APPLICATION
FOR INCLUSION OF

Plasma-derived C1 esterase inhibitor (human)

in the
WHO MODEL LIST OF ESSENTIAL MEDICINES

AND

WHO MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN

Submitted by

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<td>ADR</td>
<td>Adverse drug reaction</td>
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<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>b.w.</td>
<td>Body weight</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>C1-INH</td>
<td>C1 esterase inhibitor</td>
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<td>EML</td>
<td>Model List of Essential Medicines</td>
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<td>FFP</td>
<td>Fresh frozen plasma</td>
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<td>h</td>
<td>Hour</td>
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<td>HAE</td>
<td>Hereditary angioedema</td>
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<td>HAWK</td>
<td>Hereditary Angioedema International Working Group</td>
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<tr>
<td>HIV-1/2</td>
<td>Human immunodeficiency virus types 1 and 2</td>
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<td>HAV</td>
<td>Hepatitis A virus</td>
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<td>HBV</td>
<td>Hepatitis B virus</td>
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<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>HRQL</td>
<td>Health-related quality-of-life</td>
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<tr>
<td>iCAALL</td>
<td>International Collaboration in Asthma, Allergy and Immunology</td>
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<tr>
<td>I.M.P.A.C.T. 1</td>
<td>International, Multi-center, Prospective, Angioedema, C1-INH Trial 1</td>
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<td>I.M.P.A.C.T. 2</td>
<td>International, Multi-center, Prospective, Angioedema, C1-INH Trial 2</td>
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<tr>
<td>IRT</td>
<td>Individual replacement therapy</td>
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<td>IU</td>
<td>Unit</td>
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<td>kD</td>
<td>Kilodalton</td>
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<td>kg</td>
<td>Kilogram</td>
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<td>mL</td>
<td>Millilitre</td>
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<td>mg</td>
<td>Milligram</td>
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<tr>
<td>pdC1-INH</td>
<td>Plasma-derived C1-INH</td>
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<tr>
<td>PI</td>
<td>Prescribing information</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<td>SDP</td>
<td>Solvent detergent-treated plasma</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>μM</td>
<td>Micromolar</td>
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<td>U</td>
<td>Unit</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>WAO</td>
<td>World Allergy Organization</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Summary of the proposal

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder characterised by recurrent attacks of subcutaneous and submucosal oedema (most often involving the extremities, face, genitals and trunk). Attacks can also be associated with severe abdominal pain (due to gastrointestinal wall oedema) and life-threatening laryngeal oedema (Agostoni, Aygoren-Pursun et al. 2004). Three forms of HAE have been described: types I and II are clinically identical and result from either a deficiency (type I) or dysfunction (type II) of the plasma protein C1 inhibitor (C1-INH) (Donaldson and Evans 1963). A third type of familial angioedema is characterised by normal C1-INH levels and function, and is referred to as HAE with normal C1-INH (Craig, Aygoren-Pursun et al. 2012). C1-INH is a serine protease inhibitor, which has been shown to be an inhibitor of the classical complement pathway, the contact system, the fibrinolytic and kinin-generating pathways. The function of C1-INH in the kinin-generating pathway is directly related to the pathogenesis of HAE which involves an excess production of bradykinin, a potent vasodilatory peptide leading to the clinical symptoms of HAE (Davis 2008).

HAE attacks are extremely distressing as they often result in disfigurement and/or impaired function (for example during peripheral attacks on hands or feet). HAE-related abdominal oedema causes acute debilitating abdominal pain, which progresses to nausea, vomiting, and often diarrhoea as the attack evolves. An acute abdominal HAE attack can mimic appendicitis, a bowel rupture, or a bowel obstruction and have often led to unnecessary repeated surgery and delay in diagnosis. Attacks affecting the upper airway (laryngeal) are potentially life-threatening, since oedema can compromise the airways, leading to risk of asphyxia. Approximately 50% of all patients with HAE experience at least 1 laryngeal attack, and some patients have them repeatedly (Zuraw 2008). Prior to the development of effective therapy, the mortality rate was estimated to be 20–30% (Frank 2014). These critical clinical consequences of HAE emphasise the importance of early diagnosis and crucially, the essential need for an effective and fast-acting acute treatment option.

Furthermore, although a relatively rare disease, HAE has a significant detrimental effect on the mental and physical well-being of patients. The pain, discomfort, disfigurement, and life-threatening potential of acute attacks, compounded by the unpredictability of the disease, all result in a significant chronic burden in the form of reduced health-related quality of life (HRQL), increased incidence of depressive symptoms, reduced productivity, and missed professional and educational opportunities (Lumry, Castaldo et al. 2010).
It should be noted that emergency treatment of an acute HAE attack is extremely challenging as, unlike an allergic reaction, oedema related to HAE does not respond to epinephrine, antihistamines, or glucocorticoids (Zuraw 2008). Currently, four different products are approved for acute treatment of HAE attacks, namely plasma-derived C1-INH concentrates (pdC1-INH), conestat alfa, icatibant and ecallantide. Although all of these treatments are thought to have comparable therapeutic efficacy they differ widely in terms of clinical utility and geographical availability. In regions where these modern treatments are not available, international guidelines recommend that attacks should be treated with solvent detergent-treated plasma (SDP). If SDP is not available, then attacks should be treated with fresh frozen plasma (FFP), where safe supply is available. It should be noted that a paradoxical worsening of symptoms occasionally occurs with FFP, as it contains substrate proteins that could consume the available C1-INH and exacerbate the angioedema.

