AWMSG Secretariat Assessment Report – Limited submission

Icatibant acetate (Firazyr®) 30 mg solution for injection in pre-filled syringe

Company: Shire Pharmaceuticals Ltd

Licensed indication under consideration: Symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adolescents and children aged 2 years and older (with C1-esterase-inhibitor deficiency)

Date of licence extension: 19 October 2017

Comparator(s)

The comparators included in the company submission were:

- C1-esterase inhibitor (Berinert®)
- C1 inhibitor (Human) (Cinryze®)

Limited submission details

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

Clinical effectiveness

- Icatibant acetate (Firazyr®) was originally licensed and recommended for use in NHS Wales as an option for the symptomatic treatment of acute attacks of HAE in adults with C1-esterase-inhibitor deficiency. This submission covers the licence extension to include adolescents and children aged 2 years and older.
- The company submission includes paediatric data from a phase III, open label, nonrandomised, single arm, multicentre study (HGT-FIR-086), to evaluate the efficacy (n = 22) and safety (n = 32) of a single subcutaneous dose of Firazyr® in children and adolescents aged 2–18 years. The primary endpoints were time to onset of symptom relief and time to minimum symptoms. Overall, the median time to onset of symptom relief was 1.0 hour, with no differences between children and adolescents. More than 70% experienced symptom relief at 1.1 hours and more than 90% by 2 hours post-treatment. Overall, the median time to minimum symptoms was 1.1 hours, with similar findings for children and adolescents. Secondary endpoints (including individual symptom scores and time to initial symptom relief) supported the clinical benefit shown in the primary endpoints.
- In the HGT-FIR-086 study, Firazyr® was well tolerated; 32 treatment-emergent adverse events (TEAEs) occurred in nine people, all mild or moderate. No TEAEs were severe and none led to study discontinuation or death. Most people (90.6%) experienced injection-site reactions; however, most were of mild or moderate severity and resolved by 6 hours post-dose.
- In the HGT-FIR-086 study, the treatment response in paediatric patients was consistent with the results reported in adult patients.

- No direct comparative clinical efficacy data with Berinert® or Cinryze® are available. The company consider that indirect comparisons between the data are not feasible due to small patient numbers and differences in study design and patient populations.
- Berinert® and Cinryze® are administered intravenously and must be reconstituted before use, whereas Firazyr® is administered subcutaneously from a pre-filled syringe, which may provide a more convenient treatment option.

Budget impact

- The annual cost of treating each patient with Firazyr®, based on patients having 17 attacks a year, is [commercial in confidence figure removed] (Wales Patient Access Scheme [WPAS] price).
- The company estimate that 12 people will be eligible to receive Firazyr® in Year 1 increasing to 13 in Year 5 (based on prevalence reported in the NHS Clinical Commissioning Policy 2013 and applied to the Welsh population). The company estimate 6 people will be treated with Firazyr® based on it displacing 38% of Berinert® usage and 13% of Cinryze® usage.
- The company estimate the budget impact to be [commercial in confidence figure removed] in Year 1 to [commercial in confidence figure removed] in Year 5. This is based on the WPAS price for Firazyr® and the list prices for Berinert® and Cinryze®.
- Berinert® is associated with a WPAS. Sensitivity analysis applying a 10% discount to the list price of Berinert® resulted in a budget impact ranging from [commercial in confidence figure removed] in Year 1 to [commercial in confidence figure removed] in Year 5. Applying a 60% discount resulted in a budget impact ranging from [commercial in confidence figure removed] in Year 1 to [commercial in confidence figure removed] in Year 5.

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

- Firazyr® has 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 people eligible for treatment with Firazyr® in Wales is 63. AWTTC consider Firazyr® eligible to be appraised as an ultra-orphan medicine as the medicine has been granted EMA designated orphan status and the full population of the licensed indication is ≤ 1 in 50,000 persons. The New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 1) if they consider Firazyr® 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 associated with a significant and multifaceted disease burden. HAE attacks are painful, unpredictable and debilitating, and often require emergency medical attention. Attacks can affect a patient's daily activities, including work or schooling. Depression and anxiety are prevalent in patients with HAE. As a chronic, debilitating, and disfiguring disease, HAE can affect almost all aspects of a patient's life. Attacks affecting the hands and feet can impair a patient's ability to work and perform daily activities (e.g. typing on a computer), and because of the unpredictability of attacks, many patients refuse to travel and have anxiety. Facial attacks can be disfiguring, resulting in social stigmatization, isolation, and depression. It is estimated that patients with HAE lose 20 to 100 days of social activities per year.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	Firazyr® is the only subcutaneous preparation licensed in the UK for the treatment of acute attacks of HAE in children and adolescents aged 2–18 years.
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 Firazyr® bridges the gap to a "definitive" therapy.
The innovative nature of the medicine	Firazyr® is a first-in-class and the only bradykinin B_2 receptor antagonist available for the symptomatic treatment of acute attacks of HAE.
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)	Firazyr® may offer a more convenient treatment that is easier for patients and/or their carers to reconstitute and administer.
Added value to the patient's family (e.g. impact on a carer or family life)	Firazyr® is supplied in a prefilled syringe for subcutaneous administration, and is licensed for caregiver administration. Berinert® and Cinryze® require reconstitution and intravenous administration.
AWMSG: All Wales Medicines Strategy Group; HAE: hereditary angioedema; NMG: New Medicines Group; QALY: quality-adjusted life year.	

