

REAL-WORLD EXPERIENCE OF SUBCUTANEOUS BERINERT® 2000/3000 (C1-INH): PERSPECTIVES FROM DR ANNA SALA-CUNILL



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KEY PATIENT INFORMATION

Name: Catherine

Current age: 72 years

Sex: Female

Past medical history (other than HAE): Dyslipidaemia due to use of androgens

Year of first recorded HAE symptoms: 1967, at age 18 years

Triggers: Stress, trauma

Symptoms: Presented with severe and frequent angioedema attacks, most frequently in the abdomen, face, periphery, genitals and larynx

Family history:

- Catherine is unaware if her mother, father or other ancestral family members had the disease
- She has two daughters and one son. Two of her children have HAE. Catherine was diagnosed with HAE Type I when her son was diagnosed. These diagnoses prompted the investigation of all of the family members for HAE

Age at diagnosis: 62 years

Diagnosis: HAE Type I



PATIENT PRESENTATION

Reason for presentation: Catherine has been receiving long-term prophylactic treatment with danazol and experienced safety concerns (dyslipidaemia) and poor efficacy



2010

PATIENT PRESENTATION AND DIAGNOSIS

Date of diagnosis: 2010 (a delay of ~43 years)

Number of attacks per month: 3-4 (36 attacks per year)

Number of hospital admissions per year: 0 or 1

Laboratory testing:

- C1-INH protein level 0.049 mg/ml (reference range: 0.18-0.32 mg/ml)
- C1-INH function 30% (reference range: 70-130% of normal plasma)
- Complement C4 level 0.07 mg/ml (reference range: 0.16-0.38 mg/ml)
- Complement C1q level 0.225 mg/ml (reference range: 0.1-0.25 mg/ml)

Diagnosis: HAE Type I



2016

TREATMENT 2

Date: March 2016

Patient presentation: Spain ran out of stock of stanozolol and Catherine did not want to receive prophylaxis with C1-INH (IV), due to fear and a perceived difficulty of intravenous self-administration. Catherine chose to continue with oral androgens and initiated danazol; she was fully informed of the possible adverse events

Treatment: Danazol for long-term prophylaxis (50 mg every 24 hours)

Treatment outcome: Catherine's disease was controlled. She experienced 1 attack every 3 months.

Adverse events: Dyslipidaemia (February 2019)

Adverse event management: Danazol was decreased to 50 mg every 48 hours. Catherine's disease was less well controlled, and the dyslipidaemia did not improve



2020

TREATMENT 3

Date: June 2020

Patient presentation: Catherine's disease activity was less well controlled (2 attacks per month) since the decrease of the danazol dose (50 mg every 48 hours)

Considerations for treatment:

- Lack of disease control
- Dyslipidaemia due to androgen therapy
- Catherine is unable to self-administer plasma-derived C1-INH (IV)
- Catherine has poor venous access

Treatment: Berinert® 2000/3000 for long-term prophylaxis (SC; 4000 IU, twice a week)

Treatment outcome: Catherine's disease was well controlled; she was attack-free for the first 3 months and only experienced 1 mild peripheral attack during the past 6 months, without any adverse events. Catherine's dyslipidaemia and quality of life have also improved

Adverse events: None



Rationale for prescribing Berinert® 2000/3000 (SC):

- Berinert® 2000/3000 for subcutaneous injection is indicated for prevention of recurrent HAE attacks in adolescent and adult patients with C1-esterase inhibitor deficiency. The recommended dose of Berinert® 2000/3000 is 60 IU/kg body weight twice weekly (every 3-4 days)²
- Catherine had poor venous access and was unable to self-administer plasma-derived C1-INH (IV). She also experienced a lack of disease control and dyslipidaemia due to androgen therapy
- Catherine was prescribed Berinert® 2000/3000 as data from the COMPACT¹ clinical programme has shown that Berinert® 2000/3000:
 - Reduces attack rates by a median of 95% versus placebo³
 - Reduces attack severity versus placebo; 9% of patients treated with 60 IU/kg Berinert® experienced severe attacks versus 69% of placebo patients³
 - Produces long-term¹, statistically significant² differences in QoL measures, including EQ-5D Health State Value and Visual Analog Scale, anxiety and depression (HADS), WPAI-assessed presenteeism, work productivity loss and activity impairment, and TSQM-assessed treatment effectiveness and overall satisfaction⁴
 - Adverse events (most commonly mild and transient local site reactions) occurred in similar proportions of patients who received Berinert® or placebo³
- Moreover, the WAO/EAACI guidelines recommend C1-INH as the first-line treatment for long-term prophylaxis⁵



Biggest challenge experienced by the patient during treatment:

- Understanding their disease
- Understanding that specific, highly efficacious treatments for HAE are available that allow disease control without adverse events



Advice for the patient:

- Thoroughly explain how HAE affects your day-to-day life and any preferences you have regarding treatment
- Develop a trusting relationship with your HAE specialist to allow for co-decision making to select the most suitable therapy



Biggest challenge experienced by the clinician during treatment:

- Effectively conveying that androgens, although oral, may not be the most effective way to treat HAE and more efficacious alternatives are available



Advice for the clinician:

- Each patient is different and therefore treatment has to be individualised according to the patient's lifestyle and preferences



