Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Berinert

(C1-esterase inhibitor, human)

DE/W/0051/pdWS/002

Marketing Authorisation Holder:

CSL Behring GmbH

Rapporteur:	Germany (PEI)
Finalisation procedure (day 120):	20 July 2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Berinert 500/1500
INN (or common name) of the active substance(s):	C1-esterase inhibitor, human
MAH:	CSL Behring GmbH
Currently approved Indication(s)	Hereditary angioedema type I and II (HAE) Treatment and pre-procedure prevention of acute episodes
Pharmaco-therapeutic group (ATC Code):	B06AC01
Pharmaceutical form(s) and strength(s):	Powder and solvent for solution for injection or infusion

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed due to submission of final clinical study reports.

II. RECOMMENDATION

Submission of new paediatric data of two final clinical study reports do not change benefit-risk profile of Berinert and have therefore no impact on the SmPC. Therefore, no consequential regulatory action is required so far.

III. INTRODUCTION

On 11.09.2015, the MAH submitted two completed paediatric studies for Berinert, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Berinert and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

This paediatric worksharing procedure concerns a plasma derived C1-Esterase Inhibitor that is indicated for the treatment and pre-procedure prevention of Hereditary angioedema type I and II (HAE).

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

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

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

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

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

Berinert is provided as a powder and solvent for solution for injection/infusion. According the current SmPC posology for paediatric population is recommended with 20 IU per kilogram body weight. The reconstituted solution has to be administered by slow i.v. injection or infusion not more than 4ml/minute.

IV.2 Clinical aspects

1. Introduction

The MAH submitted final report(s) for:

Study No. CE1145_4001
Prospective open-label uncontrolled multi-center post-marketing study to assess inhibitory antibody formation in subjects with congenital C1-INH deficiency and acute hereditary angioedema (HAE) attacks treated with Berinert, a C1-Esterase Inhibitor

Study No. CE1145_5002
Patient Registry for Berinert, a C1-Esterase Inhibitor

Study CE1145_5002, the Berinert Registry, collected retrospective (since 2009) and prospective (since 2010) information on a total of 15000 infusions in 318 subjects treated with Berinert from 2009 to 2014 in 31 sites in the US and 7 sites in Europe.

2. Clinical studies

Study No. CE1145_4001

- **Description**

The current study was designed to assess whether HAE type I or II treatment with human plasma-derived C1-INH is associated with increased incidence of Antibodies that inhibit C1-INH function.

➢ Methods

- Study Objective(s)

Primary Objective

The primary objective of the study was to assess the formation of inhibitory anti-C1-INH Abs in subjects with HAE following treatment with Berinert. The study evaluated the hypothesis that the incidence of inhibitory anti-C1-INH Abs in subjects with HAE following treatment with Berinert is less than 20% of the total study population.

Secondary Objective

The secondary objective of the study was to assess the safety of Berinert in subjects with HAE following treatment with Berinert.

Exploratory Objectives

The exploratory objectives were to assess the efficacy of Berinert in subjects with HAE treated with Berinert for all types of HAE attacks, and to compare the efficacy in subjects with and without anti-C1-INH Abs.

- Study design

This was a prospective, international, multi-center, non-randomized, open-label study to investigate the formation of inhibitory anti-C1-INH Abs in subjects with HAE (type I or II) treated with i.v. Berinert.

- Study population /Sample size

60 subjects were screened and enrolled in the study. 14 subjects did not experience an HAE attack before the study ended and so did not receive study treatment. 46 subjects started and completed the active treatment period of the study.

Demography

Of the 46 subjects in the CEI145 4001 study, the majority was female (32/46; 69.6%) and all were of white race (46/46; 100%). The mean age was 38.9 years, and the mean weight and body mass index (BMI) were 71.2 kg and 25.04 kg/m2, respectively.

EU classification:

> 1 to < 2years (infants and toddlers)	0
≥ 2 to 12 years (children)	0
> 12 to < 18 years (adolescents)	**2 (4.4%)**
≥ 18 to < 65 years (adults)	42 (91.3%)
≥ 65 (geriatrics)	2 (4.4%)

Due to small numbers of paediatric and geriatric patients, no subgroup analyses by age were performed.

- Treatments

Subjects were to receive a dose of Berinert 20 IU/kg for an HAE attack requiring treatment. The duration of study participation was 9 months beginning with the first HAE attack requiring documented treatment with Berinert at the investigational site. There was no limit to the time period between screening and the first HAE attack. Once the first attack requiring treatment with Berinert occurred, subjects were to continue the study for 9 months and were expected to receive an additional 3 to 4 Berinert doses during this period.

