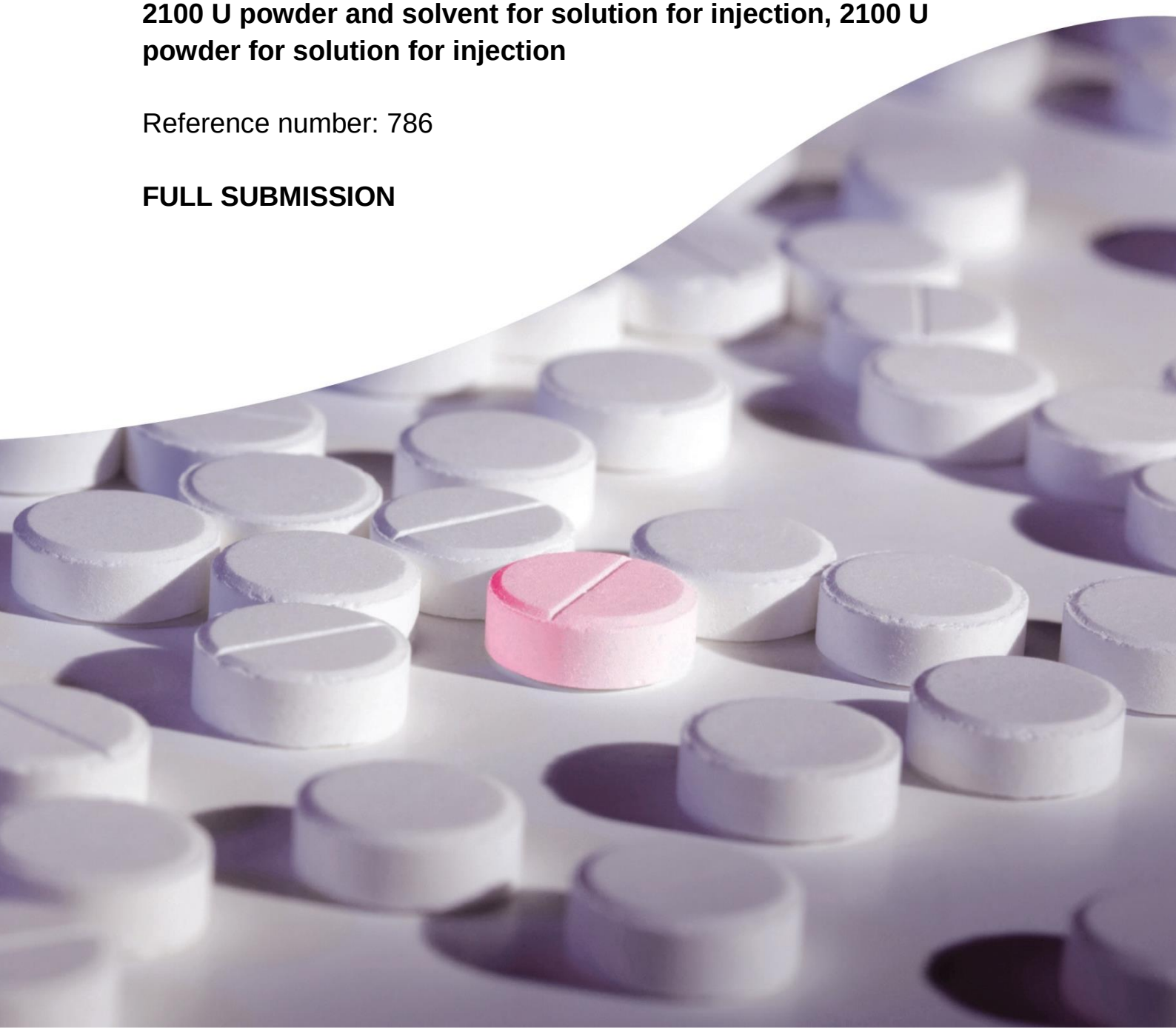
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Conestat alfa (Ruconest®)
2100 U powder and solvent for solution for injection, 2100 U powder for solution for injection

Reference number: 786

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Conestat alfa (Ruconest®) 2100 U powder and solvent for solution for injection, 2100 U powder for solution for injection. Reference number: 786. September 2018.

AWMSG Secretariat Assessment Report
Conestat alfa (Ruconest®) 2100 U powder and solvent for solution for injection, 2100 U powder for solution for injection