Treatment with pdC1-INH (to replace the functionally or quantitatively deficient C1-INH) in patients with HAE has been shown to be extremely effective for treating acute oedematous attacks at any site and is particularly effective for laryngeal attacks. pdC1-INH is also an efficacious and well-tolerated option for treating acute HAE attacks in children and pregnant and nursing women. Three pdC1-INH concentrates are currently available and approved for acute treatment of type I/II HAE in the EU, US and many other countries: Berinert® (CSL Behring GmbH, Marburg, Germany), Cinryze® (Shire Pharmaceuticals, Basingstoke, UK [acquired by Abbvie in August 2014]) and Cetor® (Sanquin, Amsterdam, the Netherlands).

Currently, pdC1-INH is the only medicinal product indicated both for the acute treatment and prevention of HAE attacks and the only treatment for HAE that is licensed for acute treatment of children (no age limit specified in the EU, limited to use in children aged 12 years and older in the US) (Craig, Aygoren-Pursun et al. 2012). In addition, pdC1-INH is approved for self-administration, allowing patients to take control of their disease and reducing the burden on healthcare resources.

The scope and relevance of this product in the acute treatment of attacks is crucial since there are no other treatments that are as broadly available with similar efficacy and safety. As the HAE defect is genetic and there are no known cures, individuals with HAE require an acute treatment plan that includes access to pdC1-INH. As of today, pd-C1INH is not available in many regions of the world, most notably in developing countries. Equitable access to and use of pdC1-INH worldwide will guarantee the same level of health to patients...
with HAE, allowing for the effective and timely treatment of HAE attacks, prevention of avoidable deaths, and a reduction in suffering and disease burden. The provision of acute C1-INH replacement therapy is essential to prevent morbidity and mortality in this group of patients who had, prior to the availability of treatment, a substantially reduced quality of life and a significant risk of mortality due to potentially life-threatening laryngeal oedema.

This application outlines the essential nature and importance of diagnosis, and the appropriate treatment of patients with type I/II HAE with pd-C1INH in order to adequately manage potentially life-threatening and/or extremely painful attacks.

1. Summary statement of the proposal for inclusion of the human, plasma-derived, pasteurized and nanofiltered C1 esterase inhibitor in the WHO EML and WHO EML for children

Plasma-derived C1 esterase inhibitor are proposed for inclusion in the World Health Organisation (WHO) Model List of Essential Medicines for acute treatment of recurrent episodes of subcutaneous and submucosal oedema (including painful abdominal and potentially life-threatening laryngeal attacks) in individuals (including pregnant/nursing women and children) with type I/II Hereditary angioedema (HAE).

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

Not applicable.

3. Name of the organization(s) consulted and/or supporting the application (endorsement letters are attached in Annex 1)

International organisations supporting the application to include pdC1-INH in the WHO Essential List of Medicines:

The US Hereditary Angioedema Association (US HAEA)
Seven Waterfront Plaza
500 Ala Moana Blvd., Suite 400
Honolulu, HI 96813
http://www.haea.org/
Contact: Anthony Castaldo
President
US HAEA and HAEi
Tel: +1 202 247 8619; a.j.castaldo@haei.org
4. **International Nonproprietary Name (INN, generic name) of the medicine**

C1 esterase inhibitor, human

5. **Formulation proposed for inclusion; including adult and paediatric (if appropriate)**

It is proposed to add the following formulation of pdC1-INH for inclusion in the complementary list of the WHO Model List of Essential Medicines (for adults and children):

Plasma-derived C1 esterase inhibitor (human),

**Powder for injection:** 500 U/IU per vial

(Note: U and IU are used interchangeably in the document when referring to doses of pdC1-INH, depending on the source/manufacturer of the product)

6. **International availability - sources, if possible manufacturers and trade names**

The companies listed below manufacture and/or distribute human plasma-derived C1-INH concentrates (trade names in brackets).
CSL Behring GmbH (Berinert®)
Emil-von-Behring-Str. 76
35041 Marburg,
Germany
Tel: +49 6421 3912

Sanquin Blood Supply Foundation (Cetor® and Cinryze®) *
Plesmanlaan 125
1066 CX Amsterdam
The Netherlands
Tel: +31 20 512 30 00
*Cinryze is distributed by Shire Pharmaceuticals (acquired by Abbvie in August 2014)
Berinert®, Cetor® and Cinryze® are comparable in terms of composition, efficacy and safety.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested as an example of a new therapeutic group

Section 11. BLOOD PRODUCTS AND PLASMA SUBSTITUTES OF HUMAN ORIGIN
Section 11.2 Plasma derived medicines
Section 11.2.3 Plasma protein
Complementary list
Human C1-inhibitor concentrate/Powder for injection: 500 U/IU per vial

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<td>Human C1-inhibitor concentrate</td>
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8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1 Epidemiological information on disease burden

8.1.1 Prevalence

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder that is commonly caused by a deficiency in functional C1-esterase inhibitor (C1-INH), which is directly involved in the pathogenesis of the disease (Donaldson and Evans 1963). Traditionally, two types of HAE have been described: the more prevalent type I HAE (about 85% of all cases), which is characterized by a deficiency in functional C1-INH, and type II HAE (about 15% of all cases), which is characterized by functionally impaired C1-INH (Bork and Davis-Lorton 2013). However, a third form of HAE characterised by normal C1-INH levels and function has been described, and is referred to as HAE with normal C1-INH (Craig, Aygoren-Pursun et al. 2012). This variant will not be discussed and future references to HAE in this document will refer exclusively to type I/II HAE.