- Outcomes/endpoints

Primary Endpoint:	Inhibitory anti-C1-INH Antibodies
Secondary Endpoints:	Any anti-C1 INH Antibodies
Efficacy Analysis:	Time to onset of relief and time to complete respolution
Safety Analysis:	Adverse events, laboratory safety parameters, vital signs, physical examination and HAE attacks

- Statistical Methods

Statistical Analysis

The primary variable was inhibitory anti-C1-INH Ab formation.
With regard to the incidence proportion of subjects with inhibitory anti-C1-INH Abs, the following comparison was of most interest: The incidence proportion needs to be below a relevant threshold, which is assumed to be 20%.
This comparison was based on the upper limit of the 2-sided 95% Wilson score confidence interval (CI).
Furthermore, additional exploratory analyses using descriptive statistics were performed.
For all other variables, descriptive statistics were calculated. Summary statistics were presented for continuous variables, by way of n, mean, standard deviation (SD), median, 25%- and 75% quantiles, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables. Point estimates and 2-sided 95% CIs were presented where appropriate.

➢ Results

In this study, subjects were considered screened if they signed the informed consent form and met the inclusion/exclusion criteria. Subjects were considered enrolled if they could receive IMP for an HAE attack but did not necessarily receive it. Sixty subjects were screened and enrolled in the study. Forty-six (76.7%) subjects started and completed the active treatment period of the study. Fourteen subjects discontinued the study because they had not experienced an HAE attack that required Berinert treatment before the study ended.

Demography
Of the 46 subjects in the study, the majority was female (32/46; 69.6%) and all were of white race (46/46; 100%). The mean age was 38.9 years, and the mean weight and body mass index (BMI) were 71.2 kg and 25.04 kg/m2, respectively.
Primary Endpoint: anti-C1-INH Antibodies
None of the 46 subjects tested positive for inhibitory anti-C1-INH Abs during the study.
Secondary Endpoint: anti-C1-INH Abs (Inhibitory or Non-inhibitory)
Thirteen (28.2%) subjects had detectable Abs at any time during the study. Thirty-three subjects (71.7%) were Ab- at all times during the study.
Nine (19.6%) subjects had detectable Abs at Day 1 (Baseline). Of these subjects, 3 had no detectable Abs post-baseline, and 6 had at least 1 detectable result for Abs post-baseline.
Ten (21.7%) subjects had at least 1 detectable result for Abs post-baseline. Of these subjects, 6 had detectable Abs on Day 1 (Baseline), and 4 had at least 1 detectable result for Abs post baseline with none detected at Day 1 (Baseline).

Efficacy
Overall, the mean TtRel per attack for all attacks was 1.418 hours (SD, 1.7601; 95% CI: 1.185, 1.652). Overall, the mean TtRel per subject for all subjects was 1.272 hours (SD, 0.8978; 95% CI: 1.005, 1.538).
For the 13 subjects (35 attacks) who tested positive for non-inhibitory anti-CI-INH Abs at any assessment during the study (including Baseline), the mean TtRel per attack was 1.508 hours (SD: 4.0700; 95% CI: 0.1100, 2.906). For the 33 subjects (186 attacks) who tested negative for non-inhibitory anti-CI-INH Abs at all assessments during the study (including Baseline), the mean TtRel per attack was 1.401 hours (SD: 0.7986; 95% CI: 1.286, 1.517).
For the 13 subjects (35 attacks) who tested positive for non-inhibitory anti-CI-INH Abs at any assessment during the study (including Baseline), the mean TtRel per subject was 1.173 hours (SD: 1.4310; 95% CI: 0.309, 2.038). For the 33 subjects (186 attacks) who tested negative for non-inhibitory anti-CI-INH Abs at all assessments during the study (including Baseline), the mean TtRel per subject was 1.311 hours (SD: 0.6001; 95% CI: 1.098, 1.523).

