AWMSG Secretariat Assessment Report – Limited submission

C1 inhibitor (human) (Cinryze®▼) 500 Units powder and solvent for solution for injection

Company: Shire Pharmaceuticals Limited

Licensed indication under consideration:
Treatment and pre-procedure prevention of angioedema attacks in children aged 2–11 years with hereditary angioedema (HAE); routine prevention of angioedema attacks in children aged 6–11 years with severe and recurrent attacks of HAE, who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Date of licence extension: 26 January 2017

Comparator(s)

- The comparator included in the company submission was human C1-esterase inhibitor (Berinert®).

Limited submission details

- The limited submission criteria were met based on a minor licence extension.

Clinical effectiveness

- C1 inhibitor (Cinryze®) was previously licensed and recommended for use in NHS Wales as an option for the treatment and pre-procedure prevention and routine prevention of angioedema attacks in adults and adolescents with HAE. This submission covers the licence extension to include children aged 2-11 years of age.
- Currently, Berinert® is the only other preparation licensed in the UK for the treatment and pre-procedure prevention of angioedema attacks in paediatric patients. Cinryze® is the only non-oral preparation licensed for the routine prevention of angioedema attacks in paediatric patients.
- The company submission includes paediatric data from a two part, phase III, double-blind, placebo controlled, multicentre study (LEVP 2005-1/A [treatment and pre-procedure prevention]; LEVP 2005-1/B [routine prevention]) and three multicentre, open-label studies (LEVP 2006-1 [treatment and pre-procedure prevention]; LEVP 2006-4 [routine prevention]; 0624-203 [treatment]) investigating the safety and efficacy of Cinryze®. One additional multicentre, randomised, single-blind, cross-over, dose-ranging study (0624-301 [routine prevention]) supported the licence extension. Together these studies included three patients

aged 2-5 years and 41 patients aged 6-11 years. To support the limited data in patients younger than six years of age, the marketing authorisation holder provided the Committee for Medicinal Products for Human Use (CHMP) with information on an additional six patients aged 3-5 years from post-marketing data.

- No direct comparative clinical efficacy data with Berinert® are available and the company consider an indirect comparison unfeasible due to low patient numbers.
- In the key study supporting the paediatric licence extension for the treatment of HAE (0624-203) the time to the beginning of unequivocal relief of the defining symptoms (primary efficacy endpoint) was less than four hours from Cinryze® initiation in all nine patients (all aged 6-11 years).
- In the key study supporting the paediatric licence extension for the routine prevention of HAE (0624-301), interim results were available from six patients (exposed to Cinryze® for 24 weeks); all aged 6-11 years. These interim results showed a clinical benefit in the primary endpoint (number of angioedema attacks) and all secondary endpoints (cumulative attack severity, cumulative daily severity, number of angioedema attacks requiring acute treatment) compared to the baseline observational period.
- HAE is a serious, debilitating and potentially fatal inherited rare disease. Due to the rarity of the disease, data in the paediatric age group (2-11 years) are very limited. Acknowledging this limitation, CHMP concluded that data from studies 0624-203 and 0624-301 demonstrated a clinically significant response on attack-relief and a reduction in the frequency and severity of attacks with Cinryze® treatment in paediatric patients and added significantly to the paediatric data from studies supporting the original marketing authorisation (LEVP 2006-1, LEVP 2005-1/A, LEVP 2006-4, LEVP 2005-1/B). CHMP also acknowledged that it would be difficult to enrol further paediatric patients into studies.
- The administration of Cinryze® was safe and generally well tolerated across the paediatric population. Most of the reported treatment-emergent adverse events were mild or moderate in intensity. No serious adverse events were considered related to Cinryze® and no patients discontinued therapy. CHMP concluded that the safety profile of Cinryze® appears to be similar across all age groups.
- Cinryze® offers a simple non-weight based dosing across all indications in paediatric patients.

Budget impact

- The company provided separate budget impact models for the use of Cinryze® in the treatment (including pre-procedure prevention) and routine prevention of angioedema attacks in paediatric patients.
- The company estimate that there are approximately 10 children aged 2-11 years with HAE in Wales; this is based on a prevalence of 1 in 50,000 (NHS England Clinical Commissioning Policy: 2016) and an under 12 years population in the UK of 9.8 million (Office of National Statistics, 2014). The population of Wales was assumed to be 5% of the total UK population.
- The company estimate the number of patients eligible to receive Cinryze® for the treatment of HAE attacks will range from 10 patients in Year 1 increasing to 12 patients in Year 5.
- Cinryze® is assumed to displace Berinert® for the treatment of HAE attacks, with market share projections of [commercial in confidence data removed] in Year 1 increasing to [commercial in confidence data removed] in Year 5, with net medicine acquisition costs ranging from £13,634 in Year 1 to £27,268 in Year 5 (based on list prices for Cinryze® and Berinert®).
- The company estimate net medicine acquisition costs for pre-procedure prevention to range from £80 in Year 1 to £160 in Year 5 (based on list prices for Cinryze® and

Berinert®). This assumes that 10% of patients undergo one procedure every year and uses the same market share projections as for the treatment of HAE attacks.