1.0 KEY FACTS

Assessment details	This is an assessment of conestat alfa (Ruconest®) for the treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.
Current clinical practice	Current treatment options include intravenous human plasma-derived C1-esterase inhibitors (Berinert® and Cinryze®) and icatibant acetate (Firazyr®), a selective competitive antagonist of the bradykinin type 2 receptor, which is administered subcutaneously. Welsh clinical expert opinion sought by AWTTC and prescribing data suggest that Berinert® and icatibant acetate are the treatment options primarily used in NHS Wales.
Clinical effectiveness	There are no efficacy or safety studies comparing conestat alfa with Berinert® or icatibant acetate. An indirect analysis was not possible due to heterogeneity between study designs and study endpoints. Three phase II/III studies showed that recombinant C1-inhibitor is superior to placebo in inducing relief from symptoms of acute angioedema attacks in patients with HAE. No specific safety concerns were identified in the phase III studies; however one case of hypersensitivity has been previously reported and therefore hypersensitivity reactions to rabbit protein cannot be excluded.
Cost-effectiveness evidence	A cost minimisation analysis (CMA) compares conestat alfa (50 units/kg) with C1-esterase inhibitor (Berinert®) (20 units/kg) and icatibant acetate (Firazyr®) (30 mg), in the first-line treatment of hereditary angioedema. The company base case suggests cost savings for conestat alfa of **[commercial in confidence figure removed]** compared with C1-esterase inhibitor (Berinert®) and **[commercial in confidence figure removed]** with icatibant acetate. A CMA has been conducted without robust evidence of equivalence of treatments. The model includes re-dosing due to inadequate response, as this rate varies by treatment, this negates the assumption of equivalence. The model time horizon is 72 hours, representing one attack.
Estimated budget impact	The company estimates that 61 patients are eligible to receive treatment with conestat alfa in Wales in Year 1. The company base case suggests cost savings of **[commercial in confidence figure removed]** in Year 1, increasing to **[commercial in confidence figure removed]** in Year 5 (based on Wales Patient Access Scheme price for conestat alfa and list price for Berinert® and icatibant alfa). The budget impact analysis assumes patients have an average of 32.84 attacks per year.

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

Additional factors to consider	AWTTC considers conestat alfa eligible to be appraised as a medicine developed specifically to treat rare diseases.

This assessment report is based on evidence submitted by Pharming Group N.V. and an evidence search conducted by AWTTC on 20 June 2018.

2.0 BACKGROUND

2.1 Condition and clinical practice

Hereditary angioedema (HAE) is a rare genetic disorder, associated with a deficiency of the protein C1-esterase inhibitor[1]. HAE attacks are recurrent, often unpredictable and can last several days if left untreated. They are characterised by localised oedematous swellings which can affect any part of the body, including the face, mouth, airway and gastrointestinal tract[2]. HAE attacks affect quality of life and angioedema swelling in the mouth and airways is life-threatening[3].

Products currently licensed for the treatment of acute angioedema attacks in adults and adolescents with HAE include:

- human-plasma derived C1-esterase inhibitors (Berinert® and Cinryze®) which are administered intravenously[4,5]
- icatibant acetate (Firazyr®), a selective competitive antagonist of the bradykinin type 2 receptor, which is administered subcutaneously[6].

Clinical expert opinion sought by AWTTC and Welsh prescribing data suggests that Berinert® and icatibant acetate are the treatment options primarily used in NHS Wales.

2.2 Medicine

The indication being assessed is the treatment of acute angioedema attacks in adults and adolescents with HAE due to C1-esterase inhibitor deficiency. Conestat alfa (2,100 U powder for solution for injection) was first licensed in October 2010 for the treatment of adults[7] and received a licence extension in March 2016 for the treatment of adolescents[8]. In January 2017 a new pharmaceutical form, 2,100 U powder and solvent for solution for injection, was added to the licence. The new pharmaceutical form is a complete kit package including solvent and administration devices and enables administration by the patient or the caregiver in the homecare setting[8]. The recommended dose of conestat alfa is one intravenous injection of 50 units/kg in people who weigh up to 84 kg[7]. For people who weigh 84 kg or more, the recommended dose is one intravenous injection of 4,200 units. If there is an insufficient clinical response, an additional dose (50 units/kg up to 4,200 units) can be administered[7].

Conestat alfa is the recombinant analogue of the human C1-esterase inhibitor and is obtained from the milk of rabbits expressing the gene encoding for human C1-esterase inhibitor[3]. Recombinant C1-inhibitor offers an alternative treatment option to plasma-derived C1-inhibitor products and icatibant acetate.

2.3 Comparators

The comparators included in the company's submission are Berinert® and icatibant acetate.

2.4 Guidance and related advice

- Maurer et al. 2018. The international WAO/EAACI guideline for the management of hereditary angioedema – The 2017 revision and update[9].

- Longhurst et al. 2015. C1 inhibitor deficiency: 2014 United Kingdom consensus document[10].
- NHS Commissioning Board Clinical Reference Group (2013). NHS Commissioning Board Clinical Commissioning Policy: Treatment of acute attacks in hereditary angiodema (adult)[1].

The All Wales Medicines Strategy Group (AWMSG) has previously recommended the use of icatibant acetate (Firazyr®), C1 inhibitor (Cinryze®) and C1-esterase inhibitor (Berinert®)[11-13].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, conestat alfa (Ruconest®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that conestat alfa (Ruconest®) may be supplied by a home healthcare provider.

3.0 CLINICAL EFFECTIVENESS

The company's submission includes evidence from three randomised, double-blind studies (C1 1310, C1 1205 and C1 1304) and their corresponding open-label extension phases[14-18]. All three studies compared the efficacy and safety of recombinant C1 inhibitor with placebo in the treatment of acute angioedema attacks in patients with HAE.

