Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Human C1 esterase inhibitor

Proprietary Product Name: Berinert

Sponsor: CSL Limited, Bioplasma Division

February 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	14 January 2010
Active ingredient(s):	Human C1 esterase inhibitor
Product Name(s):	Berinert®
Sponsor's Name and Address:	CSL Limited, Bioplasma Division189-209 Camp Road Broadmeadows Vic 3047
Dose form(s):	Powder for injection vial
Strength(s):	500 units/vial (50 U/mL)
Container(s):	Glass vial
Pack size(s):	Berinert® is supplied as a composite pack containing one vial of Berinert® and one vial of Water for Injections (10 mL). The composite pack is shrink wrapped with an administration set containing a Mix2Vial™ filter transfer set, a disposable 10 mL syringe, an infusion set, two alcohol swabs and a plaster (adhesive bandage) to form a procedure pack.
Approved Therapeutic use:	For the treatment of acute attacks in patients with hereditary angioedema (HAE)
Route(s) of administration:	Intravenous infusion
Dosage:	20 units (U) per kg body weight at an infusion rate of 4 mL per minute

Product Background

A human C1 esterase inhibitor (C1-INH) product has been registered in Germany since 1979. The product has been continuously manufactured at a Marburg, Germany site. There have been major changes in production methods over this period.

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 synthesised 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 indicated for the treatment of acute attacks in patients with hereditary angioedema (HAE). The recommended dose is 20 units (U) per kg body weight at an infusion rate of 4 mL per minute. Clinical studies demonstrate that Berinert is safe, effective and shortens the median time to onset of symptom relief for patients with HAE attacks.

Regulatory Status

Berinert P was granted orphan drug status on 10 April 2007. A copy of the orphan Drug Designation for Berinert was included within the submission. CSL Limited has elected to register the tradename Berinert rather than Berinert P which was used in the Orphan Drug Designation Application. The sponsor assures that, apart from the tradename, all aspects of Berinert are identical to those supplied within the application.

A similar application has been approved in the European Union. The product has been approved in Germany and Hungary since 1979 and Austria since 1990. Further EU countries where Berinert® has been approved in the frame of the mutual recognition procedure from late 2008 through 2009 are: Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Great Britain, Greece, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden. The product is also approved in Argentina (March 2003), Japan (June 1990) and Switzerland (October 1993). In October 2009 Berinert was approved in the USA. Applications have been made in Canada (April 2008) and in Israel (August 2008).

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The active ingredient of the medicinal product is C1 esterase inhibitor (C1-INH), obtained from human plasma. Neither a compendial nor an INN is available for the active ingredient.

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 drug substance is a **c**olourless and clear solution.

The drug substance for Berinert is manufactured by CSL Behring GmbH, located at the pharmaceutical production and research areas in Marburg, Germany.

Drug Product

The manufacturing process is as follows:

- Separation of plasma into cryoprecipitate and cryo-depleted plasma
- Adsorption of prothrombin complex and C1 esterase inhibitor
- Elution and precipitation
- Stabilization and pasteurization
- Purification
- Concentration, dialysis and final formulation

The clinical trial formula is identical to the formula for the product that is produced for marketing purposes. CSL Behring demonstrated consistency of Berinert manufacture (data from 21 full scale batches provided, showing batch to batch consistency by meeting specifications).

When reconstituted as recommended, each vial of Berinert nominally contains 50 U/mL C1 esterase inhibitor, 8.5 to 11.5 mg/mL glycine, 2.5 to 3.5 mg/mL sodium citrate and 7.0 to 10 mg/mL sodium chloride. The total protein content of the reconstituted solution is 6.5 mg/mL.

The solvent for Berinert is Water for Injections (WFI), which complies with the Ph. Eur. monograph.

The finished product comprises one vial of lyophilised powder and one diluent vial containing WFI for reconstitution. A needle-less 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 17 mL injection vials made of colourless moulded glass (type II according to Ph.Eur.). Vials are closed with stoppers made of bromobutyl rubber and sealed by combi caps. The cap is an aluminium crimp cap with punched concentric hole and integrated plastic disc made of polypropylene.

An international standard for the active ingredient (C1-INH) has not been established. For determination of the C1-INH activity, a standardized human plasma reference (SHPL) is used that is calibrated against fresh pooled plasma. The commonly used SHPL is provided commercially by Siemens Healthcare Diagnostics Products GmbH, Marburg (Germany). The C1-INH activity is determined according to the "Berichrom C1 Inhibitor" test, which is supplied by Siemens Healthcare Diagnostics Products GmbH.

Based on the available data, a shelf-life of 30 months at a storage temperature 'below +25 °C' is supported.

The packaging material meets compendial (USP, Ph.Eur.) and relevant national and international standards (DIN; ISO), as applicable, and is suitable for products to be used via parenteral administration.

Sterility aspects of the product have been reviewed. Routinely, the sterility tests are carried out in the sterility laboratory of CSL Behring GmbH. There is one back-up laboratory. Valid GMP evidence has been submitted.

Besides testing of the starting material human plasma as described in the company's Plasma Master File, no further contract laboratory is involved for conducting in-process controls or testing of the drug substance itself, except for testing of sterility at a backup laboratory. CSL will ensure the GMP clearance letters of all of the manufacturers are current at the time of registration.

Satisfactory information on the testing for pyrogens was provided.

There are no bacterial endotoxin safety related issues.

The viral safety aspects of the product have been reviewed there are no outstanding issues.

Bioavailability

The route of administration of Berinert is by intravenous infusion. The product has a systemic action hence is considered to be fully and immediately available as its site of activity.

Quality Summary and Conclusions

There are no more outstanding issues in regards to quality data. It is recommended that registration be subject to batch release conditions until the consistency of the product is demonstrated. The application was considered at the 127th meeting of Pharmaceutical Subcommittee of the Australian Drug Evaluation Committee (ADEC) on 8 July 2009 and

there were no objections on quality and pharmaceutical grounds to approval of the application, provided all outstanding issues were addressed to the satisfaction of the TGA.

III. Nonclinical Findings

Introduction

The nonclinical data provided for C1 INH included studies of primary pharmacology *in vitro* and *in vivo*, safety pharmacology in dogs, limited pharmacokinetics in rats and rabbits, acute toxicity in mice and rats, repeat-dose toxicity in rats (≤ 2 weeks), local tolerance in rabbits and antigenicity *in vitro* and *in vivo*.

It should be noted that the majority of the nonclinical safety data (safety pharmacology, acute toxicity, local tolerance (intravenous [IV]), antigenicity) provided was generated in the 1980's and was subsequently associated with a lower standard of study documentation. These studies were also written in foreign languages with only English study summaries provided. Raw study data was sometimes limited both in determination and appraisal of parameters, and legibility due to poor photocopy quality and/or poor labelling. However, despite the paucity of clearly detailed and appropriately accessible data in these studies, they are consistent with the lower study documentation of the time period, were performed in accordance with good laboratory practice (GLP), where applicable, and have provided useful information with regard to describing the safety profile of C1 INH. In addition, more recently performed and comprehensive GLP-compliant repeat-dose toxicity and subcutaneous (SC) local tolerance studies have also been provided. Moreover, studies were generally performed in relevant animal species, with adequate numbers, dose levels (based on multiples of the clinical dose), and using appropriate administration routes.

Overall, the nonclinical testing program for C1 INH was acceptable for a plasma-derived product (*ICH guideline for preclinical safety evaluation of biotechnology-derived pharmaceuticals; CPMP/ICH/302/95*).

Pharmacology

Primary pharmacology

C1 esterase inhibitor (C1 INH) belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, α_1-protease inhibitor, α_2-antiplasmin and heparin cofactor II. As with other inhibitors in this group, C1 esterase inhibitors are involved in inhibiting several major cascade systems of the human body including the complement system, the contact system, the fibrinolytic system and the coagulation cascade. Primary pharmacology studies of C1 INH provided included a company study examining its direct effects on rat and human complement *in vitro* and several publications investigating its effects in animal models of oedema, capillary leakage, sepsis and stroke *in vivo*.

C1 INH demonstrated inhibition of its primary target enzyme, the first component of the classical complement pathway (C1 esterase) in both human and rat plasma *in vitro*. The inhibitory effect of C1 INH on human (IC_{50} = 1.053 U/mL) and rat complement (IC_{50} = 1.011 U/mL) was comparable. Interestingly, these IC_{50} values were similar to C1 INH concentrations observed in the two week rat repeat dose IV toxicity study (1-1.6 U/mL), which were without adverse toxicological effects (refer to *Repeat dose toxicity* section).

C1 INH was also shown to significantly block carrageenin-induced oedema (2.5-100 U/kg (≤50%), 800 U/kg IV (almost 100%)), decrease interleukin-2 (IL-2)-induced vascular leakage (250-500 U/kg IV), enhance survival following lipopolysaccharide (LPS)-induced sepsis (100-125 U/kg/h IV for up to 4 hours; 200 U/kg IV) and reduce infarction following cortical vein occlusion (20 U/kg IV) in rats. Clot formation was also reduced and cardiovascular

function improved in a rabbit model of LPS-induced sepsis following infusion of C1 INH at 100 or 300 U/kg IV.

Overall, an inhibitory effect of C1 INH on human and rat complement *in vitro* has been demonstrated. While there is no validated nonclinical model of HAE, studies in animal disease models, including oedema formation, predominantly in rats, have provided some evidence of efficacy in several diseases where the complement and kallikrein/kinin systems are also implicated. Therefore, the rat is considered an appropriate model for human C1 INH.

Secondary and safety pharmacology

A single secondary pharmacology paper was provided which described cardioprotective effects of C1 INH in a feline model of myocardial ischemia and reperfusion. Administration of 75 U/kg IV C1 INH prior to reperfusion improved recovery of cardiac contractility, preserved cardiac endothelial function and reduced cardiac myeloperoxidase activity. Deposition of C1q (the first component of the classic complement pathway) on cardiac myocytes and coronary vessels was also demonstrated.