KEY LEARNING:

- Trust, built on an understanding of the fears and preferences of your patient, is vital to:
 - Confidently discuss treatment options
 - Ensure good adherence and consequently efficacy

*COMPACT was an international, prospective, multicentre, randomised, double-blind, placebo-controlled Phase 3 study. Patients ≥ 12 years of age with symptomatic type I or II HAE (N=90) were randomly assigned to twice-weekly treatment with Berinert® 40 IU/kg or 60 IU/kg. Patients initiated 16 weeks of active treatment or placebo and crossed over for the subsequent 16 weeks. Primary efficacy endpoint: number of attacks (investigator reported). Secondary efficacy endpoints: response rate (percentage of patients who had a $\geq 50\%$ reduction in number of attacks versus placebo), number of times rescue medication was used¹; iCOMPACT-OLE was an open-label extension of the COMPACT study, including 126 type I or type II HAE patients who had completed the Phase 3 study (n=64) or who were treatment naive (n=62) and who were randomised 1:1 to receive 40 IU/kg or 60 IU/kg Berinert® (SC) twice weekly. Primary endpoints: person-time incidence rates of related serious AEs, AEs leading to premature discontinuation, AEs of special interest (thromboembolic events and anaphylaxis), HAE attacks resulting in hospitalisation, injection-site reactions graded severe by the investigator, and the development of neutralising anti-C1-INH antibodies. Secondary endpoints: additional safety parameters, percentage of patients with time-normalised attack frequency of less than 1 attack per 4-week period, percentage of responders². ¹Point estimates with confidence intervals that excluded zero were considered statistically significant and interpreted to be indicative of a relevant treatment difference between Berinert® 2000/3000 and placebo.⁴

This patient case presentation is inspired by a real patient. To protect the patient's identity, their name and photograph have been changed.

ABBREVIATIONS

AE, adverse event; C1-INH, C1-esterase inhibitor; EAACI, European Academy of Allergy and Clinical Immunology; EQ-5D, EuroQol-5 Dimension; HADS, Hospital Anxiety and Depression Scale; HAE, hereditary angioedema; IV, intravenous; QoL, quality of life; SC, subcutaneous; TSQM, Treatment Satisfaction Questionnaire for Medication; WAO, World Allergy Organization; WPAI, Work Productivity and Activity Impairment Questionnaire.

REFERENCES

1. Craig T et al. *J Allergy Clin Immunol Pract* 2019;7:1793-1802.e2.
2. CSL Behring. Berinert 2000/3000 Summary of Product Characteristics. 2020.
3. Longhurst H et al. *N Engl J Med* 2017;376:1131-40.
4. Lumry WR et al. *Orphanet J Rare Dis* 2021;16:86.
5. Maurer M et al. *Allergy* 2018;73:1575-96.

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EU Essential Information

Berinert 500, powder and solvent for solution for injection/infusion. **Berinert 1500**, powder and solvent for solution for injection. **Qualitative and quantitative composition:** Berinert 500 contains 50 IU/ml C1-esterase-inhibitor, with a total protein content of 6.5 mg/ml. Berinert 1500 contains 500 IU/ml C1-esterase-inhibitor, with a total protein of 65 mg/ml. **Other ingredients:** glycine, sodium chloride, sodium citrate, water for injections. **Therapeutic indications:** Hereditary angioedema type I and II (HAE) for the treatment and pre-procedure prevention of acute

Please see the full Berinert® 500/1500 Summary of Product Characteristics for further details.

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EU Essential Information

Berinert 2000 / 3000, powder and solvent for solution for injection. **Qualitative and quantitative composition:** Berinert 2000/3000 contains 500 IU/ml C1-esterase-inhibitor, with a total protein content of 65 mg/ml. **Other ingredients:** glycine, sodium chloride, sodium citrate, water for injections. **Therapeutic indications:** Prevention of recurrent Hereditary Angioedema (HAE) attacks in adolescent and adult patients with C1-esterase inhibitor deficiency. **Contraindications:** Individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations or to any of the excipients listed under other ingredients. **Special warnings and precautions for use:** Traceability In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. **Hypersensitivity reactions:** If severe allergic reactions

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episodes. **Contraindications:** Hypersensitivity to the active substance or to any of the components of the product. **Special warnings and precautions for use:** In patients with known tendency towards allergies, antihistamines and corticosteroids should be administered prophylactically. If allergic or anaphylactic-type reactions occur, the administration of Berinert has to be stopped immediately (e.g. discontinue injection/infusion) and an appropriate treatment has to be initiated. Therapeutic measures depend on the kind and severity of the undesirable effect. The current medical standards for shock treatment are to be observed. Patients with laryngeal oedema require particularly careful monitoring with emergency treatment in stand-by. Unlicensed use or treatment of Capillary Leak Syndrome (CLS) with Berinert (see also section 7. Undesirable effects) is not advised. Berinert contains up to 486 mg sodium (approximately 21 mmol) per 100 ml solution. **Home-treatment and self-administration:** There are limited data on the use of this medicinal product in home- or self-administration. Potential risks associated with home-treatment are related to the administration itself as well as the handling of adverse drug reactions, particularly hypersensitivity. The decision on the use of home-treatment for an individual patient should be made by the treating