3.1 C1 1310 study (Riedl et al. 2014) and open-label extension

This phase III study enrolled 75 patients at least 13 years old (≥ 18 years old for patients outside the United States and Canada) with a clinically suspected and laboratory-confirmed diagnosis of HAE (baseline plasma C1-inhibitor activity less than 50% of normal and no evidence of acquired angioedema)[14]. Patients were eligible for treatment if: the location of the attack was peripheral, abdominal, facial and/or oropharyngeal-laryngeal; the onset of these attacks occurred within five hours before presentation to the clinic; their overall severity visual analog scale (VAS) score was ≥ 50 mm at presentation and just before dosing; and there was no evidence of regression of symptoms (i.e. no decrease ≥ 20 mm in overall severity VAS score) between presentation and dosing. Patients with life-threatening symptoms at presentation were excluded[14].

Patients were randomly assigned in a 3:2 ratio to receive recombinant C1-inhibitor (50 units/kg for patients weighing < 84 kg or 4,200 units for patients weighing ≥ 84 kg; n = 44) or placebo (n = 31)[14]. An additional dose of recombinant C1-inhibitor (50 units/kg up to a maximum of 4,200 units, open-label) could be given to patients who did not achieve the beginning of relief from symptoms and had a significant degree of pain, discomfort or disability from their symptoms four hours after dosing or at any time for life-threatening oropharyngeal-laryngeal symptoms. At the discretion of the investigator(s), patients were also allowed to receive other rescue medication at any time[14].

The primary endpoint was the time to onset of sustained relief from symptoms at the primary attack location, assessed by the responses to questions 1 and 2 in the treatment effect questionnaire at 15-minute intervals for two hours, 30-minute intervals until six hours, then at home at 8, 12 and 24 hours (see Glossary)[14]. For patients receiving rescue medication the time to beginning of relief from symptoms was censored at the last time the treatment effect questionnaire was assessed. The key secondary endpoint was time

to minimal symptoms for all attack locations, assessed by the response to question 3 in the treatment effect questionnaire (see Glossary)[14].

Treatment with recombinant C1-inhibitor resulted in a significant reduction in the time to onset of sustained relief from symptoms at the primary attack location compared with placebo, as measured by the treatment effect questionnaire (90 minutes compared with 152 minutes; $p = 0.031$)[14]. The primary endpoint remained significantly shorter for recombinant C1-inhibitor when the time to onset of relief was set to 24 hours for patients who received rescue medication or disallowed concomitant medication (4/44 patients in the recombinant C1 inhibitor group and 11/31 patients in the placebo group received rescue medication or disallowed concomitant medications). The secondary endpoint outcome, time to minimal symptoms at all attack locations, was shorter in patients who received recombinant C1-inhibitor treatment compared with patients who received placebo based on the treatment effect questionnaire, but did not reach statistical significance[14].

The open-label extension study (Li et al. 2015) was conducted to evaluate the efficacy of recombinant C1-inhibitor for repeated treatment of multiple attacks[15]. All patients who received treatment in the randomised phase were eligible for participation in the open-label phase. Forty-four patients received recombinant C1-inhibitor treatment for 224 HAE attacks; most patients received treatment for up to five attacks. The results showed that the efficacy of recombinant C1-inhibitor is maintained when administered for repeated HAE attacks and that single doses are effective in most cases[15].

3.2 C1 1205 and C1 1304 studies (Zuraw et al. 2010) and open-label extensions

Studies C1 1205 (phase II) and C1 1304 (phase III) were similar in design, entry criteria and endpoints[16]. Both studies were multi-centred; study C1 1205 was conducted in the United States and Canada, and study C1 1304 was conducted in Europe (including the United Kingdom). Across both studies seventy patients were randomised and received a single intravenous dose of recombinant C1-inhibitor or saline. All patients had functional C1-inhibitor in plasma less than 50% of normal, had an onset of attack symptoms within five hours of evaluation of eligibility, and had an overall severity visual analogue scale (VAS) score ≥ 50 mm. Eligible attack locations were abdominal, facial-oropharyngeal, laryngeal, urogenital and peripheral. Patients with acquired C1-inhibitor deficiency, a history of allergic reactions to any rabbit proteins and those presenting or developing a life-threatening attack were excluded[16].

In the North American study, 38 patients (≥ 12 years old) received treatment: 100 units/kg recombinant C1-inhibitor (n = 13), 50 units/kg recombinant C1-inhibitor (n = 12), or saline (n = 13)[16]. In the European study, 32 patients (≥ 16 years old) received treatment: 100 units/kg recombinant C1-inhibitor (n = 16) or saline (n = 16)[16].

The primary endpoint was the time to the beginning of relief of symptoms[16]. This was defined as the interval during which the VAS score at any eligible location had decreased by ≥ 20 mm compared with baseline for two consecutive score readings. A patient-reported VAS was used. Patients were asked to mark the overall severity of angioedema symptoms on a continuous scale from 0 to 100 mm, with 0 mm meaning no symptoms at all and 100 mm meaning extremely debilitating. VAS scores were recorded at the time of evaluation of the acute attack (one hour before treatment initiation), at the start of infusion (baseline) and at 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, 48 and 72 hours after treatment. The secondary endpoint was the time to minimal symptoms, which was defined as the interval during which the VAS score had decreased to < 20 mm for all anatomical locations of an attack. Patients were followed until day 90 after treatment of an acute attack unless they experienced a new attack and were enrolled in the open-label study[16].

