

AUSTRALIAN PRODUCT INFORMATION

Berinert[®] SC

(Human C1 esterase inhibitor)

1 NAME OF THE MEDICINE

Human C1 esterase inhibitor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Berinert[®] SC is available in two presentations which contain 500 IU/mL of C1 esterase inhibitor when reconstituted as directed (see **Table 1**).

Table 1: Berinert[®] SC presentations ^a

Presentation	2000 IU	3000 IU
Active ingredients (IU/vial)		
C1 esterase inhibitor	2000	3000
Reconstitution volume (mL)	4	5.6
Concentration	500 IU/mL	500 IU/mL
Total protein content (mg/mL)	65	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[®] SC 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[®] SC is produced as a sterile, pyrogen-free, freeze-dried white powder for subcutaneous injection and supplied with Water for Injections (clear, colourless) for reconstitution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Berinert[®] SC for subcutaneous injection is indicated for prevention of recurrent Hereditary Angioedema (HAE) attacks in patients aged 8 years and older with C1 esterase inhibitor deficiency.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Berinert® SC is intended for self-administration by subcutaneous injection. The patient or carer should be trained on how to administer Berinert® SC. Refer to the *Self administration and home treatment* section under **Administration**.

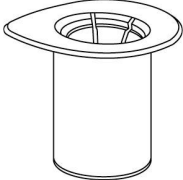


Dosage

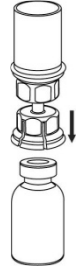
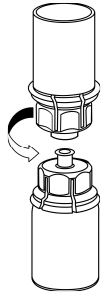

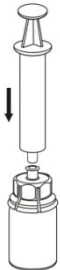
The recommended dose is 60 IU per kg body weight twice weekly (every 3–4 days).

Reconstitution

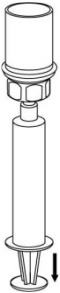
Reconstitution and withdrawal must be carried out under aseptic conditions. Reconstitution is achieved generally within 5 minutes, but may take as long as 10 minutes. Use the syringe provided with the product or a silicone-free syringe. Bring the product and diluent (Water for Injections (WFI)) vials 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.

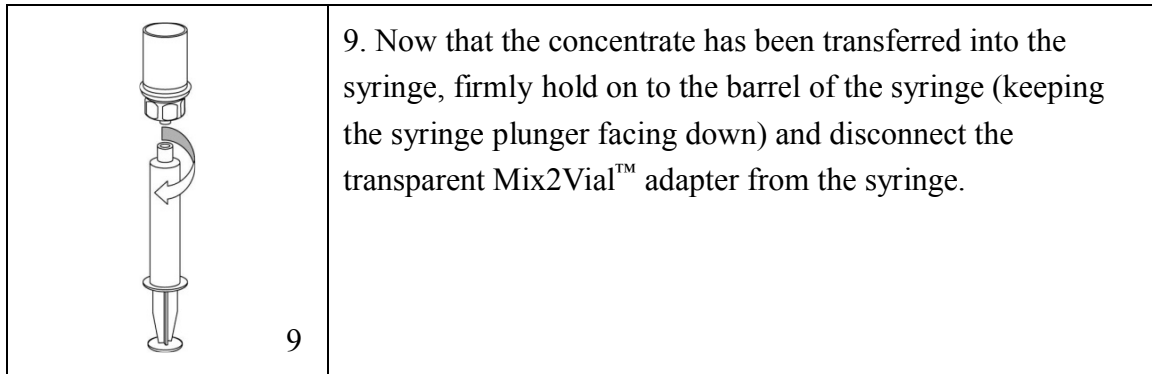
Open the carton and remove the Mix2Vial™ filter transfer set. The Mix2Vial™ filter transfer set is intended to filter the contents of a single vial of Berinert® SC only.