physician, who should ensure that appropriate training is provided and the use reviewed at intervals. **Virus Safety:** When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. **Interactions:** No interaction studies have been performed. **Incompatibilities:** Berinert must not be mixed with other medicinal products and diluents in the syringe/infusion set. **Pregnancy and lactation:** Berinert should be used during pregnancy and lactation only if clearly needed. **Undesirable effects:** Undesired reactions with Berinert are rare. Rare: Vascular disorders (development of thrombosis [in treatment attempts with high doses of Berinert for prophylaxis or therapy of CLS before, during or after cardiac surgery under extracorporeal circulation in single cases with fatal outcome]). General disorders and administration site conditions (rise in temperature, reactions at the injections site). Immune system disorders (allergic or anaphylactic type reactions). Very Rare: Immune system disorders (Shock). **Prescription status:** Prescription-only drug. **Manufacturer:** CSL Behring GmbH, Emil-von-Behring-Strasse 76, D-35041 Marburg. **Date of information:** May 2017.

in humans. In three studies, which included 344 patients, data from 36 women (50 pregnancies) were collected and no adverse events were associated with C1-INH treatment before, during or after pregnancy and women delivered healthy babies. **Breastfeeding:** There is no information regarding the excretion of Berinert in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Berinert and any potential adverse effects on the breastfed infant from Berinert or from the underlying maternal condition. **Fertility:** C1 inhibitor is a physiological component of human plasma. No studies on reproduction and developmental toxicity have been performed with Berinert in animals. **Undesirable effects:** Common: Immune system disorders (Hypersensitivity [Hypersensitivity, Pruritus, Rash and Urticaria]), Nervous system disorders (Dizziness). Very Common: Infections and infestations (Nasopharyngitis, General disorders and administration site conditions [Injection site reactions]). **Paediatric population:** The safety profile of Berinert was evaluated in a subgroup of eleven patients, 8 to < 17 years of age, in both studies (Study 3001, Study 3002) and was consistent with overall safety results. **Elderly population:** The safety profile of Berinert was evaluated in a subgroup of ten patients, 65 to 72 years of age, in both studies (Study 3001, Study 3002) and was consistent with overall safety results. **Prescription status:** Prescription-only drug. **Manufacturer:** CSL Behring GmbH, Emil-von-Behring-Strasse 76, D-35041 Marburg. **Date of information:** September 2020.

occur, the administration of Berinert must be stopped immediately (e.g. discontinue injection) and appropriate medical care must be initiated. In case of an acute HAE attack, individualized treatment should be initiated. **Thromboembolic events (TEE)** Thrombosis has occurred in treatment attempts with high doses of C1-INH i.v. for prophylaxis or therapy of capillary leak syndrome before, during or after cardiac surgery under extracorporeal circulation (unlicensed indication and dose). At the recommended s.c. doses, a causal relationship between TEEs and the use of C1-INH concentrate has not been established. **Virus Safety:** When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. **Sodium content:** Berinert 2000 IU contains less than 1 mmol sodium (23mg) per vial, that is to say essentially „sodium-free“. Berinert 3000 IU contains up to 29 mg sodium per vial, equivalent to 1.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. **Interactions:** No interaction studies have been performed. **Incompatibilities:** Berinert must not be mixed with other medicinal products and diluents. **Fertility, pregnancy and lactation:** Pregnancy There are limited data that suggest no increased risk from the use of human C1 inhibitor products in pregnant women. C1 inhibitor is a physiological component of human plasma. No studies on reproduction and developmental toxicity have been performed with Berinert in animals. No adverse effects on fertility, pre- and postnatal development are expected.

REAL-WORLD EXPERIENCE OF SUBCUTANEOUS BERINERT® 2000/3000 (C1-INH): PERSPECTIVES FROM DR MARIA PEDROSA



Maria Pedrosa, MD PhD

Consultant Allergist

Allergy Department, University Hospital La Paz, Madrid, Spain



KEY PATIENT INFORMATION

Name: Meghan

Current age: 14 years

Sex: Female

Past medical history (other than HAE): Pollinosis

Triggers: Infections, trauma, and psychological stress

Symptoms:

- Meghan experienced moderate-to-severe abdominal attacks, many peripheral attacks, and some attacks with upper respiratory involvement
- Her attacks typically lasted 3 days but some attacks, mainly peripheral, have lasted up to 5 days
- Most of the abdominal attacks, some of the peripheral attacks, and those attacks involving the respiratory tract have led to emergency room visits and, in a few cases, admission for an observation period

Family history: Father, uncle, and grandfather have been diagnosed with HAE Type I

Age at diagnosis: 7 months

Diagnosis: HAE Type I



PATIENT PRESENTATION

Reason for presentation:

- Meghan was not able to participate in school activities in the same way as her peers
- She felt unable to perform at the expected academic level
- She was anxious about the unpredictability of the disease
- Her parents were worried about letting her participate in the same activities as her brother (e.g. short trips with school and spending holiday periods alone with her grandparents)



2007

DIAGNOSIS

Date of diagnosis: 19 March 2007

Symptoms: At the age of diagnosis, Meghan was asymptomatic

Laboratory testing:

- C1-INH protein level: 6.17 mg/dL (reference range: 16–33 mg/dL)¹
- C1-INH function: 26.84% (reference range: 70–130% of normal plasma)¹
- Complement C4 level: 4.13 mg/dL (reference range: 14–60 mg/dL)¹

Diagnosis: HAE Type I



2013

TREATMENT 1

Date: 2013

Patient presentation: Meghan had been asymptomatic until age 7 when she started to experience abdominal attacks

Number of attacks per year: 8

Number of hospital admissions per year: 1–2

Treatment: Berinert® 500 IU for acute attacks (IV; 20 IU/kg)

Treatment outcome: Meghan's attacks resolved within a few hours when treatment was administered early. When treatment was delayed, her attacks lasted 24–36 hours

Adverse events: None



2014

TREATMENT 2

Date: November 2014

Patient presentation: Meghan's attacks had become more frequent (12 attacks in the previous year)

Treatment: Tranexamic acid for long-term prophylaxis (oral; 40 mg/kg; divided in three doses)

Treatment outcome: Tranexamic acid did not improve Meghan's symptoms

Adverse events: None



2015

TREATMENT 3

Date: March 2015

Patient presentation: Meghan's attack rate had increased to 3 or 4 attacks per month

Treatment: Berinert® 500 IU for acute attacks (self-administered IV; 20 IU/kg)

Treatment outcome: As treatment was self-administered at the earliest sign of an attack, attacks resolved within 1–3 hours after infusion

Adverse events: None



2015

TREATMENT 4

Date: June 2015

Patient presentation: Meghan had experienced 9 attacks in the previous 3 months. She had missed many school days, felt anxious and reported a poor QoL

Treatment: C1-INH for long-term prophylaxis (IV; 500 IU, twice weekly)

Treatment outcome: Meghan's symptoms improved and she was asymptomatic for 6 months; after which, the treatment was suspended to determine if the patient's period of increased disease activity had resolved. She was treated with on-demand therapy until June 2019

Adverse events: None



2019

TREATMENT 5

Date: June 2019

Patient presentation: Meghan had experienced 2 attacks per month in the previous 3 months. She continued to miss school days, experience anxiety and still reported a poor QoL

Treatment: Berinert® 2000/3000 for long-term prophylaxis (SC; 60 IU/kg, twice weekly)

Treatment outcome: Meghan's symptoms improved, and she was asymptomatic for 6 months; after which, the treatment was suspended to determine if the patient's period of increased disease activity had resolved and she was treated with on-demand therapy

Adverse events: Mild injection-site pain resolved without treatment after a few minutes



Rationale for prescribing Berinert® 2000/3000 (SC):

- Berinert® 2000/3000 for SC injection is indicated for the prevention of recurrent HAE attacks in adolescent and adult patients with C1-INH deficiency. The recommended dose of Berinert® 2000/3000 is 60 IU/kg body weight twice weekly (every 3–4 days)²
- Meghan had reported an increased frequency of attacks (2 attacks per month)
- The unpredictability of painful attacks limited her social life and academic potential, as well as impacting her mental health
- Data from the COMPACT^{††} clinical program has shown that Berinert® 2000/3000:
 - Reduces attack rates by a median of 95% vs placebo³
 - Reduces attack severity vs placebo; 9% of patients treated with Berinert® 60 IU/kg experienced severe attacks vs 69% of placebo patients³
 - Produces long-term,[†] statistically significant[†] differences in QoL measures, including: EQ-5D Health State Value and Visual Analog Scale, anxiety and depression (HADS), WPAI-assessed presenteeism, work productivity loss and activity impairment, and TSQM-assessed treatment effectiveness and overall satisfaction⁴
 - Adverse events (most commonly mild and transient local injection-site reactions) were similar in patients who received Berinert® and placebo³
- Moreover, the WAO/EAACI guidelines recommend C1-INH as the first-line treatment for long-term prophylaxis⁵



Biggest challenge experienced by the patient during treatment:

- Learning how to self-administer C1-INH (IV)



Advice for the patient:

- Be confident in your ability to learn how to self-administer your treatment
- Do not hesitate to communicate to your clinician the impact HAE has on your daily life
- Do not let the disease control your life but do everything you can to control the disease



Biggest challenge experienced by the clinician during treatment:

- Educating an adolescent patient on how to self-administer a non-oral treatment



Advice for the clinician:

- Consider injected therapies for routine prophylaxis in adolescents, as any perceived treatment burden is outweighed by the potential reduction in anxiety caused by the unpredictability of attacks
- Encourage your adolescent patients to self-administer their prophylactic therapies
- Monitor your patient's disease activity regularly and adjust treatment regimens, as appropriate



KEY LEARNING:

- Adolescent patients can learn to self-administer non-oral therapies
- Self-administration of long-term prophylactic treatments can improve a patient's QoL by increasing their autonomy and decreasing anxiety