Additional information

- AWTTC is of the opinion that, if recommended, icatibant acetate (Firazyr®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

Evidence search

Date of evidence search: 26 and 29 January 2018.
Date of range of evidence search: Data limits were only applied to avoid duplication of previous evidence searches. Evidence was therefore considered for the full date range.

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. Icatibant acetate (Firazyr®) 30 mg solution for injection in pre-filled syringe. Reference number: 3293. April 2018.

Appendix: Previous AWMSG secretariat assessment report (published January 2012)

This report was published as part of a previous AWMSG appraisal of icatibant acetate (Firazyr®) (Advice number 0512). The advice from this appraisal has been superseded by advice number 0818. The original appraisal documentation is included here for completeness.

AWMSG Secretariat Assessment Report – Advice no. 0512
Icatibant (Firazyr®▼) 30 mg solution for injection

This assessment report is based on evidence submitted by Shire Human Genetic Therapies on 16 September 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Icatibant (Firazyr®▼) is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1 esterase inhibitor deficiency)[1].
Dosing	Each icatibant 30 mg pre-filled syringe is intended for single use only. Icatibant is intended for subcutaneous administration preferably in the abdominal area, under the guidance of a healthcare professional. Icatibant may be self-administered or administered by a caregiver only after training in subcutaneous injection technique by a healthcare professional. The decision on initiating self-administration of icatibant should only be taken by a physician experienced in the diagnosis and treatment of hereditary angioedema. Laryngeal attacks of HAE should be managed in an appropriate medical institution after injection until the physician considers discharge to be safe. Refer to the SPC for further information regarding repeated injections and use in special populations[1].
Marketing authorisation date	11 July 2008[2].

2.0 DECISION CONTEXT

2.1 Background

Hereditary angioedema (HAE) is characterised by the occurrence of subcutaneous and submucosal swellings in any part of the skin, respiratory and gastrointestinal tracts. Abdominal HAE attacks are often associated with severe pain, vomiting, diarrhoea, and hypovolaemia[3]. Cases of asphyxiation have been reported due to laryngeal oedema[4].

Three forms of HAE have been described: types I and II (approximately 85% and 15% of HAE cases, respectively) are associated with either an absence (type I) or dysfunction (type II) of the plasma protein C1 esterase inhibitor[5]; individuals with type III HAE, which is extremely rare, have normal C1 esterase inhibitor[6]. Lack of functional C1 esterase inhibitor is thought to allow (unregulated) activation of the the kallikrein-kinin system; the early steps of the classical complement pathway, as well as the fibrinolytic system[7].

There is a paucity of data on the prevalence and incidence of HAE; in 2010 guidelines on HAE diagnosis and treatment, incidence was estimated to be 1 in 50,000 irrespective of ethnic background[5]. In their submission the company use a prevalence of 1 in 50,000, based on a 1992 estimate[8], to derive an estimate of 60 HAE patients in Wales[9]. Company-reported audit data suggests there are at least 45 patients in Wales with type I or II HAE (refer to Section 5 for further details).

Management of HAE requires an assessment of the severity, frequency and life-threatening nature of the attacks in order to develop an appropriate treatment plan; this may include long- or short-term prophylaxis as well as interventions to manage acute angioedema attacks. Acute attacks may not require any treatment if cutaneous swelling is the only present symptom[5]. By contrast, laryngeal oedema attacks can lead to life-threatening asphyxiation[4] and may require intubation[5]. Traditionally, the first-line therapy for acute HAE attacks has been intravenous infusion of plasma-derived C1 esterase inhibitor[5] (available as Berinert®; see Section 2.2).

Icatibant is a bradykinin B_2 receptor antagonist[10]; bradykinin is thought to be a key mediator of HAE attacks[7]. Icatibant is administered by subcutaneous injection, and since April 2011 has been licensed for self-administration by patients or their carers[1].

2.2 Comparators

The following comparators were originally requested by the Welsh Medicines Partnership (WMP) and agreed by the company:

- Conestat alfa (Ruconest®▼)
- C1 esterase inhibitor (Berinert®).

The company subsequently suggested that only Berinert® represented a relevant comparator, as it accounted for current routine clinical practice in Wales, and there was negligible or no use of conestat alfa in Wales.

2.3 Guidance and related advice

- Gompels *et al*, for the Primary Immunodeficiency Association (2005). C1 inhibitor deficiency: consensus document[11].
- Gompels and Lock, for the Primary Immunodeficiency Association (2005). C1 inhibitor deficiency: management[12].
- Bowen *et al* (2010). 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema[5].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission discusses evidence from three controlled phase III trials focussing on demonstrating clinical efficacy (FAST-1, FAST-2 and FAST-3) and one trial focussing on the clinical safety of icatibant (EASSI). Results of FAST-1 and FAST-2 have been jointly published in a peer-reviewed journal[13], and as of November 2011 results from FAST-3 are in press[14]. Since none of the efficacy studies use Berinert® as a comparator, the company submission also includes an indirect comparison of icatibant and Berinert®.