 <p>1</p>	<p>1. Open the Mix2Vial™ package by peeling off the lid. Do not remove the Mix2Vial™ from the blister package!</p>
 <p>2</p>	<p>2. Place the diluent (WFI) vial on an <u>even, clean surface</u> 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.</p>
 <p>3</p>	<p>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.</p>

 <p style="text-align: right;">4</p>	<p>4. Place the Berinert® SC product vial on an <u>even and firm surface</u>. 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.</p>
 <p style="text-align: right;">5</p>	<p>5. With one hand grasp the product-side of the Mix2Vial™ set and with the other hand grasp the diluent-side and unscrew the set carefully into two pieces. Discard the diluent vial with the blue Mix2Vial™ adapter attached.</p>
 <p style="text-align: right;">6</p>	<p>6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. (Generally within 5 minutes, but may take as long as 10 minutes). Do not shake.</p>
 <p style="text-align: right;">7</p>	<p>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.</p>

Withdrawal and application

 <p style="text-align: right;">8</p>	<p>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.</p>
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Note: The Mix2Vial™ is intended to filter the contents of a single vial of Berinert® SC only. If multiple vials of Berinert® SC are to be administered, a separate Mix2Vial™ must be used for each vial.

The 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

The reconstituted preparation should be administered by subcutaneous injection at a rate tolerated by the patient.

The suggested site for injection is the abdomen.

In clinical trials the injection was administered into a single site.

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

It is strongly recommended that every time Berinert® SC 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.

CAUTION: The product does not contain an antimicrobial preservative. If it is not administered immediately, it must be stored at room temperature (below 30°C) and used within 6 hours of reconstitution. 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.

Self administration and home treatment

Berinert® SC may be self-administered by the patient (or carer); this includes its administration in the home or other appropriate setting. Potential risks associated with home

treatment are related to the administration itself as well as the handling of adverse drug reactions.

Ensure that the patient / carer receives clear instructions, adequate administration training and has demonstrated the ability to perform subcutaneous injections. This should be reviewed at intervals to ensure the continued appropriate administration.

Patients / carers should be counselled regarding the appropriate course of action in case of an acute HAE attack, as individualised treatment should be initiated. See Section 4.4 Special warnings and precautions for use.

4.3 CONTRAINDICATIONS

Individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations or to any of the excipients listed in Section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions

If severe allergic or anaphylactic-type reactions occur, the administration of Berinert[®] SC should stop immediately (e.g. discontinue injection) and an appropriate treatment initiated.

In the event of an acute HAE attack, individualised treatment should be initiated.

Thromboembolic events

At the recommended subcutaneous dose, no causal relationship between thromboembolic events and the use of C1 esterase inhibitor concentrate has been established.

Thrombosis has occurred in treatment attempts with high doses of C1 esterase inhibitor intravenously for prophylaxis and during therapy of capillary leak syndrome before, during or after cardiac surgery under extracorporeal circulation (off-label indication and dose).

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[®] SC 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

Seven patients 65 to 72 years of age were included in a multicentre, randomised, double blind, placebo controlled, cross-over clinical trial (COMPACT study). Ten patients 65 to 72 years of age were included in the COMPACT extension study (see Section 5.1 Pharmacodynamic properties - Clinical trials). Results of subgroup analysis by age were consistent with overall study results.

Paediatric use

Six paediatric patients (12 to <17 years) were included in a multicentre, randomised, double blind, placebo controlled, cross-over clinical trial (COMPACT study). Ten paediatric patients (8 to <17 years) were included in the COMPACT extension study, of which 3 patients were under 12 years of age (see Section 5.1 Pharmacodynamic properties - Clinical trials). Results of subgroup analysis by age were consistent with overall study results.

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[®] SC with other medicines has not been established in appropriate studies.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

C1 esterase inhibitor is a physiological component of human plasma. No studies on fertility have been performed with Berinert[®] SC in animals.

Use in pregnancy

Berinert[®] SC should be used during pregnancy only if clearly indicated.

In the open-label COMPACT extension study, 4 pregnant women with type 1 HAE and ranging in age from 19 to 32 years received Berinert[®] SC. Patients received 40–60 IU/kg per subcutaneous administration for 4–8 weeks (9–15 doses) during the first trimester. All four women delivered healthy babies.

In an observational registry (318 subjects) data were collected on 11 pregnancies in 10 subjects (16 to 40 years of age) receiving up to 3000 IU of Berinert[®] intravenously to treat or prevent HAE attacks. No adverse events were associated with Berinert[®] treatment.