Overall, the mean TtRes per attack for all attacks was 31.890 hours (SD, 54.3926; 95% CI: 24.679, 39.101). Overall, the mean TtRes per subject for all subjects was 29.993 hours (SD: 20.0174; CI: 24.049, 35.937).
For the 13 subjects (35 attacks) who tested positive for non-inhibitory anti-CI-INH Abs at any assessment during the study (including Baseline), the mean TtRes per attack was 22.856 hours (SD: 21.0567; 95% CI: 15.622, 30.089). For the 33 subjects (186 attacks) who tested negative for non inhibitory anti-CI-INH Abs at all assessments during the study (including Baseline), the mean TtRes per attack was 33.590 hours (SD: 58.4675; 95% CI: 25.132, 42.047).
For the 13 subjects (35 attacks) who tested positive for non-inhibitory anti CI- INH Abs at any assessment during the study (including Baseline), the mean TtRes per subject was 31.015 hours (SD: 24.0803; 95% CI: 16.464, 45.567). For the 33 subjects (186 attacks) who tested negative

for non inhibitory anti CI-INH Abs at all assessments during the study (including Baseline), the mean TtRes per subject was 29.590 hours (SD: 18.5861; 95% CI: 23.000, 36.181).

Safety

A total of 52 AEs (including 2 SAEs) were reported in 15 (32.6%) subjects who received at least 1 dose of IMP at the study site (Table 1). The majority of AEs were moderate or severe in intensity, and all but 1 was reported as resolved by the end of the reporting period.

Table 1 Overall Summary of Adverse Events (Safety Set)

	Subjects Overall (N = 46)				
	n	**(%)**	**E**	**Rate/ Subject**	**Rate/ Infusion**
Adverse Events					
Any Adverse Event (AE)	15	(32.6)	52	1.13	0.24
AE occurred within 24 h of IMP administration	2	(4.3)	2	0.04	0.01
Related AEs [a]	0				
Withdrawn due to an AE	1	(2.2)	1	0.02	0.00
AE Intensity					
Mild	7	(15.2)	9	0.20	0.04
Moderate	12	(26.1)	32	0.70	0.14
Severe	3	(6.5)	11	0.24	0.05

[a] Events that are probably, possibly or definitely related to IMP, or with an unknown relationship.
Abbreviations: AE = adverse event; E = events; IMP = investigational medicinal product; n = number of subjects experiencing an event; SAE = serious adverse event.

The following list summarizes the main information of the AEs that were reported during the study:

- None of the AEs were considered related to investigational medicinal product (IMP).
- Two SAEs were reported that required hospitalization: Abortion Spontaneous (spontaneous abortion) and HAE (acute abdominal HAE attack). These SAEs were not considered related to IMP.
- One subject discontinued the IMP because she experienced an Abortion Spontaneous (spontaneous abortion), which was also reported as an SAE.
- Eleven severe AEs were reported in 3 (6.5%) subjects. Headache was the most common with 8 AEs reported in 2 subjects.

- A total of 2 AEs (Headache and Hypotension) occurred in a total of 2 subjects within 24 hours of IMP administration.
- No thromboembolic AEs were reported during the study.
- No deaths were reported during the study.

Conclusions:
Berinert showed no inhibitory anti-C1-INH Ab-forming potential in this study.
As anticipated, the presence of non-inhibitory C1-INH Abs does not appear to affect the efficacy of Berinert as assessed by TtRel and TtRes (per attack and per subject).
Safety and tolerability assessments demonstrate that Berinert was well tolerated in subjects at a dose of 20 IU/kg IV administered at the study site during this study.

Study No. CE1145_5002

➢ **Description**

Study CE1145_5002, the Berinert Registry, collected retrospective (since 2009) and prospective (since 2010) information on a total of 15000 infusions in 318 subjects treated with Berinert from 2009 to 2014 in 31 sites in the US and 7 sites in Europe.

➢ **Methods**

- Objective(s)

The main purpose of this Registry was to create a mechanism for enhanced (active) surveillance of the safety of CSL Behring's C1-esterase Inhibitor (CSLB C1-INH) in "real-world" clinical practice, and to facilitate discovery and reporting of adverse events (AEs), including potential thrombotic/thrombotic events (TEEs) and potential viral transmissions. These objectives were pre-specified before database lock.

In addition to the overall safety of CSLB C1-INH, the assessment of the safety of CSLB C1-INH administration in children younger than 12 years of age was of interest. Additional exploratory Registry objectives included the assessment of the safety and efficacy of Short-term Prophylaxis (STP) and long-term prophylaxis (LTP) using CSLB C1-INH. These were also pre-specified before database lock.

- Study design

This Registry was a multicenter, open, uncontrolled, study to collect retrospective and prospective data in a structured manner for subjects treated with CSLB C1-INH for any purpose (eg, treatment of hereditary angioedema [HAE] attacks, STP, LTP, and potential non-HAE conditions). This Registry was conducted as an observational/non-interventional study and followed subjects who received standard physician-directed treatment with CSLB C1-INH.