3.1 Placebo- and tranexamic acid-controlled studies

FAST-1 and FAST-3 are placebo controlled studies; FAST-2 uses tranexamic acid as an active control treatment[9]. Tranexamic acid was chosen as an active control for FAST-2 on the advice of the European Medicines Agency[10], but is not licensed in the UK for symptomatic treatment of acute HAE attacks[15]. In addition clinical expert opinion sought by WMP suggests that tranexamic acid is not used for this indication in Wales.

3.1.1 Study design

FAST-1 and FAST-2 were identical in terms of study design, exclusion criteria and pre-specified endpoints. Eligible patients were aged 18 years or older, and had a documented diagnosis of HAE type I or II (patients with HAE type III were excluded). Following enrolment (n = 56 for FAST-1; n = 74 for FAST-2), patients were treated at a study centre when the next eligible HAE attack presented. Patients experiencing an abdominal or cutaneous HAE attack were randomised 1:1 to icatibant (30 mg subcutaneous injection) or control treatment (placebo in FAST-1; tranexamic acid 3 g daily for two days in FAST-2). Patients with laryngeal attacks were treated with open-label icatibant, as laryngeal HAE attacks can be life-threatening and therefore treatment with placebo was considered unethical. In all cases treatment was administered by a healthcare professional[13]. Use of rescue medication (e.g. C1 esterase inhibitor, antiemetics, opiates) for the relief of any symptoms was permitted, but withheld for as long as possible (ideally for the first 8 hours) after administration of study treatment[9].

Symptoms were assessed using a 100 mm visual analogue scale (VAS, 0 mm = no symptom; 100 mm = worst possible symptom). The primary endpoint was median time to clinically significant* relief of the index symptom†. Secondary endpoints are listed in Table 1.

FAST-3 (n = 88) used a similar design to FAST-1 and FAST-2, but also included patients with mild to moderate laryngeal attacks for randomisation (to icatibant or placebo). As in FAST-1 and -2, patients with severe laryngeal symptoms received open-label icatibant. The primary endpoint of FAST-3 was the time to symptom relief, measured as the average change in VAS for three main symptoms (cutaneous swelling, cutaneous pain, or abdominal pain). Secondary endpoints are listed in Table 1.

3.2.2 Study results

Results for the primary and secondary endpoints of FAST-1, FAST-2 and FAST-3 are summarised in Table 1. In each study, treatment with icatibant resulted in a shorter time to relief of symptom(s) when compared with control treatment, but this difference did not reach statistical significance in FAST-1. The company[9] and the study investigators[13] suggested that the relatively high incidence of early use of rescue medication in the placebo arm of FAST-1 may have obscured the clinical benefit of icatibant over placebo: in the placebo treatment arm, 13 patients (45%) required rescue medication within 12 hours of treatment (3 patients [11%] in the icatibant arm required rescue medication within the same time period). By comparison, in the FAST-2 study 13% of patients in the control arm (and no patients in the icatibant treatment arm) required rescue medication within 12 hours.

* Clinically significant relief was defined as a reduction in pre-treatment VAS score of between 21 and 30 mm, depending on initial severity of the symptom, for at least three consecutive measurements.

† The most severe of three main symptoms (cutaneous swelling, cutaneous pain, or abdominal pain) was defined as the index symptom in each patient; severity was determined by baseline score on the VAS for the index symptom for purposes of assessing the primary end point.

There was a statistically significant difference between icatibant and placebo for some secondary endpoints (median time to first symptom improvement [as assessed by the patient or as assessed by the study investigator]), but not for others (median time to almost complete relief of symptoms; percentage of patients with clinically significant symptom relief at 4 hours post-treatment).