The prevalence of HAE is estimated to be approximately 1 in 50,000 persons, with no major differences due to ethnicity or gender being reported (Nzeako, Frigas et al. 2001; Bowen, Cicardi et al. 2008). Studies based on national HAE registries in Europe report a minimal prevalence ranging from 1.09 to 1.41 in 100,000 inhabitants (Roche, Blanch et al. 2005; Bygum 2009), with the actual prevalence expected to be higher. Recent reports suggest that there may be a lower prevalence of HAE in Asia (ranging from 0.1 to 9.4 in 1,000,000 inhabitants) than in Europe and North America (ranging from 0.4 in 100,000 to 1 in 50,000 inhabitants) (Lei, Shyur et al. 2011). The reasons are unknown but may include underdiagnosis or a lower prevalence in Asian populations.

8.1.2 Disease burden

Physical burden of HAE

Patients with HAE suffer from recurrent attacks of nonpruritic localised subcutaneous or mucosal oedema (most often involving the extremities, face, genitals and trunk) and abdominal pain (due to gastrointestinal wall oedema) (Bork, Meng et al. 2006). The swelling typically worsens gradually over the first 24 hours, and usually begins to resolve spontaneously over 48 to 72 h (Zuraw 2008). Abdominal attacks may be accompanied by severe pain, vomiting, and diarrhoea (Bork, Staubach et al. 2006). Laryngeal oedema (approximately 1% of all HAE attacks), may occur in up to 50% of patients and is potentially
life threatening due to obstruction of the upper airways (Bork, Hardt et al. 2003; Bork, Meng et al. 2006).

HAE is a chronic, life-altering disease that can put tremendous emotional and financial strain on patients and caregivers. Individuals with HAE require lifelong therapy and must constantly be vigilant for angioedema attacks, as any attack involving the upper airway is potentially life-threatening. As with other serious, chronic illnesses, the total disease burden of HAE includes costs to the quality of life and overall well-being of patients as well as economic costs (indirect and direct).

Health-related quality of life

In a survey conducted in 2007/2008, patients with HAE reported significantly poorer outcomes on health-related quality of life (HRQL) measurements and increased rates of depression, compared with healthy individuals (Lumry, Castaldo et al. 2010). A significant number of survey respondents (42.5%) reported at least mild symptoms and nearly twice as many reported taking psychotropic or antidepressant medication than the general population (19.5% vs 11.1%). Attenuated androgens are routinely used to manage and prevent the development of acute attacks of HAE. Chronic use of androgen therapy for HAE prophylaxis was associated with significant side effects (weight gain [70.8%], mood changes [59.7%] and agitation and sleeplessness/insomnia [45.6% for both]) that further diminished HRQL in study patients (Lumry, Castaldo et al. 2010).

Aside from the deleterious effects of HAE on the quality of life (QOL), inaccurate or delayed diagnosis of HAE can lead to undue and/or prolonged suffering for patients, lengthy or frequent hospitalizations, and unnecessary medical procedures (Agostoni, Aygoren-Pursun et al. 2004).

8.2 Assessment of current use

Acute treatment of HAE attacks with pdC1-INH is well established and recommended by organisations/international working groups such as the World Allergy Organization (WAO) (Craig, Aygoren-Pursun et al. 2012), the Hereditary Angioedema International Working Group (HAWK) (Cicardi, Bork et al. 2012) and the International Collaboration in Asthma, Allergy and Immunology (ICAALL), comprising the American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, European Association of Allergy and Clinical Immunology, and World Allergy Organization) (Lang, Aberer et al. 2012).
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), and consensus documents for the management of HAE in paediatric patients (Wahn, Aberer et al. 2012) as well as in pregnant/nursing patients (Caballero, Farkas et al. 2012).

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) and the US Hereditary Angioedema Association (HAEA) (http://www.haea.org/patients/treatments/).

pdC1-INH (Berinert®) has been used in over 600,000 treatments administered over more than 26 years (Bork, Korger et al. 2012). The recognition of the safe and efficacious treatment of patients with HAE with pdC1-INH is confirmed by regulatory authorities. It is currently approved for use in varying indications in different patient populations in the EU, USA, and many other countries.

Historically, management of HAE was limited to alleviating clinical symptoms (eg, fluid replacement, pain management) and solvent detergent or fresh frozen plasma (FFP) was utilised as a source of C1-INH (Bork and Davis-Lorton 2013). In regions where there is no access to pdC1-INH (or other newer treatments) the only treatment option for patients suffering from HAE is FFP for acute attacks. However, clinical efficacy data are limited, and plasma contains substrates that could theoretically worsen symptoms in patients with HAE (Nzeako, Frigas et al. 2001; Bowen, Cicardi et al. 2010).

Oral androgens have been used for several decades as long-term prophylaxis by HAE patients to reduce the frequency and/ or severity of attacks. The side effect profile of androgens represents the primary drawback of their use for long-term prophylaxis. Androgen therapy cannot prevent the occurrence of life-threatening upper airway edema with certainty. The risk of side effects increases with dosage and duration of androgen therapy, with common side effects including virilization, weight gain, and menstrual irregularities and less common, but serious, adverse reactions including the development of drug-induced hepatitis and hepatic neoplasms (Craig, Aygoren-Pursun et al. 2012).
8.2.1. Approved regulatory indications in the US

In the US, pdC1-INH is indicated for the treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and adolescent patients (Berinert US PI). It is also currently approved for self-administration for the treatment of acute attacks of HAE (http://www.cslbehring-us.com/s1/cs/enus/1199978939073/news/1255927936294/prdetail.htm) and for long-term prophylaxis in adults and adolescents (Cinryze US PI).