Due to the low incidence of HAE in the general population, the unpredictability of the need for treatment, and because subjects with HAE may have required CSLB C1-INH during a possibly life-threatening HAE attack, potential subjects with a known diagnosis of HAE were invited to enroll in the Registry before onset of an attack. All data were to be collected following enrolment of a subject (ie, following informed consent). Prospective data reflect events that occurred following enrolment. Retrospective data reflect events that occurred before enrolment.

Data from enrolled subjects were collected into the Registry database in the following way:

1. An enrolled subject was to report the details of his/her HAE attacks, CSLB C1-INH use, and/or AEs to the study site as per the subject's standard practice. A CSLB-developed subject diary was not provided to study subjects.
2. Each investigator was to follow and treat an enrolled subject (eg, site visits and laboratory testing) as per the investigator's standard of care.
3. Subject data were to be documented in the subject's medical records by the study site personnel as per the site's standard practice.
4. Site personnel were to periodically transfer data from the subject's medical records to the electronic case report form (eCRF) (ie, the database).
5. Data from the eCRF were to be remotely monitored.

- Study population /Sample size

Number of Subjects:

Planned: This non-interventional study aimed to describe the use of CSLB C1-INH in a cohort of individuals who used the product for any reason. Given the estimated post-marketing exposure of approximately 400 US patients as of April 2011, it was determined that data collected on ≥ 250 subjects would provide a reasonably sized experiential population.

Actual: A total of 343 subjects were enrolled across 31 sites in the US and 7 sites in Europe. These 343 subjects comprised the Full Analysis Set (FAS). Of the subjects in the FAS, 318 subjects received ≥ 1 dose of CSLB C1-INH for which data were captured. These 318 subjects comprised the Safety Set (SS). The number of CSLB C1-INH infusions that were captured per subject ranged from a single infusion to several hundred infusions.

Thirty-one (9.7%) of the 318 subjects in the SS discontinued. A discontinued subject was any subject who withdrew from participation (eg, withdrew consent or was lost to follow-up) or who was discontinued by their investigator (eg, because of an AE) before closure of the Registry on 30 April 2014. The most common reason for discontinuation was loss to follow-up, followed by withdrawal of informed consent.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

• Male or female subjects of any age.

• Any subject receiving CSLB C1-INH, for any purpose.

• Informed consent / assent.

Exclusion Criterion:

• Any subject participating in an HAE study using a C1-INH other than CSLB C1-INH.

- Treatments

  All data were to be collected following enrolment of a subject (ie, following informed consent), but data were retrospective or prospective. Retrospective data reflect events that occurred before enrolment. Prospective data reflects events that occurred following enrolment.
  The first subject who participated in the Registry provided consent on 9 April 2010. The earliest retrospective data point was dated October 2009. There was no mandatory duration of presentation in the Registry for any individual subject. Subjects were considered to have completed participation if they remained in the study until its closure on 30 April 2014. The mean duration of subject participation in the study was 21.32 months (95% CI: 20.01, 22.63)

- Outcomes/endpoints

  The following exploratory efficacy endpoints were to be assessed:

  • Breakthrough HAE attacks in subjects receiving STP and/or LTP.

  • Duration (in hours) of breakthrough HAE attacks in subjects receiving STP and/or LTP.

  • Time interval (duration in hours) between the start of a breakthrough HAE attack and the most recent STP or LTP administration of CSLB C1-INH before the breakthrough attack.

  The following were also to be assessed:

  • AEs, including TEEs.

  • Suspected adverse drug reactions.

  • Concomitant medications and plasma products, including reason(s) for administration.

  • Viral safety and occurrence of suspected viral transmission.

  • A change in treatment administration setting from a non-healthcare setting to a healthcare setting.

- **Results**

Efficacy Results

Registry Overview

This Registry collected data associated with 15,000 infusions of CSLB C1-INH from 318 treated subjects with HAE over a 5 year period (2009 to 2014). Infusions were given in healthcare and non-healthcare settings, as acute treatment of HAE attacks and prophylaxis against potential HAE attacks. Subjects ranged in age from 5 to 83 years old, including 18 subjects younger than 12 years old contributing data associated with 275 CSLB C1-INH infusions and 271 attacks. The Registry data set is comprised of both prospective data (reflective of events that occurred following enrolment) and retrospective data (reflective of events that occurred before enrolment). In this Registry, there is a greater proportion of prospective data (9148 infusions in 296 subjects) relative to retrospective data (5852 infusions in 263 subjects). Similar proportions of prospective and retrospective data were contributed by subjects younger than 12 years.