- The company estimate the number of patients eligible to receive Cinryze® for routine prevention to be one patient each year with net medicine acquisition costs of £34,736 per patient per year. This is based on a 26-week treatment duration using one 500 IU dose twice weekly. In practice, and in line with the Cinryze® Summary of Product Characteristics, routine prevention may be continued beyond six months, albeit at a reduced frequency of administration. The true net medicine acquisition cost per patient per year is therefore likely to lie between £34,736 and £69,472 (based on list prices for Cinryze® and Berinert®).
- Berinert® is associated with a Wales Patient Access Scheme (WPAS). Sensitivity analyses explored net medicine acquisition costs for the treatment of acute attacks when a 10–60% discount on the Berinert® list price was applied. Net medicine acquisition costs for Cinryze® ranged from £16,813 in Year 1 and £33,262 in Year 5 with a 10% discount applied to Berinert®, to £32,708 in Year 1 and £65,416 in Year 5 with a 60% discount.
- The company has stated that there is a national agreed price for Cinryze® in England and Wales. However, in the absence of a Wales Patient Access Scheme, this cannot be considered.

Consideration of All Wales Medicines Strategy Group (AWMSG) policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases.

- Cinryze® does not have European Medicines Agency (EMA) designated orphan status. The prevalence of HAE is estimated to be 1 in 50,000; based on this the applicant company estimate that the total number of patients eligible for treatment with Cinryze® in Wales is 62. AWTTC consider Cinryze® eligible to be appraised as a medicine developed specifically to treat rare diseases as the full population of the licensed indication is equivalent to the population for orphan status (≤ 5 in 10,000 persons [≤1,500 patients in Wales]). The New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 1) if they consider Cinryze® meets the criteria to be appraised in line with the orphan, ultra-orphan and medicines developed specifically for rare diseases policy.

Table 1. Evidence considered by NMG/AWMSG

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	HAE is a potentially life-threatening condition characterised by spontaneous, recurrent attacks of angioedema (swelling of the tissues), typically involving the abdomen, extremities, face, larynx and external genitalia. Swelling in the airway can be fatal, swelling in the abdomen can cause severe pain, nausea and vomiting, and swelling in other areas (e.g. hands/feet) can cause significant disability. HAE attacks and anxiety about future attacks impacts patients' daily activities and quality of life. The consequences of managing HAE attacks can also reduce carers' quality of life.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	Cinryze® is the only non-oral medicine licensed for routine prevention of

	angioedema attacks in children. There is advice for the use of Cinryze® in adults and adolescents (across all indications), but not for children.
Whether the medicine can reverse or cure, rather than stabilise the condition	HAE is a hereditary condition with no cure.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	There is no evidence that Cinryze® bridges the gap to a "definitive" therapy.
The innovative nature of the medicine	An alternative human C1 esterase inhibitor is already available in the UK and no other specific evidence demonstrating innovation has been presented.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	The company suggest that Cinryze® would ease patients' anxiety and reduce the severity and number of attacks, thus allowing them to continue in education and with normal daily activities.
Added value to the patient's family (e.g. impact on a carer or family life)	The company report that caregiver work time missed is comparable to that of the affected relative, with time off needed for 52% of attacks. Time off work affects the caregiver, their employer and wider society.

Additional information

AWTTC is of the opinion that, if recommended, C1 inhibitor (human) (Cinryze®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

Evidence search

Date of evidence search: 6 June 2017.
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. C1 inhibitor (human) (Cinryze®) 500 Units powder and solvent for solution for injection. Reference number: 3295. September 2017.

Appendix: Previous AWMSG secretariat assessment report (published February 2013)

This report was published as part of a previous AWMSG appraisal of C1 inhibitor (Cinryze®) (Advice number 0313). The advice from this appraisal has been superseded by advice number 2117. The original appraisal documentation is included here for completeness.