*COMPACT was an international, prospective, multicenter, randomized, double-blind, placebo-controlled Phase 3 study. Patients aged ≥12 years with symptomatic Type I or II HAE (N=90) were randomly assigned to twice-weekly treatment with Berinert® 40 IU/kg or 60 IU/kg. Patients initiated 16 weeks of active treatment or placebo and crossed over for the subsequent 16 weeks. Primary efficacy endpoint: number of attacks (investigator reported). Secondary efficacy endpoints: response rate (percentage of patients who had a ≥50% reduction in number of attacks vs placebo) and number of times rescue medication was used; [†]COMPACT-OLE was an open-label extension of the COMPACT study, including 126 Type I or II HAE patients who had completed the Phase 3 study (n=64) or who were randomised 1:1 to receive Berinert® (SC) 40 IU/kg or 60 IU/kg twice weekly. Primary endpoints: person-time incidence rates of related serious AEs, AEs leading to premature discontinuation, AEs of special interest (thromboembolic events and anaphylaxis), HAE attacks resulting in hospitalisation, injection-site reactions graded severe by the investigator, and the development of neutralising anti-C1-INH antibodies. Secondary endpoints: additional safety parameters, percentage of patients with a time-normalised attack frequency of less than 1 attack per 4-week period, percentage of responders; ^{††}Point estimates with confidence intervals that excluded zero were considered statistically significant and interpreted to be indicative of a relevant treatment difference between Berinert® 2000/3000 and placebo.

This patient case presentation is inspired by a real patient. To protect the patient's identity, their name and photograph have been changed.

ABBREVIATIONS

AE, adverse event; C1-INH, C1-esterase inhibitor; C4, complement component 4; EAACI, European Academy of Allergy and Clinical Immunology; EQ-5D, EuroQoL-5 Dimension; HADS, Hospital Anxiety and Depression Scale; HAE, hereditary angioedema; HAE-C1-INH, hereditary angioedema with deficient C1-esterase inhibitor; IV, intravenous; OLE, open-label extension; QoL, quality of life; SC subcutaneous; TSQM, Treatment Satisfaction Questionnaire for Medication; WAO, World Allergy Organization; WPAI, Work Productivity and Activity Impairment Questionnaire.

REFERENCES

1. Craig T et al. *J Allergy Clin Immunol Pract* 2019;7:1793–1802.
2. CSL Behring. Berinert® 2000/3000 Summary of Product Characteristics.
3. Longhurst H et al. *N Engl J Med* 2017;376:1131–1140.
4. Lumry W et al. *Orphanet J Rare Dis* 2021;16:86.
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physician, who should ensure that appropriate training is provided and the use reviewed at intervals. **Virus Safety:** When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. **Interactions:** No interaction studies have been performed. **Incompatibilities:** Berinert must not be mixed with other medicinal products and diluents in the syringe/infusion set. **Pregnancy and lactation:** Berinert should be used during pregnancy and lactation only if clearly needed. **Undesirable effects:** Undesired reactions with Berinert are rare. Rare: Vascular disorders (development of thrombosis [in treatment attempts with high doses of Berinert for prophylaxis or therapy of CLS before, during or after cardiac surgery under extracorporeal circulation in single cases with fatal outcome]), General disorders and administration site conditions (rise in temperature, reactions at the injections side), Immune system disorders (allergic or anaphylactic type reactions), Very Rare: Immune system disorders (Shock). **Prescription status:** Prescription-only drug. **Manufacturer:** CSL Behring GmbH, Emil-von-Behring-Strasse 76, D-35041 Marburg. **Date of information:** May 2017.

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occur, the administration of Berinert must be stopped immediately (e.g. discontinue injection) and appropriate medical care must be initiated. In case of an acute HAE attack, individualized treatment should be initiated. **Thromboembolic events (TEE)** Thrombosis has occurred in treatment attempts with high doses of C1-INH iv. for prophylaxis or therapy of capillary leak syndrome (before, during or after cardiac surgery under extracorporeal circulation (unlicensed indication and dose). At the recommended s.c. doses, a causal relationship between TEEs and the use of C1-INH concentrate has not been established. **Virus Safety:** When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. **Sodium content:** Berinert 2000 IU contains less than 1 mmol sodium (25mg) per vial, that is to say essentially sodium-free. Berinert 3000 IU contains up to 29 mg sodium per vial, equivalent to 1.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. **Interactions:** No interaction studies have been performed. **Incompatibilities:** Berinert must not be mixed with other medicinal products and diluents. **Fertility, pregnancy and lactation:** **Pregnancy:** There are limited data that suggest no increased risk from the use of human C1 inhibitor products in pregnant women. C1 inhibitor is a physiological component of human plasma. No studies on reproduction and developmental toxicity have been performed with Berinert in animals. No adverse effects on fertility, pre- and postnatal development are expected

in humans. In three studies, which included 344 patients, data from 36 women (50 pregnancies) were collected and no adverse events were associated with C1-INH treatment before, during, or after pregnancy and women delivered healthy babies. **Breastfeeding:** There is no information regarding the excretion of Berinert in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Berinert and any potential adverse effects on the breastfed infant from Berinert or from the underlying maternal condition. **Fertility:** C1 inhibitor is a physiological component of human plasma. No studies on reproduction and developmental toxicity have been performed with Berinert in animals. **Undesirable effects:** Common: Immune system disorders (Hypersensitivity [Hypersensitivity, Pruritus, Rash and Urticaria]), Nervous system disorders (Dizziness). Very Common: Infections and Infestations (Nasopharyngitis), General disorders and administration site conditions (Injection site reactions). **Epidemiologic population:** The safety profile of Berinert was evaluated in a subgroup of eleven patients, 8 to < 17 years of age, in both studies (Study 3001, Study 3002) and was consistent with overall safety results. **Elderly population:** The safety profile of Berinert was evaluated in a subgroup of ten patients, 65 to 72 years of age, in both studies (Study 3001, Study 3002) and was consistent with overall safety results. **Prescription status:** Prescription-only drug. **Manufacturer:** CSL Behring GmbH, Emil-von-Behring-Strasse 76, D-35041 Marburg. **Date of information:** September 2020.