Table 1. Summary of efficacy endpoints for FAST-1, -2 and -3

FAST-1			
Primary end point	**Icatibant**	**Placebo**	**p value**
Median time to clinically significant relief of the index symptom (hours)	2.5	4.6	0.142
Secondary end points			
Median time to first symptom improvement – (non-laryngeal, assessed by patient) (hours)	0.8	16.9	< 0.001
Median time to first symptom improvement (hours) (non-laryngeal, assessed by study investigator)	1.0	5.7	< 0.001
Median time to almost complete relief of all symptoms (hours)	8.5	19.4	0.08
Patients with clinically significant symptom relief at 4 hours post-treatment (%)	67	46	0.18
FAST-2			
Primary end point	**Icatibant**	**Tranexamic acid**	**p value**
Median time to clinically significant relief of the index symptom (hours)	2.0	12.0	< 0.001
Secondary end points			
Median time to first symptom improvement – (non-laryngeal, assessed by patient) (hours)	0.8	7.9	< 0.001
Median time to first symptom improvement (non-laryngeal, assessed by study investigator) (hours)	1.5	6.9	< 0.001
Median time to almost complete relief of all symptoms (hours)	10.0	51.0	< 0.001
Patients with clinically significant symptom relief at 4 hours post-treatment (%)	80	31	< 0.001
FAST-3			
Primary end point	**Icatibant**	**Placebo**	**p value**
Median time to TOR 50+ three-symptom composite VAS (non-laryngeal) (hours)	2.0	19.8	< 0.001
Secondary end points			
Median time to first symptom improvement – TOR 30+ VAS score single symptom (hours)	1.6	16.2	< 0.001
Median time to first symptom improvement – TOR 30+ (non-laryngeal, assessed by patient) (hours)	0.8	3.5	< 0.001
Median time to first symptom improvement – TOR 30+ (non-laryngeal, assessed by investigator) (hours)	0.9	3.4	< 0.001
Median time to almost complete relief of all symptoms - TOR 90+ (hours)	7.0	33.9	0.016
Median time to TOR 50+ 5-symptom composite (laryngeal, blinded) (hours)	2.5	N/A	N/A
TOR: time to onset of symptom relief, VAS: visual analogue scale. Refer to the Glossary for definitions of TOR 30+, 50+ and 90+.			

For all three studies, results from the open-label phases suggested that efficacy of icatibant was maintained during subsequent HAE attacks. Median time to relief of symptoms was similar for attacks treated in the open-label phase and in the controlled phase (first attack). Results available from FAST-1 and FAST 2 demonstrate that only a minority of attacks (16/109 for FAST-1, 10/122 for FAST-2) required treatment with more than one dose of icatibant[9].

3.2 Supportive study EASSI

This open-label single dose study focuses on the safety of icatibant, but also provides supportive results for efficacy; time to TOR 50+ and time to TOR 30+ were measured as secondary endpoints (see Section 3.4 for study design and safety results). Importantly, this was the only study in the company submission where patients self-administered icatibant. Results from the EASSI study show times to TOR 50+ and TOR 30+ that are comparable with those observed in the pivotal FAST studies, where icatibant was administered by a healthcare professional (Table 2)[9].

Table 2. Time to symptom relief in the EASSI and FAST studies

Study*	Median time to TOR 30+ (hours)	Median time to TOR 50+ (hours)
EASSI	2.0	2.0
FAST-1	2.5	2.5
FAST-2	2.0	2.0
FAST-3	1.5	2.0
*All data for FAST studies is from the blinded phase of the studies; EASSI was an open-label study.		

A patient questionnaire carried out as part of the EASSI study was completed by all 31 patients Icatibant was viewed as easy or very easy to inject by 87.5% of patients; 87.5% were satisfied or very satisfied with how self-administration relieved their HAE symptoms, and 94.6% preferred self-administration to attending a clinic.

3.3 Comparative effectiveness of icatibant and Berinert®

In the absence of any head-to-head clinical comparisons of icatibant and Berinert®, the company provided an indirect comparison of the aforementioned placebo-controlled trials of icatibant with a randomised, double-blind, placebo controlled trial of Berinert® (IMPACT-1)[16]. The primary endpoint of IMPACT-1 was the time from start of treatment to patient-defined onset of symptom relief, which is comparable to some of the secondary endpoints assessed in the FAST trials. To account for variations in results across trials, and differences in precise endpoint definition, indirect comparisons were conducted using different combinations of trial and endpoint data. The results of 45 different comparisons show that icatibant was more effective than Berinert® in the majority of analyses, although few comparisons showed a significant difference between the two treatments[9]. For more detailed results, refer to Appendix 1, Table 1.

3.4 Clinical safety

EASSI is an ongoing, open-label phase IIIb multicentre study, exploring the clinical safety of icatibant self-administration. At the time of submission, 31 patients had been recruited and trained to self-administer icatibant, and a total of 36 icatibant treatments had been received, 31 of which were self-administered. Of this population, 32% of patients experienced at least one adverse event. The most commonly reported adverse event was recurrence of HAE symptoms, which occurred in 29% of self-treated attacks and 40% of healthcare professional-treated attacks[9]. Injection site reactions were observed in the majority of patients receiving icatibant, but all were resolved without intervention[9,10].

Safety data from the FAST studies (in which icatibant was administered by a healthcare professional, rather than self-administered as in the EASSI study) showed similar outcomes to the results of the EASSI study. Symptoms of angioedema were reported in 9 patients (16.1% overall, 4 icatibant [14.8%], 5 [17.2%] placebo) in FAST-1 and in 16 patients (21.6% overall, 10 icatibant [27.8%], 6 [15.8%] tranexamic acid) in FAST-2. In the same two studies, injection site reactions were reported in 96.3% and 97.2% of patients in the icatibant arms, respectively[13], but as in the EASSI study, these all resolved without the need for intervention[9]. Post-marketing experience with icatibant since its original marketing authorisation in 2008 does not appear to have identified any additional safety concerns[9].

