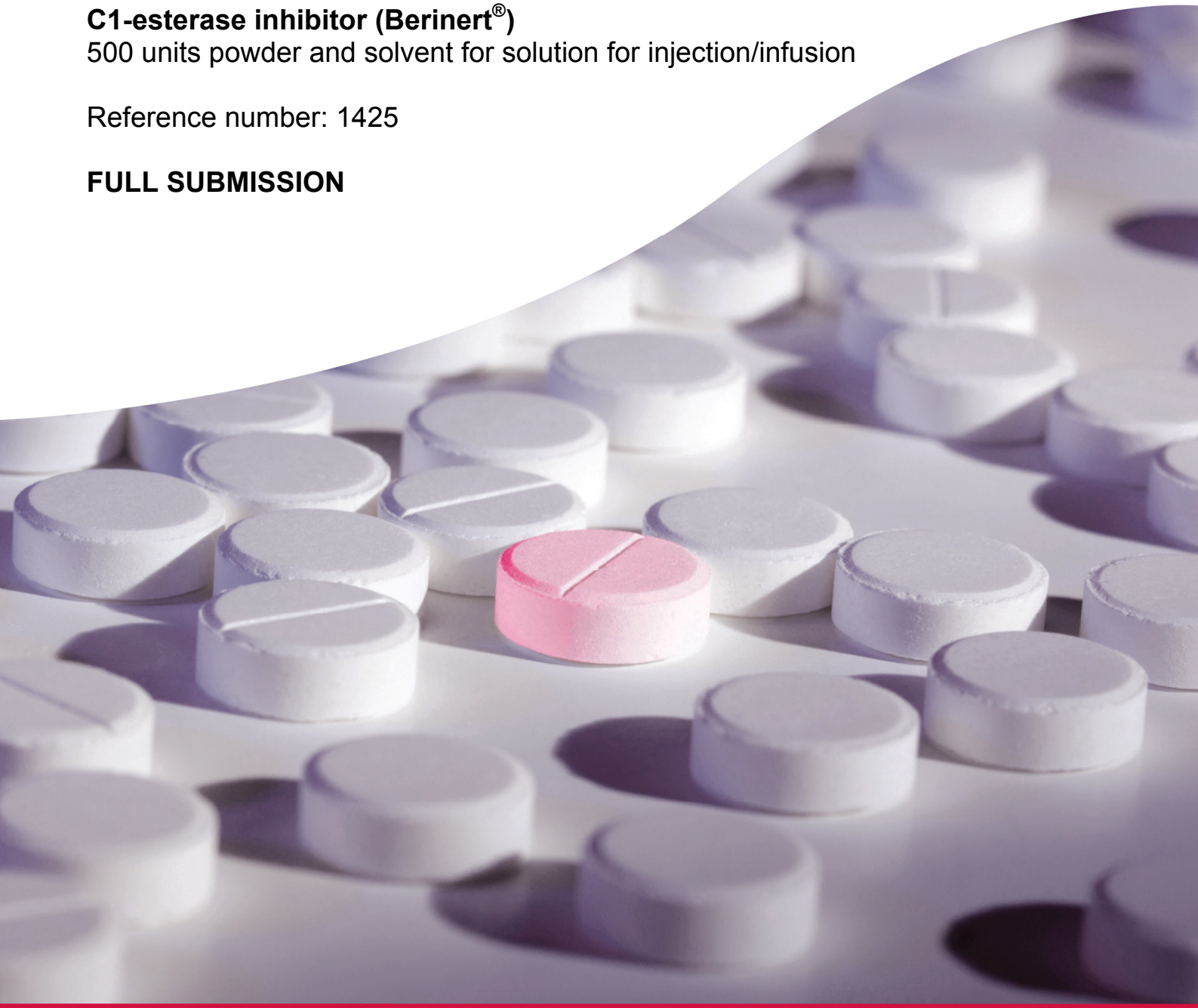
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

C1-esterase inhibitor (Berinert®)
500 units powder and solvent for solution for injection/infusion

Reference number: 1425

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
C1-esterase inhibitor (Berinert®) 500 units powder and solvent for solution for injection/infusion

This assessment report is based on evidence submitted by CSL Behring UK Ltd on 1 February 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Treatment of acute episodes of hereditary angioedema type I and II[2].
Dosing	20 units per kilogram body weight[2].
Marketing authorisation date	29 January 2009[2].