Analysis of Attacks Overall and by Age Group

Characteristics of HAE attacks included anatomic location, intensity, and trigger. Abdominal HAE attacks affected the highest percentage of subjects (78.4% of subjects overall), and accounted for the most common anatomic location (40.9% of attacks). Laryngeal HAE attacks, the attacks with the highest potential to be life-threatening, were experienced at least once by a substantial percentage of subjects (27.9% of subjects overall), but accounted for the smallest percentage of overall attacks (2.0%). Regardless of anatomic location, the greatest percentage of subjects experienced at least 1 severe attack (74.8% of subjects overall), but severe attacks occurred least commonly (14.9% of attacks). Attack triggers were most often (75.8% of attacks) non-identifiable (spontaneous), being reported by the highest percentage of subjects (87.2% of subjects overall).

There were notable differences with regard to anatomic location and intensity in subjects younger than 12 years old, relative to the overall study population. A smaller percentage of subjects in this age group experienced laryngeal attacks (5.9% of paediatric subjects). Relative to the overall population, attacks in paediatric subjects were less likely to be documented as mild (19.2% relative to 31.6% of attacks in subjects overall). No paediatric subjects had exclusively mild attacks, while 9 subjects (3.0%) of the overall population had only mild attacks.

Hereditary angioedema attack location and intensity were also compared in subjects overall who experienced lower or higher incidence rates of attacks (≤ 2 or > 2 attacks per month, respectively). Facial and laryngeal attacks were more commonly reported in subjects who had a lower incidence rate of attacks. A lower incidence rate of attacks was also associated with an increased percentage of severe attacks and a decreased percentage of mild attacks, relative to subjects with a higher incidence rate of attacks.

Short-term Prophylaxis

A total of 79 subjects received 149 infusions of CSLB C1-INH categorized as STP to prevent potential post-procedure HAE attacks. Of these, 3 subjects who were younger than 12 years old

received 4 CSLB C1-INH infusions as STP. The median dose per STP infusion in subjects overall was 14.60 IU/kg (dose by body weight) or 1000 IU (absolute dose).

In all, there were 52 breakthrough attacks in 27 subjects within 7 days of CSLB C1-INH infusions categorized as STP. When attacks occurring within 7 days of CSLB C1-INH infusions categorized as STP were analyzed, the mean time interval between STP infusion and breakthrough attack was 85.9 hours (95% CI: 75.14 to 96.59 hours). The cumulative percent of STP infusions followed by breakthrough attacks were 5%, 7% and 12% on days 1, 2 and 3, respectively, and 35% on day 7. Taken together, these data suggest that subjects may be at lower risk for an HAE attack in the 3 days immediately following a single STP infusion, relative to later time points.

Long-term Prophylaxis

A total of 47 subjects received 4082 infusions of CSLB C1-INH categorized as LTP. No infusions of CSLB C1-INH categorized as LTP were documented in subjects younger than 12 years old. The median dose per LTP infusion was 13.77 IU/kg (dose by body weight) or 1000 IU (absolute dose).

In all, there were 246 breakthrough attacks in 47 subjects within 7 days of an infusion categorized as LTP (more attacks per subject than were observed for infusions categorized as STP). The mean time interval between an infusion categorized as LTP and a breakthrough attack was 73.65 hours (95% CI: 69.57, 77.73 hours), consistent with the trend toward a slightly shorter mean attack-free time interval than was observed following STP dosing. The cumulative percent of LTP infusions followed by breakthrough attacks occurring within 1, 2, 3, and 7 days of regular LTP dosing were < 0.005% (15 attacks), 1% (61 attacks), 3% (133 attacks), and 6% (246 attacks). However, the cumulative percent of LTP infusions followed by breakthrough attacks increased to 6% (226 attacks) within 5 days of regular LTP dosing, with modest increases on day 6 (an increase of 11 attacks) and day 7 (an additional increase of 9 attacks).

These data suggest that a regularly administered LTP regimen confers a slightly greater protective effect against HAE attacks in the days immediately following administration of CSLB C1-INH, relative to later time points.

Safety Results:

Overview of Adverse Events

Of the 296 subjects who received ≥ 1 prospective dose of CSLB C1-INH during participation in the Registry, 85 subjects (28.7%) experienced a total of 252 AEs. As no AE data were reported for retrospective infusions, a post-hoc set of analyses was conducted based upon subjects who contributed at least one prospective data point and based upon prospective infusions. This analysis set is considered most relevant and of primary importance in understanding the safety profile of CSLB C1-INH as captured in the Registry. Adverse events were generally mild to moderate in intensity. Most AEs (243/252) were considered unrelated to CSLB C1-INH, including 234 events assessed as “not related” and 9 events assessed as “unlikely related”.

