PUBLIC SUMMARY DOCUMENT
Product: ICATIBANT, injection, 30 mg in 3 mL (as acetate), single use pre-filled syringe, Firazyr®
Sponsor: Shire Australia Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission sought an Authority Required listing for treatment of laryngeal/oro-pharyngeal and severe abdominal attacks of acute hereditary angioedema (HAE) for patients with confirmed diagnosis of C1-esterase inhibitor deficiency.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Icatibant was TGA registered on 3 September 2010 for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).

4. Listing Requested and PBAC's View

Authority required

Supply for anticipated emergency treatment of laryngeal/oro-pharyngeal and severe abdominal attacks of acute hereditary angioedema (HAE) for patients with confirmed diagnosis of C1-esterase inhibitor deficiency with treatment initiated by a specialist immunologist or other relevant specialist.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Hereditary angioedema is a rare, potentially fatal, autosomal dominant disease caused by deficiency of C1 esterase inhibitor (C1-INH) due to mutations of the C1-INH gene. HAE is characterised by spontaneous, unpredictable and recurrent attacks of oedema of the extremities, face, trunk abdominal viscera and upper airways that can be painful and debilitating.

Icatibant is proposed as an alternative treatment, administered subcutaneously, of potentially life-threatening acute episodes of hereditary angioedema.

6. Comparator

The submission nominated C1-INH (Berinert®) as the comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

Five randomised double-blind controlled trials were included in the submission – FAST-1, FAST-2, IMPACT.1, Kunschak and Zuraw. The submission presented an indirect comparison of icatibant and C1-INH with placebo as the common reference, using the icatibant study (FAST-1) and the C1-INH studies (Zuraw, Kunschak, IMPACT.1).

The PBAC noted that none of the studies presented in the submission included self administered icatibant.

The table below details the published trials presented in the submission.

Trial ID / First author	Protocol title / Publication title	Publication citation
Icatibant vs Placebo (Icatibant vs Tranexamic acid)		
FAST-1 (FAST-2) Reidl M (2008)	Icatibant, a selective bradykinin B2 receptor antagonist, proves effective and safe in treating the symptoms of hereditary angioedema (HAE) attacks.	*J Allergy Clin Immunol*, 2008;21:S103
C1-INH vs Placebo		
IMPACT.1 Craig TJ et al	Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks.	*J Allergy Clin Immunol*: (available online Sept 2009 as an epublication)
Bernstein JA et al.	Treatment of acute abdominal and facial attacks of hereditary angioedema (HAE) with human C1 esterase inhibitor (C1-INH): Results of a global, multicenter, randomized, placebo-controlled, Phase II/III Study (IMPACT.1).	*J Allergy Clin Immunol*, 2008; 121 (3): 795. Abstract LB16.
Kiessling P et al.	Treatment of hereditary angioedema with human C1 esterase inhibitor: results of a global, multicentre, randomised, placebo-controlled, phase II/III dose-finding study of acute abdominal and facial attacks (IMPACT.).	*Clin Experimental Immunol*, 2008; 154 (Suppl. 1):143-144, Abstract P220B.
Kunschak M et al. (1998)	A randomized, controlled trial to study the efficacy and safety of C1-Iinhibitor concentrate in treating hereditary angioedema.	*Transfusion,* 1998;38:540-9.
Waytes AT et al. (1996)	Treatment of hereditary angioedema with a vapour-heated C1-Iinhibitor concentrate.	*NEJM*, 1996;334 (25):1630-1634
Zuraw BL et al. (2008)	Results of a randomized double-blind controlled study of nanofiltered C1-inhibitor for the treatment of HAE attacks.	*Annals of Allergy, Asthma & Immunology*, 2008;1 (Suppl 1):A7 (abstract 16).

8. Results of Trials

FAST-1: Efficacy of icatibant vs placebo.

ATTACKS RANDOMISED (NON-LARYNGEAL)

The results for time to onset of symptom relief-based on composite visual analogue scale (VAS) score showed that there was a statistically significant difference, between icatibant and placebo, in time to onset of symptom relief (using the composite VAS score) after censoring of patients before the onset of relief at 120 hours (1.5 hrs vs 9.0 hrs; p = 0.01) and at time rescue medication was taken (1.5 hrs vs 8.0 hrs; p = 0.024).