8.2.2. Approved regulatory indications in the EU

pdC1-INH (Berinert®) was first approved for the treatment of HAE attacks in Germany 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 (Berinert SPC; http://www.cslbehring.com/PRelease/Berinert-Approved.htm?tabSelections=1255923338766&currentPage=3). European health authorities have also approved the self-administration of pdC1-INH for the treatment of HAE attacks (Berinert and Cinryze SPC), 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 (Cinryze®) (http://www.cslbehring.com/s1/cs/enco/1151517263302/news/1255931201677/prdetail.htm).

8.2.3. Approved Regulatory Indications in Australia

pdC1-INH is indicated for treatment (Berinert® + Cinryze®) and pre procedure prevention (Cinryze®) of angioedema attacks in adults and adolescents with C1 inhibitor deficiency and routine prevention (Cinryze®) of angioedema attacks in adults and adolescents with frequent attacks of hereditary angiodema (HAE), who are intolerant to or insufficiently protected by oral therapy by the Therapeutics Goods Administration (TGA) of Australia. (http://www.tga.gov.au/pdf/auspar/auspar-berinert.pdf, www.tga.gov.au/word/.../auspar-c1-esterase-inhibitor-130729.docx).

8.2.4. Approved Regulatory Indications in Canada

Based on the Health Canada review of data on quality, safety, and efficacy, Health Canada considered that the benefit/risk profile of Berinert® was favourable for the treatment of acute abdominal or facial attacks of HAE of moderate and severe intensity and for Cinryze®
for routine prevention of angioedema attacks in adult and adolescents with hereditary angioedema (HAE).


8.2.5. **Approved Regulatory Indications in other parts of the world**

pdC1-INH is approved for the treatment of acute HAE attacks in other countries including Argentina, Brazil, Israel, Japan, Mexico, Puerto Rico, Russia, and South Korea. It is also available in New Zealand, Saudi Arabia and the UAE on named-patient-basis or special access programs.

8.3. **Target population**

Patients with type I/II HAE lacking functional C1-INH suffer from recurrent attacks of nonpruritic localized subcutaneous or mucosal oedema, most commonly affecting the extremities, face, bowels, abdomen, genitalia or upper respiratory tract (Zuraw 2008). Attacks affecting the cutaneous tissue can be very disfiguring and cause distressing symptoms, which can last for several days if left untreated (Bork, Staubach et al. 2008). HAE attacks in the abdomen can cause very severe pain (Bork, Staubach et al. 2006) whilst swelling of the upper respiratory mucosa poses the greatest risk because it can lead to death due to asphyxiation (Bork, Hardt et al. 2003). In the past, mortality rates of up to 30% have been reported as a result of asphyxiation, in untreated cases of HAE (Frank 1976). Acute replacement with pdC1-INH has been shown to lead to immediate and reliable relief of all symptoms (usually within 30 minutes of intravenous injection) (Craig, Levy et al. 2009).

Because of recurrent attacks, compared with healthy individuals, patients with HAE have a significantly poorer quality-of-life, increased rates of depression, and reduced productivity in the form of missed time at work and school, with lasting negative impacts on career and educational prospects (Lumry, Castaldo et al. 2010).

As HAE is a genetic disease with no known cure, individuals with HAE require a management plan that includes provisions of access to pd-C1INH for acute treatment of attacks. Establishment of plans for acute treatment by the relatives or the patients themselves (self-administration) will allow patients to gain control of the disease leading to a significantly better quality of life (Bygum, Andersen et al. 2009).
9. **Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)**

The treatment recommendations for acute treatment of HAE attacks outlined below are based on EU and US prescribing information, and are also advocated in the WAO Guidelines for the Management of HAE (Craig, Aygoren-Pursun et al. 2012).

**Adults (including pregnant/nursing women)**
Treatment of acute HAE attacks:
20 IU/kg body weight (b.w.) (Berinert®) or 1000 U (Cinryze®)

**Children**
Treatment of acute HAE attacks:
20 IU/kg b.w. (Berinert®) or 1000 U (Cinryze®, for children 12 years and above)

According to the WAO guidelines (Craig, Aygoren-Pursun et al. 2012), pdC1-INH is the only HAE treatment recommended as first-line therapy for:

- treatment of acute HAE attacks at all body sites in a broad patient population comprising all age groups (including pregnant/nursing women and children of any age)

- self-administration for acute treatment of attacks of HAE in adults (including pregnant/nursing women) and children, provided patients or caregivers have been adequately trained to provide intravenous infusion.

Currently, pdC1-INH is the only approved drug for type I/II HAE on-demand treatment in childhood (in the EU, 12 years and older in the US).

Recent changes to product licences allowing self-administration (home therapy) of pdC1-INH have provided additional options for the management of HAE. Researchers have noted the benefits of self-administered pdC1-INH therapy on the quality of life (both the physiological and psychological aspects) of patients (Bygum, Andersen et al. 2009; Kreuz, Martinez-Saguer et al. 2009).
10. **Summary of comparative effectiveness in a variety of clinical settings**

10.1 **Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)**

The clinical evidence for the effectiveness of pdC1-INH for the acute treatment of HAE attacks has been extensively reviewed in clinical studies and by regulators worldwide (see Section 8.2).