A single GLP-compliant safety pharmacology study of C1 INH was performed in dogs. The limited summary provided, small number of dogs examined, absence of concurrent control animals and reporting of individual recordings or traces only, precluded a more thorough assessment of this study. Nonetheless, successive 500, 1000 and 2000 U/kg IV doses of C1 INH (cumulative dose 3500 U/kg) had no remarkable effects on the cardiovascular, respiratory and body temperature parameters examined. A mild effect on some haematological values (erythrocyte, leukocyte and platelet counts) was noted at 2000 U/kg, which resolved by the study end. Effects on platelet aggregation were inconsistent. However, a decrease in coagulation time was observed at all doses in two out of three dogs, which did not resolve by the end of the study.

Overall, this study suggests that administration of large C1 INH doses (≤2000 U/kg IV) to dogs are not associated with any significant cardiovascular, respiratory, body temperature or haematological effects. The clinical significance of the decreased coagulation time observed at all doses would appear limited given this effect was confined to two of three dogs, the large clinical safety margin still evident at the lowest effect dose (500 U/kg; 25-fold proposed clinical dose of 20 U/kg on a U/kg comparison basis only) and absence of similar coagulation effects in rats given 200 U/kg/day for 6 to 14 days (10-fold clinical dose on a U/kg comparison basis; 2-fold clinical dose based on AUC, refer to *Relative exposure* section).

Pharmacokinetics

Traditional absorption, distribution, metabolism, excretion (ADME) studies were not performed for C1 INH, however conventional pharmacokinetic assessment of biotechnology derived pharmaceuticals, including plasma-derived products, is generally not required (*CPMP/ICH/302/95*).

Pharmacokinetic data provided was confined to single dose IV or subcutaneous (SC) absorption studies in rats, rabbits and humans, and toxicokinetic data in rats. While limited, this data defined the absorption profile of C1 INH in the primary toxicology test species (rat and rabbit) and provided an assessment of systemic exposure in the pivotal rat repeat-dose toxicology study. No information about the pharmacokinetic profile of C1 INH in dogs was provided.

In all species, the volume of distribution was low (about 12 mL in rats, 170 mL in rabbits and 3.2 L in HAE subjects[1]) after a single IV dose, suggesting confinement primarily to the

[1] Based on 70 kg person

intravascular space, as expected for a high molecular weight (105 kDa) glycoprotein. When adjusted for bodyweight, these values were similar in rats (60-120 mL/kg[2]), rabbits (61 mL/kg) and humans (45 mL/kg).

The systemic clearance of C1 INH was faster in rats (4.5-9 mL/h/kg[2]) compared to HAE patients (1.0 mL/h/kg) and rabbits (1.6 mL/h/kg). As expected, a much shorter half-life was observed in rats (9 hours) compared to HAE patients (36 hours) and rabbits (34 hours).

Relative exposure

Table 1. Estimated systemic exposure to C1 INH in pharmacokinetic or toxicity studies

Species	Dose (U/kg) /Route	$C^{\#}/C_{max}$ (U/mL)	Exposure multiple	AUC (U.h/mL)	Exposure multiple
Wistar Rat	200* IV	1.06-1.62[#]	-	-	-
CD Rat	200 IV	-	-	**36.4**	1.8
CHB Rabbit	200 IV	7.53	-	150.96	7.4
	200 SC	1.70	-	115.2	5.6
HAE patient	20 IV	-	-	**20.5**[†]	

$C^{\#}$ = 24 hours after last dose (day 6, 10 or 14); *200 U/kg/day for 6-14 days; [†]Based on the AUC of 15.4 U.h/mL at 15 U/kg and assuming dose linearity.

Clinical exposure parameters were limited to AUC values in HAE patients given a 15 U/kg IV (not 20 U/kg as proposed) C1 INH dose. Assuming dose linearity, a 20 U/kg C1 INH dose to HAE patients would be associated with an AUC value of 20.5 U.h/mL. Toxicokinetic data for the pivotal 2 week rat repeat-dose toxicity was limited to determination of C1 INH plasma levels at 24 hours after the 6th, 10th and 14th doses. Nonetheless, given the availability of C1 INH single dose pharmacokinetic parameters for CD rats at 200 U/kg IV, and the absence of a cumulative effect on C1 INH plasma levels following repeated dosing at 20-200 U/kg/day in Wistar rats, this AUC value (36.4 U.h/mL) was employed for exposure comparison. On this basis, exposure in the pivotal rat repeat dose IV study is anticipated to be around 2-fold that expected clinically. While several assumptions are made in order to determine this safety margin, the alternative approach, of using dose (U/kg) or BSA (U/m^2) normalised dose comparisons, would fail to take into account the significantly different elimination profiles of C1 INH in rats and humans, and most likely markedly overestimate clinical safety margins for this species. In the absence of pharmacokinetic data in dogs, the highest IV dose in the dog safety pharmacology study (2000 U/kg) is 100 times the proposed clinical dose (20 U/kg).

Toxicology

Acute toxicity

The acute toxicity of C1 INH was examined in mice and rats given a single IV bolus dose. This study was GLP-compliant, employed typical rodent species, adequate numbers, doses chosen to achieve 'multiples' of the intended clinical dose and employed the intended clinical administration route. Doses of up to around 4800-5700 U/kg and 2700 U/kg IV in mice and rats, respectively were not associated with any deaths. Similarly, with the exception of cachexia observed at the 4800-5700 U/kg mouse dose during days 7-14, no remarkable clinical signs or necropsy findings were observed. While thorough assessment of this study

[2] Based on 100-200 g weight estimate, weight not provided in study

was precluded by the limited English summary provided, these results suggest that C1 INH is well-tolerated as an IV bolus dose of up to around 2400-2900 U/kg in two rodent species. These doses were associated with large multiples (120-145-fold) of the intended clinical dose, even when a 4-fold factor was introduced to account for potential rat interspecies clearance differences (>30-fold).

Repeat Dose Toxicity

The repeat dose toxicity of C1 INH was evaluated in a single 14 day GLP compliant IV study in rats. Dose level selection was based on "a multiple of the clinical dose" with doses administered up to 200 U/kg/day IV for 6-14 days. However, in the absence of any dose-limiting toxicity, it is likely that higher doses could have been employed. Although overall animal numbers were adequate (15/sex/group), only 5 rats/sex/group were evaluated at each sampling period (day 7, day 11 and day 15), suggesting numbers were low for a pivotal study. In contrast, the duration of this study is considered adequate given the likely infrequent administration of C1 INH, as an emergency treatment modality, and limitations associated with longer-term exposure to a human plasma protein, such as antibody development. Thus, in addition to standard toxicological evaluation, antibody generation was also assessed in this study.

There were no deaths. No remarkable clinical signs or adverse effects on food consumption or body weight were observed. There were no treatment-related findings in ophthalmoscopic or clinical laboratory (haematology, clinical chemistry and urinalysis) investigations. Post-mortem examinations also revealed no treatment-related macroscopic observations or adverse effects on organ weights. Microscopic findings associated with repeated dosing at the injection site (phlebitis/periphlebitis/thrombophlebitis and/or perivascular haemorrhage) were observed in the majority of animals. Given these lesions were observed in both control and treated animals, they were attributed to mechanical irritation rather than a direct toxic effect of C1 INH.

The measurement of rat antibody response against human C1 INH produced no clear results. While occasional antibody titres were detected, these values were associated with considerable scatter. It was noted that the presence of C1 INH in the samples might have lead to the formation of antigen-antibody complexes, obscuring the detection of the antibodies against C1 INH.

Overall, C1 INH appeared well-tolerated at IV doses up to 200 U/kg/day for up to 14 days in rats. Based on systemic exposure (AUC), this dose represents only a 2-fold safety margin over the intended dose in HAE patients (refer to *Relative Exposure* section). Nonetheless, no evidence of C1 INH-related toxicity has been observed in this study.

Genotoxicity, carcinogenicity and reproductive toxicity

No genotoxicity, carcinogenicity, or reproductive toxicity studies were conducted with C1 INH. This is acceptable for a human plasma-derived product. Long-term repeat dose toxicity studies are usually impracticable due to the formation of antibodies to this class of product.

Local tolerance

Potential local irritation of C1 INH was examined in GLP compliant rabbit studies using both the intended clinical route of administration (IV injection) and the subcutaneous route. Despite the limited study data available, CN 1NH appeared well-tolerated both locally and systemically following a single IV dose at 1500 U/kg. Similarly, only a mild, short-term local irritant effect of 25 U/kg and 75 U/kg SC C1 INH in rabbits was observed.

No injection site reactions were reported in the single-dose IV toxicity studies in rats and mice. Similarly, injection site findings in the 2 week rat repeat IV dose toxicity were limited to mechanical irritation effects, which were observed in all dose groups.

Antigenicity

An immunisation study investigating the presence of novel antigenic determinants, potentially induced by a pasteurisation step in Berinert manufacture, did not reveal any evidence for neoantigenicity in the *in vitro* Ouchterlony test and *in vivo* passive cutaneous anaphylaxis model in guinea pigs.

The presence or absence of antibody formation in the two week rat repeat dose IV toxicity study could not be confirmed.

Nonclinical Summary and Conclusions

A limited but adequate nonclinical testing program was provided for C1 INH.

The efficacy profile was well-defined with demonstrated inhibition of the complement pathway *in vitro* and in animal models of disease involving the complement and kallikrein/kinin systems.

Toxicology studies demonstrated that C1 INH was well tolerated in GLP compliant acute and short-term repeat dose toxicity studies in rodents and local tolerance studies in rabbits. Although clinical exposure margins were low (2-fold) in the pivotal 2 week rat study, no evidence of toxicity was observed in this and at much higher doses in the acute study. This low safety margin may be acceptable for a human plasma-derived substance anticipated for infrequent emergency use.

There are no nonclinical objections to the registration of Berinert as proposed by the sponsor.

IV. Clinical Findings

Introduction

Data in this dossier on the candidate formulation include one study of C1-INH pharmacokinetics, one randomised placebo-controlled study of safety and efficacy and an uncontrolled follow-up extension program with slightly widened entry criteria. The preparation was designated in Australia as an Orphan Drug for the claimed indication in April 2007.