In a retrospective case collection study, 22 pregnant women with type I HAE and ranging in age from 20 to 38 years received C1 esterase inhibitor doses of 500 or 1000 IU per intravenous administration for the treatment of acute attacks before, during, and/or after pregnancy (total of 35 pregnancies). No adverse events were associated with C1 esterase inhibitor treatment before, during, or after pregnancy.

Animal reproductive and development toxicity studies have not been conducted with Berinert[®] SC.

Use in lactation

Berinert[®] SC should be given to a nursing mother only if clearly needed. There is no information regarding the excretion of Berinert[®] SC in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Berinert[®] SC and any potential adverse effects on the breastfed infant from Berinert[®] SC.

In a retrospective case collection study, breastfeeding was documented for neonates from 21 of 35 births with a median duration of 4.8 months (ranging from 1 to 34 months). Mothers were treated postpartum with C1 esterase inhibitor doses up to 1000 IU per intravenous administration for the treatment of acute HAE attacks. No adverse events to the mothers were associated with C1 esterase inhibitor treatment after pregnancy. No information regarding the effect on the breastfed infant was reported.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical studies experience

Of the 90 subjects randomised in the COMPACT study, 86 subjects received at least 1 dose of Berinert[®] SC and 86 subjects received at least 1 dose of placebo (**Table 2**). A total of 5081 injections of Berinert[®] SC and placebo were administered over a range of 3 to 19 weeks (median of 16.6 weeks for Berinert[®] SC; median of 16.3 weeks for placebo).

Table 2: Adverse Reactions in >4% of Subjects treated with Berinert[®] SC subcutaneously

MedDRA System Organ Class	Adverse Reaction	Berinert [®] SC			Placebo (N = 86)
		60 IU/kg (N = 43)	40 IU/kg (N = 43)	Overall (N = 86)	
		n (%)	n (%)	n (%)	n (%)
General disorders and administration site conditions	Injection site reactions ^a	15 (34.9)	12 (27.9)	27 (31.4)	21 (24.4)
Immune system disorders	Hypersensitivity (Hypersensitivity, pruritus, rash and urticaria)	3 (7.0)	2 (4.7)	5 (5.8)	1 (1.2)
Infections and infestations	Nasopharyngitis	8 (18.6)	1 (2.3)	9 (10.5)	6 (7.0)
Nervous system disorders	Dizziness	0 (0.0)	4 (9.3)	4 (4.7)	1 (1.2)

N = number of subjects receiving the treatment; n = number of subjects experiencing ≥1 event.

^a Includes the terms: injection site bruising, coldness, discharge, erythema, haematoma, haemorrhage, induration, oedema, pain, pruritus, rash, reaction, scar, swelling, urticaria, warmth.

Of the injection site reactions occurring after treatment with Berinert[®] SC subcutaneously, 95.0% were of mild intensity and 82.5% resolved within 1 day of onset.

Table 3 presents the frequencies of adverse reactions on a per-patient basis for Berinert[®] SC administered subcutaneously according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) or unknown (cannot be estimated from the available data).

Table 3: Frequency of adverse reactions for Berinert[®] SC administered subcutaneously estimated on a per-patient basis

MedDRA System Organ Class	Adverse Reaction	Frequency
General disorders and administration site conditions	Injection site reactions	Very common
Immune system disorders	Hypersensitivity (Hypersensitivity, pruritus, rash and urticaria)	Common
Infections and infestations	Nasopharyngitis	Very common
Nervous system disorders	Dizziness	Common

Overall, safety data from the open-label COMPACT extension study, consisting of 64 rollover patients and 62 non-rollover patients, was consistent with the safety data from the randomised, double-blind, placebo-controlled, crossover routine prophylaxis trial (COMPACT study).

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. Doses up to 117 IU/kg have been administered subcutaneously twice weekly in a fixed-dose clinical study and were well tolerated.

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 is a plasma glycoprotein which belongs to the group of serine protease inhibitors that includes antithrombin III, alpha₁-protease inhibitor, alpha₂-antiplasmin and heparin cofactor II. Its concentration in human plasma is approximately 240 mg/L. 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.

Beriner[®] has been shown to inhibit the classical complement activity in both human (IC₅₀ = 1.05 IU/mL) and rat (IC₅₀ = 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 Beriner[®] SC to patients with C1 esterase inhibitor deficiency (hereditary angioedema; HAE) replaces the missing or malfunctioning protein.