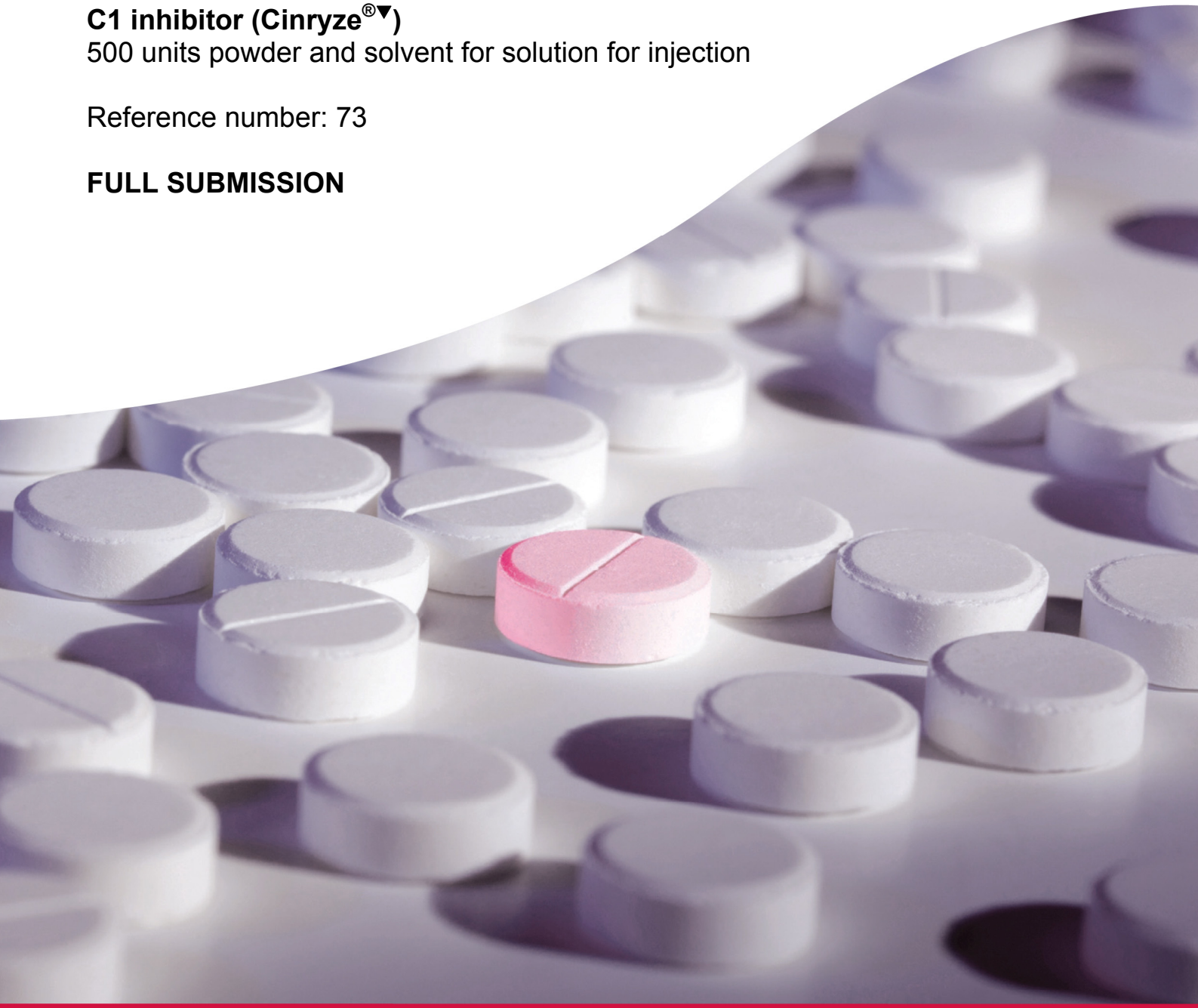
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

C1 inhibitor (Cinryze®▼)
500 units powder and solvent for solution for injection

Reference number: 73

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
C1 inhibitor (Cinryze®▼) 500 units powder and solvent for solution for injection

This assessment report is based on evidence submitted by ViroPharma Ltd on 24 August 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	C1 inhibitor (Cinryze®▼) for the treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with hereditary angioedema. 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 patients who are inadequately managed with repeated acute treatment[2].
Dosing	For treatment of angioedema attacks: 1,000 units at the first sign of the onset of an acute attack. A second dose of 1,000 units may be administered if the patient has not responded adequately after 60 minutes. For patients experiencing severe attacks, particularly laryngeal attacks, or if initiation of treatment is delayed, the second dose can be given sooner than 60 minutes. For routine prevention of angioedema attacks: 1,000 units every three or four days is the recommended starting dose. The dosing interval may need to be adjusted according to individual response. For pre-procedure prevention of angioedema attacks: 1,000 units within 24 hours before a medical, dental or surgical procedure. For treatment, routine prevention and pre-procedure prevention in adolescents the dose is the same as for adults[2].
Marketing authorisation date	15 June 2011[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 2.1 in 10,000 and 1 in 50,000 have been estimated[3–6]. In their submission, the applicant company uses a prevalence of 1 in 50,000 to derive an estimate of 60 HAE patients in Wales, and state that there are presently 50 patients diagnosed[1]. The company acknowledge that there may be a number of undiagnosed patients[1,7].

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 inhibitor (C1-esterase inhibitor, C1-INH)[3,8]. HAE type III is extremely rare and does not appear to be associated with C1 inhibitor absence or dysfunction. C1 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 inhibition, spontaneous or trigger-induced activation of these pathways leads to swelling[2].

Licensed products for the treatment of HAE attacks include the plasma-derived C1 inhibitors Cinryze®▼ and Berinert®; icatibant (Firazyr®▼; a selective competitive antagonist of the bradykinin type 2 receptor); and conestat alfa (Ruconest®▼; a recombinant C1 inhibitor analogue)[2,9–11]. Cinryze®▼ is also licensed for routine and pre-procedure prevention of HAE attacks[2]; antifibrinolytic agents (eg oral tranexamic acid) or attenuated androgens (eg danazol) are currently used off-label for routine prophylaxis of HAE attacks.

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was C1-esterase inhibitor (Berinert®). The company have also included data on the comparative effectiveness of icatibant for the treatment of acute HAE attacks[1].

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[12].
- 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[13].
- Grigoriadou et al (2009). Clinical Immunology Review Series: An approach to the patient with angio-oedema[8].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of icatibant and conestat alfa:

- 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[14].
- 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[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details from four clinical trials (two double-blind, placebo-controlled and two open-label, single-arm) which describe the efficacy and safety of Cinryze®▼ for the treatment, pre-procedure prevention and routine prevention of HAE attacks[1,16–19].