Pharmacokinetics

Study CE1145_2001 was an opportunistic evaluation of the pharmacokinetics of the candidate preparation. It included 40 paediatric or adult patients with hereditary angioedema (HAE) presenting at a specialized clinic, either for management of a HAE episode or for a regular prophylactic dose.

The investigator-initiated study report documents that the dose and timing of administration of C1-INH to patients prior to the test dose was incomplete, necessitating approximations for adjusting the measured levels. However HAE is a relatively uncommon condition so better studies are unlikely to be forthcoming. Furthermore, there are two previous estimates of C1-INH pharmacokinetics, but using different preparations, with which the results of this study can be supplemented. Reliable information on its pharmacokinetics would of course be valuable to guide use of C1-INH but dose and timing of administration of the agent would in practice, be determined mainly by the clinical circumstances.

The study involved a single dose of 500-1500 Units of reconstituted lyophilized powder. It used 28 different batches of the product. Advice from the quality evaluator should be sought

on the likely batch-to-batch variability. The preparation was administered intravenously as a bolus infusion (a further description was not provided in the study report). Blood samples were drawn pre-administration and up to 72 hours post-administration. Additional rapid early sampling was planned for a sub-set of patients but this was undertaken in only two patients, both children, and in them it was incomplete.

C1-INH activity was analysed by a chromogenic assay (Berichrom® C1-Inhibitor, Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) and this was the value primarily used in data analysis. However, C1-INH antigen levels were also analysed by an ELISA ("NOR partigen®, Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). No details of assay performance appear to have been provided for either method.

There was a total of 40 individuals of whom 6 were aged <18 years, 31 were female, 25 were receiving C1-INH “on demand” and 15 were receiving regular prophylaxis. In 5 of the latter the time and dose of the previous dose was unknown and an approximation was used to adjust the measured levels.

No measurement of endogenous C1-INH activity and protein level was made specifically to identify the type of HAE present in each patient.

There is large inter-individual variability in all parameters but least in volume of distribution. There was no obvious difference in values between the age groups or types of treatment.

Levels of antigen correlated only approximately with measured C1 esterase inhibition for most individuals and for 5 subjects low functional activity but high antigen levels presumably indicated that they were examples of the Type II disorder.

In addition to the tabulated parameters, an *in vivo* recovery (IVR) was calculated as both the % increase from baseline plasma concentration (Classical IVR) and as the % increase from baseline plasma concentration per dose expressed as U/kg body weight (bw) (Incremental IVR).

Due to the fluctuations in the endogenous C1-INH activity levels, the IVR was calculated using the maximum increase in C1-INH concentration within 4 hours after study drug administration.

As the haematocrit value was not measured, a plasma volume of 41% was assumed for all subjects; the values obtained were tabulated in the same format as were the PK parameters.

There was no clear difference in mean IVR between children and adults but those patients receiving C1-INH prophylactically seemed to have greater increases in plasma levels (i.e. IVR) than did those receiving treatment “on demand.”.

Summary

The pharmacokinetics of the candidate preparation, characterized as C1-esterase inhibitory activity, were determined in an investigator-initiated study in 40 opportunistically assembled patients undergoing routine treatment in a specialized clinic. The doses administered in this studies varied as determined by unspecified clinical considerations but were in the range 500-1500 Units.

The derived pharmacokinetic parameters showed considerable inter-individual variability but generally demonstrated a volume of distribution consistent with intra-vascular retention, a low clearance and half-life ($t_{1/2}$) of ~36 hours.

Drug Interactions

No studies of drug interactions were provided in the submission.

Pharmacodynamics

No studies of pharmacodynamics were provided in the submission.

Efficacy

The pivotal study included in the dossier is a randomised, placebo-controlled trial of efficacy of a single dose of the candidate formulation in aborting an acute episode of HAE. This is supplemented by an open label multiple dose extension study, available to those who had participated in the controlled trial together with other patients as detailed below. Other material presented consists of anecdotal reports.

Pivotal Study

Study CE1145_3001 was a randomized, placebo-controlled double-blind study in 126 patients aged ≥6 years with HAE documented by centrally performed assay of C1 esterase function and/or antigen. Those presenting with a moderate to severe, acute facial or abdominal episode received a single intravenous dose of C1-INH or placebo. The study was conducted in accordance with the International Conference on Harmonization (ICH) Good

Clinical Practice (GCP) and appears to have been reasonably conducted and documented. There was 1 major protocol violation in ITT populations for each of the placebo and 10 Units/kg bw groups; one placebo patient received rescue medication before 4 hours post-dose, the other was admitted despite a positive drug screen. There were 201 minor deviations which were about twice as common in the placebo group as in the active treatment groups Patients with laryngeal manifestations were excluded to avoid their being randomised to receive placebo. In this study each patient contributed data from the treatment of only one episode. Data from subsequent episodes could be used for the extension study CE1145_3003 (see below). The treatment was to be given within 5 hours of the beginning of the episode.

Concomitant medication was minimized during the study but prophylactic agents such as androgens and tranexemic acid could be continued at an unchanged dose.

Further administration of blinded test infusions could be given as rescue medication when initial response was considered to be insufficient. This was not to be done until 4 hours had elapsed from the time of the initial treatment.

The **primary efficacy endpoint** was the time to onset of relief of symptoms as defined by the patient's responses to standardized enquiry by the investigator on the following schedule: every 15 min for the first 2 hours, every 30 min for the subsequent 2 hours, thence at 5, 6, 7, 8, 12, 16, 20 and 24 hours after start of administration of the study medication.

Subjects who received rescue study medication before onset of symptom relief were counted as non-responders for analysis of the primary endpoint.

Secondary efficacy endpoints were

- The reduction in the proportion of subjects in whom at least 1 of the clinical HAE symptoms present at baseline, worsened in intensity between 2 and 4 hours after start of study medication administration.
- The reduction in the number of vomiting episodes within 4 hours after start of study medication

The initial study plan was for randomisation (1:1:1) to receive placebo, C1-INH 10 Units/kg bw or 20 Units/kg bw. Following a planned interim analysis after a total of 35 patients had been treated in the placebo and C1-INH groups, the Data Safety Monitoring Board (DSMB) recommended that the 10 Units/kg bw group be discontinued due to futility[*]. Delays in implementing this decision resulted in little effect being manifested in the numbers included in the three groups; the ITT population finally comprised 124 patients. The group distributions within the study of those enrolled are shown in Table 2.

Overall 65% of patients were included in the four hour safety population without rescue medication.

In the ITT population, demographic and disease characteristics of the ITT population were generally similar in the Berinert and placebo groups. The placebo group was of lower weight but this was not likely to be clinically relevant as the dose given was specified as Units/kg

[*] *Futility in this sense, indicates that significance is unlikely to be reached by accumulating further observations.*

bw. However, more patients receiving placebo were identified as suffering from Type I HAE[**] than were those receiving the candidate preparation 20 Units /kg bw.

The time to subjective onset of symptom relief was the primary efficacy variable and both mean and median durations were substantially less for the Berinert 20 Units/kg bw group than those for the placebo group (Figure 1).

[**] *In Type I HAE the genetic defect results in low or absent levels of the gene product whereas in Type II levels of protein are not reduced but esterolytic activity is low. A rare Type III is described in which both protein activity and protein level are normal and thus it is presumably not relevant to the therapy under discussion.*

Table 2: Study CE1145_3001.

Population	Number (%) of subjects			
	Placebo	**Berinert 10 U/kg bw**	**Berinert 20 U/kg bw**	**Overall**
Total number of inclusions	42 (100)	40 (100)	43 (100)	127 (100) [a]
Total number of subjects	42 (100)	40 (100)	43 (100)	126 (100) [b]
Randomized population	42 (100)	40 (100)	43 (100)	125 (99.2)
Not completing [c] but evaluable [d]	10 (23.8)	8 (20.0)	14 (32.6)	32 (25.4)
ITT population	42 (100)	39 (97.5)	43 (100)	124 (98.4)
PP population	41 (97.6)	38 (95.0)	42 (97.7)	121 (96.0)
Safety populations				
4-hour safety population	41 (97.6)	39 (97.5)	43 (100)	126 (100) [e]
After 4-hour safety population without rescue medication	18 (42.9)	26 (65.0)	35 (81.4)	82 (65.1) [e]
	Placebo + Berinert 20 U/kg bw	**Berinert 10 U/kg bw + Berinert 10 U/kg bw**	**Berinert 20 U/kg bw + Placebo**	**Overall**
After 4-hour safety population with rescue medication	23 (54.8)	13 (32.5)	8 (18.6)	44 (34.9)

ITT = intention-to-treat; PP = per-protocol

[a] Includes 2 subjects who were not randomized.

[b] Includes 1 additional subject who was not randomized.

[c] No completion of treatment phase and/or follow-up or missing data on completion.

[d] Included in the ITT population.

[e] One subject in the Placebo group, 1 subject in the Berinert 10 U/kg bw group and 1 non-randomized subject were additionally included in the Overall population as they received >15 U/kg bw Berinert.

The DSMB recommendation to discontinue the 10 Units/kg bw group was vindicated. A non-parametric ranked-sum test of the difference between placebo and the 20 Units/kg bw groups was significant (p=0.00253) whereas that between the placebo and 10 Units/kg bw groups was not (p=0.2731) (see Table 3 below). However, presentation of the results was biased by the fact that those who required either a rescue second injection of test preparation or other medication for symptomatic relief were given an arbitrary *time to relief* of 24 hours.

Two stipulated secondary efficacy variables supported the conclusion indicated by the primary variable. Significantly fewer patients experienced worsening symptoms and fewer episodes of vomiting (see Tables 4 and 5 below).