Pharmacodynamics

In untreated patients, insufficient levels of functional C1 esterase inhibitor lead to increased activation of C1, which results in decreased levels of complement component 4 (C4). The administration of Berinert[®] increases plasma levels of C1 esterase inhibitor in a dose-dependent manner and subsequently increases plasma concentrations of C4. The C4 plasma concentrations after subcutaneous administration of 60 IU/kg of Berinert[®] SC were in the normal range (160 to 380 mg/L).

Clinical trials

The efficacy, safety, pharmacokinetics and quality of life (QoL) of Berinert[®] SC as a prophylaxis regime to prevent HAE attacks has been demonstrated in two phase III clinical trials.

COMPACT study

The first trial was a multicentre, randomised, double blind, placebo controlled, crossover study (COMPACT study). The study assessed 90 adult and adolescent subjects with symptomatic HAE type I or II. The median (range) age of subjects was 40 (12 to 72) years; 60 subjects were female and 30 subjects were male. Subjects were randomised to receive either 60 IU/kg or 40 IU/kg Berinert[®] SC in one 16 week treatment period and placebo in the other 16 week treatment period. Patients subcutaneously self-administered Berinert[®] SC or placebo 2 times per week. Efficacy was evaluated for the last 14 weeks of each treatment period. Eligible patients were also able to participate in an open-label extension study for up to 140 weeks. Approximately half of the subjects enrolled in the extension study participated in the COMPACT study (64/126, 50.8%), which contributed to the similarities between study populations.

Twice per week subcutaneous doses of 60 IU/kg or 40 IU/kg resulted in a significant difference in the time-normalised number of HAE attacks (the rate of attacks) relative to placebo (**Table 4**). The time-normalised number of HAE attacks in subjects dosed with 60 IU/kg was 0.52 attacks per month compared with 4.03 attacks per month while receiving placebo ($p < 0.001$). The time-normalised number of HAE attacks in subjects dosed with 40 IU/kg was 1.19 attacks per month compared with 3.61 attacks per month while receiving placebo ($p < 0.001$).

Table 4: Time-normalised number of HAE attacks (number/month)

	60 IU/kg Treatment Sequences (N = 45)		40 IU/kg Treatment Sequences (N = 45)	
	Berinert® SC	Placebo	Berinert® SC	Placebo
n	43	42	43	44
Mean (SD)	0.53 (0.771)	4.02 (2.308)	1.22 (2.310)	3.61 (2.088)
Min, Max	0.0, 3.1	0.6, 11.3	0.0, 12.5	0.0, 8.9
Median	0.29	3.75	0.29	3.81
LS Mean (SE)*	0.52 (0.261)	4.03 (0.263)	1.19 (0.327)	3.61 (0.327)
95% CI for LS Mean*	(0.00, 1.04)	(3.51, 4.55)	(0.54, 1.85)	(2.96, 4.26)
Treatment difference (within-subjects)	60 IU/kg Berinert® SC– Placebo		40 IU/kg Berinert® SC– Placebo	
LS Mean* (95% CI)	-3.51 (-4.21, -2.81)		-2.42 (-3.38, -1.46)	
p-value*	< 0.001		< 0.001	

CI = confidence interval; HAE = hereditary angioedema; N = number of randomised subjects;
n = number of subjects with data; SD = standard deviation; LS = Least squares, SE = standard error.

* From a mixed model.

The median (25th, 75th percentile) percentage reduction in the time-normalised number of HAE attacks relative to placebo was 95.1% (79.0, 100.0) on 60 IU/kg and 88.6% (69.6, 100.0) on 40 IU/kg among subjects with evaluable data in both treatment periods.

The percentage of responders (95% CI) with a $\geq 50\%$, $\geq 70\%$ and $\geq 90\%$ reduction in the time-normalised number of HAE attacks was higher on Berinert® SC relative to placebo (see **Table 5**).