ATTACKS NOT RANDOMISED (SINGLE OPEN-LABEL ICATIBANT) – LARYNGEAL

The median time to observable regression of visual symptoms (as measured by the investigator) appeared to vary between the non-randomised icatibant treatment arms

(laryngeal vs non-laryngeal attacks). These outcomes were not the primary outcomes of the FAST-1 trial and the icatibant laryngeal arm data represented evidence from a single treatment arm.

IMPACT.1, Kunschak and Zuraw: Efficacy of C1-INH vs placebo.

Data from the IMPACT.1 trial demonstrated evidence for the efficacy of C1-INH 20U/kg in the absence of any new attack occurring in this treatment group before complete resolution of the previous attack, indicating an absence of rebound angioedema. This endpoint was not examined in the icatibant trial, FAST-1.

Patients in the Kunschak trial appeared to experience a longer time to symptom relief compared to the other trials. However, only the symptoms with the longest time-to relief were included in the analysis.

Zuraw reported that the time to onset of unequivocal relief from the angioedema symptom was reduced in the treated arm (2 hours) compared to the placebo arm (>4 hours).

Indirect comparison of effectiveness (FAST-1, Kunschack, IMPACT.1. and Zuraw)

The clinical assessment of symptom relief varied across the trials included in the indirect comparison. This and other differing characteristics among the trials may reflect the apparent heterogeneity in treatment effect observed, among the placebo arms across the trials and among the C1-INH active treatments across the trials. These differences made it difficult to conduct a robust assessment of comparative effectiveness between icatibant and C1-INH concentrate.

The results for time to complete resolution (Kunschak and IMPACT.1.) or "almost complete" resolution (FAST-1) of symptoms are summarised below. No data were provided for Zuraw.

Time to complete or almost complete resolution of attack symptoms

Trial ID	Treatment arm	N	Time to (almost) complete resolution		p value vs placebo
FAST-1	Icatibant	27	Median hrs (25%, 75% IQR)	8.5 (2.5, 31.5)	p=0.08
	PBO	29		19.4 (10.2, 55.7)	
IMPACT. 1	C1-INH 20U/kg	39	Median hrs (range)	4.92 (0.47-1486)	p=0.02
	C1-INH 10U/kg	43		20.00 (0.47-1486)	NS
	PBO	42		7.79 (0.33 - 1486)	
Kunschak	C1-INH 25U/kg	11	Median hrs (25%, 75% IQR)	14.08 (3.00, 29.08)	NR
	PBO	12		26.00 (25.00, 50.83)	NR

NS = Not statistically significant; IQR = Inter quartile range; NR = Not reported; PBO = placebo

The results were difficult to interpret given that the time estimates may be substantially affected by the use of rescue medication which could have varied among the trials – both in timing and extent of use. Furthermore, the endpoints vary in terms of degree of resolution and the times for complete resolution in the icatibant FAST-1 trials may be longer than those observed for "almost complete resolution".

In an informal indirect comparison, the results of use of rescue medications (C1-INH and symptomatic therapy) and response rate at 4 hours post treatment favour C1-INH 25U/kg over icatibant. It is unclear how many patients had multiple attacks within either study.

Overall, compared with placebo, C1-INH demonstrated a statistically significant difference in time to complete resolution whereas time to "almost complete resolution" favoured icatibant although this difference was not statistically significant.

For PBAC's comments on these results, see Recommendation and Reasons.

The PBAC noted there were no available data from direct trials comparing icatibant with C1-INH concentrate and given the heterogeneity among the trials considered for the indirect comparison, a robust comparative assessment of their toxicity profiles was difficult.

A summary of the safety data from the FAST-1 and FAST-2 trials showed:

-Nearly all patients (>96%) receiving icatibant experienced injection site reactions, compared to approximately 25% of patients in the comparator groups;
-In FAST-1, all (100%) icatibant treated patients experienced erythema; 23 patients (85.2%) experienced swelling; 18 patients (66.7%) experienced warm sensation, 6 patients (22.2%) experienced burning and 5 patients (18.5%) experienced both itching and cutaneous pain. In patients with laryngeal symptoms at baseline, there were 8 severe injection site reactions of erythema (100.0%) and 6 events of swelling (75.0%);
-In FAST-2, more patients in the icatibant arm experienced adverse events (excluding injection site reactions) than did patients in the tranexamic acid arm (50.0% versus 36.8%). A total of 4 patients (5.4 %) experienced 6 severe adverse events, all of which were considered 'unrelated' to the study treatment.