Figure 1: Study CE1145_3001

I - Kaplan-Meier curves for time to onset of relief of HAE symptoms, as determined by subject's assessment (ITT population)

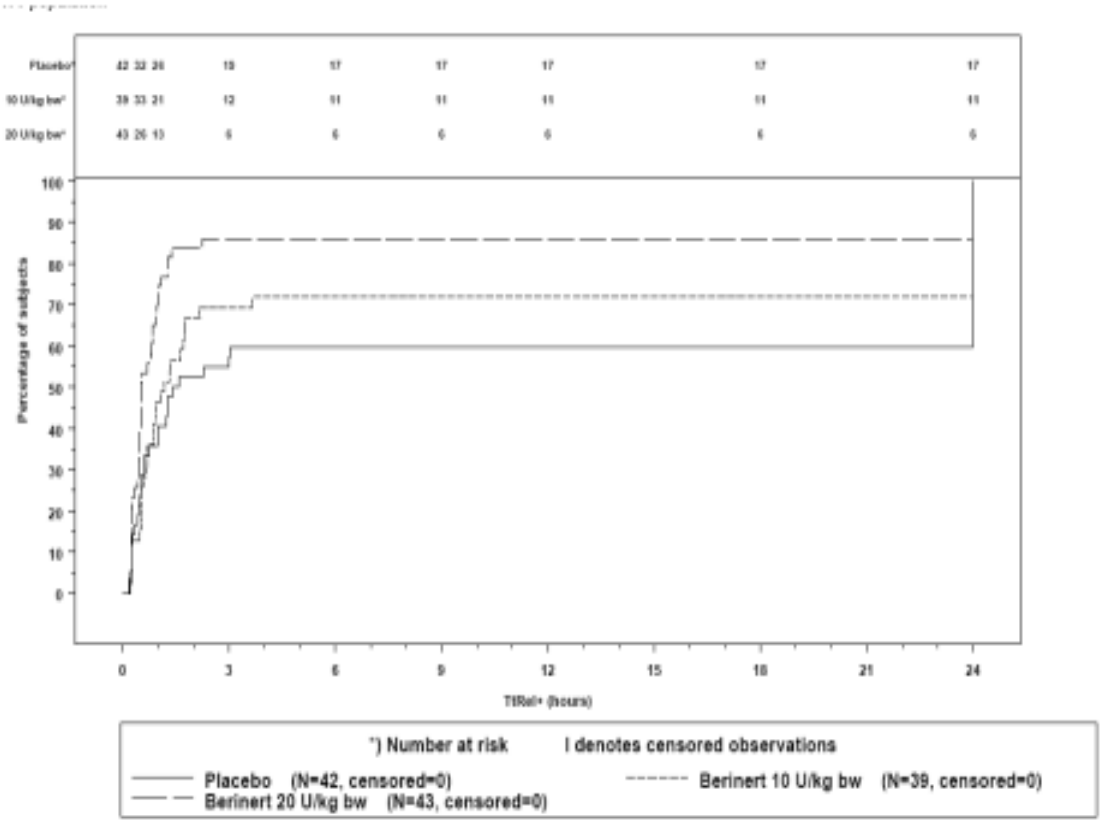


Table 3:

Table 13 - Time to onset of relief of HAE symptoms (abdominal or facial), as determined by subject's assessment (ITT population)

Statistic	Time to onset of relief of HAE symptoms [hours]			
	Placebo (N=42)	Berinert 10 U/kg bw (N=39)	Berinert 20 U/kg bw (N=43)	p-value 20 U/kg bw – Placebo
Mean (SD)	10.27 (11.481)	7.47 (10.513)	3.89 (8.202)	
Median (range)	1.50 (0.20-24.00)	1.17 (0.17-24.00)	0.50 (0.17-24.00)	0.00253[a]

Notes: The Berinert 10 U/kg bw group was ceased for futility after the first interim analysis.

Note: The comparison of time to onset of relief of HAE symptoms (abdominal or facial) between the treatment groups was biased (see mean and SD) due to subjects requiring study rescue medication or analgesics/anti-emetics/open-label C1-INH/FFP during first 4 hours after start of study medication. Time to onset of relief was set to 24 hours (poor/failure outcome) in case the subject received rescue study medication after 4 hours after start of treatment or received analgesics/anti-emetics/open-label C1-INH/FFP during the first 4 hours after start of study medication.

N = total number of subjects; SD = standard deviation

[a] One-sided two-sample Wilcoxon test

Table 4: Proportion of Subjects with worsened intensity

T ıportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after start of study medication (ITT population)

Study population	Number (%) of subjects			
	Placebo (N=42)	Berinert 10 U/kg bw (N=39)	Berinert 20 U/kg bw (N=43)	p-value 20 U/kg bw – Placebo
Total number of subjects with any HAE symptom at baseline with intensity >0	**42 (100)**	**39 (100)**	**43 (100)**	
Worsened intensity (Yes)	13 (31.0)	8 (20.5)	2 (4.7)	0.0014[a]

Note: The Berinert 10 U/kg bw group was ceased for futility after the first interim analysis.
N = total number of subjects
[a] Fisher's exact test

Table 5: Number of Vomiting Episodes

- Number of vomiting episodes within 4 hours after start of treatment (ITT population)

Statistic	Placebo (N=42)	Berinert 10 U/kg bw (N=39)	Berinert 20 U/kg bw (N=43)	p-value 20 U/kg bw – Placebo
Mean (SD)	0.8 (2.59)	0.2 (0.77)	0.1 (0.41)	
Median (range)	0 (0-16)	0 (0-4)	0 (0-2)	0.0329[a]

Note: The Berinert 10 U/kg bw group was ceased for futility after the first interim analysis.
N = total number of subjects; SD = standard deviation
[a] One-sided Wilcoxon test

Extension Study

Study CE1145_3003 is an open label extension study of Study CE1145_3001 continuing at the time of the report (November 2007), conducted in fifteen of the US and Canadian centres involved in the above placebo-controlled trial. After the 24 hours observation period following administration of the test preparation, patients enrolled in the extension study were to be treated with the C1-INH preparation 20 Units/kg bw, for each subsequent attack with which they presented at the centre. In addition to patients enrolled in Study CE1145_3001, patients otherwise eligible when screened but not included due to laryngeal oedema, could be enrolled in the extension. Observations made after administrations of C1-INH were similar to those in the preceding study and were documented on patients' case report forms.

A total of 355 attacks in 39 patients provided interim data on response and on safety.

The demographic characteristics of enrolled patients were similar to those for Study CE1145_3001 and again the underlying disorder was predominantly (~90%) Type I HAE considered both as the proportion of patients involved or as the proportion of attacks. Only six patients with laryngeal oedema were entered and they experienced ten treated episodes. Mild attacks were also treated in this extension study and 67 of the 355 episodes were so described.

The median time elapsing between the beginning of the episode and administration of C1-INH ranged from 2.9-7.1 hours (Table 6).

Table 6: Study CE1145_3003

Ta ne from estimated start of HAE attack until start of study treatment (per attack) at baseline (ITT population)

Type of HAE attack	Statistic	Time [hours] Attacks (N=355)
Abdominal	**n**	**242**
	Mean (SD)	10.3 (10.07)
	Median	6.4
	Range	0 - 64
Peripheral	**n**	**94**
	Mean (SD)	10.3 (9.24)
	Median	7.1
	Range	1 - 59
Laryngeal	**n**	**10**
	Mean (SD)	2.6 (0.97)
	Median	2.3
	Range	2 - 5
Facial	**n**	**8**
	Mean (SD)	8.4 (7.79)
	Median	5.6
	Range	2 - 25
Other	**n**	**1**
	Mean (SD)	2.9 (—)
	Median	2.9
	Range	—

N = total number of attacks; n = number of attacks with available data; SD = standard deviation

There was large inter-patient and inter-attack variation in the time to subjectively assess onset of relief but as can be seen from the medians (see Table 7 below), half of patients and half of the attacks had started to improve within half an hour and the median for patients was almost identical with that found in the 20 Units/kg bw group in Study CE1145_3001.

Table 7

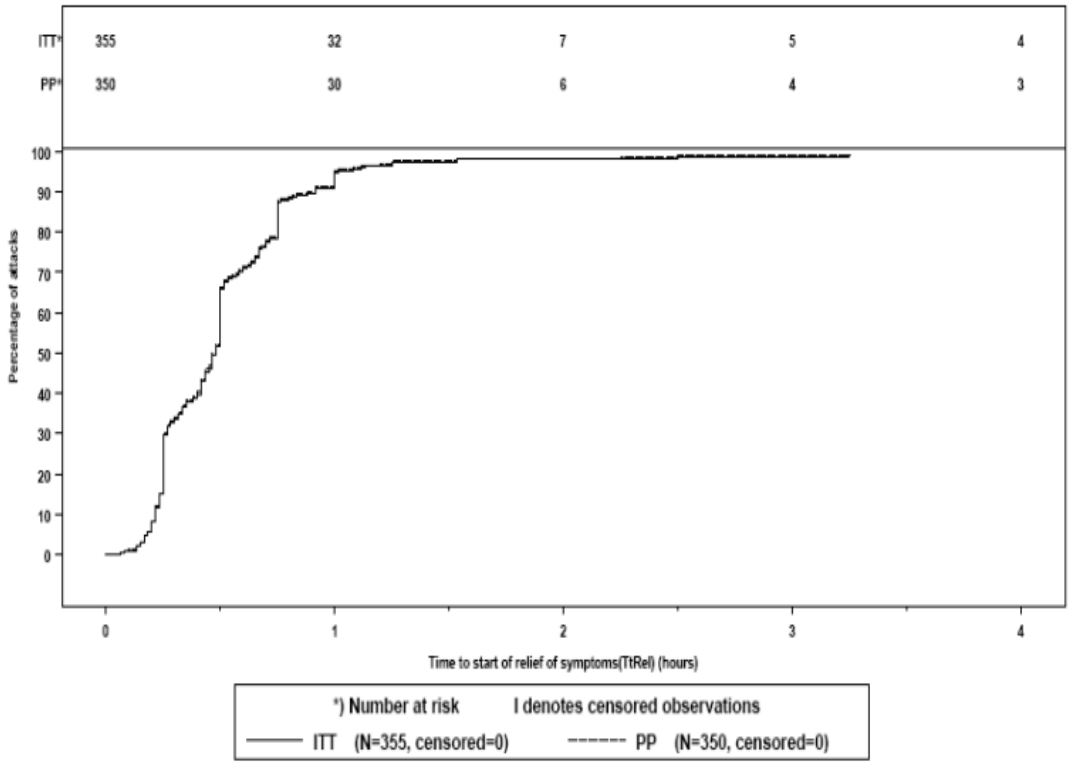
Table 15 - Time to onset of relief of HAE symptoms, as determined by subject's assessment (ITT population)

Statistic	Time to onset of relief of HAE symptoms [hours]	
	Subjects[a] (N=39)	Attacks (N=355)
Mean (SD)	13.90 (79.508)	2.13 (26.459)
Median (range)	0.48 (0.2; 497.0)	0.48 (0.1; 497.0)
Two-sided 95% CI for median	[0.37; 0.54]	[0.43; 0.50]

N = number of subjects/attacks with available data for time to onset of relief of HAE symptoms;
CI = confidence interval
[a] Analysis of average per subject included imputed values

This also is illustrated by the Kaplan-Meier Curve for the per attack analysis which also demonstrates the skewed distribution with 4 attacks still unimproved at 4 hours post treatment (Figure 2).