3.1 Treatment of acute attacks

3.1.1 CHANGE Part A

CHANGE Part A (also called LEVP 2005-1/A) was a randomised, double-blind, placebo-controlled, multicentre phase III trial designed to determine the efficacy and safety of Cinryze®▼ for the treatment of acute HAE attacks[1,16]. A total of 71 patients

≥ 6 years of age with a confirmed diagnosis of HAE were randomised 1:1 to treatment with either 1,000 units of Cinryze®▼ (n = 36) or placebo (n = 35) administered intravenously over 10 minutes. Only patients with moderate or severe attacks (self-assessed) that involved the abdomen, face or external genitalia were eligible for treatment. Pregnant patients and patients presenting with attacks of laryngeal angioedema were excluded, and were administered Cinryze®▼ as part of an open-label extension study (CHANGE 2; see Section 3.1.2). The primary endpoint was time from administration of study drug to unequivocal relief of symptoms, defined as three consecutive reports of improvement, as reported by the patient. Severity was assessed every 15 minutes. If the patient did not report unequivocal relief at 60 minutes, a second dose was administered. If four hours without unequivocal relief elapsed, assessment was discontinued and the patient was offered rescue therapy with Cinryze®▼ as part of the open-label extension study[16].

For the primary endpoint analysis of the intent-to-treat dataset (n = 71), the time to onset of unequivocal relief was reduced in the Cinryze®▼ arm (two hours) compared with the placebo arm (more than four hours; estimated success ratio: 2.05; 95% confidence interval [CI]: 1.01,4.16; p = 0.048). After completion of treatment, three patients were deemed by an independent, blinded expert to have not suffered true angioedema attacks; for the remaining 68 patients (35 in the Cinryze®▼ arm and 33 in the placebo arm), the estimated median time to onset of unequivocal relief was two hours in the Cinryze®▼ arm compared with more than four hours in the placebo arm (estimated success ratio: 2.41; 95% CI: 1.17,4.95; p = 0.02). A second dose of study drug was administered to 23 patients in the Cinryze®▼ arm and 28 patients in the placebo arm at 60 minutes. Onset of unequivocal relief did not occur within four hours for 14 (40%) patients in the Cinryze®▼ arm[16].

3.1.2 CHANGE 2

The CHANGE 2 study (also called LEVP 2006-1) enrolled patients (n = 113) ≥ 1 year old that had completed CHANGE Part A or had been previously excluded. This phase III, open-label, single-arm, multicentre trial was designed to evaluate the efficacy and safety of repeat use of Cinryze®▼ for the treatment of HAE attacks (including laryngeal) and for pre-procedure prophylaxis (see Section 3.3). Pregnant and breast feeding women were eligible to participate. Of 609 attacks in 101 patients treated, 412/609 (68%) achieved the primary endpoint of unequivocal relief (at least three consecutive post-treatment reports of improvement) within 60 minutes of the first dose of Cinryze®▼ (1,000 units) and 529/609 (87%) achieved unequivocal relief within four hours. For the subset of laryngeal attacks, 50/84 (59.5%) achieved unequivocal relief within 60 minutes and 65/84 (77.4%) achieved unequivocal relief within four hours of the first-dose of Cinryze®▼[17].

3.2 Routine (long-term) prevention

3.2.1 CHANGE Part B

CHANGE Part B (also called LEVP 2005-1/B) was a 24-week, phase III, randomised, double-blind, placebo-controlled, multicentre, crossover trial to determine the efficacy and safety of Cinryze®▼ for routine prevention of acute HAE attacks. Participants of CHANGE Part A were eligible for Part B if they had a history of at least two attacks per month. Patients (n = 24) were randomised 1:1 to twice-weekly injections of Cinryze®▼ (1,000 units) or placebo, and crossed over to complete two 12-week periods. The primary endpoint was the number of attacks during each therapy period, as reported by the patient. One patient from each arm was excluded from the efficacy analysis as they did not complete the first 12-week period of the study. The average normalised frequency of attacks in the Cinryze®▼ group was 6.26, compared with 12.73 for the placebo group (difference of 6.47; 95% CI: 4.21–8.73, p < 0.001)[16].

3.2.2 CHANGE 3

CHANGE 3 (also called LEVP 2006-4) was an open-label, single-arm, multicentre study of the efficacy and safety of Cinryze®▼ for routine prevention of acute HAE attacks. Patients (n = 146) ≥ 1 year old with HAE and suffering ≥ 1 attack per month or with a history of laryngeal angioedema were administered Cinryze®▼ (1,000 units) every 3–7 days. The median number of attacks at baseline was 3.0 per month; this was significantly reduced during the study period to 0.19 ($p < 0.001$; median treatment duration of 248 days [range: 173–507 days])[19].

3.3 Pre-procedure prevention

Participants of CHANGE Part A and CHANGE 2 were eligible for pre-procedure Cinryze®▼. Data for all patients that received Cinryze®▼ prior to medical, dental or surgical procedures in these studies were collated. A total of 41 patients ≥ 6 years of age received Cinryze®▼ for 91 procedures. A single dose (1,000 units) was administered for 87 procedures, with two doses administered for the remaining four. Within 72 hours of dosing, two HAE attacks were reported (2% of procedures)[18].