A systematic literature review of studies that evaluated the efficacy and safety of one of the available pdC1-INH concentrates (Berinert®) for the treatment and prophylaxis of patients with HAE has been recently published (Bork, Steffensen et al. 2013). Details of pivotal RCTs and a selection of studies documenting the efficacy of pdC1-INH for the acute treatment of HAE attacks in a variety of clinical settings are provided in **Annexes 2 and 3**. These include studies of pdC1-INH for treatment of adults (including pregnant/nursing women) and children as well as for self-administration.

Currently, four different products are licensed as therapeutic options for acute treatment of HAE attacks (based on well-controlled clinical trials), namely pdC1-INH (Berinert®, Cinryze®/Cetor®), conestat alfa (Ruconest®) icatibant (Firazyr®) and ecallantide (Kalbitor®).

In regions where these modern treatments are not available, international guidelines recommend that attacks should be treated with solvent detergent-treated plasma (SDP). If SDP is not available, then attacks should be treated with FFP (where safe supply is available).

However, these recommendations are based on observational reports of the effectiveness of FFP rather than on blinded, well-controlled trials (Prematta, Gibbs et al. 2007; Bowen, Cicardi et al. 2010; Bork and Davis-Lorton 2013). Furthermore, there is a greater risk of transmission of blood-borne pathogens in FFP compared to pdC1-INH products which have undergone stringent purification procedures. It should also be noted that a paradoxical worsening of symptoms can occur with FFP, as it contains substrate proteins that could consume the available C1-INH and exacerbate the angioedema (Nzeako, Frigas et al. 2001) (Nzeako, Frigas et al. 2001). Indeed, physicians have observed significant cases of worsening of angioedema after administration of FFP than expected by chance alone (Kalaria and Craig 2013).

Though no head-to-head studies have been carried out with the modern acute HAE treatments, the comparable therapeutic efficacy of these treatments is acknowledged by international guidelines on HAE treatment with all obtaining an equal recommendation level (Craig, Aygoren-Pursun et al. 2012).
There are, however, differences in the clinical utility and geographical availability of these products (Table 1). Ruconest®, Kalbitor® and Firazy® are not licensed for use in children and cannot be given in pregnancy, unlike pdC1-INH. In addition, Kalbitor® is only licensed in the US.

**Table 1: Treatments available for treatment of acute HAE attacks**

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<tr>
<th>HAE treatment</th>
<th>Acute (on demand) clinical usage (patient population)</th>
<th>World-wide registration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 2–12 yrs</td>
<td>Age 12–18 yrs</td>
</tr>
<tr>
<td>pdC1-INH (as a class) (Berinert®, Cinryze®/Cetor®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>***Argentina, Australia, Brazil, Canada, Iceland, Israel, Japan, Liechtenstein, Mexico, Norway, Puerto Rico, Russia, South Korea, Switzerland, Turkey, USA **</td>
<td></td>
</tr>
<tr>
<td></td>
<td>**Colombia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>***New Zealand, Saudi Arabia, UAE</td>
<td>**Cetor® previously sold in Egypt, Iran and Indonesia</td>
</tr>
<tr>
<td>Icatibant (Firazy®)</td>
<td>No, studies ongoing</td>
<td>No</td>
</tr>
<tr>
<td>Ecallantide (Kalbitor®)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Conestat alfa (Ruconest®)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

¹ Comprising the following countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom.

* Although licensed, pdC1-INH might not be available in some countries because of pending pricing and/or reimbursement approval.
** Application planned.
*** Available in these countries on named-patient-basis or special access program.

11. **Summary of comparative evidence on safety**

Since 1985, cumulatively more than 550,000,000 IU of pdC1INH (Berinert) have been sold worldwide, corresponding to an estimated exposure of more than 30,000 patient years. The safety of pdC1-INH as a class is considered to be well established. The most important identified and potential risks for pdC1-INH (according to prescribing information) are...
hypersensitivity reactions, thromboembolic events and the theoretical risk of transmission of infectious agents.

Many studies have been conducted that provide convincing evidence on the safety of pdC1-INH as a life-saving therapeutic product. See Annex 4 for a comprehensive table of studies demonstrating the safety of pdC1-INH in various patient populations. In addition, each pdC1-INH product placed on the market has had to demonstrate product-specific safety to the relevant regulators. A description of the general safety considerations is set out in the EMEA’s core Summary of Product Characteristics (SPCs) and FDA Prescribing Information (PIs). Safety data are also regularly evaluated and updated in the respective sections of the product labelling (Berinert US PI; Cinryze PI). Suspected adverse drug reactions for medicinal products authorised in the EU through the centralised procedure are published by EMA in the ‘European database of suspected adverse drug reaction reports’ available at www.adrreports.eu; this database is updated regularly. No reports have been made for Berinert® though there have been a number of reports for Cinryze®.

Adverse events (AE) occurring in the pivotal trials and extension studies of pdC1-INH are presented in Annex 5. Most AEs reported in the pivotal multinational randomised trial (I.M.P.A.C.T.1) which evaluated pdC1-INH (Berinert®) were reflective of the underlying disease and type of attack. The most commonly reported AEs in patients receiving pdC1-INH 20 U/kg were nausea, abdominal pain and dysgeusia. No AEs or serious AEs (SAEs) leading to discontinuation occurred within 4 hours after study treatment in any of the patients treated with pdC1-INH (Annex 6).

In the open-label extension trial (I.M.P.A.C.T.2), pdC1-INH was well tolerated during repeat administrations, with no drug-related SAEs reported (Craig, Bewtra et al. 2011) (Annex 6). AEs were reported in 25/57 (43.9%) patients and most were mild or moderate in intensity. AEs possibly related to treatment were reported in 8/57 (14.0%) patients and in 9/1085 (0.8%) attacks. One patient discontinued from the study due to an infusion-related reaction.