Figure 2: Study CE1145_3003 - Kaplan-Meier curves for time to onset of relief of HAE symptoms, as determined by subject's assessment - Per-attack analysis (ITT-attacks and PP-attacks populations)



Other Studies

Study CE1145_6001 was a retrospective record review of management during 33 pregnancies of 20 women with HAE. Manifestations of HAE are known to increase in frequency during pregnancy due to increased oestrogen dominance. Treatment of 13 of the patients was by regular prophylactic administration of C1-INH and 7 received it on demand. In the absence of a control group and due to the retrospective acquisition of data, little can be said about efficacy of the treatment apart from an indication that the clinicians' opinions were that the on demand treatment was effective in all of the 13 patients but that regular

prophylactic administration completely prevented attacks in only one of the seven patients treated prophylactically.

Summary

A parallel group, placebo-controlled, randomized, double-blind trial compared the effect of administration of 20 Units/kg bw intravenously of the test formulation of C1-INH vs placebo, on progress of a single attack of HAE in each of 85 patients (43 C1-INH; 42 placebo).

The median time to onset of relief as assessed by the patient, was significantly less in those treated with C1-INH than in the placebo-treated group.

This study included a 10 Units/kg bw dose group but cessation of enrolment was recommended for futility after an interim analysis and the truncated group was not significantly different from the placebo group in time to onset of response.

An open, uncontrolled extension was undertaken by 33 of the patients in the above controlled trial, together with 6 otherwise eligible patients who had presented with laryngeal oedema and were excluded to avoid receiving placebo. These patients received 20 Units/kg bw to treat all further attacks (total of 39 individuals suffering 355 attacks). The median time to onset of relief was almost identical to that in the 20 Units/kg bw group in the controlled study, suggesting that the response was not lost following repeated administration.

A retrospective record review of treatment of acute attacks in 20 women through 33 pregnancies gave anecdotal support to treatment of attacks "on demand" in this situation but prophylactic administration was said to have completely suppressed attacks in only 1 of 7 women so treated.

Safety

Pivotal Study

For **Study CE1145_3001**, a summary of all adverse events experienced by >1 patient in the first 4 hours following injection is tabulated (Table 8). There were fewer such gastrointestinal events in the active treatment groups, presumably due to a therapeutic benefit, but no other convincing difference between the groups is seen. Dysgeusia was noted in 3 patients receiving active treatment but in none receiving placebo.

Rescue medication was given after observation for 4 hours in 44 patients in the form of C1-INH or placebo, to bring the total dose administered to 20 Units/kg bw in all cases. More placebo patients required rescue than in the active treatment groups but delayed manifestations considered to relate to HAE were more common in the active treatment groups. Delayed or persisting gastrointestinal symptoms were more frequent in placebo patients not given rescue medication than in such patients initially receiving active treatment (Table 9). Dysgeusia after 4 hours was reported in 2 rescued patients.

Table 8: Study CE1145_3001

- 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 10 U/kg bw (N=39)	Berinert 20 U/kg bw (N=46)
Number of subjects with at least 1 AE	**18 (43.9)**	**10 (25.6)**	**9 (19.6)**
Gastrointestinal disorders	13 (31.7)	3 (7.7)	5 (10.9)
Nausea	5 (12.2)	1 (2.6)	3 (6.5)
Abdominal pain	3 (7.3)	1 (2.6)	2 (4.3)
Diarrhea	4 (9.8)	1 (2.6)	0
Vomiting	3 (7.3)	1 (2.6)	1 (2.2)
Lip swelling	1 (2.4)	1 (2.6)	0
General disorders and administration site conditions	3 (7.3)	5 (12.8)	2 (4.3)
Pain	1 (2.4)	4 (10.3)	1 (2.2)
Edema peripheral	0	1 (2.6)	1 (2.2)
Face edema	1 (2.4)	1 (2.6)	0
Musculoskeletal and connective tissue disorders	4 (9.8)	4 (10.3)	1 (2.2)
Muscle spasms	2 (4.9)	4 (10.3)	1 (2.2)
Nervous system disorders	2 (4.9)	2 (5.1)	2 (4.3)
Dysgeusia	0	1 (2.6)	2 (4.3)
Headache	2 (4.9)	1 (2.6)	0

Notes: The Berinert 10 U/kg bw group was ceased for futility after the first interim analysis.
This table includes only SOCs with individual preferred terms that occurred in >1 subject overall.
N = total number of subjects

Table 9: Study CE1145_3001

- 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 (N=18)	Berinert 10 U/kg bw (N=26)	Berinert 20 U/kg bw (N=38)	Placebo + Berinert 20 U/kg bw (N=23)	Berinert 10 U/kg bw + 10 U/kg bw (N=13)	Berinert 20 U/kg bw + Placebo (N=8)
Number of subjects with at least 1 AE	**9 (50.0)**	**9 (34.6)**	**11 (28.9)**	**14 (60.9)**	**5 (38.5)**	**5 (62.5)**
Congenital, familial and genetic disorders	0	4 (15.4)	5 (13.2)	3 (13.0)	1 (7.7)	1 (12.5)
Hereditary angioedema	0	4 (15.4)	5 (13.2)	3 (13.0)	1 (7.7)	1 (12.5)
Nervous system disorders	0	1 (3.8)	3 (7.9)	4 (17.4)	0	3 (37.5)
Headache	0	1 (3.8)	3 (7.9)	4 (17.4)	0	3 (37.5)
Dysgeusia	0	0	0	1 (4.3)	0	1 (12.5)
Gastrointestinal disorders	5 (27.8)	1 (3.8)	2 (5.3)	8 (34.8)	4 (30.8)	1 (12.5)
Abdominal pain	1 (5.6)	1 (3.8)	1 (2.6)	1 (4.3)	1 (7.7)	0
Diarrhea	2 (11.1)	0	1 (2.6)	3 (13.0)	0	0
Nausea	2 (11.1)	0	0	4 (17.4)	1 (7.7)	0
Vomiting	0	0	0	4 (17.4)	0	0
Abdominal distension	0	0	0	0	1 (7.7)	1 (12.5)
Infections and infestations	1 (5.6)	1 (3.8)	2 (5.3)	1 (4.3)	1 (7.7)	0
Upper respiratory tract infection	0	1 (3.8)	1 (2.6)	0	0	0
General disorders and administration site conditions	3 (16.7)	1 (3.8)	0	5 (21.7)	0	0
Pain	1 (5.6)	0	0	2 (8.7)	0	0
Musculoskeletal and connective tissue disorders	1 (5.6)	0	1 (2.6)	5 (21.7)	0	1 (12.5)
Back pain	0	0	0	3 (13.0)	0	1 (12.5)
Muscle spasms	0	0	0	2 (8.7)	0	0

Note: The Berinert 10 U/kg bw group was ceased for futility after the first interim analysis.
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; Source: Table 12.13 and Table 12.23

No serious adverse events or deaths were reported in the 4 hours post injection period. In the post 4-hour period, 4 patients experienced a serious adverse event, in all cases being manifestations of HAE. No routine assessment of laboratory results was undertaken in this study.

Extension Study

The bulk of safety data comes from **Study CE1145_3003** which pertains to treatment of 355 HAE attacks, but it should be noted that these occurred in 39 patients of whom all but 6 provided data for the comparison with placebo detailed above. Thus the number of individuals in the total exposed group is increased very little, while the number of administrations is added to substantially.

A greater percentage of patients reported at least 1 adverse event than was the case in the preceding controlled phase but this would be due to repeated exposure over time and the difference disappears if the adverse events are stated as per attack (Tables 10 and 11).

Table 10: Study CE1145_3003

Tal ımmary of AEs occurring in at least 5% of subjects by preferred term and system organ class (safety subject population)

System Organ Class/Preferred Term	Subjects (N=39)
Number of subjects with at least 1 AE	**16 (41.0)**
Congenital, familial and genetic disorders	3 (7.7)
Hereditary angioedema	3 (7.7)
Infections and infestations	8 (20.5)
Nasopharyngitis	3 (7.7)
Upper respiratory tract infection	2 (5.1)
Vulvovaginal mycotic infection	2 (5.1)
Nervous system disorders	5 (12.8)
Headache	4 (10.3)

Data are sorted alphabetically by SOC and by frequency of preferred term within each SOC.

Table 11: Study CE1145_3003

Table 26 - Summary of AEs associated with ≥2 attacks (safety attacks population)

Syst Class/Preferred Term	Attacks (N=355)
Number of attacks associated with at least 1 AE	35 (9.9)
Congenital, familial and genetic disorders	3 (0.8)
Hereditary angioedema	3 (0.8)
Gastrointestinal disorders	9 (2.5)
Abdominal pain	5 (1.4)
Abdominal distension	3 (0.8)
Nausea	3 (0.8)
Infections and infestations	14 (3.9)
Upper respiratory tract infection	4 (1.1)
Nasopharyngitis	3 (0.8)
Vulvovaginal mycotic infection	2 (0.6)
Nervous system disorders	8 (2.3)
Headache	7 (2.0)
Reproductive system and breast disorders	4 (1.1)
Dysmenorrhoea	4 (1.1)

Data are sorted alphabetically by SOC and by frequency of preferred term within each SOC.