2.0 DECISION CONTEXT

2.1 Background

Hereditary angioedema (HAE) is characterised by recurrent nonpruritic oedema of the skin and submucosal tissues, and is associated with pain, nausea, vomiting, diarrhoea and life-threatening airway swelling[3]. There is a paucity of data on the prevalence of HAE; figures between 1 in 10,000 and 1 in 50,000 have been estimated[3–6]. In their submission, the applicant company suggest that there are 87 HAE patients in Wales, based on a reported 47 patients diagnosed with the disease[7] and assuming a diagnosis rate of 54%[1].

Three forms of HAE have been described; types I and II (approximately 85% and 15% of HAE cases, respectively) are clinically identical, but are associated with either an absence (type I) or dysfunction (type II) of the plasma protein C1-esterase inhibitor (also called C1 inhibitor or C1-INH)[3,8]. HAE type III is extremely rare and does not appear to be associated with C1-esterase inhibitor absence or dysfunction. C1-esterase inhibitor exerts local anti-inflammatory effects by binding to and inactivating kallikrein and factors XIa and XIIa, inhibiting the contact system and coagulation pathway[2,8]. Without C1-esterase inhibition activation of these pathways leads to swelling of subcutaneous tissues, bowel walls and upper airways[9].

Licensed products for the treatment of HAE attacks include the plasma-derived C1-esterase inhibitors Berinert® and Cinryze®▼; icatibant (Firazyr®▼; a selective competitive antagonist of the bradykinin type 2 receptor); and conestat alfa (Ruconest®▼; a recombinant C1-esterase inhibitor analogue)[2,10–12].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were Cinryze®▼, icatibant and conestat alfa.

2.3 Guidance and related advice

- Cicardi et al (2012). Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group[13].
- Bowen et al (2010). 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema[3].
- Eidelman F (2010). Hereditary angioedema: New therapeutic options for a potentially deadly disorder[14].
- Grigoriadou et al (2009). Clinical Immunology Review Series: An approach to the patient with angio-oedema[8].

AWMSG has previously issued recommendations for the use of C1 inhibitor (Cinryze®▼), icatibant and conestat alfa:

- C1 inhibitor (Cinryze®▼) is recommended as an option for use within NHS Wales for the treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with hereditary angioedema, and routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of hereditary angioedema who are intolerant to or insufficiently protected by oral prevention treatments or who are inadequately managed with repeated acute treatment[15].
- Icatibant (Firazyr®▼) is recommended as an option for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1 esterase inhibitor deficiency). This recommendation applies only in circumstances where the approved Wales patient access scheme is utilised[16].
- In the absence of a submission from the holder of the marketing authorisation, conestat alfa (Ruconest®▼) cannot be endorsed for use within NHS Wales for the treatment of acute angioedema attacks in adults with hereditary angioedema due to C1 esterase inhibitor deficiency[17].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission refers to a systematic review of studies that investigated the use of Berinert® for the treatment and prophylaxis of patients with HAE; this is yet to be published, but interim results are available in poster format[1,18,19]. The systematic review and the company submission included details of the pivotal study IMPACT 1, a randomised, placebo-controlled trial of Berinert® (10 or 20 units/kg) for the treatment of a single acute HAE attack of the abdomen or face[20], and an open-label extension of this study (IMPACT 2), designed to assess Berinert® (20 units/kg) for the treatment of an acute HAE attack of any body location[21]. These studies are described individually below. The company submission also included supportive data from trials of Berinert® in pregnant and breast feeding women[22,23]; for self-administration at home (including children and adolescents)[24,25]; and for patients refractory to danazol prophylaxis[26]; these are not discussed further[1].