No safety issues associated with C1-INH concentrate were identified in IMPACT.1 or Kunschak and Zuraw provided inadequate data on safety. The submission noted that C1-INH concentrate has been used extensively and is considered to have a good safety profile.

9. Clinical Claim

The submission described icatibant as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over C1-INH concentrate, noting the limitations of the indirect evidence.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented two economic analyses.

1) A modelled evaluation of the cost-effectiveness of C1-INH concentrate vs best supportive care (without C1-INH concentrate being available). The model replicated an HAE attack (of both laryngeal and severe abdominal types, respectively) for each treatment arm, and assigned probabilities of hospitalisation and death.

The incremental cost per life year gained (LYG) for both sites pooled (laryngeal and abdominal) was calculated to be less than $15,000.

2) A cost-minimisation analysis of icatibant vs C1-INH concentrate. Two alternative calculations of equi-effective doses were presented, determined on the basis of total dose used per attack. These were: that 1.12 (x30 mg) injections of icatibant (av. requirement per

attack) would replace 2.31 or 3.97 (x500 U) vials of C1-INH concentrate, depending on whether trial-based or practice-based dosing was used.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost per year to the PBS to be less than $10 million in Year 5. The PBAC considered the financial implications were underestimated.

12. Recommendation and Reasons

The PBAC considered that there is a clinical need for an effective treatment for hereditary angioedema (HAE) for administration outside the emergency setting. However, the appropriate setting for icatibant on the PBS is uncertain, given the recommendation for registration by the Advisory Committee on Prescription Medicines (ACPM) that "it was clinically appropriate in view of the supporting safety data to allow patient self administration." The sponsor's Pre-PBAC Response noted that the ACPM recommendation for home administration was unexpected and that the submission had been prepared in the context of treatment under medical supervision only.

The PBAC noted that the requested restriction was narrower than the ACPM recommended indication and the Australian Society of Clinical Immunology and Allergy (ASCIA) guidelines. These guidelines recommend the use of icatibant for mild abdominal pain, as well as for peripheral attacks, The clinician representative from ASCIA at the hearing stated that ASCI recommends the use of icatibant in the following situations:

- patients with a history of laryngeal or severe abdominal attacks;
- patients in remote locations;
- families where there are multiple HAE sufferers where it is necessary to have one injection on hand due to the higher probability of an attack
- ASCIA recommend individual and specific care plans for each patient which will include the option for the patient to call the treating physician or immunologist at the onset of an attack and discuss if self administering Firazyr is suitable
- ASCIA recommends a follow up visit with the physician in person or over the phone soon after an attack where Firazyr has been self administered

The clinician assured the Committee in the hearing that ASCIA would be willing to work with the PBAC to ensure that PBS usage complied with the PBS restriction.

The PBAC noted that it is not possible to construct a PBS restriction around a patient's location. Members were also concerned that it was impractical to suggest that patients be required to experience severe abdominal pain before administering icatibant. It places the responsibility on the patient to have to make clinical decisions as to whether they were experiencing an attack serious enough to warrant its use. Furthermore, the term 'severe' abdominal attacks' requires a subjective assessment by the patient and also partially defeats the purpose of early intervention by self-administration, which is to stop an attack progressing to such a point. The PBAC thus considered there was considerable potential for utilisation outside the intended restriction.

The PBAC noted that the appropriate comparator can no longer be simply defined as C1-INH concentrate, but more might be accurately described in this setting as "delayed treatment with C1-INH concentrate, where necessary". Further there is no evidence demonstrating the

effectiveness or safety of icatibant actually undertaken in the self-administration setting ie. effectiveness and safety are assumed to be applicable from trials undertaken in the hospital setting, where icatibant is administered under medical supervision and patient conditions are monitored.