Table 5: Percentage reduction in time-normalised number of HAE attacks on Berinert® SC relative to placebo

	Percentage reduction in time-normalised number of HAE attacks on Berinert® SC relative to placebo		
	$\geq 50\%$	$\geq 70\%$	$\geq 90\%$
Responder (%)^a			
60 IU/kg (n=40)	90.0	82.5	57.5
40 IU/kg (n=42)	76.2	66.7	42.9
≥ 40 IU/kg (95% CI) (n=82)	82.9 (73.4, 89.5)	74.4 (64.0, 82.6)	50.0 (39.4, 60.6)

^a Percentages are based on the number of subjects included in the analysis.

n = number of subjects with data; CI = confidence interval;

A subject is classified as a responder if the percentage reduction is $\geq 50\%$.

The proportion of subjects that had ≥ 1 HAE attack per 4 week period on placebo and < 1 HAE attack per 4 week period on Berinert® SC was 71.1% on 60 IU/kg and 53.3% on 40 IU/kg.

A total of 40.0% of subjects on 60 IU/kg and 37.8% of subjects on 40 IU/kg were attack-free, and the median rate of HAE attacks per month was 0.29 on both doses. The maximum rate of HAE attacks per month was 3.1 on 60 IU/kg and 12.5 on 40 IU/kg.

Berinert[®] SC resulted in a significant difference in the time-normalised number of uses of rescue medication (the rate of rescue medication use) relative to placebo. The 60 IU/kg dose resulted in a mean rate of rescue medication use of 0.32 uses per month compared with 3.89 uses per month with placebo. The 40 IU/kg dose resulted in a mean rate of rescue medication use of 1.13 uses per month compared with 5.55 uses per month with placebo.

Results of subgroup analysis by age (12 to <17, 17 to < 65, and ≥65 years) were consistent with overall study results.

Post-hoc analysis of exploratory endpoints demonstrated QoL and treatment satisfaction improved with Berinert[®] SC treatment compared with placebo treatment, with significant improvements from baseline observed for the treatment satisfaction questionnaire for medication (TSQM); domain - Effectiveness and Overall satisfaction and for the work productivity and activity impairment (WPAI) questionnaire; domain - Presenteeism, Productivity Loss and Impairment.

The results of subject reported outcome measures provide evidence that routine prophylaxis with subcutaneous Berinert[®] SC was effective, enabled subjects with HAE to be more active and productive, and increased overall satisfaction with treatment. Thus, Berinert[®] SC may importantly reduce the burden of HAE as identified in a published patient survey.

COMPACT extension study

The second phase III clinical trial (COMPACT extension study) was a multicentre, randomised, open-label parallel study, which provides long-term efficacy and safety data (and allowed continued treatment to subjects who had completed the COMPACT study). The COMPACT extension study included subjects with age range 8–72 years and included 10 subjects <18 years of age (3 were <12 years) and 10 subjects ≥ 65 years. The study assessed 126 subjects with symptomatic HAE type I or II for efficacy, safety, PK and QoL. Seventy six subjects were female and 50 subjects were male; the median (range) age of subjects was 41.0 (8–72) years. Subjects were randomised to receive either 60 IU/kg or 40 IU/kg Berinert[®] SC subcutaneously over a 24-week fixed dose treatment period, followed by individualised dose adjustment over a 28-week treatment period. Subjects who experienced frequent HAE attacks during the fixed dose period were eligible for dose increases.

Patients that were enrolled into the study had a mean monthly attack rate of 4.3 in the 3 months prior to entry and were treated for a mean of 1.5 years. A total of 44 subjects (34.9%)

had more than 2 years of exposure. The mean steady state C1 esterase inhibitor functional increased from 30.4% baseline to 52.0% for the 40 IU/kg treatment group and 28.3% baseline to 66.6% for the 60 IU/kg treatment group.

The incidence of adverse events was low and similar in both dose groups. Event rates of 11.3 and 8.5 adverse events per patient-year were reported during treatment with 40 IU/kg and 60 IU/kg Berinert[®] SC respectively. The majority of adverse events reported were mild in severity and were resolved within 24 hours of appearance.

The median rate of HAE attacks was 1.3 and 1.0 attacks per year in the 40 IU/kg and 60 IU/kg treatment groups respectively. The median number of use of rescue medication was 0.2 and 0.0 times per year in the 40 IU/kg and 60 IU/kg treatment groups respectively.