It was concluded from these studies that pdC1-INH has a favourable safety profile, which is in agreement with the numerous observational studies conducted with pdC1-INH (Bork, Steffensen et al. 2013).

The descriptive tolerability of intravenous pdC1-INH (Cinryze®) in patients with HAE was assessed across the Cinryze® clinical trial programme (total of >14,500 Cinryze® infusions in 262 patients across two randomised trials and three open-label studies) (Cinryze EPAR
2011). AEs occurring in pivotal studies are presented in Annex 5. Intravenous pdC1-INH was well tolerated when used to treat or prevent HAE episodes. Rash was the only common (frequency ≥1 to <10 %) AE with a suspected (possibly, probably or definitely) relationship to treatment with intravenous pdC1-INH in patients with HAE (Cinryze SPC). The rash typically involved the upper extremities, chest, abdomen or injection site, and none of the rashes were serious. Other uncommon (frequency ≥0.1 to <1 %) adverse events with a suspected relationship to pdC1-INH (Cinryze®) included hyperglycaemia, dizziness, headache, venous thrombosis, hot flush, cough, nausea, vomiting, diarrhoea, abdominal pain, contact dermatitis, erythema, pruritus, joint swelling, arthralgia, myalgia, chest discomfort and pyrexia.

No head-to-head data are available comparing the safety of pdC1-INH use against alternative treatments for acute HAE attacks. Historically, FFP has been used for the treatment of HAE. However, as previously mentioned, FFP contains substrates that could theoretically worsen symptoms in patients with HAE. Indeed, a recent survey to evaluate the risks associated with treatments for HAE revealed that physicians observed a significant worsening of HAE attacks after FFP administration than expected by chance alone (Kalaria and Craig 2013).

Furthermore, there is a greater risk of viral transmission with FFP administration compared with the other HAE treatments and it is also associated with anaphylactic reactions (Kalaria and Craig 2013). With regard to the newer HAE treatments, a summary of reported AEs for pdC1-INH and its comparators are provided in Annex 6.

As an example for safety information in product information texts, the safety sections from the SPCs of Berinert® and Cinryze® are provided below:

**Berinert®**

4.8 Undesirable effects

The following adverse reactions are based on post marketing experience as well as scientific literature. The following standard categories of frequency are used: very common (≥ 1/10), common, (≥ 1/100 and < 1/100), uncommon (≥ 1/1,000 and < 1/100), rare (≥ 1/10,000 and < 1/1,000), very rare: < 1/10,000 (including reported single cases). Undesired reactions with Berinert® are rare.
In treatment attempts with high doses of Berinert® for prophylaxis or therapy of Capillary Leak Syndrome (CLS) before, during or after cardiac surgery under extracorporeal circulation (unlicensed indication and dose), in single cases with fatal outcome.

Cinryze®

4.8 Undesirable effects

Summary of the safety profile

The only common adverse reaction observed following Cinryze® infusion in clinical studies was rash; descriptions of rash characteristics were non-specific, but were typically described as involving the upper extremities, chest, abdomen, or injection site. None of the rashes were serious, and none led to discontinuation of medicinal product.

Tabulated list of adverse reactions

Adverse reaction frequency was estimated primarily based on summation of unique Cinryze®-related adverse events reported across 8 completed clinical studies in HAE subjects. This includes data from two placebo-controlled studies, three open-label studies, and three compassionate-use subjects. There were a total of 385 subject exposures involving over 14,500 infusions of Cinryze® in these studies.

Adverse reactions with suspected relationship (i.e. determined by the investigator to be possibly, probably, or definitely related) to treatment with Cinryze® are classified by MedDRA System Organ Class and absolute frequency in Table 1. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000).
Description of selected adverse reactions

Among reports of venous thrombosis, the most common underlying risk factor was presence of an indwelling catheter.

Local reactions at the injection site were uncommon. In clinical studies local reactions (described as pain, bruising, or rash at the injection/catheter site, venous burning or phlebitis) occurred in association with approximately 0.2% of infusions.

Paediatric population

Across 8 completed clinical studies, there were 46 unique paediatric subjects enrolled and exposed to Cinryze® (2–5 years, n=3; 6–11 years, n=17; 12–17 years, n=26). Among these children, the only adverse reactions with Cinryze® included headache, nausea, pyrexia, and infusion site erythema. None of these adverse reactions were severe, and none led to discontinuation of medicinal product. Overall, the safety and tolerability of Cinryze® are similar in children and adults.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

- Range of costs of the proposed medicine
Prices for human pdC1-INH concentrates are not listed in the WHO International Drug Price Indicator Guide, or other international sources, such as the UNICEF or Médecins sans Frontières price information services. The price for Berinert® ranges from 1.32$/IU in South-America, 1.43$/IU in Europe, 2.01$/IU in Australasia to 3.13$/IU in North-America, with an average world market price of 1.61$ per IU (805$ per 500 IU pack) in September 2014 (Source: CSL Behring, analysis conducted September 2014).

The recommended dose for acute attacks is 1000 IU (Cinryze®) or 20 IU/kg (Berinert®). The cost per treatment would range for an adult (75kg) from approx. 1,320$/1,980$ in South-America to 3,130/4,695$ in North-America for the fix dose of 1000IU or the 20IU/kg body-weight based dose respectively – assuming the above-mentioned average prices of Berinert®. It is assumed that prices for emerging or under-developed countries would be at the lower end of the range.

