Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Angela Timoney FRPharmS
NHS SCOTLAND

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

SMC No. (476/08)

Shire Human Genetic Therapies

10 February 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

icatibant acetate (Firazyr®) is accepted for use within NHS Scotland.

Indication under review: Symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).

Icatibant treatment resulted in symptom relief in patients suffering acute abdominal, cutaneous and/or laryngeal attacks of hereditary angioedema.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of icatibant. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).

Dosing Information

The recommended dose is a single slow subcutaneous injection of icatibant 30 mg. In case of insufficient relief or recurrence of symptoms, a second injection can be administered after six hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection can be administered after a further six hours. No more than three injections should be administered in a 24 hour period.

It is intended for use under the guidance of a healthcare professional and may be self-administered or administered by a caregiver only after training in subcutaneous injection technique by a healthcare professional. Patients with laryngeal attacks should be managed in an appropriate medical institution after injection until the physician considers discharge to be safe.

Product availability date

July 2008. Icatibant acetate was granted orphan status in February 2003

Summary of evidence on comparative efficacy

Hereditary angioedema (HAE) is an autosomal dominant disease caused by the absence or dysfunction of C1-esterase inhibitor. It is characterised by episodic attacks of oedema resulting in subcutaneous and submucosal swelling in any part of the skin and the respiratory and gastrointestinal tracts. These attacks are related to the increased release of bradykinin which is the key mediator in the development of clinical symptoms. Icatibant is a synthetic decapeptide that acts as a selective competitive bradykinin-B2 receptor antagonist.[1]

Three randomised, double-blind, multicentre, controlled phase III studies (FAST-1, FAST-2, and FAST-3) have assessed the efficacy of icatibant in the treatment of acute attacks of HAE. All three studies recruited adults ≥18 years of age with a diagnosis of type I or II HAE presenting with a current attack of moderate to very severe severity affecting cutaneous or abdominal areas. Patients were randomized in a 1:1 ratio to start treatment with icatibant or placebo (FAST-1 and FAST-3), or icatibant or tranexamic acid (FAST-2), within six hours of the time at which the attack reached moderate severity. Patients presenting with laryngeal attacks were given open-label icatibant in FAST-1 and FAST-2, whereas in FAST-3, patients with mild to moderate laryngeal attacks were randomised to icatibant or placebo, while those with a severe attack received open-label icatibant. Study medications were administered in a double-blind, double-dummy manner with icatibant as a single subcutaneous injection of 30mg/3mL, and tranexamic acid as 1g orally three times daily for 2 days. Rescue therapy (e.g. analgesia, anti-emetic, or C1 esterase inhibitor concentrate) was permitted but was withheld for as long as possible, ideally for at least 8 to 9 hours after study-drug administration. Prophylactic androgens were permitted but dosage was to be stable or reduced. These controlled phases of

the studies were followed by open-label extensions during which subsequent attacks of HAE could be treated with icatibant. During the open-label extensions, up to three injections of icatibant could be given for an attack.[2,3]

The primary efficacy endpoint in FAST-1 and FAST-2 was the median time to clinically significant relief of the index symptom. The index symptom was the one (cutaneous swelling, cutaneous pain, or abdominal pain) that was scored highest on a 100mm visual analogue scale (VAS, with 0mm = no symptom and 100mm = worst possible symptom) by the patient. If the patient had a combination of symptoms that included abdominal pain, then abdominal pain was classified as the index symptom. A clinically significant change was defined as a reduction from pre-treatment values of 21 to 30mm, depending upon initial severity, and the time to meet this endpoint was the first of three consecutive measurements in which the clinically significant reduction was achieved. In FAST-3, the primary efficacy measure was the time from blinded treatment administration to a 50% reduction in symptom severity, measured using a mean composite VAS score, which was a composite of three symptom domains (abdominal pain, cutaneous pain, and cutaneous swelling). The primary endpoint was met in the FAST-2 and FAST-3 studies, and time to clinically significant index symptom relief was numerically lower in FAST-1, although this did not reach statistical significance. The table below presents the primary endpoints and selected secondary endpoints of all three studies for patients presenting with non-laryngeal attacks.