The data from both randomised studies were pooled and analysed[16]. The mean overall VAS score decreased more rapidly in both recombinant C1-inhibitor groups compared with the saline group. Median time to onset of symptom relief was 66 minutes (95% confidence interval [CI] 61 to 122 minutes; $p < 0.001$) with 100 units/kg recombinant C1-inhibitor, 122 minutes (95% CI 72 to 136 minutes; $p = 0.013$) with 50 units/kg recombinant C1-inhibitor and 495 minutes (95% CI 245 to 520 minutes) with saline. Comparing only the 50 units/kg dose of recombinant C1-inhibitor versus placebo in the North American study showed a median time to onset of symptom relief of 122 minutes with recombinant C1-inhibitor and 258 minutes for placebo ($p < 0.001$)[3]. The results from both studies are considered clinically relevant[3]. The secondary endpoint outcome for the pooled analysis was supportive and showed a statistically significant ($p \leq 0.001$) reduction in time to minimal symptoms with both recombinant C1-inhibitor doses compared with saline[16]. Statistical significance could not be assessed for the 50 units/kg dose versus placebo in the North American study[3].

The open-label extension studies (Riedl et al. 2013 and Moldovan et al. 2012) were conducted to assess the safety and efficacy of repeated recombinant C1-inhibitor treatment for recurrent attacks[17,18]. In the European extension study, patients received a single vial of recombinant C1-inhibitor (2,100 units) with an investigator option for two additional 2,100 unit doses within four hours as clinically required[17]. The overall median dose was 34 units/kg[17]. In the North American extension study, patients received 50 units/kg dose of recombinant C1-inhibitor with an option for an additional dose within four hours (50 units/kg) based on clinical response[18].

In the European extension study, 57 patients received treatment for 194 HAE attacks (range between one and more than six attacks per patient)[17]. In the North American extension study, 62 patients received treatment for 168 attacks (range one to eight attacks per patient)[18]. The results showed that the efficacy of recombinant C1-inhibitor was maintained throughout subsequent attacks[17,18].

3.3 Safety

There are no safety data comparing conestat alfa with Berinert® or icatibant acetate. The phase II/III studies and the open-label extension studies outlined in section 3.1 and 3.2 did not highlight any specific safety concerns. In particular, there were no significant safety concerns in relation to thrombosis, antibodies to conestat alfa or antibodies to host related impurities[3]. Adverse reactions were usually mild to moderate and the most common adverse reaction observed after administration of recombinant C1-inhibitor was headache[7]; rates were similar in the placebo and recombinant C1 inhibitor groups[19]. Overall the rate of treatment emergent adverse events was similar or slightly lower than in the placebo-treated group[3].

Although no hypersensitivity reactions were reported in the phase II/III studies, an earlier phase I study reported one case of hypersensitivity in a person with a pre-existing rabbit allergy. The risk of hypersensitivity, in particular in patients allergic to rabbits, is highlighted in the Summary of Product Characteristics as well as the potential for cross-reactivity between cow milk and rabbit milk[7].

3.4 AWTTC critique

- No evidence is available that directly compares the clinical effectiveness and safety of conestat alfa with Berinert® or icatibant acetate. The European Medicines Agency considers that placebo-controlled studies are acceptable and in line with recommendations in the Committee for Medicinal Products for Human Use (CHMP) scientific advice[3]. However, this did necessitate the exclusion of patients with life-threatening attacks. An indirect comparison is hindered by the

heterogeneity between placebo-controlled trials and inconsistencies in trial endpoints.

- There are no clinical tests that can objectively assess the severity of an HAE attack. As a result, the primary endpoints from the studies were assessed by patient-reported methods: the VAS score and the treatment effect questionnaire[16]. The CHMP accepted the use of the VAS score as it has been used in the evaluation of other treatments for HAE attacks[3]. Similarly, the treatment effect questionnaire was requested by regulatory authorities[14].
- Studies C1 1205 and C1 1304 were the key studies supporting the UK marketing authorisation for conestat alfa. Both studies included a dose higher than the currently licensed dose. The CHMP concluded that pooled data from these two studies and their open-label extensions demonstrated similar success rates for patients receiving 50 units/kg (with the option for a second dose) and patients receiving 100 units/kg. Only 10% of patients required an additional 50 units/kg dose[3].
- Hereditary angioedema is a life-long condition with some patients experiencing numerous attacks each year. In the key studies patients were followed for three months or for a small number of attacks. Longer term data on clinical efficacy and safety are lacking.
- Conestat alfa, Berinert® and icatibant acetate are licensed for home treatment and self-administration[4,6,7]. Conestat alfa is available as a complete kit package which includes solvent and administration devices[7]. This facilitates administration by the patient or the caregiver in the home care setting, but like Berinert® it requires administration by intravenous injection[4]. Icatibant acetate is administered subcutaneously and is available as a pre-filled syringe[6]. These differences in administration may influence the choice of treatment for patients who receive treatment at home. Differences in licensed indications and licensed ages may also influence choice of treatment, with Berinert® also being indicated for pre-procedure prevention of HAE attacks.
- Conestat alfa is a recombinant C1-inhibitor derived from the milk of rabbits whereas Berinert® is derived from human plasma. Conestat alfa removes the possible risk of transmission of blood-borne pathogens and there is less concern over its availability as it does not require donor plasma[3,19].