• **Comparative cost-effectiveness**

In addition to pdC1-INH (Berinert®, Cinryze®, Cetor®), alternative therapies available for the acute management of HAE are plasma, icatibant (Firazyr®), conestat alfa (Ruconest®) and ecallantide (Kalbitor®). Although FFP is readily available and affordable, it remains an option only when other therapies are unavailable (WAO guidelines) (Craig, Aygoren-Pursun et al. 2012) as clinical efficacy data are limited, and it is known to pose safety concerns (Bowen, Cicardi et al. 2010).

With regards to the newer treatments, a comparison of costs is challenging as a variety of factors need to be taken into account:

• Although all the treatments had similar efficacy (Craig, Aygoren-Pursun et al. 2012) they differ, however, by the doses administered per patient (with dosing either based on body weight or as a fixed dose).

• The price per administration is also determined in part by the need for re-dosing since evidence of effect achievement by the first dose differs amongst therapeutic alternatives, as reflected in the different product labels.

• In the case of conestat alfa, pre-treatment allergy tests and differential facility needs for therapy administration (conestat alfa may only be administered in a hospital setting) also need to be considered, contributing to the cost of administration.
Currently, the only publically accessible cost-effectiveness analysis for the different HAE treatments have been provided by CSL Behring and Viropharma Ltd (the manufacturers of the two available pdC1-INH concentrates [Berinert® and Cinryze®]) for assessment by the All Wales Medicines Strategy Group (AWMSG) group (All Wales Therapeutics and Toxicology Centre January 2013).

A decision analytic model for the use of Cinryze® in the treatment of acute HAE attacks was carried out with Berinert® and icatibant (Firazyr®) as comparators. Costs included medication acquisition, administration and replenishment of medication, and additional inpatient care costs. Unit costs were taken from the British National Formulary (British Medical Association 2012), Personal Social Services Research Unit (Personal Social Services Research Unit 2010) and NHS Reference Costs (Department of Health 2011). In the base case analyses, Cinryze® and its comparators are assumed to be therapeutically equivalent due to a lack of direct comparative data and difficulties in conducting indirect treatment comparisons using available data. The base case analyses provided by the company therefore amount to cost minimisation analyses (CMA). The results for the treatment of acute attacks are presented in Table 2.

**Table 2. Estimated five-year costs of treatment of acute attacks**

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Total five-year costs per patient</th>
<th>Plausibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case:</strong> Cinryze® vs. Berinert®</td>
<td>£75,083</td>
<td>£73,323 (32% probability of being cost-saving)</td>
</tr>
<tr>
<td>Therapeutic equivalence List prices used</td>
<td></td>
<td>Assumptions of equivalence? Berinert® dosing based on expert opinion of use in practice Repeat dosing issues?</td>
</tr>
<tr>
<td><strong>Scenario:</strong> Cinryze® vs. icatibant</td>
<td>£75,083</td>
<td>£77,054 (71% probability of being cost-saving)</td>
</tr>
<tr>
<td>Therapeutic equivalence List prices used</td>
<td></td>
<td>Assumptions of equivalence? Repeat dosing issues? icatibant approved by AWMSG based on formally agreed discount, not list price**</td>
</tr>
</tbody>
</table>

Under an assumption of therapeutic equivalence and assuming current list prices, Cinryze®, at the recommended dose, is more costly than Berinert® and less costly than icatibant for the treatment of acute attacks. The results of this analysis suggest that pdC1-INH is a more cost-effective option than icatibant. It is also likely that icatibant and conestat alfa would be less cost-efficient than pdC1-INH based on reported requirements for redosing in clinical trials (RuconestSPC ; Cicardi, Banerji et al. 2010; Craig, Bewtra et al. 2011)
13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Currently, three human pdC1-INH concentrates are manufactured by CSL Behring and Sanquin under the trade names Berinert®, Cinryze® and Cetor®, respectively. pdC1-INH concentrates are approved for the treatment of acute HAE attacks by pharmaceutical regulators in most regions of the world, including the EU, Turkey, Argentina, Australia, Brazil, Canada, Iceland, Israel, Japan, Liechtenstein, Mexico, Norway, Puerto Rico, Russia, South Korea, Switzerland, and USA. It is also available in New Zealand, Saudi Arabia and the UAE on named-patient-basis or special access programmes.


Currently, no pharmacopoeia requirements exist for C1-INH concentrates due to limited worldwide use and the small number of manufacturers (Over, Kramer et al. 2013). Therefore, manufacturers analyse their pdC1-INH products using their own specific analytical methods based on the European Pharmacopoeia and the United States Pharmacopoeia Monograph requirements for other plasma proteins.

15. Proposed (new/adapted) text for the WHO Model Formulary

15.1 Proposed new text for the WHO Model Formulary

SECTION 11: Blood products and plasma substitutes
11.2 Plasma fractions for specific use
11.2.3 Plasma proteins

Plasma-derived C1 esterase inhibitor (human) concentrate

_Power and solvent for solution for injection/infusion: 500 IU per vial_

Purified, pasteurized, lyophilized, nanofiltered concentrate of C1 esterase inhibitor derived from human plasma.

_Uses:_ Replacement therapy for C1-INH functional deficiency in type I/II hereditary angioedema.

_Contraindications:_ known hypersensitivity to any of the components of the product.
Precautions:

- Antihistamines and corticosteroids should be administered prophylactically in patients with known tendency towards allergies.
- Administration of pdC1-INH to be stopped immediately (and appropriate treatment to be initiated) if allergic or anaphylactic-type reactions occur.
- Patients with laryngeal oedema should be carefully monitored with emergency treatment on stand-by.
- Unlicensed use or treatment of Capillary Leak Syndrome (CLS) with pdC1-INH is not advised.
- Use of pdC1-INH in patients on a controlled sodium diet to be carefully considered.
- Patients with known risk factors for thrombotic events (including indwelling catheters) should be monitored closely.