Table: Primary endpoints and selected outcome data from the FAST-1, FAST-2, and FAST-3 studies. [2,3]

	FAST-1		**FAST-2**		**FAST-3**	
	Icatibant	**Placebo**	**Icatibant**	**Tranexamic Acid**	**Icatibant**	**Placebo**
n	27	29	36	38	43	45
Median time to clinically significant relief of index symptom (hours)[a]	2.5 , p=0.14	4.6	2.0	12	1.5	18.5
Median time to 50% reduction in composite VAS score (hours)[b]	2.5, p=0.02	7.0	2.0	15	2.0	19.8
Response rate: proportion of patients achieving primary endpoint at 4 hours (%)	67, p=0.18	46	80	31	74, p<0.0001	31
Median time to almost complete relief of symptoms (hours)[c]	8.5, p=0.08	19.4	10	51	8.0, p=0.012	36

Unless quoted, p-values for comparisons were <0.001.
[a] Primary endpoint in FAST-1 and FAST-2. Secondary endpoint in FAST-3
[b] Primary endpoint in FAST-3. Post-hoc analyses in FAST-1 and FAST-2.
[c] Almost complete relief of symptoms (when VAS was between 0 and 10mm)

In the FAST-3 study, owing to small patient numbers, there were insufficient data to compare icatibant (n=3) and placebo (n=2) in the treatment of mild to moderate laryngeal attack. Furthermore, of the two patients randomised to placebo, one patient progressed to severe symptoms and so received open-label icatibant, and the second patient required icatibant as rescue medication. The median time to onset of symptom relief was 2.5 hours for patients

randomised to icatibant. In total there were 21 patients with laryngeal symptoms treated with icatibant (including 5 patients presenting with severe symptoms, and 11 patients in the open-label extension phase). The median time to onset of symptom relief was 2.3 hours.[3] Another 11 patients with laryngeal symptoms received open-label icatibant in the FAST-1 (n=8) and FAST-2 (n=3) studies. Median time to first symptom improvement, as reported by the patients, was 0.6 and 1.0 hours, respectively. Three of these patients required rescue medication within 24 hours of icatibant administration.[2]

Summary of evidence on comparative safety

The majority of patients given icatibant reported local injection-site reactions, e.g. erythema and swelling, most of which were mild to moderate in severity and self-limiting, resolving within four hours of administration.[2,3]

Worsening or recurrence of angioedema was reported by 15%, 28%, and 11% of patients allocated to icatibant, and 17%, 16%, and 22% allocated to control, in the FAST-1, FAST-2 and FAST-3 studies respectively. None of these were considered related to treatment.[2,3]

Interim results of an ongoing multicentre, open-label, uncontrolled study, primarily exploring the safety of self-administration of icatibant has not identified any further safety issues in the 56 patients, 48 of whom were icatibant experienced at study outset, treated to date. Local, self-limiting injection-site reactions were reported in the majority of patients, and worsening or recurring symptoms of HAE were recorded in 23% (n=13/56) of patients.[4]

Summary of clinical effectiveness issues

Icatibant is an orphan product for the treatment of acute attacks in patients with type I or II HAE.

There are some limitations with the evidence supporting the use of icatibant in the treatment of acute HAE. The sample sizes in the studies are small but in the context of this orphan indication are considered reasonable. The high rate of injection-site reactions experienced by patients receiving icatibant may have compromised blinding. The primary outcome used in the clinical studies was based on changes in symptom severity as measured using a VAS. There are no accepted standard outcome measures for treatment of HAE, and use of VAS has not been validated for this condition. 'Significant symptoms improvement' was defined differently in FAST-3 (reduction in a composite score of all three main symptoms), compared with FAST-1 and FAST-2 (reduction in an index symptom). The use of the composite score in FAST-3 addressed a criticism that assessment of an index symptom does not account for the range of symptoms that a patient may experience during an attack.

In FAST-2 and FAST-3, superiority in terms of a faster onset of symptomatic improvement was demonstrated for icatibant compared with control (tranexamic acid, and placebo respectively). However there was no significant difference between the treatment arms in FAST-1. When the data from FAST-1 and FAST-2 were analysed post hoc to compare the time to 50% reduction in VAS score, the primary endpoint of FAST-3, there was consistency between studies with a benefit for icatibant.