3.5 WMP critique

- No evidence is available that directly compares the clinical effectiveness of icatibant with relevant comparators. Therefore the company have conducted an indirect comparison of the FAST studies from the icatibant clinical trial programme, with a placebo-controlled study of similar design assessing Berinert®. Such an analysis should be interpreted with caution, as endpoints chosen for comparison were similar but not identical. Furthermore, allowable use of rescue medication differed from trial to trial, as did characteristics of the patient populations[9]. Nevertheless, the analysis conducted explores a wide range of treatment comparisons to account for this heterogeneity. The results suggest there is no statistically significant difference in efficacy between icatibant and Berinert®[9].
- The advantages of self-administration of icatibant (see below) should be interpreted with the caveat that throughout the clinical trial programme discussed in this ASAR, only the EASSI study (a supportive study in terms of efficacy) included patients self-administering icatibant (n=31); in all other studies icatibant was always administered by a healthcare professional. Clinical outcomes in the EASSI study were consistent with those reported in the FAST pivotal efficacy studies, which the company suggests shows icatibant to be equally effective whether self- or healthcare professional-administered.
- Self-administration of icatibant offers several potential benefits in clinical practice, including a reduced time to treatment administration following HAE attack onset and a reduction in the number of HAE attacks for which patients need to attend accident and emergency (A&E) departments. In relation to the latter point however, patients receiving icatibant for the first time or patients who have suffered a laryngeal attack should still attend a medical institution for treatment or observation respectively[1]. In a patient satisfaction questionnaire carried out as part of the EASSI study, patients expressed a very high (94.6%) preference for self administration over attending clinic/A&E for treatment[9].
- Icatibant is administered subcutaneously from a pre-filled syringe[1], whereas Berinert® is delivered by intravenous injection or infusion and must be reconstituted before use[17], thus allowing for faster time to treatment with icatibant.
- In the pivotal studies FAST-1 and FAST-2, a single HAE symptom had to be considered as “primary” for the purposes of endpoints. This is somewhat artificial given the mix of symptoms with which HAE patients can present, but unavoidable in the context of conducting a robust clinical trial. Time to relief of non-primary symptoms was assessed as a secondary endpoint.

- In the FAST studies, immunogenicity was recorded in 3/82 HAE attacks treated with icatibant; all cases were transient and efficacy was maintained[9]. By contrast, the company highlight that C1 esterase inhibitor treatments such as Berinert® can be immunogenic[9], but cite a case report detailing the development of antibodies in only a single patient[18]. Therefore the proportion of patients that may develop an antibody reaction to Berinert® is not clear.

4.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of icatibant (Firazyr®▼) compared against C1-INH (Berinert®)[9]. As there is no difference between treatments in terms of the QALY gains generated by the model, the company has presented what is essentially a cost minimisation analysis.

A simple decision analytic model has been developed, which is intended to represent the mean average costs and outcomes associated with a single moderate to severe HAE attack over a period of 96 hours. In the absence of direct comparative trial data for icatibant and Berinert®, a wide range of indirect treatment comparisons have been conducted around the FAST clinical trials of icatibant and the IMPACT-1 trial of Berinert®[9,16]. These provide relative estimates of the time to onset of symptom resolution, from which the company has concluded there are no statistically significant differences in this outcome between icatibant and Berinert®. As icatibant may be self-administered via pre-filled syringes, a key contributor to the differential overall costs is the requirement for treatment in the acute (A&E) hospital setting and subsequent admission to hospital. A range of costing approaches has been employed for Berinert®, the base case analysis being based on the weight distribution of patients recruited to the FAST clinical trials. See Appendix 2 for further details.

The company has provided further analyses which remain confidential.

4.1.2. Results.

The results of the base case analyses are summarised in Table 3. The base case model predicted icatibant treatment to reduce mean duration of symptoms by around 2.5 hours compared with Berinert®, which does not translate into a difference in QALYs between treatments over the time horizon of analysis; therefore only costs are presented.

Assuming the full list price for icatibant, when Berinert® is dosed based on the patient weight distribution observed in the FAST trials, or when based on expert opinion, treatment with icatibant is estimated to be less costly than Berinert® treatment. However, assuming the Berinert® dosing observed in a UK audit of HAE patients (45 Welsh patients), treatment with icatibant is estimated to be more costly than treatment with Berinert® (by around £200 per attack treated).

The company provided details of a probabilistic sensitivity analysis based around the base case analysis, which demonstrates cost savings and very little difference in QALY gains between treatments (favouring icatibant by less than a quality-adjusted hour). Supplementary univariate sensitivity analyses provided by the company indicate that icatibant at full list price remains cost saving irrespective of the proportion of patients assumed to self administer while ever the dose of Berinert® is based on expert opinion. WMP-conducted analyses indicate that icatibant at full list price is more costly than Berinert®, irrespective of the proportion of patients assumed to self administer icatibant, while ever the dose of Berinert is based on the UK audit data.