In addition, the PBAC considered that there is limited evidence and high uncertainty surrounding the evidence presented in the submission to support use of icatibant in the hospital/emergency setting. The PBAC noted that there are no studies directly comparing icatibant and C1-INH, and the indirect studies were not sufficiently exchangeable to be useful for an indirect comparison. The claim of non-inferiority between icatibant and C1-INH concentrate is made on the basis of an informal comparison and the submission did not conduct a formal indirect comparison between icatibant and C1-INH due to the apparent heterogeneity between the trials.

The PBAC considered the individual results suggested that icatibant may not be as effective as C1-INH in preventing rebound oedema, as in the FAST-1 trial occasional post icatibant angioedema attacks required treatment with C1-INH. In contrast, results from the IMPACT.1 study indicated that acute treatment with C1-INH protects patients with HAE from rebound angioedema attacks. The sponsor's pre-sub-committee response notes that whilst there were no reports of rebound oedema in the IMPACT.1 study, worsening of symptoms after initiation of C1-INH was reported in 2/27 patients. In the FAST 1 study, HAE reported as an AE included inadequate initial treatment, worsening or recurrence of a treated attack or the emergence of a new attack, and was also observed in 2/27 patients. Given the differences in definitions between the trials, the pre-sub-committee response concludes that it is difficult to compare the incidence of rebound across the studies. The PBAC noted that the half-life of C1-INH is considerably longer than icatibant (icatibant $t_{1/2}$ =1-1.5 hrs, C1-INH concentrate $t_{1/2}$ = 32 hrs).

The PBAC concluded that the data presented in the submission were insufficient to support a claim of non-inferiority against C1-INH, and that the cost-minimisation approach was therefore not adequately supported.

The appropriate dose of C1-INH is also unclear. The submission stated that the dosing regimen that would be expected to be used in clinical practice is: 500 U for patients <50kg, 1000 U, for patients 50-100kg, 1500 U, for patients ≥100kg. This represents a range of doses between 10 U/kg and 20 U/kg, depending on the patient's actual weight. Further, the submission presented two alternative calculations of equi-effective doses, determined on the basis of total dose used per attack. These are: that 1.12 (x30mg) injections of icatibant (av. requirement per attack) will replace 2.31 or 3.97 (x500U) vials of C1-INH concentrate, depending on whether trial-based or practice-based dosing is used. Additionally, the cost-minimisation assumes no leakage or wastage of PBS-funded icatibant which is unrealistic.

The ESC advised that the FAST trials (used to calculate the average dose requirement per attack for icatibant) included the treatment of less severe attacks (including cutaneous and mild abdominal attacks), which might reasonably be expected to require fewer doses than the more severe attacks specified in the proposed PBS restriction. This concern is supported by the fact that when only laryngeal attacks in the FAST trials are considered, the average number of doses required per attack was 1.17.

Further, the cost-minimisation approach against C1-INH assumed that all use of icatibant would be in a hospital setting and is therefore not appropriate given the potential for self-administration. Thus in addition to the uncertainty about the claim of non-inferiority, there was also considerable uncertainty about the submission's calculation of equi-effective doses for icatibant and C1-INH concentrate.

The PBAC noted further that the validity of the cost-minimisation approach would also require acceptance of the cost effectiveness analysis presented in the submission for C1-INH concentrate. The PBAC agreed with ESC advice that the results of this cost effectiveness analysis, including the calculation of the cost per life year gained, are not valid given the concerns with the model structure and inputs, and are highly uncertain.

The PBAC considered the submission's estimate of utilisation to be highly uncertain and a likely underestimate because of the high likelihood of usage outside the intended population. Further, this estimate did not include the initial distribution of icatibant injections (prior to an attack but in anticipation of a severe attack).

The PBAC therefore rejected the submission because of insufficient evidence in the proposed setting to support the clinical place of the therapy and uncertain cost-effectiveness.

The PBAC indicated a willingness to meet with the sponsor, ASCIA and patient groups to determine the appropriate clinical setting for icatibant on the PBS.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Shire Australia appreciate the PBAC's view that there is a clinical need for an effective treatment like icatibant outside the emergency setting. Shire thank the PBAC for a constructive stakeholder meeting held in September and is committed to working with the PBAC, ASCIA and patient groups to determine the appropriate clinical setting for icatibant on the PBS.