There are no comparative data for the use of icatibant in laryngeal attacks, one of the most clinically important manifestations of HAE because of the life-threatening nature of the symptoms.

The main treatment used in NHS Scotland for acute attacks of HAE is infusion of human C1-esterase inhibitor concentrate (Berinert® or from fresh frozen plasma). Treatment is generally given in hospital Accident and Emergency (A&E) Departments. A recombinant analogue of C1-esterase inhibitor, conestat alfa, is licensed for this indication but has been not recommended by SMC for use in NHS Scotland. Less effective alternatives that are used in the treatment of acute HAE attacks include tranexamic acid and the androgen danazol (used off-label).

While the predominant treatment for acute attacks of HAE in NHS Scotland is C1-esterase inhibitor concentrate, at the time of study design there was no licensed medicinal product so it was not considered an appropriate control by the regulatory authorities. Tranexamic acid was therefore used in FAST-2, and placebo in FAST-1 and FAST-3. The daily dose of tranexamic acid used was less than the maximum recommended by its marketing authorisation (1,500mg three times daily).

The company submitted an indirect comparison of icatibant and a C1-esterase inhibitor concentrate (Berinert®), using the Bucher methodology. A large number of comparisons was made in an attempt to account for the studies' heterogeneity and methods used for handling data in patients who required rescue medication, making the results difficult to interpret. Expert statistical advice sought by SMC concluded that there was no significant difference between icatibant and Berinert® for the outcomes compared.

Icatibant has several potential advantages for both the patient and the service. C1-esterase inhibitor must be administered by intravenous infusion or slow bolus injection. Icatibant is presented as a pre-filled syringe and is licensed for self-administration by subcutaneous injection. This may enable patients to treat attacks early outside the A&E setting and could result in a shorter time between onset of symptoms and initiation of treatment. This may be a particular benefit for patients who live in areas distant from a major A&E department. However, appropriate patient education would be needed to support self-administration; in the study of icatibant self-administration, patients required training in both the assessment of acute attacks and in self-administration

Icatibant is not derived from human donor blood, therefore does not carry the risk of blood-borne pathogen transmission associated with C1-esterase inhibitor. Potential disadvantages of icatibant are that it is not approved for use in children or pregnant women due to the lack of safety data; puberty and pregnancy have been noted as triggers for HAE attacks.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing icatibant with Berinert®. The submission acknowledged that this could also be seen as a cost-minimisation analysis because the estimated quality-adjusted life years (QALY) gain was small.

A model was developed based on a decision analytic framework for adult patients with C1-esterase inhibitor deficiency treated for moderate to severe attacks of type I and II HAE. The time horizon of the model was the duration of one attack of HAE (assumed to be 96 hours). In the model patients experience a moderate to severe attack which is either (i) laryngeal or (ii) non-laryngeal (cutaneous, peripheral, or abdominal). Patients either:

- have therapy administered in A&E, following which the patient is either discharged or admitted, or
- self-administer, and either require no further care or attend A&E with the possibility of admission.

QALYs were estimated for each intervention by combining data for the time to onset of symptom relief from an indirect comparison with utility weights for two health states: (i) during an attack (i.e. the period of time before the onset of symptom relief), and (ii) after recovery (i.e. after onset of symptom relief). The indirect comparison used the Bucher method.

Utilities came from 8 clinicians completing an EQ-5D to reflect their perception of the patient's experience of an attack.

The analysis included costs for drug acquisition; administration, monitoring and supportive care; hepatitis A and B vaccinations; self-administration training and adverse events.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was given on the price of icatibant as part of a home delivery package. Based on the PAS, icatibant was estimated to lead to a saving of £813 per patient, mainly due to differences in drug acquisition, monitoring, administration training and adverse event costs. Based on the indirect comparison there is no significant difference in effectiveness between the treatments in terms of QALY gain per attack (0.0000852 QALY in favour of icatibant).