There were 9 AEs in 6 subjects considered related to CSLB C1-INH (inclusive of 2 events in 1 subject with missing event causality).

Of all AEs documented in the Registry, there were 34 serious adverse events (SAEs) in 14 subjects; out of 34 SAEs, 15 SAEs were HAE attacks, 9 of which occurred in a single individual. All SAEs were considered unrelated to CSLB C1-INH with the exception of 1 occurrence of DVT that was considered related. The event occurred in a HAE type III subject with an indwelling subclavian venous access port. Although the event was assessed as “probably related”, it had a plausible alternative causality (ie, the indwelling subclavian venous access port).

The overall AE rate in subjects contributing prospective data was 0.85 events per subject and 0.03 events per infusion.

Safety of CSLB C1-INH Prophylaxis

Of the 100 subjects who contributed prospective data and who received ≥ 1 dose of CSLB C1-INH for prophylactic treatment during participation in the Registry, 16.0% of subjects experienced ≥ 1 AE (63 events in 16 subjects) and 5.0% of subjects experienced an SAE (5 events in 5 subjects) after use of CSLB C1-INH for prophylactic treatment. Most events were considered unrelated to CSLB C1-INH by investigators, with 56 events in 13 subjects considered “not related” and 2 events in 2 subjects considered “unlikely related”. All events were captured as prospective data.

Events were mostly mild or moderate for both acute and prophylactic treatment. Events of mild intensity were experienced by the highest percentage of subjects with acute treatment (19.0% of subjects; 111 events) and with prophylactic treatment (10.0% of subjects; 17 events). Events of severe intensity were experienced by the lowest percentage of subjects with acute treatment (4.6% of subjects; 24 events), and with prophylactic treatment (3.0% of subjects; 3 events).

The safety profile of prophylactic CSLB C1-INH was similar to acute therapy when event rates per subject and per infusion were assessed. Subjects receiving acute treatment had an AE rate per subject of 0.66, and subjects receiving prophylaxis had an AE rate per subject of 0.63. Subjects experienced the same AE rate per infusion (0.03), regardless of whether they received acute treatment or prophylaxis.

Safety of CSLB C1-INH in Subjects < 12 Years Old

There were 18 subjects younger than 12 years old who were treated with 275 CSLB C1-INH infusions. There were 3 AEs documented in 3 subjects in this age group (toothache; nasopharyngitis; ankle fracture). No SAEs were documented in children younger than 12 years old. Rates of AEs per subject were lowest in subjects younger than 12 years old (0.18 events per subject in 17 subjects with prospective data). Subjects aged 12 to < 17 had the next lowest AE rate per subject (0.76 events per subject in 21 subjects with prospective data). Rates of AEs per infusion were also lowest in subjects younger than 12 years old (0.02 events per infusion). Subjects aged 17 to < 65 had the next lowest AE rate per infusion (0.03 events per infusion).This is of particular note considering subjects younger than 12 years old received the highest median dose of CSLB C1-INH (15.6 IU/kg in subjects aged < 12 years; 13.3 to 14.7

IU/kg in subjects aged between 12 and 64 years). Together, this suggests that CSLB C1-INH use is generally well tolerated in young paediatric patients.

Safety of Berinert by Age Group

Adverse Events by age subgroup (subjects with ≥ 1 prospective dose of Berinert)

Age group	N, Subjects	N, AEs	Rate per Subject	Rate per Infusion
> 1 to < 2 years (infants and toddlers)	0	0	0	0
≥ 2 to < 12 years (children)	17	3	0,18	0,02
≥ 12 to < 17 years (adolescents)	21	16	0,76	0,04
≥ 17 to < 65 years (adults)	235	214	0,91	0,03
≥ 65 (geriatrics)	23	19	0,83	0,02

Administration Setting and Failure to Self-infuse

Administration setting was documented for 14,819 CSLB C1-INH infusions, including retrospective and prospective infusions. The majority of all CSLB C1-INH infusions that had a documented administration setting were received in a non-healthcare setting (14,072 infusions). Infusions received in a non-healthcare setting (eg, at home) were self-administered by subjects or administered by their friends or caregivers.

The reasons for change in CSLB C1-INH administration setting from a non-healthcare to healthcare setting were documented. Failure to self-infuse, defined as the inability to find a vein or inject CSLB C1-INH into an iv port, was reported in 13 cases (6 subjects; 1.9% of all subjects in the SS). Taken together, these data (ie, 13 self-infusion failures out of 14,072 non-healthcare infusions) result in an estimate of < 1 case of failure to self-infuse per 1000 self-infusions.