Table 3. Company-reported results of the cost-minimisation analysis of icatibant versus Berinert® for a single HAE attack

	Icatibant	Berinert®	Difference
Base case analysis – Berinert® costs based on patient weight distribution in FAST trials			
Drug costs	£1,546.20	£1,954.62	-£408.41
Administration, monitoring, supportive care costs	£33.36	£215.69	-£182.32
Hepatitis vaccination	£0.00	£0.38	-£0.38
Self-administration training	£0.14	£2.29	-£2.15
Adverse events /allergy testing	£0.00	£0.00	£0.00
Average total cost	£1,579.71	£2,172.97	-£593.26
Alternative Berinert® costing approaches			
Average total cost– Berinert® dosing based on expert opinion	£1,577.38	£1,754.44	-£177.06
Average total cost – Berinert® dose as per Welsh audit data	£1,577.38	£1,378.39	+£198.99

4.1.3 WMP critique

Strengths of the economic evidence include:

- In the absence of direct comparative data, the company has made significant efforts to estimate the relative effectiveness of icatibant and Berinert®. A wide range of indirect comparisons have been conducted in an attempt to account for differences in the trial populations, the use of rescue medications, and definitions of endpoints.
- The company has attempted to conduct a CUA (the preferred type of analysis) before assuming a cost minimisation approach. Different methods of estimating relevant utility weights have been explored.

Limitations of the economic evidence include:

- There are no direct comparative data for icatibant and Berinert®. The available trial data relate to different endpoints and demonstrate substantial variation in the time to symptom relief for the placebo arms, which the company suggests may be due to differences in trial populations and use of rescue medication. Caution is required in the interpretation of indirect treatment comparisons in the context of such possible heterogeneity.

- The indirect comparisons conducted by the company relate to various measures of time to onset of symptom resolution only. The basis of the probabilities of self-administration, need for attendance at A&E and probabilities of hospital admission following A&E attendance are not clearly defined. These probabilities become more relevant when the Berinert® dosing assumed in the model is based on actual doses used in Welsh practice, as in this costing scenario icatibant treatment is estimated to be more costly than Berinert® treatment.
- The model is intended to reflect mean average costs and outcomes associated with one HAE attack; however, it is not clear that all lifetime costs of icatibant treatment have been incorporated, as the first ever treatment with icatibant should be administered by a healthcare professional (which would probably occur in the acute hospital setting).

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost-effectiveness of icatibant in the symptomatic treatment of HAE.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and Methods

The company notes that the HAE prevalence estimates in the literature range from 1 in 10,000 to 1 in 50,000 (which would be equivalent to 300 and 60 patients in Wales respectively) and has assumed the latter. Based on company-sought expert opinion, it is assumed there would be one to two new cases of HAE diagnosed each year. Reportedly based on a recent UK audit, there are 45 patients with type I or II HAE registered at University Hospital of Wales, Cardiff[9]. Although laryngeal attacks can be life-threatening, the company notes that mortality rates due to such attacks are very low and therefore have assumed that no deaths occur over a five-year period. The company assumes three HAE attacks per patient per year (by contrast, the economic model assumes six treatable HAE attacks), and the number of syringes of icatibant and vials of Berinert® required to treat each attack is based on use and patient body weight distributions observed in the FAST clinical trials (as assumed in the base case economic model). Uptake of icatibant is assumed by the company to be 45% in year 1, rising to 65% in year 5.

Results of the company's budget estimates are presented in Table 2. The company estimates cost savings from the use of icatibant based on the current list price. Additional data has been provided by the company which remains confidential, and therefore has not been included in the Table 2.

No further scenario / sensitivity analyses have been conducted by the company around the budget impact estimates. However, the company has highlighted additional cost savings related to reduced need for A&E attendance with icatibant treatment versus Berinert® treatment.

Table 2. Company-reported budget impact estimates for icatibant treatment versus Berinert®

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of HAE patients	46	47	48	49	50
Total number of treatable HAE attacks per year	138	141	144	147	150
Anticipated use of icatibant (%)	45	50	55	60	65
Icatibant treatment costs – based on current list price	£86,630	£98,348	£110,484	£123,039	£136,013
Berinert® treatment costs – based on weight distributions in FAST trials	£122,616	£139,202	£156,380	£174,151	£192,514
Net costs – Full list price	-£35,987	-£40,855	-£45,896	-£51,115	-£56,501

5.1.2 WMP critique of the company's budget impact estimates

The company has employed data from the immunology services department at University Hospital of Wales, Cardiff to determine likely numbers of patients eligible for treatment in Wales. This is lower than estimates for Wales based on prevalence figures, and appears to exclude patients treated at other centres. The Berinert® cost estimates reported above are based on the dosing of Berinert® using the distribution of patient weights in the FAST trials; however, the UK audit, used by the company to determine eligible patient numbers, indicates that actual Berinert® dosing in Welsh practice is somewhat less than would be estimated based on patient body weight in the FAST trials. The company's economic model demonstrates a Berinert® acquisition cost per attack of £1,954 using doses based on the weight distribution of patients in the FAST icatibant trials, and £1,164 using the patient doses obtained from patients in the Welsh audit. This compares with acquisition costs of £1,546 for icatibant using the current list price. Irrespective of the actual acquisition cost assumed for icatibant, the cost estimates for Berinert® appear subject to considerable uncertainty, and the company has elected to use the most costly approach to costing Berinert® in the budget impact analyses. The budget impact analyses may therefore be biased against Berinert® and the reported net costs associated with the use of icatibant misrepresented. There are other costs associated with treatment of HAE attacks, such as attendance at A&E, etc., which are included in the economic model but are not considered in the budget impact analysis.