The indirect comparison provided suggests that icatibant is non-inferior to C1-esterase inhibitor (Berinert®). There is inherently more uncertainty with an indirect comparison than with a 'head-to-head' trial and the mixed treatment comparison method would have been more robust than the Bucher method. However, since this would have added only one further trial to the evidence base, it would be unlikely to change the conclusion. Given the cost savings predicted, the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Primary Immunodeficiency Association
- Hereditary Angioedema Patient Association

Additional information: guidelines and protocols

An international consensus guideline on the management of acute attacks of hereditary angioedema was published in 2010. The guideline advocated the early treatment of acute attacks, and recommended that plasma-derived C1 esterase inhibitor (Berinert®), icatibant, or ecallantide (not licensed in the UK) should be used to treat cutaneous swellings of the face and neck, or abdominal attacks, or attacks involving the larynx. Due to the lack of comparative studies, no agent was considered better. In instances in which none of the recommended first-line therapies are available, the use of solvent detergent-treated plasma, or fresh frozen plasma could be considered. Doubling the dose of long-term prophylactic treatments (attenuated androgens or tranexamic acid) were also suggested as an option; however it was acknowledged there were limited data to support this recommendation. Supportive care with intravenous fluids and analgesia are considered essential but do not modify the outcome of an attack. The guideline envisaged that patients should be offered home therapy programs, analogous to haemophilia services.

In a UK consensus guideline commissioned by the Primary Immunodeficiency Association and published in 2005 (predating the availability of icatibant and licensing of C1 esterase inhibitor), the management of acute attacks was described. Treatment options were selected based on the severity of the acute attack. Attenuated androgen, stanozolol or danazol, were considered options for episodes of peripheral swelling only, as they can shorten the duration of the attack. In cases of upper airway swelling, the recommendation was to use C1 esterase inhibitor concentrate 500 to 1,500 international units. It was suggested that abdominal oedema be managed with non-steroidal anti-inflammatory drugs for pain relief, and that severe attacks be treated with C1 esterase inhibitor. As an alternative to C1 esterase inhibitor, fresh frozen plasma or solvent detergent-treated plasma may be used, however data for solvent-treated plasma's efficacy was scarce. Tranexamic acid 1g four times daily for 48 hours was listed as an option, but no specific guidance was given as to its place in therapy.

Additional information: comparators

The C1-esterase inhibitor Berinert® is predominantly used in NHS Scotland. Danazol (off-label) and tranexamic acid are also used for treating acute HAE attacks. Conestat alfa is licensed for acute treatment of HAE but has not been recommended by SMC for use in NHS Scotland.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Icatibant	**30mg subcutaneous injection, repeated to a maximum of three doses per attack.**	**1,395 to 4,185**
Conestat alfa	50units/kg intravenous injection.	2,800
Human C1-esterase inhibitor (Berinert®)	20units/kg intravenous injection or infusion.	1,650
*Danazol capsules	200mg orally two or three times daily	Up to 3/day
Tranexamic acid 500mg tablets	1,000mg to 1,500mg orally two to three times daily	Up to 1/day

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS (November 2011) except oral medicines, from eVadis on 23 November 2011. Weight based doses calculated from an adult bodyweight of 70kg.
*Danazol capsules are unlicensed for the treatment of acute HAE attacks.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 95 patients, rising to 115 by year 5. Company estimates of market share were commercial in confidence. The gross impact on the medicines budget was estimated at £242K in year 1 and £427K in year 5. The net medicines budget impact, taking into account savings on the costs of existing medicines, was estimated to be a cost savings of £16K in year 1 and £28K in year 5. The estimated cost savings due to implementation of the PAS were greater.

The company also estimated some savings on the administration costs of existing treatments but these are not included in the figures above.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1) Shire Human Genetic Therapies. SPC – Firazyr 30mg solution for injection in pre-filled syringe. [online] Available from http://www.medicines.org.uk [Last updated 21 April 2011].
2) Cicardi M, Banerji A, Bracho F, Malbran A et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med. 2010; 363: 532-41. http://dx.doi.org/10.1056/NEJMoa0906393
3) Lumry WR, Li HH, Levy RJ, Potter PC et al. Randomized placebo-controlled trial of the bradykinin B_2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol. 2011; 107: 529-37.
4) Center for Drug Evaluation and Research. Medical Review – Icatibant (application number: 022150). [online] Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [Last updated 25 August 2011].

This assessment is based on data submitted by the applicant company up to and including 16 January 2012.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.