Viral Safety

No subject was reported to have an adverse experience reflective of new infection with blood-borne viruses including HIV, HBV, HCV, or Parvovirus B19 during participation in the Registry. Because the Registry was designed to document the use of CSLB C1-INH according to local standard of care, there was no requirement for investigators to conduct viral testing. No post-baseline viral testing was documented as a part of the Registry. Therefore, the viral safety of CSLB C1-INH cannot be rigorously assessed using the Registry data set.

Thromboembolic Events

Thromboembolic events were identified using the Embolic and Thrombotic Events SMQ. There were a total of 2 TEEs reported as part of 9,148 prospective infusions documented in the Registry. This resulted in an observed rate of 2 TEEs in 9,148 prospective infusions, or a rate/subject of 0.007 and a rate/infusion of 0.0002. Both TEEs were documented as SAEs. One TEE was considered related to CSLB C1-INH; however, the event had a plausible alternative causality (ie, an indwelling subclavian venous access port).

3. Discussion on clinical aspects

Conclusions:

• Study CE1145_5002, the Berinert Registry, collected retrospective (since 2009) and prospective (since 2010) information on a total of 15,000 infusions in 318 subjects treated with CSLB C1-INH from 2009 to 2014 in 31 sites in the US and 7 sites in Europe.

• CSLB C1-INH doses per infusion varied substantially depending on subjects' age group, geographic location, and HAE attack characteristics. The highest mean and median doses were used for subjects of the youngest age group, for subjects residing in the US, for treating laryngeal and facial HAE attacks, and for severe HAE attacks of any anatomic location.

• A total of 2 TEEs were reported. One of the TEEs, a DVT, was considered possibly related to CSLB C1-INH; this event had a plausible alternative causality (an indwelling iv catheter).

• No cases of viral transmission were reported.

• CSLB C1-INH appeared safe in young paediatric HAE subjects aged < 12 years (range: 5 to 11 years), with rates of AEs per subject and per infusion numerically lower than for HAE subjects of older age groups despite the youngest age group having received the highest median by-weight dose.

• The safety of CSLB C1-INH infusions in short-term and long-term HAE prophylaxis was similar to that of acute therapy.

• CSLB C1-INH appeared effective as long-term prophylaxis, with the rate of 0.53 HAE attacks per month. Overall median LTP dose was 13.77 IU/kg or 1000 IU per infusion (based on 4082 infusions in 47 subjects). An apparent dose-dependent trend of prophylactic efficacy was observed.

• CSLB C1-INH appeared effective as STP or pre-procedural prophylaxis with cumulative percent of STP infusions followed by breakthrough HAE attacks on days 1, 2 and 3 after infusion of 5%, 7%, and 12%, respectively. Overall the median STP dose was 14.60 IU/kg or 1000 IU per infusion (based upon 149 infusions in 79 subjects). Similar to LTP, an apparent dose dependency of this effect was observed.

• The results of long-term observation in the Registry supported the favorable safety profile of CSLB C1-INH when administered in a broad population of subjects with ages ranging from 5 to 83 years of age. This favorable safety profile was observed when CSLB C1-INH was administered at home or in a healthcare setting either as prophylaxis or acute therapy.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

The MAH submitted final clinical study reports of two post marketing studies including paediatric subjects with congenital C1-INH deficiency. Via the paediatric worksharing procedure a potential impact by the use of Berinert on safety or efficacy of the paediatric population should be identified. In study CE1145_4001 only 2 subjects between 12 and 18 years (adolescents) were enrolled whereas the registry study CE1145_5002 included 18 children below 12 years and 21 adolescents between 12 and 17 years.

Main objective of study CE1145_4001 was the assessment of (inhibitory) antibodies following treatment with Berinert as well as an efficacy and a safety analysis. The study revealed no inhibitory anti-C1-INH Ab potential and other antibodies against C1-INH didn´t appear to affect the efficacy of Berinert. Due to the small number of paediatric patients no subgroup analysis was performed. The data show no influence to the well-established safety and efficacy profile of Berinert and therefore, no changes to the SmPC with regard to the paediatric population are considered necessary.

Main objective of study CE1145_5002, a registry study, was the post-authorisation surveillance of the safety of Berinert and the discovery and reporting of adverse events, including potential thromboembolic events (TEEs) and potential viral transmission. Additionally, the assessment of the safety in children younger than 12 years was of special interest.