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REAL-WORLD EXPERIENCE OF SUBCUTANEOUS BERINERT® 2000/3000 (C1-INH): PERSPECTIVES FROM DR THOMAS BUTTGEREIT



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KEY PATIENT INFORMATION

Name: Beth

Current age: 36 years

Sex: Female

Past medical history (other than HAE):

- Hypertension: In 2018, Beth was prescribed ACE inhibitors for her hypertension, which worsened her HAE disease activity. The ACE inhibitor was later changed to a calcium antagonist
- Poor dental status: Dental/surgical procedures are known to induce attacks and require the use of pre-procedural prophylactic treatments¹

Triggers: Stress at school (1995-2003), dental surgery (i.e. July 2017)

Symptoms: Lip swelling, abdominal pain and erythema marginatum (typical clinical presentation)

Family history:

- Unknown: Parents died in a car accident. Beth was raised by her grandparents. Grandmother reports that Beth's mother had sporadic swelling during her adolescence without diagnosis

Age at diagnosis: 15 years

Diagnosis: HAE Type I



PATIENT PRESENTATION

Reason for presentation: Blood pressure medications (such as ACE inhibitors) taken since 2018 have impacted Beth's HAE disease activity



1995

TREATMENT 1

Date: 1995

Patient presentation: Cylated erythema and swelling of the lip. Note: At this time, Beth's HAE was undiagnosed

Treatment: Antihistamines (4 mg dimetindene) and systemic corticosteroids (100 mg prednisolone)

Treatment outcome: No response, persistence of lip swelling for 4 hours. Note: The lack of response is not surprising as bradykinin-mediated angioedema does not respond to antihistamines. Lack of response to antihistamines can help differential diagnosis

Adverse events: None



2000

DIAGNOSIS

Date of diagnosis: July 2000

Number of attacks per year: 8

Number of hospital admissions per year: 2-3

Laboratory testing:

- C1-INH protein level 0.05 mg/ml (reference range: 0.18-0.32 mg/ml)²
- C1-INH function 40% (reference range: 70-130% of normal plasma)²

- Complement C4 level 0.09 mg/ml (reference range: 0.16-0.38 mg/ml)²

Diagnosis: HAE Type I



TREATMENT 2

Date: 2000

Treatment: Berinert® 500/1500 for acute attacks (IV; 20 IU/kg; usually once or twice a month)

Treatment outcome: Acute attacks controlled with on-demand treatment

Adverse events: None

COMMON ATTACK FACED BY BETH

Date: 2009

Patient presentation: Abdominal attack with severe pain and erythema marginatum

Treatment: Berinert® 500/1500 (IV; 20 IU/kg)

Treatment outcome: Regression of abdominal pain

Adverse events: None

Frequency at which patient faced this type of attack: 7-14 times a year



2009

TREATMENT 3

Background: In July 2017, Beth experienced an attack in her lip after dental surgery

Date: October 2017

Patient presentation: Dental surgery required due to cavities

Treatment: Berinert® 500/1500 for pre-procedural prophylaxis (IV; 1000 IU, <6 hours prior to dental surgery)

Treatment outcome: Successful prevention of post-procedural attacks. Beth was advised to administer pre-procedural prophylaxis ahead of any future surgeries

Adverse events: None



2020

TREATMENT 4

Date: December 2020

Patient presentation: Beth has been treating acute attacks with on-demand Berinert (IV), but reports increased frequency of attacks (5 attacks per month), poor disease control (AECT=6) and impaired QoL (AE-QoL=83)

General health, wellbeing and lifestyle before starting treatment:

- Beth is a young, open-minded, well-educated, busy woman with an active life style and several hobbies (hiking, mountain biking, etc.)
- The unpredictability of painful abdominal attacks severely limited her social life
- Beth wishes to start a family

Considerations for treatment:

- Increased frequency of attacks
- Tendency to develop frequent tooth infections

Treatment: Berinert® 2000/3000 for long-term prophylaxis (SC; 3000 IU, every 3-4 days)

Treatment outcome:

- Absence of attacks
- Increased QoL (AE-QoL=26) and disease control (AECT=15)

Adverse events: None



Rationale for prescribing Berinert® 2000/3000 (SC):

- Berinert® 2000/3000 for subcutaneous injection is indicated for prevention of recurrent HAE attacks in adolescent and adult patients with C1-esterase inhibitor deficiency. The recommended dose of Berinert® 2000/3000 is 60 IU/kg body weight twice weekly (every 3-4 days)³
- Beth reported an increased frequency of attacks (5 attacks per month), poor disease control (AECT=6) and impaired QoL (AE-QoL=83)
- The unpredictability of painful abdominal attacks severely limited her social life and she was prone to developing tooth infections
- Beth also wishes to start a family