Neither presentation raises further concern. There was no formal investigation of effect of C1-INH on laboratory values in this study.

Other Study

Study CE1145_6001was **t**he retrospective record review in 20 pregnant women who were treated with C1-INH. It concerned treatments delivered over the period June 1997-September 2005 so that two different formulations would have been used. There are no data on adverse

events in general. No laboratory deviations out of keeping with pregnancy were found. Seventeen of the children had HAE but there were no birth defects.

Viral Safety

Viral safety of the candidate formulation was said to be assessed in **Studies CE1145_3001** and **3003** by documenting seroconversion from pre-infusion to approximately 12 weeks post-infusion for HIV-1 & -2 and hepatitis viruses A, B and C, and by PCR at 7-9 days for Parvovirus 19. However this material is presented in a confused and in parts contradictory way which was subsequently clarified by the sponsor.

Virus safety data are so far available for 82 subjects in Study CE1145_3001, for 36 subjects in Study CE1145_3003 and for 37 subjects participating in both studies

Shifts between pre- and post-administration findings were found in 5 patients as set out in Table 12.

Table 12:

Tab 'irus safety results in subjects with shifts from negative to positive test results in Studies CE1145_3001 and CE1145_3003

Study Time point	Anti-HAV IgG			Anti-Parvovirus IgG-R	HBS antigen
	Subject 8001 [a] (8303 [b])	Subject 8003 [a] (8302 [b])	Subject 12009 [a] (12309 [b])	Subject 29001 [a] (29301 [b])	Subject 50001 (NA)
CE1145_3001					
Baseline	Negative	Negative	Negative	18.00 (normal)	Negative
Follow-up	Positive	Positive	Positive	-	Positive
CE1145_3003					
Baseline	Positive	Positive	Positive	29.00 (high)	NA
Follow-up	Positive	Positive	Positive	-	NA

- = missing value; NA = not applicable because the subject did not participate in Study CE1145_3003.

[a] Subject number in Study CE1145_3001.

[b] Subject number in Study CE1145_3003.

[*] *One subject (Subject 50001) shifted from negative to positive (borderline results) at Week 12 for HBS antigen. However, a seroconversion was excluded on the basis of a letter from the Investigator who tested the subject negative after the Week 12 follow-up.*

The sponsor stated that no conversions involved HIV-1 or -2, HCV or HBV although the latter statement contrasts with the HBV surface antigen conversion noted elsewhere in the text and is noted in Table 12. Anti-HBS, anti-HBc and HBsAg tests were negative in the Day 7-9 samples. Hepatitis B serology testing at the study site in March 2007 (approximately 2 months after Week 12) did not show any evidence of hepatitis B, all hepatitis B markers were negative, and no increase in hepatic enzymes could be detected.

The pre- and post-treatment anti-Parvovirus titres are not discussed.

Postmarketing Surveillance

There has been considerable use of the pasteurized product. From its introduction in 1985 to 31 December 2007, a total 208,965,800 Units have been issued. Using 500 Units as the standard dose this equates to ~418,000 administrations. This very probably overestimates the number of administrations and of course the number of patients receiving the product would be very much less due to multiple dosing.

A total of 57 reports of suspected ADRs were collected from the worldwide market during this time period. These include allergic/anaphylactic reactions (7 cases), chills and fever (2), lack of effect (9), suspected virus transmission (5) and thrombosis (14). It is stated that all 5 reports of suspected viral transmission were not confirmed but presentation of the viral test results do not engender total confidence on this aspect of safety evaluation. Of the 14 reports of thrombosis, 12 were derived from cases involving administration of high doses to ill patients for the unapproved indication of the capillary leak syndrome. The remaining 20 reports were of events considered to be not related to the administration of Berinert.

Summary

The documented experience with Berinert is limited and conclusions concerning safety must therefore be tentative. However, it appears to be well tolerated in clinical use at the recommended dose.

In the pivotal placebo-controlled study, crude figures for adverse events in the 4 hours immediately following injection and in the subsequent period of observation were lower in patients receiving the active preparation than in those receiving placebo. This is plausibly explained as due to amelioration of symptoms of the HAE attack being treated.

The extension phase of the pivotal study which involved treating subsequent attacks in almost entirely the same population, did not suggest previously unrecorded adverse events.

Although the numbers are small, dysgeusia was an interesting adverse event noted in 3 patients initially receiving Berinert and in 1 patient in the placebo group, after receiving 20 mg/kg bw as rescue medication.

In a retrospective record review of 33 pregnancies in 20 women, 17 of the babies had HAE but there were no birth defects recorded.

In the pivotal study and its extension, an effort was made to detect possible transmission of HIV, Hepatitis viruses A, B, & C and Parvovirus19. Results are presented confusingly and the conclusion reached that there is no evidence of viral transmission is therefore not completely convincing. Elaboration by the sponsor was provided.

Clinical Summary and Conclusions

The pharmacokinetics of the candidate preparation, characterized as C1-esterase inhibitory activity, were determined in an investigator-initiated study in 40 opportunistically assembled patients undergoing routine treatment in a specialized clinic. The derived pharmacokinetic parameters showed considerable inter-individual variability but generally demonstrated a volume of distribution consistent with intra-vascular retention, low clearance and $t_{1/2}$ of ~36 hours.

A parallel group, placebo-controlled, randomized, double-blind trial compared the effect of administration of 20 Units/kg bw intravenously of the test formulation of C1-INH vs placebo, on progress of a single attack of HAE in each of 85 patients (43 C1-INH;42 placebo).

The median time to onset of relief as assessed by the patient, was significantly less in those treated with C1-INH than in the placebo-treated group.

This study included a 10 Units/kg bw dose group but suspension of enrolment was recommended after an interim analysis for futility and this truncated group was not significantly different to the placebo group in time to onset of response.

An ongoing open-label, uncontrolled extension study is being undertaken by 33 of the patients in the above controlled trial, together with 6 otherwise eligible patients who had presented with laryngeal oedema and were excluded to avoid receiving placebo. These

patients received 20 Units/kg bw to treat all further attacks, a total of 39 individuals suffering 355 attacks. The median time to onset of relief was almost identical to that in the 20 Units/kg bw group in the controlled study, suggesting that the response was not lost following repeated administration.

A retrospective record review of treatment of acute attacks in 20 women through 33 pregnancies gave anecdotal support to treatment of attacks "on demand" in this situation but prophylactic administration completely suppressed attacks in only 1 of 7 women so treated.

The documented experience with Berinert is limited and conclusions concerning safety must therefore be tentative, however it appears to be well tolerated in clinical use at the requested dose.

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The extension phase of the pivotal study involved treating subsequent attacks in almost entirely the same population, did not suggest previously unrecorded adverse events.

Although the numbers are small, dysgeusia was an interesting adverse event noted in 3 patients initially receiving Berinert and in 1 patient in the placebo group, after receiving 20 mg/kg bw as rescue medication.

In a retrospective record review of 33 pregnancies in 20 women, 17 of the babies had HAE but there were no birth defects recorded.

In the pivotal study and its extension, an effort was made to detect possible transmission of HIV, Hepatitis viruses A, B, & C and Parvovirus19. Results are presented confusingly and the conclusion reached that there is no evidence of viral transmission is not completely convincing. Elaboration and clarification was subsequently provided by the Sponsor .

Recommendation

In view of the drug's Orphan Status, the uncommon but potentially fatal nature of the disease and the reasonable evidence of efficacy, albeit from only on small trial, it is recommended that Berinert be approved for marketing for the treatment of acute attacks of hereditary angioedema at the recommended dose of 20 Units/kg body weight, intravenously.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendation:

Quality

Human C1 esterase inhibitor (C1-INH) is a highly purified, pasteurised, lyophilised concentrate derived from human plasma. C1-INH is a soluble single chain glycoprotein containing 478 aa residues organised into three beta sheets and 8 or 9 alfa sheets.

Each vial contains 500 U C1-INH, 50 to 80 mg total protein, and glycine, sodium citrate and sodium chloride as excipients. Impurity limits, release specifications, the manufacturing process, process controls, and viral inactivation procedures are all satisfactory. There are no current quality objections to registration.

Nonclinical

A limited but adequate nonclinical testing program was provided for C1-INH.

C1-INH belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, α_1-protease inhibitor, α_2-antiplasmin and heparin cofactor II. As with other inhibitors in this group, C1 esterase inhibitors are involved in inhibiting several major cascade systems of the human body including the complement system, the contact system, the fibrinolytic system and the coagulation cascade.

C1-INH is a major inhibitor of the activated serine proteinases C1r and C1s, kallikrein and coagulation factors XIIa and XIa. The efficacy profile was well-defined with demonstrated inhibition of the complement pathway *in vitro* and in animal models of disease involving the complement and kallikrein/kinin systems

Toxicology studies included acute toxicity in rodents, repeat dose toxicity in rats, and local tolerance in rabbits. Toxicology studies demonstrated that C1 INH was well tolerated in GLP compliant acute and short-term repeat dose toxicity studies in rodents and local tolerance studies in rabbits. Although clinical exposure margins were low (2-fold) in the pivotal 2 week rat study, no evidence of toxicity was observed in this and at much higher doses in the acute study. This low safety margin may be acceptable for a human plasma-derived substance anticipated for infrequent emergency use.

There are no nonclinical objections to the registration of Berinert as proposed by the sponsor.

Clinical

Clinical studies supporting registration of this C1-INH product were one pharmacokinetic study (Study CE1145_2001), one pivotal efficacy study (Study CE1145_3001), an open extension of the pivotal study (Study CE1145_3003) which provides the bulk of the safety data, and a retrorespective record review of management of pregnant women with HAE (Study CE1145_6001).