The study results show that the rates of Adverse Events in subjects younger than 12 years and in adolescents were lower than in the older age groups though they received a higher median dose of Berinert. This suggests that Berinert is in general well tolerated in paediatric patients.

Overall, the favourable benefit-risk profile of Berinert did not change with regard to the use in the paediatric population and therefore, no changes to the SmPC or Patient Leaflet are recommended.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable

VII. CMS COMMENTS

Beside one agreement the following comment from a CMS was received:

It is agreed that the B/R for Berinert remains positive and unchanged, also in the paediatric population, however we recommend that paediatric data be included in the SmPC.

In the first Article 46 paediatric WS procedure for Berinert (DE/W/0051/pdWS/001) there were data on 15 HAE subjects aged < 18 years and these had been treated with 20 IU/kg for acute HAE attacks. Of these, only one (aged 10 years) was <12 years old. Resulting from that procedure, no paediatric data were included in the Berinert SmPC.

In the current procedure, from the Berinert registry (study 5002), there are efficacy and safety data from 18 children below 12 years (range 5 to 11 years) and 21 adolescents between 12 and 17 years which represents a substantial increase in available data especially in subjects <12 years old.

Currently there are no data from the paediatric population included in the Berinert SmPC. In order to make the paediatric data accessible and also as this is a rare disease with little paediatric data available, in our opinion a summary of efficacy and safety data, including dosages used, from the paediatric population in the Berinert studies should be included in the Berinert SmPC. This would also be consistent with the SmPCs of the other two plasma derived C1-inhibitor concentrates approved in the EU (Cinryze and Cetor) which both contain information in the SmPC on the paediatric population.

VIII. ASSESSMENT OF RESPONSES

MAH´s response to comment from CMS

pdC1-INH (Berinert®) was first approved for the treatment of HAE attacks in Germany already in 1979, and in further EU countries in the frame of the Mutual Recognition Procedure from late 2008 through 2010. It is now approved for the treatment of all types of acute HAE attacks in adults (including pregnant/nursing women), adolescents, children and neonates in Europe.

In addition the European health authorities have also approved the self-administration of pdC1-INH for the treatment of HAE attacks, for pre-procedure prevention (short-term prophylaxis) of acute episodes of HAE in adult and paediatric patients undergoing medical, dental or surgical procedures and for long-term prophylaxis.

The use of pdC1-INH is also endorsed in documents focusing on specific aspects of HAE therapy, including the International Home Therapy Consensus Document (Longhurst, Farkas et al. 2010, [1]), and consensus documents for the management of HAE in paediatric patients (Wahn, Aberer et al. 2012, [2]).

In addition, C1-INH treatment is recognised as an effective therapeutic option for HAE by patient organisations such as the International Patient Organization for C1-Inhibitor Deficiencies (HAEi) (http://www.haei.org/node/594, [3]) and the US Hereditary Angioedema Association (HAEA) (http://www.haea.org/patients/treatments/, [4]).

Therefore, based on the above mentioned selection of publications as well as available consensus documents and numerous webpages, it is concluded that specific paediatric population information is easily accessible for the health care professionals as well as for the patient.

Furthermore and in agreement with the authorities CSL Behring is also of the opinion that the current valid SPC of Berinert® properly reflects all necessary information in order to allow an effective and safe use in the target population (including paediatric patients). Therefore it is the philosophy of CSL Behring, especially in such times with a tendency of information overload for the health care professionals, to focus in the frame of updates only on new and formerly unknown information which could have an impact on the safe and effective use of the CSL Behring products. In accordance with our internal processes besides the ongoing safety monitoring during clinical trials also in the end phase all available data were carefully analysed and discussed within an interdisciplinary team. By doing this it can be ascertained that upcoming new safety and efficacy information will be included in product specific core documents and after submission and approval by the authorities will be available for the target user without delay.

The currently included paediatric safety and efficacy information is considered to be adequate also in the light of the newly submitted final clinical study reports of two post marketing studies. CSL Behring will continue to monitor the safety and efficacy and will update the SPC as soon as new and formerly unknown information arise.

IX. FINAL MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

The RMS supported the MAH view. The clinical information provided within this application is does not reveal any impact on the positive/benefit risk ratio of Berinert regarding the use in the paediatric population. The current SmPC wording reflecting paediatric efficacy and safety information is considered appropriate. As no modification of section 4.2 or 4.3 is considered necessary and no clinically relevant efficacy and safety aspects can be identified, maintaining of the current wording in accordance with the recommendation of the SmPC-Guideline is suggested.