- Beth was prescribed Berinert® 2000/3000 as data from the COMPACT¹¹ clinical programme has shown that Berinert® 2000/3000:
 - Reduces attack rates by a median of 95% versus placebo⁴
 - Reduces attack severity versus placebo; 9% of patients treated with 60 IU/kg Berinert® experienced severe attacks versus 69% of placebo patients⁴
 - Produces long-term, statistically significant differences in QoL measures, including EQ-5D Health State Value and Visual Analog Scale, anxiety and depression (HADS), WPAI-assessed presenteeism, work productivity loss and activity impairment, and TSQM-assessed treatment effectiveness and overall satisfaction⁵
 - Adverse events (most commonly mild and transient local site reactions) occurred in similar proportions of patients who received Berinert® or placebo⁵

Moreover, the WAO/EACI guidelines recommend C1-INH as the first-line treatment for long-term prophylaxis¹



Biggest challenge experienced by the patient during treatment:

- Understanding the need for short- and long-term prophylactic treatment
- Experiencing an increased frequency of attacks (5 attacks per month), poor disease control (AECT=6) and impaired QoL (AE-QoL=83) before initiating Berinert® (SC)
- Learning to identify and treat an attack as early as possible



Advice for the patient:

- New therapeutic options in HAE allow patients to live a near-normal life as well as reduce the burden of the disease and its treatment
- Stay in touch with your physician to learn about the latest therapeutic options



Biggest challenge experienced by the clinician during treatment:

- Sharing decision making on the need for long-term prophylaxis
- Obtaining the exact medical and treatment history to identify trigger factors



Advice for the clinician:

- Avoid using ACE inhibitors/ARBs in patients with HAE because these drugs can worsen disease activity
- Consider disease-related QoL, disease control and disease activity in your treatment decision making
- Be aware that some patients experience prodromal signs (e.g. erythema marginatum); erythema marginatum should not be mistaken for urticaria
- Consider prescribing short-term prophylaxis before procedures that may induce attacks (e.g. dental surgery)



KEY LEARNING:

- A detailed history of secondary diagnoses and medications is important when treating HAE
- Consideration of disease-related QoL, disease control and attack frequency is critical to evaluate the need for long-term prophylaxis

*COMPACT was an international, prospective, multicentre, randomised, double-blind, placebo-controlled Phase 3 study. Patients ≥12 years of age with symptomatic type I or II HAE (N=90) were randomly assigned to twice-weekly treatment with Berinert® 40 IU/kg or 60 IU/kg. Patients initiated 16 weeks of active treatment or placebo and crossed over for the subsequent 16 weeks. Primary efficacy endpoint: number of attacks (investigator reported). Secondary efficacy endpoints: response rate (percentage of patients who had a ≥50% reduction in number of attacks vs placebo) and number of times rescue medication was used¹. ¹COMPACT-OLE was an open-label extension of the COMPACT study, including 126 type I or type II HAE patients who had completed the Phase 3 study (n=64) or who were treatment naïve (n=62) and who were randomised 1:1 to receive 40 IU/kg or 60 IU/kg Berinert® (SC) twice weekly. Primary endpoints: person-time incidence rates of related AEs, AEs leading to premature discontinuation, AEs of special interest (thromboembolic events and anaphylaxis). HAE attacks resulting in hospitalisation, injection-site reactions graded severe by the investigator, and the development of neutralising anti-C1-INH antibodies. Secondary endpoints: additional safety parameters, percentage of patients with a time-normalised attack frequency of less than 1 attack per 4-week period, percentage of responders². Point estimates with confidence intervals that excluded zero were considered statistically significant and interpreted to be indicative of a relevant treatment difference between Berinert® 2000/3000 and placebo⁵.

This patient case presentation is inspired by a real patient. To protect the patient's identity, their name and photograph have been changed.

ABBREVIATIONS

ACE, angiotensin-converting enzyme; AE, adverse event; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; ARB, angiotensin II receptor blocker; C1-INH, C1-esterase inhibitor; EACI, European Academy of Allergy and Clinical Immunology; EQ-5D, EuroQol-5 Dimension; HADS, Hospital Anxiety and Depression Scale; HAE, hereditary angioedema; IV, intravenous; OLE, open-label extension; QoL, quality of life; SC, subcutaneous; TSQM, Treatment Satisfaction Questionnaire for Medication; WAO, World Allergy Organization; WPAI, Work Productivity and Activity Impairment Questionnaire.

REFERENCES

- Maurer M et al. *Allergy* 2018;73:1575-1596.
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- CSL Behring. Berinert 2000/3000 Summary of Product Characteristics. 2020.
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- Lumy WR et al. *Orphanet J Rare Dis* 2021;16:86.

This is EU essential information only. For national prescribing information please see your country specific product information/package insert that comes with the product.

It may be that the situation as given in the prescribing information specific for your country is different with regard to indications, contraindications, license holder etc. Please contact our local labelling representative for further information.

EU Essential Information

Berinert 500, powder and solvent for solution for injection/infusion. **Berinert 1500**, powder and solvent for solution for injection.