Pharmacokinetics

Study CE1145_2001 is an investigator initiated evaluation of pharmacokinetics of the C1-INH product proposed for registration. The study included 40 paediatric or adult patients with hereditary angioedema presenting at a specialized clinic for management of HAE episode or for prophylactic dose. A single dose of 500-1500 U was administered. Blood samples were drawn pre-administration and up to 72 hours post-administration. CI-INH activity was analysed primarily with a chromogenic assay. C1-INH antigen levels were also analysed by ELISA. There is large inter individual variation in all parameters. There were no obvious differences in values between age groups or types of treatment. Estimated volume of distribution was consistent with intravascular retention of the product, median systemic clearance was approximately 1.0 mL(kg x h) (~70 mL/h for a person weighing 70 kg)and median elimination half life was around 36 hours.

Efficacy

Study CE1145_3001 is a randomised, placebo controlled, parallel group study in 126 patients aged 6 years and older with HAE documented by a centrally performed assay of C1 esterase function and/or antigen. Subjects presenting with a moderate to severe, acute, facial or

abdominal HAE episode received a single dose of C1-INH or placebo. Laryngeal oedema was an exclusion criterion. A possible second infusion after 4 hours, to bring the total C1-INH dose to 20 U/kg, was allowed as rescue medication. Concomitant medications were minimised during the study. The initial study plan was for C1-INH 10 U/kg or 20 U/kg treatment arms but the 10 U/kg treatment arm was discontinued due to futility after an interim analysis. The primary efficacy endpoint was time to onset of relief of symptoms from evaluated attacks (abdominal or facial) by patient's response to standardised enquiry. Secondary endpoints were proportion of subjects in whom clinical HAE symptoms worsened between 2 and 4 hours after study medication and number of vomiting episodes within 4 hours after start of study therapy.

Figure 1 shows Kaplan-Meier curves for time to relief of symptoms, the primary efficacy endpoint. Mean and median time to onset was significantly less in the CI-INH 20U/kg group than placebo group. In the ITT population, mean time to onset of symptom relief was 3.89 hours in the 20U/kg group, 7.47 hours in 10U/kg group and 10.27 hours in the placebo group (although those requiring a rescue injection were arbitrarily assigned a 24 hour time to relief). The difference between placebo and 20U/kg was statistically significant (p= 0.00253) whereas the difference between placebo and 10 U/kg was not (p=0.2731).

C1-INH 20U/kg also showed superiority to placebo for the secondary endpoints.

Worsened intensity of clinical HAE symptoms between 2 -4 hours after start of study medication was reported, in the ITT population, in 31% of placebo, 20.5% of 10 U/kg and 4.7% of 20 U/kg groups (20U/kg vs placebo p value 0.00014). Mean number of vomiting episodes within 4 hours after start of study medication, in ITT population, was 0.8 in placebo group, 0.2 in 10 U/kg group and 0.1 in 20 U/kg group (20U/kg vs placebo p = 0.0329).

Study CE1145_3003 is an open label extension study continued in 15 centres that had been involved in Study CE1145_3001. A total of 33 patients who had previously received study medication, and 6 otherwise eligible patients who had presented with laryngeal oedema, were treated with C1-INH 20U/kg for each subsequent attack in the extension phase. A total of 355 attacks in 39 patients were reported in an interim report with a defined cut-off date. Demographic characteristics were similar to the previous study. There was large inter-patient and inter-attack variation in time to onset of relief of HAE symptoms but the median time was similar in this study and Study CE1145_3001.

Study CE1145_6001 was a record review of 33 pregnancies of 20 women with HAE. Manifestations of HAE are known to increase in frequency during pregnancy. Thirteen of the women received C1-INH regularly and 7 received C1-INH on demand. Clinicians' opinion was that on demand treatment was effective in all 13 patients but that regular prophylactic administration completely prevented attacks in only 1 of the 7 patients.

Safety

In the pivotal study CE1145_3001, a total of 126 patients were included in 4 hour safety population and 82 (65%) were included in the after 4 hour safety population without rescue medication. Adverse experiences after 4 hours showed that gastrointestinal disorders more frequent in the placebo compared to C1-INH groups. Dysgeusia was reported within 4 hours in 3 subjects who received C1-INH. This persisted in 1 subject and was reported in one subject after rescue with 20U/kg.

No serious adverse event or deaths reported in the 4 hour post injection period. The 4 serious AE reported after 4 hours were manifestations of HAE.

In Study CE1145_3003 there was safety experience from 355 attacks but all but 6 of the 39 subjects had been enrolled in the pivotal study. There was no evidence of previously unrecorded AE in this study.

In studies CE1145_3001 and CE1145_3003 there was some assessment of transmission of HIV, Hepatitis A, B & C and Parvovirus. Although the conclusion was reached that there is no evidence of viral transmission the clinical evaluator considered the results were presented in a confusing way.

In the retrospective record review of 33 pregnancies in 20 women, 17 of the children had HAE but there were no birth defects.

In post-marketing experience there have been 14 reports of thrombosis, 12 of which were involved administration of high doses for capillary leak syndrome.

The clinical evaluator has supported registration of C1-INH, Berinert, for the treatment of acute attacks of in patients with hereditary angioedema. The recommended dose is 20 U/kg body weight.

Risk-Benefit Analysis

A single, randomised, double blind controlled study supports the efficacy of C1-INH at a dose 20 unit/kg bw, on the progress of a single attack of HAE in 85 subjects (43 C1-INH, 42 placebo). An open, uncontrolled extension was undertaken in 33 of the patients in the controlled study, together with 6 otherwise eligible patients who had presented with laryngeal oedema. Conclusions concerning safety are tentative but, however, it appeared to be well tolerated in the clinical studies at the proposed dose. The delegate concurred with the clinical recommendation that there is reasonable support for registration of C1-INH for this rare but serious condition.

In the pivotal study there were only 3 children in the 3 -<12 year age group and 10 subjects in the 12 - <17 years. The proposed PI statement is "*Safety and efficacy in children has not been systematically evaluated. There were no apparent differences in safety and efficacy profiles as compared to adults"*.

The US FDA has recently has recently registered C1 Esterase Inhibitor (Human), Berinert, for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult or adolescent patients. The ADEC were requested to comment on whether the indication approved by FDA is preferred to the indication proposed in Australia.

The FDA approval letter noted a 20% incidence of treatment emergent anti-C1 esterase inhibitor antibodies observed in the open label extension study. The sponsor should comment on this observation in the pre-ADEC response. The sponsor should also comment on postmarketing commitments associated with the FDA approval, including the establishment of a HAE patient registry. The clinical evaluator noted the results of assessment of viral transmission in the pivotal and extension clinical studies was confusing. The Sponsor was requested to comment on this issue in the pre-ADEC response.

The Delegate proposed to approve the registration of Berinert for:
the treatment of acute attacks in patients with hereditary angioedema (HAE)
The recommended dose is 20 U per kg body weight.

The sponsor responded that the above FDA observation is based on interim immunogenicity data that the FDA specifically requested on an ad-hoc basis during the review of CSL Behring's Berinert submission. More importantly, the sponsor confirmed that there was no evidence of neutralizing antibodies that could be detected in any of the individual subjects

samples tested above the assay cut-off (33.4%) to anti-C1 antibodies. The occurrence of autoantibodies to treatment-naïve patients to C1-INH (and Fresh Frozen Plasma) has been observed in both acquired and hereditary angioedema. Antibodies to C1-INH might be induced physiologically in subjects with HAE. The physiological role of such antibodies is currently unknown. The sponsor maintained that these antibodies do not represent a risk to the subjects. Complete immunogenicity data from the extension study will be available in the final clinical study report. It was also noted that that evaluation of immunogenicity will be the objective of one of the FDA Postmarketing Commitment (PMC) studies. The sponsor believes that C1-INH antibody development is not of concern for patients treated with Berinert. However, CSL Behring will continue to collect information regarding this in the PMC study.

The sponsor also responded that at the FDA's request, a registry of patients treated with Berinert for any indication will be established in the U.S. in order to obtain general information about the patients and the administered treatment to further elucidate HAE and its treatment with C1 Esterase Inhibitor and to identify and characterise potential associated risks. This registry will be maintained for the first 3 years post licensure. The sponsor plans to have the registry implemented within 6 months of product licensure and expects to enrol up to 100 patients into the registry. The registry will permit a mechanism for enhanced detection of thrombotic or thromboembolic events as well as viral safety. Annual reporting of the overall status of the registry will be performed. A final report will be submitted to the FDA 12 months after completion of the registry project at the latest. A draft protocol outline and patient registry questionnaire are currently under FDA review. In summary, the PMC studies requested by the FDA will permit further evaluation of Berinert's efficacy and safety, in addition to 30 years of commercial experience with Berinert.

The sponsor responded that overall, shifts from negative to positive viral safety test results at any time during or between both Studies CE1145_3001 and CE1145_3003 were recorded in 5 subjects. Shifts from negative at baseline to positive at follow-up were reported for anti-HAV IgG in 3 subjects (Subjects 8001, 8003, 12009) and for HBS antigen in 1 subject (Subject 50001). However, virus transmission and seroconversions were excluded in all cases for the following reasons:

The 3 subjects with shifts in anti-HAV IgG test results were retested with more specific quantitative tests. For Subjects 8001 and 8003, the negative results for baseline and the positive results for Week 12 in hepatitis A IgG were confirmed. However, Polymerase Chain Reaction (PCR) testing of the Day 7-9 samples did not show any evidence of hepatitis A. For both subjects, vaccination and passive immunization against hepatitis A as well as the administration of immunoglobulins was excluded by the Investigator. Permutation of the samples cannot be ruled out. Re-testing of samples of Subject 12009 confirmed the positive results for Week 12 but also showed positive borderline results for baseline Hepatitis A IgG. In addition, PCR testing of the Day 7- 9 samples did not show any evidence of hepatitis A virus infection. In case of an HAV infection, both IgG and IgM are known to increase to positive values. Since anti-HAV IgM remained negative in all tests for all 3 subjects, this suggests that no HAV infection occurred at time of application of the study drug.