3.4 Comparative effectiveness

The company state that there are no head-to-head studies that directly compare the efficacy of Cinryze®▼ and Berinert® for the treatment of acute HAE attacks, and that an indirect comparison is hindered by the unavailability of a uniform scale for assessing symptom relief and diverse clinical endpoints used for the related trials. The company have used the endpoint of median time to onset of clinical relief from two open-label and two randomised controlled trials to provide an indirect comparison of Cinryze®▼ (CHANGE 2[17]), Berinert® (IMPACT 2[20]) and icatibant (FAST-1 and FAST-2[21]) (see Appendix 1, Table 1A)[1].

Study designs and outcomes for the phase III clinical trials of Cinryze®▼ (Change Part A[16] and CHANGE 2[17]), Berinert® (IMPACT 1[22] and IMPACT 2[20]) and icatibant (FAST-1, FAST-2[21] and FAST-3[23]) for the treatment of acute HAE attacks are included in Appendix 1, Table 1B.

As Berinert® and icatibant are not licensed for pre-procedure or routine prevention of HAE attacks, a comparison has not been made.

3.5 Comparative safety

No comparative safety data for Berinert® or icatibant have been provided by the applicant company.

The safety of Cinryze®▼ was evaluated in all Cinryze®▼ clinical trials described above; more than 14,500 doses of Cinryze®▼ have been administered to 385 individual patients in all completed, controlled and open-label clinical studies[1,16–19]. As noted in the Summary of Product Characteristics (SPC), rash is the most commonly reported adverse event (AE) associated with Cinryze®▼ treatment[2]. Two serious AEs that were considered to have an unknown relationship to study drug were reported in one study (exacerbation of major chronic depression and musculoskeletal chest pain)[19]. Three deaths were reported during the open-label studies, none of which were considered to be related to study drug[17,19]. No patients discontinued study drug due to an AE in any of the clinical studies[1,2,4,16–19].

3.6 AWTTC critique

- No evidence is available that directly compares the clinical effectiveness and safety of Cinryze®▼ with Berinert® or icatibant for the treatment of acute HAE attacks. An indirect comparison is hindered by the unavailability of a uniform scale for assessing symptom relief and diverse clinical endpoints in the trials for the individual products. Limited data (from a single secondary endpoint) have been used in the indirect comparison provided by the company[1]; these results

should be interpreted with caution. The trend towards longer time to onset of both symptom and complete relief with Cinryze®▼ than with Berinert® or icatibant shown in Appendix 1, Table 1B should also be interpreted with caution.

- Berinert® and icatibant are not licensed for pre-procedure prevention of HAE attacks or routine prevention of HAE attacks in patients who are intolerant to or insufficiently protected by oral prevention treatments, or who are inadequately managed with repeated acute treatment.
- The rate of repeat dosing (or requirement for rescue medication) varied between the trials of Cinryze®▼, Berinert® and icatibant for the treatment of acute HAE attacks (see Appendix 1, Table 1B); however, the scheduling for repeat dosing differed between trial protocols so figures cannot easily be compared[16,17,20–23]. An increased need for repeat dosing may increase costs and discomfort for the patient.
- Berinert® is licensed for use in patients of any age, whereas Cinryze®▼ is licensed for adolescents and adults, and icatibant is licensed only for adults[2,9,11].
- The Committee for Medicinal Products for Human Use (CHMP) state that the decision to exclude patients that were deemed not to have had a true angioedema attack from the efficacy dataset of CHANGE Part A is not supported[4]. Intent-to-treat data have been provided for the primary endpoint but are borderline significant (p = 0.048).
- Cinryze®▼, Berinert® and icatibant are licensed for home treatment and self-administration. According to the SPCs, appropriate training of patients or caregivers by trained healthcare professionals should be performed in order to minimise the potential risks[2,9,11]. The applicant company state that training in self-administration is offered[1].
- There are differences in the reconstitution and administration of Cinryze®▼, Berinert® and icatibant. For each 1,000 unit dose of Cinryze®▼, two vials (500 units per vial) must be reconstituted with water and administered intravenously[2]. The dose of Berinert® (500 units per vial) is calculated according to body weight, reconstituted with water and administered intravenously[9,10]. Icatibant is available in a pre-filled syringe which should be administered as a single subcutaneous injection[11].
- No long-term safety data for Cinryze®▼ are available. It should be noted that Cinryze®▼ and Berinert® are blood-derived products; therefore, despite standard measures for prevention, the possibility of transmitting infective agents cannot be totally excluded[2,9]. The applicant company states that Cinryze®▼ benefits from an additional nanofiltration process through two sequential 15 nm filters, removing both potential enveloped and non-enveloped viral and theoretical prion-sized particles. Further, they have established a patient registry to characterise the safety and use of Cinryze®▼ in routine clinical practice[1]. Administration of Berinert® has not been shown to be associated with transmission of viruses, irrespective of treatment duration[20,22,24,25].
- As proteins of human plasmatic origin, there is an inherent immunogenic risk with Cinryze®▼ and Berinert®; however, there has been no evidence of clinically relevant anti-C1 inhibitor antibody development in the Cinryze®▼ or Berinert® trials described[4,20,22,24,25].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes two decision analytic models for the use of Cinryze®▼: one for use in the treatment of acute HAE attacks and one for use as routine prevention. Berinert® is the primary comparator in both models, with icatibant used as a comparator in scenario analysis for the acute treatment model. The company has not provided a modelled analysis for the use of Cinryze®▼ in pre-procedure prevention, due to a lack of data to inform modelling. However, costs have been provided for pre-procedure prevention, assuming the same doses of Cinryze®▼ and Berinert® used for treatment of acute attacks[1].