Qualitative and quantitative composition: Berinert 500 contains 50 IU/ml C1-esterase-inhibitor, with a total protein content of 6.5 mg/ml. Berinert 1500 contains 500 IU/ml C1-esterase-inhibitor, with a total protein of 65 mg/ml. **Other ingredients:** glycine, sodium chloride, sodium citrate, water for injections. **Therapeutic indications:** Hereditary angioedema type I and II (HAE) for the treatment and pre-procedure prevention of acute

episodes. **Contraindications:** Hypersensitivity to the active substance or to any of the components of the product. **Special warnings and precautions for use:** In patients with known tendency towards allergies, antihistamines and corticosteroids should be administered prophylactically. If allergic or anaphylactic-type reactions occur, the administration of Berinert has to be stopped immediately (e.g. discontinue injection/infusion) and an appropriate treatment has to be initiated. Therapeutic measures depend on the kind and severity of the undesirable effect. The current medical standards for shock treatment are to be observed. Patients with laryngeal oedema require particularly careful monitoring with emergency treatment in stand-by. Unlicensed use or treatment of Capillary Leak Syndrome (CLS) with Berinert (see also section "7. Undesirable effects") is not advised. Berinert contains up to 486 mg sodium (approximately 21 mmol) per 100 ml solution. **Home-treatment and self-administration:** There are limited data on the use of this medicinal product in home- or self-administration. Potential risks associated with home-treatment are related to the administration itself as well as the handling of adverse drug reactions, particularly hypersensitivity. The decision on the use of home-treatment for an individual patient should be made by the treating

physician, who should ensure that appropriate training is provided and the use reviewed at intervals. **Virus Safety:** When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. **Interactions:** No interaction studies have been performed. **Incompatibilities:** Berinert must not be mixed with other medicinal products and diluents in the syringes/infusion set. **Pregnancy and lactation:** Berinert should be used during pregnancy and lactation only if clearly needed. **Undesirable effects:** Undesired reactions with Berinert are rare. Rare: Vascular disorders (development of thrombosis [in treatment areas with high doses of Berinert for prophylaxis or therapy of CLS before, during or after cardiac surgery under extracorporeal circulation in single cases with fatal outcome]). General disorders and administration site conditions (rise in temperature or reactions at the injections site). Immune system disorders (allergic or anaphylactic type reactions). Very Rare: Immune system disorders (Shock). **Prescription status:** Prescription-only drug. **Manufacturer:** CSL Behring GmbH, Emil-von-Behring-Strasse 76, D-35041 Marburg. **Date of information:** May 2017.

Please see the full Berinert® 500/1500 Summary of Product Characteristics for further details.

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EU Essential Information

Berinert 2000 / 3000, powder and solvent for solution for injection. **Qualitative and quantitative composition:** Berinert 2000/3000 contains 500 IU/ml C1-esterase-inhibitor, with a total protein content of 6.5 mg/ml. **Other ingredients:** glycine, sodium chloride, sodium citrate, water for injections. **Therapeutic indications:** Prevention of recurrent Hereditary Angioedema (HAE) attacks in adolescent and adult patients with C1-esterase inhibitor deficiency. **Contraindications:** Individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations or to any of the excipients listed under other ingredients. **Special warnings and precautions for use:** **Traceability:** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. **Hypersensitivity reactions:** If severe allergic reactions

occur, the administration of Berinert must be stopped immediately (e.g. discontinue injection) and appropriate medical care must be initiated. In case of an acute HAE attack, individualized treatment should be initiated. **Thromboembolic events (TEE):** Thrombosis has occurred in treatment attempts with high doses of C1-INH. IV, for prophylaxis or therapy of capillary leak syndrome before, during or after cardiac surgery under extracorporeal circulation (unlicensed indication and dose). At the recommended s.c. doses, a causal relationship between TEEs and the use of C1-INH concentrate has not been established. **Virus Safety:** When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. **Interactions:** Berinert must not be mixed with other medicinal products and diluents in the syringes/infusion set. **Pregnancy and lactation:** Berinert should be used during pregnancy and lactation only if clearly needed. **Undesirable effects:** Undesired reactions with Berinert are rare. Rare: Vascular disorders (development of thrombosis [in treatment areas with high doses of Berinert for prophylaxis or therapy of CLS before, during or after cardiac surgery under extracorporeal circulation in single cases with fatal outcome]). General disorders and administration site conditions (rise in temperature or reactions at the injections site). Immune system disorders (allergic or anaphylactic type reactions). Very Common: Infections and infestations (Nasopharyngitis). General disorders and administration site condition (Injection site reactions). **Paediatric population:** The safety profile of Berinert in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Berinert or any potential adverse effects on the breastfed infant from Berinert or from the underlying maternal condition. **Fertility, pregnancy and lactation:** Pregnancy: The safety profile of Berinert was evaluated in a subgroup of eleven patients, 8 to <17 years of age, in both studies (Study 3001, Study 3002) and was consistent with overall safety results. **Elderly population:** The safety profile of Berinert was evaluated in a subgroup of ten patients, 65 to 72 years of age, in both studies (Study 3001, Study 3002) and was consistent with overall safety results. **Prescription status:** Prescription-only drug. **Manufacturer:** CSL Behring GmbH, Emil-von-Behring-Strasse 76, D-35041 Marburg. **Date of information:** September 2020.

Please see the full Berinert® 2000/3000 Summary of Product Characteristics for further details.

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