The proportion of subjects that were HAE attack-free throughout the study duration with a maximum exposure of >2.5 years was 34.9% and 44.4% in the 40 IU/kg and 60 IU/kg treatment groups respectively. In a post-hoc analysis of the 21 subjects receiving 40 IU/kg > 2 years, 16 (76.2%) were HAE attack-free during months 25 to 30 of treatment. Of the 23 subjects receiving 60 IU/kg > 2 years, 19 (82.6%) were HAE attack-free during months 25 to 30 of treatment.

Results of subgroup analysis by age (≤ 17 years and > 17 years; < 65 years and ≥ 65 years) were consistent with overall study results.

The COMPACT extension study confirms results of the placebo controlled COMPACT study and demonstrates the long term safety and efficacy of Berinert[®] SC replacement therapy for routine prophylaxis to prevent HAE attacks, therefore reducing the need for rescue medication.

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

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic (PK) characteristics of Berinert[®] SC when administered subcutaneously were derived using population PK methods on pooled data from three clinical studies (study 1001; phase I healthy subject PK and safety study; COMPACT phase I/II patient PK and safety study; and the COMPACT phase III study) in healthy subjects and HAE patients. After inclusion of the COMPACT extension study, the population PK parameters derived using the previously developed PK model remain unchanged and the C1 esterase inhibitor functional activity was similar across all studies following Berinert[®] SC administration for both 40 IU/kg and 60 IU/kg dose.

Studies have not been conducted to evaluate the PK of C1 esterase inhibitor in specific patient populations stratified by gender, race, or the presence of renal or hepatic impairment. The population analysis, evaluating age (8 to 72 years), was found not to influence the PK of C1 esterase inhibitor.

Absorption

Following twice weekly subcutaneous dosing, Berinert[®] SC is slowly absorbed, with a median (95% confidence interval; CI) time to peak concentration of approximately 59 hours (23, 134). Based on a median (95% CI) apparent plasma half-life of 69 hours (24, 250), steady state for C1 esterase inhibitor is expected within 3 weeks of dosing. A mean (95% CI) steady state trough functional C1 esterase inhibitor of 48% (25.1, 102) is expected after twice weekly subcutaneous administration of 60 IU/kg Berinert[®] SC. The mean (95% CI) relative bioavailability of Berinert[®] SC after subcutaneous administration was estimated to be approximately 43% (35.2, 50.2).

Distribution

The population mean (95% CI) apparent volume of distribution of Berinert[®] SC was estimated to be approximately 4.33 L (3.51, 5.15).

Excretion

The population mean (95% CI) clearance of Berinert[®] SC was estimated to be 83 mL/hr (72.7, 94.2). C1 esterase inhibitor clearance was found to be positively correlated with total body weight. The steady state PK of Berinert[®] SC was found to be independent of dose between 20–80 IU/kg in HAE subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with Berinert[®] SC.

Carcinogenicity

No carcinogenicity studies have been conducted with Berinert[®] SC.

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.

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 carton packaging.

Reconstituted product

The product does not contain an antimicrobial preservative. If it is not administered immediately, it must be stored at room temperature (below 30°C) and used within 6 hours of reconstitution. The reconstituted product should only be stored in the vial.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°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[®] SC powder for injection and Water for Injections in glass vials with latex-free rubber closures closed with an aluminium seal and a plastic flip-top cap.

Berinert[®] SC 2000 IU and 3000 IU presentations are supplied as:

- 1 vial with powder
- 1 vial with Water for Injections (2000 IU: 4 mL, 3000 IU: 5.6 mL)
- 1 Mix2Vial[™] filter transfer set 20/20
- One administration pack containing:
 - 1 disposable syringe (2000 IU: 5 mL, 3000 IU: 10 mL)
 - 1 hypodermic needle
 - 1 subcutaneous injection set
 - 2 alcohol swabs
 - 1 non-sterile plaster (adhesive bandage).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine 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 26–30%.

CAS number

80295-38-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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9 DATE OF FIRST APPROVAL

12 July 2018

10 DATE OF REVISION

3 September 2021

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2, 6.5	Update Water for Injections nominal volume
4.6, 5.1	Editorial changes