5.2 Comparative unit costs

Table 3 includes example drug acquisition costs for licensed treatments for acute HAE attacks based on their current list prices.

Table 3. Examples of drug acquisition costs for licensed treatments for acute HAE attacks

	Example dose regimen	Cost per course
Icatibant (Firazyr®▼) 30 mg pre-filled syringe	30 mg subcutaneous injection*	£1,395
Human plasma C1 esterase inhibitor (Berinert®) 50 U/mL	20 U per kg by slow intravenous injection or infusion	£550 to £2,200, depending on body weight
* Dose may be repeated every six hours up to a maximum of three injections in 24 hours See relevant Summaries of Product Characteristics for full dosing details. Costs are based on BNF[19] and MIMS[20] list prices as of 17 October 2011. This table does not imply therapeutic equivalence of the drugs or the stated doses.		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that icatibant is not suitable for shared care within NHS Wales.

6.2 Ongoing studies

The company submission highlights that the EASSI study and the open-label phase of FAST-3 are both ongoing; dates of study completion are not known. No other ongoing studies were highlighted.

GLOSSARY

TOR 30+
Median time to onset of clinically significant relief of the index symptom, defined as a 30% reduction from pre-treatment values.

TOR 50+
Median time to onset of clinically significant symptom relief, defined as a 50% reduction from pre-treatment values.

TOR 90+
Median time to almost complete symptom relief, defined as the earliest time point at which the visual analogue scale score was 0–10 mm for at least three consecutive measurements for all symptoms.

Visual Analogue Scale (VAS)
A method of measuring patient-reported symptoms. Patients rate their symptom on a scale of 0 mm (no symptom) to 100 mm (worst possible symptom).

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Appendix 1. Additional clinical information

Table 1. Results of an indirect comparison of icatibant and Berinert®

Analysis	Number of HR estimates < 1 (favours Berinert®)	Number of HR estimates > 1 (favours icatibant)	Mean HR*	Median HR*	Minimum HR*	Maximum HR*	Icatibant significantly better†	Icatibant significantly worse†
Icatibant vs Berinert® 10 IU/kg	0	45	2.169	2.192	1.069	3.387	29	0
Icatibant vs Berinert® 20 IU/kg	8	37	1.381	1.387	0.717	2.099	2	0
Icatibant vs Berinert® 20 IU/kg, like-for-like comparisons only	4	11	1.133	1.127	0.717	1.715	0	0

HR: hazard ratio.
*HR estimates greater than 1 imply a result in favour of icatibant, whilst HR estimates less than 1 favour the comparator.
† "Significantly better" is the number of comparisons (out of 45) where the entire 95% confidence interval for the HR lies above 1 (favours icatibant), whereas "significantly worse" is the number of comparisons (out of 45) where the 95% confidence interval for the HR lies below 1 (favours comparator).

Appendix 2. Additional health economic analysis Information

Table 1. Health economic analysis detail[9]

Base case model		Appropriate?
Comparator(s)	Icatibant (Firazyr®▼) is compared against human plasma C1 esterase inhibitor concentrate Berinert®.	Yes.
Population	Adult patients who experience moderate or severe HAE attacks (either cutaneous/peripheral/abdominal; or laryngeal) that require symptomatic treatment.	Yes, in line with the licensed indication[1].
Analysis type	A base case cost minimisation analysis has been provided on the basis of no significant difference evident in the time to onset of symptom resolution based on available evidence, and the economic model generated minimal differences in QALY gains (less than a quality-adjusted hour) between icatibant and Berinert®. A decision analytic model was developed in which patients may experience either a cutaneous/peripheral/abdominal attack or a laryngeal attack. Patients treated with icatibant self administer the drug using pre-filled syringes, whereas all Berinert® recipients must be treated in the hospital setting. Non-laryngeal attacks treated with icatibant may resolve; if not, patients are required to attend A&E. Once in A&E patients who resolve successfully are discharged home, or else admitted. All laryngeal attacks require attendance at A&E.	CUA is the preferred type of analysis, which the company has attempted to undertake. It would be reasonable to assume a cost minimisation approach in the absence of any differences in outcomes. The modelled pathway relates to symptomatic treatment only.
Perspective	The NHS in Wales and personal social services (PSS).	The analysis considered direct medical costs only.
Time horizon	The base case analysis assumes a 96 hour time horizon covering a single HAE attack, based on the time taken to onset of symptom resolution observed in the icatibant clinical trials. The company states this approach has been adopted because of the high variability in the frequency of HAE attacks between patients over their lifetime.	HAE is a chronic condition and the company submission highlights that laryngeal HAE attacks can be life threatening. In such circumstances a lifetime time horizon of analysis would normally be appropriate. The company states that a time horizon of analysis covering just one HAE attack was considered more appropriate than a lifetime time horizon due to the variability in the number of attacks per year; however, it is of note that the company employs estimates of the average lifetime number of attacks to estimate resource use and costs per HAE attack associated with administration of the comparator for the economic model and for the budget impact analysis.