4.0 COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-minimisation analysis (CMA) comparing conestat alfa (50 units/kg) with Berinert® (20 units/kg) or icatibant acetate (30 mg), in the first-line treatment of acute HAE attacks.

A simple decision analytic model is used to estimate the difference in cost between conestat alfa (50 units/kg) with Berinert® (20 units/kg) or icatibant acetate (30 mg). The model adopts an NHS/Personal Social Services in Wales perspective and a time horizon of 72 hours. In the model it is assumed that conestat alfa and the comparators are used in a first-line context. Patients enter the model when an acute attack occurs. Initial dose and re-dosing due to inadequate response to the first treatment are included in the model[19]. A mean weight of 76.9 kg was assumed for the calculating medicine doses according to ONS snapshot data for the 'average Briton'[20]. This assumes a 50:50 split between male and female patients. The company reported that there is no evidence to suggest that HAE is more prevalent in males or females.

Costs for a full course of treatment were calculated as the sum of the costs of medicine acquisition, based on patient weight, and administration. Medicine administration costs were calculated by weighting the home and hospital administration cost with the probability of receiving treatment in each of the locations. The cost of hospital administration for the re-dosing period is assumed to be included in the initial treatment period, as the patient would be occupying the hospital bed regardless of receiving additional treatment or monitoring. All treatments are supplied in vials or a pre-filled syringe (conestat alfa Wales Patient Access Scheme [WPAS] price **[commercial in confidence figure removed]** per vial; Berinert® £550 per vial; icatibant acetate list price £1,395 per pre-filled syringe).

Administration costs include the administration of treatment, assessment and monitoring during and at the end of treatment. Home administration cost are £120.75, based on 70% requiring 4 hours community nurse time, and 30% self-injecting at no cost. Hospital administration cost are £106.81, based on 50:50 emergency department non-admitted visits, and a clinical haematology outpatient attendance. The emergency department non-admitted visit costs are for NHS walk-in centres as the company reported that most treatments are given outside of the emergency departments. Unit personnel costs were derived from Personal Social Services Research Unit costs for the UK[21].

Re-dosing (patients requiring rescue therapy after initial treatment) occurred for 9.3% of conestat alfa patients, 18.6% of Berinert®, and 17.83% for icatibant acetate patients. These inputs were identified with a pragmatic literature search and inputs were selected based on the views of two key opinion leaders based in France and Italy. Only one set of re-dosing was assumed, therefore patients received a maximum of two doses in the 72-hour period; this was based on discussions with clinicians within a Cardiff hospital where patients see a positive reaction from the first or second dose. It was assumed that 75% of patients would be treated at home[22]. No discounting was applied given the short time horizon of the model.

The company conducted sensitivity analyses to test the influence of parameter uncertainty on the robustness of the base case results. They explore the impact of varying the average patient weight and source of re-dosing rates.

4.1.2 Results

The results of the base case analysis and sensitivity analyses for HAE are given in Table 1. Conestat alfa is less costly in the base case and in the majority of sensitivity/scenario analyses conducted. Dosing is based on a mean weight of 76.9 kg; requiring two vials of conestat alfa, four vials of Berinert®, or one pre-filled syringe of icatibant acetate. In the scenario of the average weight of 75 kg only three vials of Berinert® are costed.

Table 1. Results of the base case analysis and scenario/sensitivity analyses

Scenario	Costs	Conestat alfa (list)	Conestat alfa (WPAS)	Berinert® (list)	Icatibant (list)	Difference per patient Berinert®	Difference per patient icatibant acetate	Plausibility
Base case								
Conestat alfa versus Berinert® or icatibant acetate	Medicine acquisition costs	£1,640	¶¶	£2,609	£1,644			Not plausible as all treatments are available to Welsh NHS at a discount as per WPAS.
	Staff time and hospital resources	£126	¶¶	£134	£133			
	Total costs	£1,765	¶¶	£2,743	£1,777	−£978 list prices ¶¶	−£12 list prices ¶¶	
Sensitivity analysis: average weight 75 kg instead of 76.9 kg								
Conestat alfa versus Berinert® or icatibant acetate	Medicine acquisition costs	£1,640	¶¶	£1,957	£1,644			Plausibility is dependent on the average weight of people with HAE. No evidence on average weight of people with HAE has been reported.
	Staff time and hospital resources	£126	¶¶	£134	£133			
	Total costs	£1,765	¶¶	£2,091	£1,777	−£326 list prices ¶¶	−£12 list prices ¶¶	
Scenario analysis: re-dosing (0.2% conestat alfa; 1.1% Berinert®; 17.2% icatibant acetate)								
Conestat alfa versus Berinert® or icatibant acetate	Medicine acquisition costs	£1,503	¶¶	£2,224	£1,635			Plausibility is based on clinical evidence for re-dosing and if the re-dosing rates reflect Welsh clinical practice.
	Staff time and hospital resources	£117	¶¶	£118	£133			
	Total costs	£1,620	¶¶	£2,342	£1,768	−£722 list prices ¶¶	−£147 list prices ¶¶	
Scenario analysis: equal re-dosing rates 0.2%								
Conestat alfa versus Berinert® or icatibant acetate	Medicine acquisition costs	£1,503	¶¶	£2,204	£1,398			Plausibility is based on clinical evidence for re-dosing and
	Staff time and hospital resources	£117	¶¶	£117	£117			