Subject 29001: The baseline result for Parvovirus IgG-R was negative and in subsequent tests (baseline result in Study CE1145_3003) was positive. However, the results of antiparvovirus IgM as well as PCR were negative in all tests.

For Subject 50001 with a shift in HBS antigen test result, a seroconversion was excluded on the basis of a letter from the investigator who tested the subject negative after the Week 12 follow-up. Hepatitis B serology testing at the study site in March 2007 (approximately 2

months after Week 12) did not show any evidence of hepatitis B virus infection, all hepatitis B markers were negative, and no increase in liver function tests (ASAT, ALAT) could be detected.

In all cases, virus transmission as a cause for these shifts were examined and ruled out based on retesting of samples obtained prior to treatment with more sensitive tests as well as on additional follow-up information from the study sites and the absence of any disease manifestations. In conclusion, the findings from the variety of tests and clinical information do not support virus transmission in the abovementioned cases. The sponsor will continue to collect viral safety data in the HAE patient registry in the US. To date, there have been no confirmed cases of virus transmission in subjects using Berinert in the postmarketing surveillance of this product.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended the following indication be approved

> *Berinert is indicated for the treatment of acute attacks in patients with hereditary angioedema (HAE)*

The ADEC agreed with the clinical evaluator and the Delegate that Study CE1145_3001 demonstrated the efficacy of C1 esterase inhibitor (Berinert) at a dose of 20unit/kg and has a satisfactory safety profile. The Committee also determined that since the mechanism of disease is the same in laryngeal and cutaneous attacks as in abdominal and facial attacks, there is no need for the indication to be limited to the latter. The Committee was satisfied with the sponsor's pre ADEC response regarding the virus transmission in subjects using Berinert. The Committee also noted that there was no increase risk of thrombo-embolic events with Berinert used for treatment of HAE emerging from postmarketing surveillance.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Berinert, powder for injection which contains 500 U Human C1 Esterase Inhibitor per vial. Berinert is indicated for:

the treatment of acute attacks in patients with hereditary angioedema (HAE).

Attachment 1. Product Information

Product Information

Berinert®

Australia

NAME OF THE MEDICINE
Human C1 esterase inhibitor, powder for injection.

DESCRIPTION
Berinert® is a highly purified, freeze-dried C1 esterase inhibitor concentrate derived from human plasma. It contains 500 units (U) of C1 esterase inhibitor per vial (50 U/mL). One unit is equal to the amount of C1 esterase inhibitor in 1 mL of human plasma, which is equivalent to approximately 240 mg/L of plasma. It is produced as a sterile, pyrogen-free, freeze-dried white powder for intravenous injection after reconstitution with the supplied Water for Injections.

The Berinert® manufacturing process includes pasteurisation (at 60°C for 10 hours) and hydrophobic interaction chromatography to reduce the potential for pathogen transmission.

Berinert® is provided in a pack containing 2 vials, 1 containing 500 U of freeze-dried Berinert® powder, and the other containing 10 mL of Water for Injection. When reconstituted as recommended, each vial nominally contains 50 U/mL C1 esterase inhibitor, 8.5 to 11.5 mg/mL glycine, 2.5 to 3.5 mg/mL sodium citrate and 7.0 to 10 mg/mL sodium chloride. The total protein content of the reconstituted solution is 6.5 mg/mL.

Berinert® contains highly purified and concentrated C1 esterase inhibitor. 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 40%. C1 esterase inhibitor is mainly synthesised in the liver.

PHARMACOLOGY
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 U/mL) and rat (IC_{50} = 1.01 U/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® 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

Pharmacokinetics

Pharmacokinetic properties have been investigated 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® ranging from 500 U to 1,500 U.

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 %/U/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 %/U/kg body weight).

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

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

Efficacy and Safety

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® 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® 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®.

Subjects were randomised to either receive a 10 U/kg body weight dose of Berinert® (39 subjects), a 20 U/kg dose of Berinert® (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 U/kg dose of Berinert® 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® 20 U/kg group (4.9 hours) than in the placebo group (7.8 hours).

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

Berinert® was further evaluated in a prospective, open-label, uncontrolled, multicentre extension study in subjects who had participated in the pivotal Phase III study or were screened for the pivotal phase III study and experienced a life–threatening laryngeal attack prior to enrolment. In this study attacks at any body location were treated. Subjects received a 20 U/kg body weight dose of Berinert® and were observed until onset of relief of HAE symptoms.

At the time of the first interim analysis a total of 39 subjects (age ranging from 10 to 53 years) with 355 HAE attacks had been treated. There were 33 subjects with abdominal attacks, 5 subjects with facial attacks, 19 subjects with peripheral attacks, and 6 subjects with laryngeal attacks.

The median subject-reported time to onset of symptom relief was shortest for laryngeal attacks (0.4 hours) and longest for facial attacks (0.8 hours). A 20 U/kg body weight dose of Berinert® was effective in achieving a rapid onset of relief of HAE symptoms in subjects suffering from various types of HAE attacks and in achieving complete resolution of HAE symptoms within 24 hours in the majority of subjects. Similar efficacy results were demonstrated for 242 abdominal attacks and 8 facial attacks as compared to 34 abdominal and 9 facial attacks in the pivotal study.

Adverse reactions encountered during the clinical trials are outlined under **ADVERSE EFFECTS**.

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

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

PRECAUTIONS
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® 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® is not advised.

Berinert® contains up to 48.6 mg sodium per vial. This is to be taken into consideration for patients on a controlled sodium diet.

Refer to **DOSAGE AND ADMINISTRATION** section for further precautions regarding administration of Berinert®.

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, virus removal and inactivation procedures are included in the manufacturing process. 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.

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

Use in pregnancy
The safety of Berinert® 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® should be used during pregnancy only if clearly needed.

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

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

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

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

Carcinogenicity
No carcinogenic studies have been conducted with Berinert®

Genotoxicity
No genotoxicity studies have been conducted with Berinert®.

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

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

ADVERSE EFFECTS
Undesired reactions with Berinert® are rare.

Clinical Studies Experience

The most common adverse events (AEs) reported in subjects up to 4 hours after receiving 20 U/kg body weight Berinert® in the pivotal phase III study and the first interim analysis of the extension study were nausea, dysgeusia, abdominal pain and headache.

The most common AEs reported in subjects up to 9 days after infusion with 20 U/kg body weight Berinert® 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 1 provides a summary of AEs in >1 subject overall by preferred term and system organ class.

Table 1: 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 20 U/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 2 provides a summary of AEs in > 1 subject overall by preferred term and system organ class (after 4-hour safety populations).

Table 2: 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 (N=18)	Berinert 20 U/kg body weight (N=38)	Placebo + Berinert 20 U/kg body weight (N=23)	Berinert 20 U/kg body weight + Placebo (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® for treatment of HAE include allergic/anaphylactic reactions, injection-site pain, injection-site redness, chills and fever.

In treatment attempts with high doses (>90 U/kg body weight) of Berinert® 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.

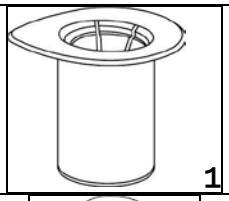
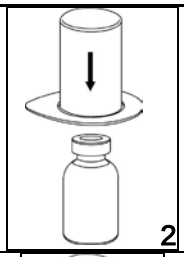
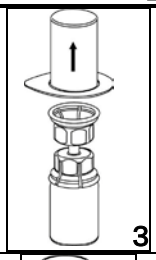
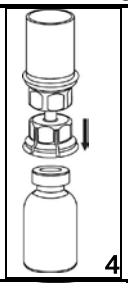
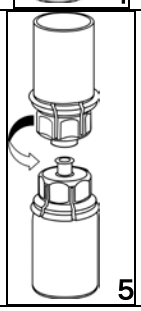
DOSAGE AND ADMINISTRATION

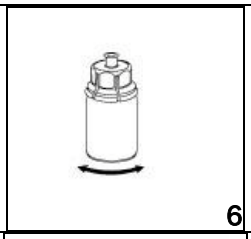
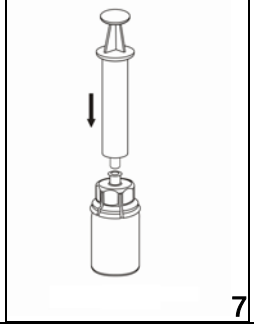
Dosage

The recommended dose is 20 units (U) per kg body weight.

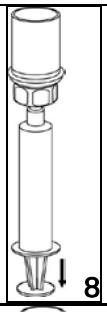
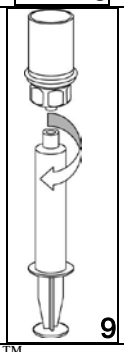
Reconstitution

Reconstitution and withdrawal must be carried out under aseptic conditions. 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.

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

	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 concentrate into the syringe by pulling the plunger back slowly.
	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® only. If multiple vials of Berinert® are to be administered, a separate Mix2Vial™ must be used for each vial.

The solution should be clear or 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

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

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

It is strongly recommended that every time Berinert® 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 2-8°C and used within 24 hours of reconstitution. Any unused solution must be discarded appropriately. Use in one patient on one occasion only.

OVERDOSAGE

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 U/kg body weight) of Berinert® in newborns and young children with congenital heart anomalies during or after cardiac surgery under extracorporeal circulation.

PRESENTATION

Each product package consists of one carton containing the single-use vial of Berinert® and one 10 mL vial of Water for Injection, and a second carton containing one Mix2Vial™ filter transfer set, a disposable 10 mL syringe, an infusion set, two alcohol swabs and a plaster (adhesive bandage).

STORAGE CONDITIONS

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

NAME AND ADDRESS OF THE SPONSOR AND DISTRIBUTOR

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POISON SCHEDULE OF THE MEDICINE

Unscheduled

Date of Therapeutic Goods Administration approval: 14 January 2010
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