For the acute treatment model, monthly attack rate and the duration and severity of attacks are based on Welsh expert opinion and a Spanish burden of illness (BOI) study[26], due to a reported lack of Wales-specific data. For the routine prevention model, patients are maintained on Cinryze®▼ or Berinert® and can experience a mild, moderate or severe HAE attack in any monthly cycle, which are all assumed to be treated with Berinert®. Data on mean attack rate, severity and duration are taken from the CHANGE 3 open-label trial[19], the Spanish BOI study[26] and the placebo-controlled CHANGE Part A and Part B trials[16].

Costs included medication acquisition, administration and replenishment of medication, and additional inpatient care costs. Medication dosing estimates for acute treatment are based on Welsh clinical expert opinion. For routine prevention, Berinert® dosing is also based on expert opinion, and Cinryze®▼ dosing is based on dosing observed in the CHANGE 3 trial[19]. Unit costs were taken from the British National Formulary (BNF)[27], Personal Social Services Research Unit (PSSRU)[28] and NHS Reference Costs[29]. Utility values used in the model are derived from the Spanish BOI study[26]. Costs and outcomes beyond one year were discounted at 3.5%.

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). A five-year time horizon of analysis is used[1].

4.1.2 Results of the company analyses

The results for the treatment of acute attacks, for routine prevention and pre-procedure prevention are presented in Tables 1, 2 and 3, respectively.

Table 1. Estimated five-year costs of treatment of acute attacks

Scenarios	Total five-year costs per patient			Plausibility
	Cinryze®▼	Comparator	Difference	
Base case: Cinryze®▼ vs. Berinert® Therapeutic equivalence List prices used	£75,083	£73,323	**+£1,760** (32% probability of being cost-saving)	Assumptions of equivalence? Berinert® dosing based on expert opinion of use in practice Repeat dosing issues?
Scenario: Cinryze®▼ vs. icatibant Therapeutic equivalence List prices used	£75,083	£77,054	**-£1,971** (71% probability of being cost-saving)	Assumptions of equivalence? Repeat dosing issues? Icatibant approved by AWMSG based on formally agreed discount, not list price[14]

Table 2. Estimated five-year costs of routine prevention of HAE attacks

Scenarios	Total five-year costs per patient			Plausibility
	Cinryze®▼	Comparator	Difference	
Base case: Cinryze®▼ vs. Berinert® Therapeutic equivalence List prices used Berinert® dosing twice-weekly based on expert opinion of use in practice, Cinryze®▼ dosing 1.4 times weekly based on trial data	£483,858	£564,259	**-£80,401** (88% probability of being cost-saving)	Assumptions of equivalence? Berinert® not licensed for use in routine prevention but expert opinion indicates used in low numbers Cinryze®▼ dosing based on trial data which conflicts with SPC and expert opinion?
Scenario: Cinryze®▼ vs. Berinert® Therapeutic equivalence List prices used Dosing for both based on expert opinion of use in practice	£679,396	£564,259	**+£115,137**	Assumptions of equivalence? Berinert® not licensed for use in routine prevention – dosing based on expert opinion of use in practice? Cinryze®▼ dosing aligned with SPC-recommended dose.
Scenario: Cinryze®▼ vs. Berinert® Therapeutic equivalence List prices used Berinert® dosing twice-weekly based on 3 vials twice weekly, as for SPC-dose for treatment of attacks in patients weighing ≥ 75 kg. Cinryze®▼ dosing 1.4 times weekly based on trial data	£483,858	£832,587	**-£348,729**	Assumptions of equivalence? Berinert® not licensed for use in routine prevention. SPC dose refers to acute attacks, and conflicts with expert opinion? Cinryze®▼ based on trial data which conflicts with SPC and expert opinion?
Scenario: Cinryze®▼ vs. Berinert® Berinert® less effective than Cinryze®▼ by 5–30% List prices used Berinert® dosing twice-weekly based on expert opinion of use in practice, Cinryze®▼ dosing 1.4 times weekly based on trial data	£483,858		Cinryze®▼ dominates	Assumptions of relative effectiveness? Cinryze®▼ dosing based on trial data which conflicts with SPC and expert opinion?
Scenario: Cinryze®▼ vs. Berinert® Berinert® prevents all attacks, Cinryze®▼ reduces monthly attack rate to 0.5 as per base case List prices used Berinert® dosing twice-weekly based on expert opinion of use in practice, Cinryze®▼ dosing 1.4 times weekly based on trial data	£483,858 (4.57 QALYs)	£536,656 (4.67 QALYs)	ICER: £551,000 saved per QALY foregone*	Assumptions of relative effectiveness? Extreme scenario of improved Berinert® effectiveness Cinryze®▼ dosing based on trial data which conflicts with SPC and expert opinion? * Note: the ICER reflects both lower costs and lower effectiveness of Cinryze®▼