The applicant company also performed a limited indirect comparison of the efficacy endpoints of Berinert®, Cinryze®▼, icatibant and conestat alfa studies for the treatment of acute HAE attacks[1].

3.1 Systematic review

A systematic search of electronic databases up to December 2011 was performed to identify all studies that evaluated the efficacy and safety of Berinert® for the treatment and prophylaxis of patients with type I and II HAE. The data were found to be inappropriate for a meta-analysis. Of the 95 studies included (2,073 patients), 58 evaluated Berinert® for the treatment of acute HAE attacks (one randomised, controlled trial [IMPACT 1], 6 observational studies and 51 descriptive studies). Across the

studies, treatment with Berinert® was consistently associated with rapid onset of symptom relief and timely resolution of symptoms in adults and children[18,19].

3.2 IMPACT 1

IMPACT 1 was a randomised, double blind, parallel group, placebo-controlled, three-arm, multicentre phase II/III trial designed to assess the efficacy and safety of Berinert® 10 or 20 units/kg for the treatment of an acute HAE attack of the abdomen or face. Patients ≥ 6 years old with type I or II HAE (n = 125) were randomised 1:1:1 to receive a single intravenous infusion of Berinert® 20 units/kg (n = 43), Berinert® 10 units/kg (n = 40) or placebo (n = 42) on presentation of an acute moderate to severe abdominal or facial attack. Treatment was administered within five hours of the attack reaching moderate intensity. Four hours after administration, patients that had insufficient or no symptom relief received a second dose of double-blind treatment (referred to as "rescue study medication"; Berinert® 20 units/kg for the placebo arm, Berinert® 10 units/kg for the Berinert® 10 units/kg arm and placebo for the Berinert® 20 units/kg arm). For each patient, only a single attack was treated and evaluated. The primary endpoint of median time to onset of symptom relief was significantly shorter with Berinert® at a dose of 20 units/kg than with placebo (0.5 versus 1.5 hours, respectively; p = 0.0025). The secondary outcomes consistently supported the efficacy of the 20 units/kg dose. Fewer patients in the Berinert® 20 units/kg arm received rescue medication than in the placebo arm (18.6% versus 57.1%, respectively)[20].

3.3 IMPACT 2

IMPACT 2 was an open-label, uncontrolled, multicentre phase III extension of the IMPACT 1 trial, designed to provide additional efficacy and safety data for the long-term use of Berinert® for the treatment of subsequent HAE attacks at any body location and of any severity. Patients ≥ 6 years old with type I or II HAE (n = 57) received a single intravenous dose of Berinert® 20 units/kg for each attack. Patients were in the study for a median duration of 24 months. The median time from start of treatment to onset of symptom relief (primary endpoint) was 0.46 hours in the per patient analysis. Times to onset of relief were comparable for all body locations. The median time to complete resolution (patient-assessed and measured as a secondary endpoint) was 15.5 hours. Of 1,085 attacks, 1,073 (99%) were resolved with a single 20 units/kg dose of Berinert®[21].

3.4 Comparative effectiveness

The applicant company states that there are no head-to-head comparisons of Berinert® with other products used for the treatment of acute HAE attacks. An indirect comparison of efficacy endpoints from trials of Berinert® (IMPACT 1[20] and IMPACT 2[21]), Cinryze®▼ (CHANGE Part A[27] and CHANGE 2[28]), icatibant (FAST-1, FAST-2[29] and FAST-3[30]) and conestat alfa (C1 1205-01 and C1 1304-01[31]) for the treatment of acute HAE attacks is included in Appendix 1, Table 1. The company suggests that for the endpoint of median time to onset of symptom relief, Berinert® compares favourably with Cinryze®▼, icatibant and conestat alfa[1].

3.5 Comparative safety

No comparative safety data for Cinryze®▼, icatibant or conestat alfa have been provided by the applicant company.