Scenario	Costs	Conestat alfa (list)	Conestat alfa (WPAS)	Berinert® (list)	Icatibant (list)	Difference per patient Berinert®	Difference per patient icatibant acetate	Plausibility
	Total costs	£1,620	¶¶	£2,322	£1,515	−£701 list prices ¶¶	£105 list prices ¶¶	if the re-dosing rates reflect Welsh clinical practice.
Scenario analysis: equal re-dosing rates 18.6%								
Conestat alfa versus Berinert® or icatibant acetate	Medicine acquisition costs	£1,779	¶¶	£2,209	£1,654			Plausibility is based on clinical evidence for re-dosing and if the re-dosing rates reflect Welsh clinical practice.
	Staff time and hospital resources	£134	¶¶	£134	£134			
	Total costs	£1,913	¶¶	£2,743	£1,789	−£830 list prices ¶¶	£125 list prices ¶¶	
Scenario analysis: proportion of patients eligible for home treatment set to 0%								
Conestat alfa versus Berinert® or icatibant acetate	Medicine acquisition costs	£1,640	¶¶	£2,609	£1,644			Plausibility depends on Welsh clinical practice.
	Staff time and hospital resources	£107	¶¶	£107	£107			
	Total costs	£1,746	¶¶	£2,716	£1,751	−£970 list prices ¶¶	−£4 list prices ¶¶	
Scenario analysis: proportion of patients eligible for home treatment set to 25%								
Conestat alfa versus Berinert® or icatibant acetate	Medicine acquisition costs	£1,640	¶¶	£2,609	£1,644			Plausibility depends on Welsh clinical practice.
	Staff time and hospital resources	£113	¶¶	£116	£116			
	Total costs	£1,753	¶¶	¶¶	£1,759	£972 list prices ¶¶	−£7 list prices ¶¶	

Conestat alfa medicine acquisition cost is based on Wales Patient Access Scheme (WPAS) price, Berinert® and icatibant acetate acquisition costs are based on the list prices.
¶¶ commercial in confidence figure removed

Four scenarios of equal rates of re-dosing were tested, only the lowest and highest rates are reported in Table 1 as in all four scenarios conestat alfa was no longer cost saving compared to icatibant acetate. When equal rates of re-dosing are applied, icatibant acetate becomes the cost-saving treatment option.

Berinert® is associated with a WPAS. Sensitivity analyses exploring a 10%–60% discount on the list price of Berinert® resulted in a cost saving of £794 per patient for conestat alfa when applying a 10% discount and an additional cost of £511 per patient

for conestat alfa when applying a 60% discount. Conestat alfa is no longer cost saving at a 45% discount for Berinert®.

Icatibant acetate also has a WPAS. Sensitivity analyses exploring a 10%-60% discount on the list price of icatibant acetate resulted in a cost saving of £76 per patient for conestat alfa when applying a 10% discount and an additional cost of £898 per patient for conestat alfa when applying a 60% discount. Conestat alfa is no longer cost saving at a 10% discount for icatibant acetate (conestat alfa costs £76 per patient more).

The results of the sensitivity and scenario analysis show that cost savings with conestat alfa are most sensitive to re-dosing rates and cost of treatments.

4.1.3 AWTTC critique

The reliability of the CMA is dependent on the extent to which conestat alfa is considered to be therapeutically equivalent to the comparators. The company justified the use of a CMA, as opposed to a cost-utility analysis (CUA), on the basis that no head-to-head trials have been carried out and the evidence available reports inconsistent primary and secondary endpoints.

In the absence of well-designed equivalence trials and/or evidence of close comparability of other effects, (impact on health-related quality of life, adverse events, patient preference, adherence and survival), AWTTC considers a CMA to be an inappropriate approach in this instance.

Strengths and limitations of the economic analysis include:

- The company's justification for using a CMA is not appropriate as it is not based on robust evidence of equivalence.
- The model incorporates inadequate response from initial treatment at differing rates for the three therapies therefore demonstrating that the therapies are not equivalent in efficacy. A CUA would be more appropriate to incorporate the impact of rescue medication and potential hospitalisation due to inadequate response of initial treatment.
- The population was based on an average weight of 76.9 kg based on statistics for the whole UK population in 2010 (the calculated average of women at 70.2 kg and men at 83.6 kg)[20]. The patient characteristics reported in the clinical evidence do not report mean weight so it is not clear if the weight of patients with HAE is comparable to the general population. A lower weight of 75 kg was tested in the sensitivity analysis. Given that the lower weight resulted in a lower cost for Berinert® as one less vial was required it would be useful to see how varying the re-dosing in a lower weight population affects the results.
- In four of the clinical trials of conestat alfa[14,15,17,18] a higher proportion of women (ranging from 59% to 65% of trial population) was reported, however the model does not include sex of the patients, and any differences in weight between the sexes. The model assumes 75% of patients were treated at home in the base case; this is based on an evaluation of hospital emergency department visits in a hospital in Portugal, which reported that 25% of patients had recurrent emergency department visits and/or hospital admissions.
- The time horizon was 72 hours to reflect one acute attack. However, patients with HAE are reported to have numerous attacks per year (average 32.84 per patient in the budget impact analysis) and these can potentially result in hospitalisation. The model should include the need for attendance at A&E following home administration if symptoms do not improve or involve the larynx, and if an overnight stay is required[1]. Furthermore, it is not clear how re-dosing costs are

applied to patients who were treated at home as these would likely require an A&E visit.

- In the model the emergency medicine visits are based on type 4 non-admitted visits which apply to NHS walk-in clinics.

4.2 Review of published evidence on cost-effectiveness

A literature search by AWTTC identified two publications relevant to this submission. A conference abstract of a CMA comparing Berinert®, Cinryze®, icatibant acetate and conestat alfa in patients with HAE. This CMA was based on the treatments having similar efficacy, but with differing doses and need for re-dosing. However, the frequency for re-dosing was estimated as 1% for Berinert®, 30% for Cinryze®, 7% for icatibant acetate, and 10% for conestat alfa. Using these re-dosing estimates, conestat alfa was not the cost-effective option; Berinert® was found to be the least costly therapy. As this was an abstract no details of the sources of inputs or any sensitivity analyses have been included[23].

A CUA from the Polish healthcare system perspective compared conestat alfa (50 units/kg) and Berinert® (20 units/kg) with placebo in the treatment of acute attacks in adults with HAE over a 1-year time horizon[24]. The evaluation found quality-adjusted life-year (QALY) results of 0.0261 QALYs for conestat alfa and 0.0262 QALYs for Berinert®. The unit costs of conestat alfa were higher than Berinert® (€1,175 vs. €933). The cost of treating an attack was higher for Berinert® than conestat alfa (€92 vs. €60). The results report that conestat alfa was cheaper than Berinert® (€419 vs. €755), and therefore more cost-effective, although with incremental cost-effectiveness ratios compared to placebo. However, the fact that no comparative clinical data and quality of life estimates during attacks were available, the sources of efficacy and utility inputs are unclear, and as treatments are not compared with each other, but to placebo, this limits the usefulness of this analysis.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company has estimated that there will be 61 patients with HAE in Wales. This estimate is based on Welsh government population statistics[25] and global prevalence data published by Lumry 2013[26]. To calculate the number of patients who require treatment in Wales, the company has combined prevalence estimates, with a HAE-adjusted mortality rate of 1.41%[27]. An assumed market share of 4% in Year 1, increasing to 15% in Year 5 is further applied to estimate the number of patients likely to be prescribed conestat alfa in Wales for the indication covered in the submission. The company provides a breakdown of how Berinert® and icatibant acetate is likely to be displaced as a result. It was assumed that the original market share of Berinert® and icatibant acetate was a 50:50 split. The costs are based on an average number of attacks of 32.84 per year[28].

5.1.2 Results

The budget impact is presented in Table 2. The company estimates that introduction of conestat alfa would lead to an overall saving of £176,673 in Year 1, increasing to £236,364 in Year 5 when both Berinert® and icatibant acetate are displaced by conestat alfa.

Table 2. Company-reported costs associated with use of conestat alfa for the treatment of HAE

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	61	61	61	61	61
Sub-population of eligible patients (indication under consideration)	61	61	61	61	61
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine allowing for discontinuations	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without new medicine (no discounts applied)	£4,329,651	£4,329,651	£4,329,651	£4,329,651	£4,329,651
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£0	£0	£0	£0	£0
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
Source of re-dosing rates	-£159,358	-£224,606	-£224,606	-£210,175	-£210,175
Adjusted patient average weight	-£133,830	-£165,000	-£165,000	-£129,256	-£129,256
20% lower market share	-£37,007	-£162,350	-£162,350	-£199,357	-£199,357
20% higher market share	-£125,343	-£199,357	-£199,357	-£273,371	-£273,371
50% lower average number of attacks	-£88,336	-£125,343	-£125,343	-£118,182	-£118,182
50% higher average number of attacks	-£265,009	-£376,030	-£376,030	-£354,546	-£354,546
Alternative source of number of attacks (average 8.5 attacks. Source: Bouillet et al. 2011)	-£45,728	-£64,885	-£64,885	-£61,178	-£61,178
¶¶ commercial in confidence figure removed					

The company estimate that the net resource implications in year 1 will be a saving of £9,316, £10,376 in years 2 and 3, and £6,778 in years 4 and 5. This includes home and hospital administration costs for initial and re-dosing based on the re-dosing rates of 9.3% of conestat alfa patients, 18.6% of Berinert®, and 17.83% for icatibant acetate. These costs were not tested in the sensitivity analyses.