Table 3. Estimated cost per procedure for pre-procedure prevention of HAE attacks

Scenarios	Costs per procedure			Plausibility
	Cinryze®▼	Comparator	Difference	
Base case: Cinryze®▼ vs. Berinert® Therapeutic equivalence List prices used	£1,336	£1,283	**+£53**	Assumptions of equivalence? Dosing same as prevention of acute attacks, based on expert opinion of use in practice

4.1.3 AWTTC critique

There is a lack of direct comparative data for Cinryze®▼ and the comparators currently in use in Wales. 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. There is uncertainty in the assumed dose and hence the cost of Cinryze®▼ for routine prevention; this has resulted in scenarios in which Cinryze®▼ is estimated to be more costly or cost-saving versus comparators. Collectively, the economic evidence provided by the company appears subject to considerable uncertainty.

Strengths of the economic evidence:

- In the absence of comparative data for Cinryze®▼, and in the reported absence of Wales-specific data on attack frequency, severity and duration, the company has made efforts to seek expert opinion from clinicians working in the main treatment centre in Wales to inform parameter estimates. The structure of the models developed by the company adequately represents the current treatment pathway in Wales.

Limitations of the economic evidence:

- There is a lack of comparative data for Cinryze®▼. 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. Scenarios exploring assumed greater relative effectiveness for Cinryze®▼ report it to be dominant over Berinert® in the routine prevention setting, as would be expected. An extreme supplementary scenario analysis provided by company that assumes Berinert® prevents all attacks results in Cinryze®▼ being both less costly and less effective.
- There is considerable uncertainty around the assumed treatment doses and costs. For the acute treatment model, the company has adopted expert opinion on dosing, which for Cinryze®▼ is aligned with the SPC-recommended dose. However, for the base case routine prevention model, the company has assumed a Cinryze®▼ dose frequency of 1.4 times per week, based on the CHANGE 3 trial, which is lower than the SPC-recommended and expert opinion-based dose frequency. The base case model therefore predicts cost savings compared with Berinert®, but scenarios in which the expert opinion and SPC-recommended dose frequencies are assumed predict additional costs compared with Berinert® (see Tables 1 and 2).
- In addition, it is unclear whether there are differences between Cinryze®▼ and the comparators in the need for repeat dosing in the treatment of acute attacks. In the CHANGE 2 trial 30.9% of Cinryze®▼ recipients needed repeat doses[17], compared with 1.1% of Berinert® recipients in the IMPACT 2 trial[20]. The extent to which these differences are driven by the trial protocols is unclear.
- Data on attack severity and utilities are based on a Spanish study due to a reported absence of Welsh data, which may introduce uncertainty. However, there would be little impact from this in the context of assumed therapeutic equivalence and the cost minimisation analyses that have been presented.

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 Cinryze®▼ within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on clinical expert estimates, the company reports that there are currently 50 patients diagnosed with HAE in Wales that are risk of acute attacks. Of these, 10% are intolerant to or insufficiently protected by oral prevention treatments, or are inadequately managed with repeated acute treatment, and hence would be eligible to receive Cinryze®▼ for routine prevention. The company also estimates that there will be one new diagnosis per annum and a maximum of one death over the following five years. Clinical experts estimated that up to 25 procedures per year would require pre-procedure prevention. A gradual increase in market share at a constant rate is assumed, rising from 5% to 25% for treatment of acute attacks and from 8% to 40% for routine prevention and pre-procedure prevention in year five[1].

5.1.2 Results

The company anticipates incremental costs resulting from using Cinryze®▼ in place of current options for the treatment of acute attacks and in pre-procedural prevention, and reduced costs from using Cinryze®▼ in place of (off-label) Berinert® for routine prevention. The net costs for all patients in each of the licensed indications are summarised in Table 4.

Table 4. Company-reported costs associated with use of Cinryze®▼ for the treatment of HAE.

	Year 1			Year 2			Year 3			Year 4			Year 5		
	AT	PPP	RP	AT	PPP	RP	AT	PPP	RP	AT	PPP	RP	AT	PPP	RP
Number of patients	51	25*	5	52	26*	5	52	26*	5	53	27*	5	54	27*	5
Uptake (%)	5%	8%	8%	10%	16%	16%	15%	24%	24%	20%	32%	32%	25%	40%	40%
Treated patients	2	–	0	4	–	0	6	–	1	9	–	2	14	–	2
Total cost for all Welsh patients															
A: Current costs (using comparators only)	£798,699	£32,597	£613,486	£811,277	£33,110	£623,147	£823,855	£33,623	£632,808	£836,433	£34,137	£642,469	£849,011	£34,650	£652,130
B: Anticipated costs (using Cinryze®▼ and comparators)	£799,574	£32,704	£606,493	£813,055	£33,327	£608,942	£826,564	£33,955	£611,171	£840,100	£34,585	£613,179	£853,663	£35,219	£614,967
Net budget impact (B-A)	£875	£107	–£6,992	£1,778	£217	–£14,205	£2,709	£331	–£21,637	£3,667	£448	–£29,290	£4,652	£569	–£37,163

AT: acute treatment; PPP: pre-procedure prevention; RP: routine prevention
* Number of procedures
Note: number of patients or procedures presented has been rounded to nearest integer and costs to nearest pound

5.1.3 AWTTC critique

- The company has made reasonable effort to characterise the epidemiology and treatment pathway of HAE in Wales using Welsh expert opinion.
- As the budget impact analysis is based on the total cost estimates generated in the economic models, the same limitations and uncertainties reported above would apply to the budget impact estimates provided.
- The net cost resulting from the use of Cinryze®▼ in place of Berinert® in pre-procedure prevention appears to be calculated for all procedures, ie based on 100% market share and not on the expected 8% uptake.
- Collectively, the budget impact estimates would appear subject to considerable uncertainty.