In the IMPACT 1 study, 9/46 (19.6%) patients that received Berinert® 20 units/kg reported an adverse event (AE) within four hours of treatment compared with 18/41 (43.9%) that received placebo. The most common AEs (occurring in > 1 patient) were nausea, diarrhoea, abdominal pain and muscle spasms. The frequencies of these were all lower with Berinert® 20 units/kg than with placebo. No serious AEs were reported within four hours of treatment and there were no treatment discontinuations dues to AEs[20]. The systematic review by Bork et al states that Berinert® is well-tolerated and is safe for use in children and pregnant women[18].

3.6 AWTTC critique

- No evidence is available that directly compares the clinical effectiveness and safety of Berinert® with Cinryze®▼, icatibant or conestat alfa for the treatment of acute attacks of HAE types I and II. An indirect comparison is hindered by diverse clinical end points from trials and the lack of availability of a uniform scale for assessing symptom relief. Efficacy data from individual clinical trials of these four treatments have been included by the company in the indirect comparison provided (see Appendix 1, Table 1); these should be interpreted with caution. International guidelines on HAE treatment conclude that these treatments have comparable therapeutic efficacy, and have awarded equal recommendation[6].
- The company suggest that the rate of repeat dosing is lower with Berinert® than with Cinryze®▼, icatibant and conestat alfa for the treatment of acute HAE attacks in the trials described, stating that a decreased need for repeat dosing may reduce costs and discomfort for the patient. Whilst the rate of repeat dosing observed in IMPACT 2 was 1%, 18.6% of patients that received 20 units/kg of Berinert® in the IMPACT 1 trial required "rescue study medication", which is higher than observed in trials of icatibant and conestat alfa (see Appendix 1, Table 1)[12,20,21,29,30]. These results should also be interpreted with caution as the scheduling for repeat dosing differed between trial protocols, so figures cannot easily be compared.
- Berinert® is licensed for use in patients of any age, whereas Cinryze®▼ is licensed only for adolescents and adults, and icatibant is only licensed for adults[2,10,11].
- Berinert®, Cinryze®▼ and icatibant are licensed for home treatment and self-administration. This is suggested to prevent a delay in seeking emergency department treatment. According to the Summaries of Product Characteristics (SPCs), appropriate training of patients or caregivers by trained healthcare professionals should be performed in order to minimise the potential risks[2,10,11].
- There are differences in the reconstitution and administration of Berinert®, Cinryze®▼, conestat alfa and icatibant. Doses of Berinert® (500 units per vial) and conestat alfa (2,100 units per vial) are calculated according to body weight, reconstituted with water and administered intravenously[2,12]. For each 1,000 unit dose of Cinryze®▼, two vials (500 units per vial) must be reconstituted with water and administered intravenously[11]. Icatibant is available in a pre-filled syringe which should be administered as a single subcutaneous injection[10].
- Berinert® has been licensed since January 2009 and has been shown to be well-tolerated[2,19]. It should be noted that Berinert® and Cinryze®▼ are blood-derived products; therefore, despite standard measures for prevention, the possibility of transmitting infective agents cannot be totally excluded[2,11]. Administration of Berinert® has not been shown to be associated with transmission of viruses, irrespective of treatment duration[18–21]. In addition, as a protein of human plasmatic origin, there is an inherent immunogenic risk; however, there has been no evidence of clinically relevant anti-C1 inhibitor antibody development in the trials described[4,18–21].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost minimisation analysis (CMA) of Berinert® within its licensed indication for the treatment of acute attacks of HAE type I and II[1]. The comparators used were icatibant, Cinryze®▼ and conestat alfa. The company based their analyses on an assumption of therapeutic equivalence between Berinert® and its comparators. A cost utility analysis was also discussed, where disutility due to delayed response and need for repeat dosing was included in the model. However, given very small differences in estimated quality-adjusted life-years (QALYs), this was not pursued further[1].

