facial HAE. Subjects ranged in age from 6 to 72 years of age.

The study objectives were to show that Berinert® IV shortens the time to onset of relief of symptoms of an abdominal or facial attack compared to placebo and to compare the efficacy of two different doses of Berinert® IV.

Subjects were randomised to either receive a 10 IU/kg body weight dose of Berinert® IV (39 subjects), a 20 IU/kg dose of Berinert® IV (43 subjects), or a dose of placebo (42 subjects) by slow intravenous infusion (4 mL per minute) within 5 hours of an attack.

Subjects treated with a 20 IU/kg dose of Berinert® IV experienced a highly significant reduction ($p = 0.0025$) in the median time to onset of relief from symptoms of an HAE attack (30 minutes) as compared to placebo (90 minutes).

The median time to complete resolution of HAE symptoms was significantly shorter ($p = 0.0237$) in the Berinert® IV 20 IU/kg group (4.9 hours) than in the placebo group (7.8 hours).

The study demonstrated that a 20 IU/kg body weight dose of Berinert® IV was significantly more efficacious than a 10 IU/kg body weight dose of Berinert® IV or placebo. Additionally, the 10 IU/kg body weight dose of Berinert® IV did not show a clinically significant difference compared to placebo.

Berinert® IV was further evaluated in a prospective, open-label, uncontrolled, multicentre extension study conducted at 15 centres in the US and Canada in subjects who had participated in the pivotal phase III study for the treatment of acute abdominal or facial attacks in subjects with HAE.

The purpose of this extension study was to provide Berinert® IV to subjects who had participated in the pivotal study and who experienced any type of subsequent HAE attack (i.e., abdominal, facial, peripheral, or laryngeal).

The safety analysis of the open-label extension study included a total of 57 subjects (19 males and 38 females, age range: 10 to 53 years) with 1085 HAE attacks treated with 20 IU/kg body weight dose of Berinert® IV per attack, who were observed at the study site until onset of relief of HAE symptoms, and were followed up for adverse reactions for 7 to 9 days following treatment of each HAE attack.

During the extension study, 51 subjects experienced 747 abdominal attacks, 21 subjects experienced 51 facial attacks, 30 subjects experienced 235 peripheral attacks, and 16 subjects experienced 48 laryngeal attacks. Some study subjects may have experienced HAE attacks in more than one location.

An analysis of laryngeal HAE attacks showed that the median time to initial onset of symptom relief and median time to complete resolution in the per-attack analysis were 0.25 hours and 8.4 hours, respectively (see **Table 4**), which were the shortest times among the various attack locations.

Table 4: Time to initial onset of symptom relief and time to complete resolution of HAE symptoms for laryngeal attacks

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

CI = confidence interval; HAE = hereditary angioedema; N = number of attacks.

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

There were no clinically relevant or consistent data suggesting that gender, age group, race/ethnic group, type of HAE, routine use of androgens, or presence of detectable anti-C1 esterase inhibitor antibodies had an effect on the time to initial or complete relief of symptoms following Berinert® IV.

The prospective open-label extension study demonstrated that, in comparison to untreated historical control data retrospectively collected at a study centre in Germany over a 20 year period, the Berinert® IV 20 IU/kg body weight dose appeared to be effective in ameliorating laryngeal HAE attacks by achieving complete resolution of HAE symptoms within 24 hours from attack onset in the majority of subjects. The treatment effects observed with Berinert® IV in the extension study are consistent with the findings from the placebo-controlled efficacy trial.

Adverse reactions encountered during the clinical trials are outlined under section 4.8 Adverse effects (undesirable effects)**.**

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic properties of Berinert® IV have been investigated in two studies.

In the first study, the pharmacokinetics (PK) of Berinert® IV were evaluated in an open-label, uncontrolled, single-centre study in 40 subjects (6 patients <18 years) with either mild or severe HAE. The 25 subjects with mild HAE were treated on demand for an acute attack; the 15 subjects with severe HAE were treated on a prophylactic basis. All subjects received a single intravenous injection of Berinert® IV ranging from 500 IU to 1500 IU.

The median *in vivo* recovery (IVR) was 86.7%. The IVR for children was slightly higher (98.2%) than for adults (82.5%). Patients with severe attacks had a higher IVR (101.4%) compared to patients with mild attacks (75.8%).

The median increase in C1 esterase inhibitor activity was 2.3%/IU/kg body weight. 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 vs 2.1%/IU/kg body weight).

The maximum concentration of C1 esterase inhibitor activity in plasma was reached within 0.8 hours after administration of Berinert® IV 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).

The second study, a phase 1 study conducted in 15 healthy adult subjects, provided PK data that was used to assess the relative bioavailability of the Berinert® IV 1500 IU presentation and 500 IU presentation. Comparable bioavailability of the two presentations of Berinert® IV was demonstrated. For C1 esterase inhibitor antigen concentrations, the maximum observed plasma concentration (Cmax) and area under the curve to the last quantifiable concentration (AUC0-last) geometric mean ratios (90% confidence intervals (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 the 1500 IU presentation and 500 IU presentation was 87.7 hours and 91.4 hours respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with Berinert® IV.

Carcinogenicity

No carcinogenicity studies have been conducted with Berinert® IV.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Glycine

Sodium citrate

Sodium chloride

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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Reconstituted product

Berinert® IV contains no antimicrobial preservative.

If Berinert® IV 500 IU is not administered immediately, it must be stored at 2–8°C and used within 24 hours of reconstitution.

If Berinert® IV 1500 IU is not administered immediately, it must be stored at 2–8°C and used within 8 hours of reconstitution.

The reconstituted product should only be stored in the vial.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not freeze. Protect from light. Do not use after the expiry date.

6.5 NATURE AND CONTENTS OF CONTAINER

Each presentation includes Berinert® IV powder for injection and Water for Injections in glass vials with latex-free rubber stoppers closed with an aluminium seal and a plastic flip-off cap.

Berinert® IV 500 IU and Berinert® IV 1500 IU presentations are supplied as:

- 1 vial with powder
- 1 vial with Water for Injections (500 IU: 10 mL, 1500 IU: 3 mL)
- 1 Mix2Vial™ filter transfer set 20/20
- One administration pack containing:
    - 1 disposable syringe (500 IU: 10 mL, 1500 IU: 5 mL)
    - 1 infusion set
    - 2 alcohol swabs
    - 1 non-sterile plaster (adhesive bandage)

Not all presentations may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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

CAS number

80295-38-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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14 January 2010

10 DATE OF REVISION

05 February 2019

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	PI reformatted in line with TGA requirement
All sections	Product name changed from "Berinert®" to "Berinert® IV"
4.7	Information about effects on ability to drive and use machines added
6.2	Information about incompatibilities added
6.5	Information about nature of container added