5.2 Table of comparative unit costs

Table 5 provides example comparative costs for treatments used in the management of HAE. Oral treatments are unlicensed for use, but have been used for pre-procedure prevention and routine prevention. Cinryze®▼ is licensed for use in routine prevention only where oral treatments provide insufficient protection or are not tolerated, or in patients who are inadequately managed with repeated acute treatment[2].

Table 5. Examples of costs of HAE acute attack treatment, and pre-procedure and routine prevention.

Treatment	Example dose*	Approximate cost per patient/procedure
Cinryze®▼ Injection, 500 unit vial	**Acute attacks**: 1,000 units as a single dose **Pre-procedure prevention**: 1,000 units up to 24 hours before procedure **Routine prevention**: 1,000 units every 3–4 days, interval between doses adjusted according to response	**Acute attacks** and **pre-procedure prevention**: £1,336 per attack/procedure **Routine prevention**: £121,910–£162,547 per annum
Berinert® Injection, 500 unit vial	**Acute attacks**: 20 units/kg	£1,650†
Icatibant (Firazyr®▼) Injection (10 mg/ml), 3 ml pre-filled syringe	**Acute attacks**: 30 mg as a single dose	£1,395
Conestat alpha (Ruconest®▼) Injection, 2,100 unit vial	**Acute attacks**: 50 units/kg as a single dose	£2,800†
Tranexamic acid (non proprietary) Oral, 500 mg tablets	**Pre-procedure prevention (unlicensed):** 1–1.5 g 2–3 times daily started several days before the procedure and continued for 2–5 days afterwards	**Pre-procedure prevention**: £0.35–£0.78 per patient per day
Danazol (Danol®) Oral, 100 and 200 mg capsules	**Pre-procedure (unlicensed):** initially 200 mg 2–3 times daily, then reduced according to response	**Pre-procedure prevention**: £1.08–£1.62 per patient per day
Costs based on BNF list prices as of 23 September 2012[27] * Based on BNF dosing instructions[27] † Calculated based on average adult body weight of 70 kg, to nearest whole vial. This table does not imply therapeutic equivalence of the stated treatments and doses. See all relevant SPCs for full dosing details[2,9–11,30–32].		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, Cinryze®▼ 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 6–12 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 and 21 September 2012
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to ultra-orphan medicines

The applicant company suggest that the use of Cinryze®▼ might meet the AWMSG criteria for ultra-orphan status. Ultra-orphan medicines are orphan drugs that are licensed for the treatment of diseases with a prevalence of less than 1 in 50,000 persons in the European Union (EU) at the time of submission of the designation application to the European Medicines Agency. CHMP reports a prevalence of 2.1 per 10,000 EU population[4].

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Appendix 1. Additional clinical information

Table 1A. Company-provided indirect comparison of the study design and efficacy endpoint "median time to onset of clinical relief" for clinical trials of Cinryze®▼, Berinert® and icatibant for the treatment of acute HAE attacks[1]

Treatment	Trial reference	Study design	Patient numbers	Efficacy endpoint	Time to endpoint (mins)
Cinryze®▼	CHANGE 2 (LEVP 2006-1, Riedl et al)[17,33]	Open-label, single-arm, multicentre	101	Median time to onset of clinical relief (secondary endpoint, self-assessed)	15–45
Berinert®	IMPACT 2 (Craig et al)[20]	Open-label, single-arm, multicentre	43	Median time to onset of symptom relief (primary endpoint, self-assessed)	28
Icatibant	FAST-1 (Cicardi et al)[21]	Randomised, double-blind (versus placebo), multicentre	56	Median time to clinically significant relief of the index symptom (primary endpoint, assessed using VAS)	150
	FAST-2 (Cicardi et al)[21]	Randomised, double-blind (versus TXA), multicentre	74		120
TXA: tranexamic acid, VAS: visual analogue scale					

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

Treatment	Trial	Study design	Patient numbers	Efficacy endpoint	Median time to endpoint (hours)*		Significance (p value)	Rate of repeat dosing in treatment arm
					Treatment	Placebo		
Cinryze®▼ (1,000 units)	CHANGE Part A (LEVP 2005-1/A, Zuraw et al, 2010)[16]	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[17])	Open-label, single-arm, multicentre	113	Median time to beginning of unequivocal relief	0.75			30.9%
Berinert® (20 units/kg)	IMPACT 1 (Craig et al, 2009)[22]	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)[20]	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			
Icatibant (30 mg)	FAST-1 (Cicardi et al, 2010)[21]	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)[21]	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)[23]	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	

TXA: tranexamic acid
* Results should be interpreted with caution due to the heterogeneity between clinical endpoints
† Per protocol data set