The CMA mainly incorporated the weighted costs of the comparator treatments (i.e. taking into account the assumed need for repeat dosing) and the resources used for the administration of these therapies (staff time and overhead costs), where applicable. All analyses provided by the company employ a confidential discount applied to the list price for Berinert®, as agreed in a Wales Patient Access Scheme (WPAS). Repeat dosing rates were based on the SPCs for conestat alfa and icatibant, and the open-label trials for Berinert® and Cinryze®▼ (IMPACT 2 and CHANGE 2), respectively[10,12,21,28]. Sensitivity analyses were also conducted, reducing the repeat dosing frequencies of comparators by 50% and exploring the Berinert® dose requirements based on body weight. Resource use due to severity of attacks was not considered due to the assumption of equivalent efficacy. The model considered a one-year time horizon.

4.1.2 Results of the company analyses

The results of the base case analysis are presented in Table 1.

4.1.3 AWTTC critique

There is a lack of direct comparative data for Berinert® and the comparators. A key assumption of the analysis is the expected need for re-dosing among the different comparators, which are based on trial data and may be influenced by trial protocols. Sensitivity analyses have been conducted to explore alternative re-dosing assumptions but all retain a lower rate for Berinert® compared to the comparators.

Limitations of the economic evidence:

- There is a lack of direct comparative data for Berinert® and the comparators. The base case analyses provided by the company are based on the assumption of therapeutic equivalence in the absence of robust comparative data, which is a source of uncertainty.
- A low attack rate was assumed in the analysis (2.3–3.1 attacks per year) based on expert opinion of the proportion of attacks treated per year. This is a source of uncertainty, and results appear sensitive to the assumed attack rate, which is not further explored.
- There is assumed to be a greater need for re-dosing among the comparators compared with Berinert®, based on re-dosing rates recorded in clinical trials. It is unclear whether or not the assumed rates of re-dosing, that favour Berinert® in all analyses, would be observed in practice.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of Berinert® within its current licensed indications.

Table 1. Estimated annual acquisition costs per patient

[Commercial in confidence data removed]

5.0 SUMMARY OF THE EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on data from an unpublished audit of HAE treatment in Wales, 2010[7], the company reports that there are currently 47 patients with diagnosed HAE attending clinics. Assuming a diagnosis rate of 54%, the company estimates that 87 patients have the condition in Wales, which brings the estimated prevalence in line with HAE prevalence in other countries (between 1:10,000 to 1:50,000). This number is estimated to increase to 89 in 2016 with Welsh population growth. Based on an expected steady increase in diagnosis rate to 60.5%, the company estimates that the total number of diagnosed patients will rise steadily to reach around 54 patients in 2016[1].

5.1.2 Results

The results of the company's budget impact analysis are summarised in Table 2 (information provided as commercial in confidence).

Table 2. Company-reported costs associated with the use of Berinert® for the treatment of acute attacks of HAE type I and II

	Year 1 (2012)	Year 2 (2013)	Year 3 (2014)	Year 4 (2015)	Year 5 (2016)
Number of eligible patients (assuming 100% uptake)	47	50	52	53	54
Net costs					
Administration and monitoring	-	-	-	-	-
Primary care	-	-	-	-	-
Secondary & tertiary care	-	-	-	-	-
Staffing	-	-	-	-	-
Infrastructure	-	-	-	-	-
Personal social services	-	-	-	-	-
Overall total cost	*	*	*	*	*
* Commercial in confidence data removed					

5.1.3 AWTTC critique

- The price of Berinert® assumed in the company's budget impact analysis is the WPAS-approved discounted price.
- The results represent the total costs, assuming all patients will be treated with Berinert®, rather than the incremental cost of using Berinert®. As icatibant and Cinryze®▼ are already recommended as options for use in NHS Wales, Berinert® prescribing rates may be subject to change.
- These budget impact estimates are based on the base case CMA. Any uncertainties and limitations of the economic evidence highlighted in section 4.1.3 therefore also apply to the budget impact analysis.

5.2 Table of comparative unit costs

Table 3 provides example comparative acquisition costs for HAE acute attack treatments, based on current list prices. Both Berinert® and icatibant have an approved WPAS, which provides a confidential discount on their list prices.