5.1.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact. The company has also factored mortality into the calculations.
- The budget impact considerations are limited to acquisition and administration costs only; other resource use is not included (e.g. monitoring costs and costs associated with adverse events).
- Berinert® and icatibant acetate are both associated with a WPAS. The company did not explore potential discounts to Berinert® and icatibant acetate.

5.2 Comparative unit costs

Comparative unit costs based on list price are provided in Table 3.

Table 3. Examples of medicine acquisition costs

Regimens	Unit cost	Example doses	Approximate costs per patient per acute attack, no re-dosing*
Conestat alfa	¶ per 2,100 unit vial	Body weight up to 84 kg: 50 units/kg for 1 dose by intravenous injection Body weight 84 kg or more: 4,200 units for 1 dose by intravenous injection	¶†
Berinert®	¶ per 500 unit vial	20 units/kg	¶
Icatibant acetate	¶ per 30 mg pre-filled syringe	30 mg subcutaneous injection	¶

* The licences for conestat alfa and icatibant acetate allow repeat dosing[6,7].
†Assumes two vials per dose (any patient > 42 kg would require two vials).
¶ Approved WPAS price: confidential figures removed.
See relevant Summaries of Product Characteristics for full licensed indications and dosing details[4,6,7].
Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.

WPAS: Wales Patient Access Scheme

6.0 ADDITIONAL FACTORS TO CONSIDER

6.1 AWMSG's policy for orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

Conestat alfa does not have European Medicines Agency (EMA) designated orphan status; this was withdrawn in 2010. The company estimates that the number of patients eligible for treatment in Wales is 61, though this figure may be higher due to problems in diagnosing HAE. AWTTC considers conestat alfa eligible to be appraised as a medicine developed specifically to treat rare diseases.[29]

New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 4) if they consider conestat alfa is an orphan/ultra-orphan equivalent medicine.

Table 4. 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.	Patients who experience acute attacks associated with HAE generally experience significant limitations with daily activities and reduced quality of life. Abdominal attacks are associated with pain, nausea, vomiting and diarrhoea, which can progress to requiring hospitalisation. Swelling of the face can be very serious due to risk of upper airway obstruction. Laryngeal angioedema is rare, but it the most serious because it can lead to asphyxiation and death.
Whether the medicine addresses an unmet need (for example, no other licensed medicines).	Conestat alfa is a recombinant C1-inhibitor and offers an alternative treatment option to human plasma-derived C1-inhibitor. Conestat alfa therefore removes the risk of the potential transmission of blood-borne pathogens and does not require blood donor and therefore there is less concern around availability. Conestat alfa can be self-administered using an administration kit which includes solvents and administration devices.
Whether the medicine can reverse or cure, rather than stabilise the condition.	Conestat alfa does not reverse or cure angioedema attacks in patients with HAE.
Whether the medicine may bridge a gap to a "definitive" therapy (for example, gene therapy) and that this "definitive" therapy is currently in development.	Conestat alfa does not bridge a gap to a definitive therapy.
The innovative nature of the medicine.	Conestat alfa is obtained from the milk of rabbits expressing the gene encoding for C1-inhibitor. Conestat alfa is an alternative treatment to human plasma-derived C1-inhibitor and therefore removes the risk of the potential transmission of blood-borne pathogens.
Added value to the patient which may not adequately be captured in the QALY (for example, 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).	This criterion is not applicable as the company has submitted a cost-minimisation analysis not a cost-utility analysis.
Added value to the patient's family (for example, impact on a carer or family life).	Conestat alfa can be administered at home with or without a healthcare professional. This could potentially reduce the burden of the patient's family by allowing the patient to receive treatment in a place of their choice and avoid a visit to the hospital. Conestat alfa can also be self-administered which allows for quicker administration and recovery, limiting the impact of an attack on family life.
HAE: hereditary angioedema	

GLOSSARY

Treatment effect questionnaire
A questionnaire to assess HAE symptoms over time[14]. At each time point for each affected anatomic location, patients were asked three questions which assessed the severity of their symptoms, whether their symptoms had begun to decrease notably, and whether their symptoms were minimal (barely noticeable). The three questions and choice of answers are detailed below:

1. To what extent has the overall severity of your [relevant attack location] HAE attack changed since you received the infusion? This was measured using a seven point categorical scale ranging from “much worse” to “much better”.
2. Has the intensity of your [relevant attack location] HAE attack symptoms begun to decrease noticeably since you received the infusion? The choice of answers were “yes” or “no”.
3. At this moment, are your [relevant attack location] HAE attack symptoms minimal (barely noticeable)? The choice of answers were “yes” or “no”.

The primary endpoint based on the treatment effect questionnaire was defined as the time between dosing and the first time point at which the patient reported all of the following for the primary attack location:

- a response of “a little better”, “better” or “much better” to question 1
- a response of “yes” to question 2
- persistence of improvement at the next assessment time point (i.e. the same or better response to question 1 and a response of “yes” to question 2).

The secondary endpoint based on the treatment effect questionnaire was defined as the time between dosing and the first time point at which the patient reported a response of “yes” to question 3 for all attack locations[14].

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