Table 1 (continued)

Base case model		Appropriate?
Discount rate	No discounting has been assumed due to the short time horizon of analysis.	Appropriate, if a short time horizon of analysis is considered acceptable. It should be noted that costs of immunisation against hepatitis A and B, extending up to 5 years in the future for patients treated with Berinert® treatment have been included in the estimate of an average cost of treatment per HAE attack for the comparator.
Efficacy	There are no direct comparative trial data available for icatibant and Berinert®. Therefore a wide range of indirect treatment comparisons have been undertaken to define relative time to onset of symptom relief/improvement using hazard ratios.	In the absence of direct comparative data, indirect treatment comparisons may be appropriate. However, the company has noted that the median time to onset of symptom relief varied substantially across the included trials, possibly due to differences in patient characteristics, the definitions of endpoints and the use of rescue medication. The company has employed various methods to adjust for the use of rescue medication, etc. but caution is required in interpretation of meta-analyses in the context of substantial heterogeneity. The company has reported 45 different hazard ratios relating to onset of symptom resolution, estimated via a wide range of indirect treatment comparisons across the FAST-1, -2 and -3 icatibant trials and the IMPACT-1 trial of Berinert®. In two of these comparisons, onset of symptom relief was statistically significantly shorter with icatibant than with Berinert®, and in no cases was Berinert® significantly better than icatibant. The company therefore concludes that a cost minimisation analysis (assuming equivalence in outcomes) would be appropriate (although these data are subsequently used in a CUA). It should be noted that no clinical data are presented in relation to important outcomes such as need for attendance at A&E following self administration of icatibant, need for admission for overnight stay following A&E attendance, etc. The sources of the probabilities of these events are not discussed in the company submission and appear not to be tested in any sensitivity analyses.
Adverse effects	Adverse events, such as injection site reactions following icatibant administration, and headache and muscle spasm following Berinert® administration, are assumed not to impact significantly on patient health-related quality of life or NHS resource utilisation and costs. The model therefore does not incorporate adverse events	Yes, the cost and patient impact of the main adverse events identified are likely to be minimal relative to the costs and impact of HAE attack treatment.

Table 1 (continued)

	Base case model	Appropriate?
Utility values	Utility values for health states during an attack and after onset of symptom relief are applied. Two unpublished sources of utility values have been considered: one based on expert opinion in which clinicians were asked to score HR-QoL of HAE attacks using the EQ-5D; and an estimation of utility values based on VAS scores obtained from the FAST clinical trials.	The two methods of determining utility weights for the health states included in the model produce very different estimates. Those based on expert opinion produce a utility decrement associated with a HAE attack of 0.293 compared with those based on VAS scores from the FAST trials, which produces a decrement of 0.666. However, as the modelled time horizon relates only to the course of symptom resolution for one attack, the actual difference in the resultant QALYs between icatibant and Berinert® treatment is approximately zero, irrespective of the method used to estimate utility weights.
Resource use and cost	Resource use and costs relate to drug acquisition costs for icatibant and Berinert®, plus analgesic and antiemetic treatments, the costs of administration in the A&E setting, the costs of one overnight hospital stay for those whose symptoms do not resolve adequately to permit discharge. In addition, the cost of hepatitis vaccination is included for Berinert® recipients. The company has provided additional analyses which remain confidential.	Acquisition costs for Berinert® have been estimated using three different approaches: weight distribution of patients in the FAST trials, company-sought expert opinion on likely number of vials per patient, and number of vials per patient based on an audit of 45 Welsh patients (not verified). Appropriate published unit costs appear to be used. It should be noted that the future (5 years hence) costs of ongoing hepatitis vaccination booster has been rolled into the average cost of each attack treated with Berinert®. However, the first time use of icatibant must be provided by a healthcare professional and it is not clear that this cost has been incorporated into the average cost of an attack treated by icatibant. The current list price per icatibant pre-filled injection is listed in Table 3, Section 5. The company has provided additional confidential analyses.
Uncertainty and scenario analyses	The company provides alternative approaches to costing Berinert®. A probabilistic sensitivity analysis has been conducted based around the base-case model parameters.	The company reports one-way scenario analyses relating to acquisition costs. Probabilistic sensitivity analysis has been conducted, but this relates to the base case model parameters. Therefore no sensitivity analyses have been presented in the context of the company's proposed patient discount scheme. There has been no exploration of the impact of uncertainty based around the assumed probabilities of self-administration, resolution of symptoms, hospital admission following A&E attendance, the basis of which are not clearly defined.
Model provided?	Yes.	Yes.

A&E: accident and emergency; CUA: cost-utility analysis; HAE: hereditary angioedema; HR-QoL: health-related quality of life; QALY: quality-adjusted life year; RCT: randomised controlled trial; VAS: visual analogue scale.