Table 3. Examples of costs of HAE acute attack treatment

Treatment	Example dose	Approximate cost per dose*
Berinert® Injection, 500 unit vial	20 units/kg	£1,650†
Cinryze®▼ Injection, 500 unit vial	1,000 units	£1,336
Icatibant (Firazyr®▼) Injection (10 mg/ml), 3 ml pre-filled syringe	30 mg	£1,395
Conestat alfa (Ruconest®▼) Injection, 2,100 unit vial	50 units/kg	£2,800†

*Costs based on BNF list prices as of 23 September 2012[32], assuming one dose required per attack – note that repeat dosing may be required for some attacks.
†Calculated based on average adult body weight of 70 kg, to nearest whole vial
This table does not imply therapeutic equivalence of the medicines and doses listed.
See all relevant SPCs for full dosing details[2,10–12].

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, Berinert® is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next six months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Dates of evidence search: 14 September 2012, 21 September 2012 and 8 March 2013.
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1. Additional clinical information

Table 1. Indirect comparison of the study design and efficacy outcomes of the phase III clinical trials of Cinryze®▼, Berinert®, icatibant and conestat alfa for the treatment of acute HAE attacks

Treatment	Trial	Study design	Patient numbers	Efficacy endpoint	Median time to endpoint (hours)*		Significance (p value)	Requirement for second dose in treatment arm
					Treatment	Placebo		
Berinert® (20 units/kg)	IMPACT 1 (Craig et al, 2009)[20]	Randomised, double-blind, placebo-controlled, multicentre	85†	Median time to onset of relief	0.5	1.5	0.0025	18.6%
				Median time to complete resolution	4.92	7.79	0.237	
	IMPACT 2 (Craig et al, 2011)[21]	Open-label, single-arm, multicentre	57	Median time to onset of symptom relief	0.46			1%
				Median time to complete resolution of symptoms	15.5			
Cinryze®▼ (1,000 units)	CHANGE Part A (LEVP 2005-1/A, Zuraw et al, 2010)[27]	Randomised, double-blind, placebo-controlled, multicentre	68	Median time to onset of relief	2	> 4	0.02	65.7%
				Median time to unequivocal relief	12.3	25	0.004	
	CHANGE 2 (Riedl et al, 2012[28])	Open-label, single-arm, multicentre	113	Median time to beginning of unequivocal relief	0.75			30.9%
Icatibant (30 mg)	FAST-1 (Cicardi et al, 2010)[29]	Randomised, double-blind (versus placebo), multicentre	56	Median time to first symptom improvement	0.8	16.9	< 0.001	22%§
				Median time to clinically significant relief	2.5	4.6	0.14	
				Median time to almost complete relief	8.5	19.4	0.08	
	FAST-2 (Cicardi et al, 2010)[29]	Randomised, double-blind (versus TXA), multicentre	74	Median time to first symptom improvement	0.8	7.9	< 0.001	17%
				Median time to clinically significant relief	2	12	< 0.001	
				Median time to almost complete relief	10	51	< 0.001	
	FAST-3 (Lumry et al, 2011)[30]	Randomised, double-blind, placebo-controlled, multicentre	88	Median time to first symptom improvement	1.5	18.5	< 0.001	7%
				Median time to almost complete relief of all symptoms	8.0	36.0	0.012	
Conestat alfa (50 & 100 units/kg)	C1 1205-01 and C1 1304-01 (Zuraw et al, 2010)[31]	Randomised, double-blind, saline-controlled, multicentre	73	Median time to the beginning of relief of symptoms	2.0 (50 units/kg)	8.25	< 0.001	SPC pooled: 10%[12]
					1.1 (100 units/kg)		0.013	

TXA: tranexamic acid
* Results should be interpreted with caution due to the heterogeneity between clinical endpoints
† Patient number = Number of patients in 20 units/kg treatment arm + number of patients in placebo arm
§ Second dose was ”rescue therapy”, including C1-esterase inhibitor, antiemetic agents or opiates