Home therapy and 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.

Pregnancy, breastfeeding and fertility:

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effects of pdC1-INH on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. No maternal or embryofetal effects of treatment were observed in reproductive studies in rats at dose levels up to 28 times the recommended human dose (1000 U) based on an average adult body weight of 70 kg. No adverse effects on fertility, pre- and postnatal development are expected in humans. Therefore, pdC1-INH should be given to a pregnant woman only if clearly needed.

Breastfeeding

It is unknown whether pdC1-INH is excreted in human milk, but due to its high molecular weight, the transfer of pdC1-INH into breast milk seems unlikely. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue the pdC1-INH therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
C1-INH is a physiological component of human plasma. Therefore, no studies on reproduction and developmental toxicity have been performed in animals and no adverse effects on fertility, pre- and postnatal development are expected in humans.

**Transmissible agents:** The possibility of transmitting infective agents cannot be totally excluded when medicinal products prepared from human blood or plasma are administered, despite stringent measures to ensure that all infective agents are eliminated. Appropriate vaccination (hepatitis A and B) should be generally considered for patients in regular/repeated receipt of human plasma-derived products. It is strongly recommended that every time pdC1-INH is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

**Dose:** Acute angioedema attacks, 20 IU per kg body weight (Berinert®) or 1000 U (Cinryze®).

NB: The dose for treatment in adolescents is the same as for adults.

**RECONSTITUTION AND ADMINISTRATION.** According to manufacturer’s directions.

**Adverse effects:** Berinert®: Rare occurrences of thrombosis development, raised temperature and reactions at the injection side, allergic or anaphylactic-type reactions (e.g. tachycardia, hyper- or hypotension, flushing, hives, dyspnoea, headache, dizziness, nausea) and shock (very rare). Cinryze®: Common occurrences of rash; uncommon occurrences of hyperglycaemia, dizziness, headache, thromboembolic events, phlebitis, venous burning, cough, nausea, vomiting, diarrhoea, abdominal pain, joint swelling, arthralgia, myalgia, injection site rash/erythema, infusion site pain, chest discomfort and pyrexia.

### 15.2 Proposed new text for the WHO Model Formulary for Children

**Plasma-derived C1 esterase inhibitor (human) concentrate**

**ATC code:** B06AC01

*Powder and solvent for solution for injection/ infusion: 500 IU per vial*

Purified, pasteurized, lyophilized, nanofiltered concentrate of C1 esterase inhibitor derived from human plasma.

**Indications:** Replacement therapy for C1-INH functional deficiency in type I/II hereditary angioedema (treatment of acute episodes).

**Contraindications:** Known hypersensitivity to any of the components of the product.

**Precautions:**

- Antihistamines and corticosteroids should be administered prophylactically in patients with known tendency towards allergies.
• Administration of pdC1-INH to be stopped immediately (and appropriate treatment to be initiated) if allergic or anaphylactic-type reactions occur
• Patients with laryngeal oedema should be carefully monitored with emergency treatment on stand-by
• Unlicensed use or treatment of Capillary Leak Syndrome (CLS) with pdC1-INH is not advised
• Use of pdC1-INH in patients on a controlled sodium diet to be carefully considered
• Patients with known risk factors for thrombotic events (including indwelling catheters) should be monitored closely.

Home therapy and 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.

Transmissible agents: The possibility of transmitting infective agents cannot be totally excluded when medicinal products prepared from human blood or plasma are administered, despite stringent measures to ensure that all infective agents are eliminated. Appropriate vaccination (hepatitis A and B) should be generally considered for patients in regular/repeated receipt of human plasma-derived products. It is strongly recommended that every time pdC1-INH is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Dose:
Acute angioedema attacks.

Slow intravenous injection or infusion (4 mL/min):

CHILDREN, 20 IU per kg body weight (Berinert®) or 1000 U (Cinryze®, for patients 12 years and older).

RECONSTITUTION AND ADMINISTRATION. According to manufacturer’s directions.

Renal impairment: Dose reduction not required.
Hepatic impairment: Dose reduction not required.
Adverse effects: Berinert®: Rare occurrences of thrombosis development, raised temperature and reactions at the injection side, allergic or anaphylactic-type reactions (e.g. tachycardia, hyper- or hypotension, flushing, hives, dyspnoea, headache, dizziness, nausea)
and shock (very rare). Cinryze®: **Common** occurrences of rash; **uncommon** occurrences of hyperglycaemia, dizziness, headache, thromboembolic events, phlebitis, venous burning, cough, nausea, vomiting, diarrhoea, abdominal pain, joint swelling, arthralgia, myalgia, injection site rash/erythema, infusion site pain, chest discomfort and pyrexia; **rare** occurrences of thrombosis development, raised temperature and reactions at the injection site, allergic or anaphylactic-type reactions (e.g. tachycardia, hyper- or hypotension, flushing, hives, dyspnoea, headache, dizziness, nausea); **very rare** shock.

**Interactions with other medicines (**indicates severe**): No interaction studies have been performed.
16. Literature references


All Wales Therapeutics and Toxicology Centre (January 2013). AWMSG Secretariat Assessment Report. C1 inhibitor (Cinryze®) 500 units powder and solvent for solution for injection. Reference number: 73. .


