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 2011

1. Purpose of Application

The submission sought an Authority required listing for anticipated emergency treatment of an acute attack of hereditary angioedema (HAE) in a patient with confirmed diagnosis of C1-esterase inhibitor deficiency.

2. Background

At the July 2010 meeting, the PBAC rejected a submission to list icatibant as an Authority required benefit for supply for anticipated emergency treatment of laryngeal/oro-pharyngeal and severe abdominal attacks of acute hereditary angioedema for patients with a confirmed diagnosis of C1-esterase inhibitor deficiency, with treatment initiated by a specialist immunologist or other relevant specialist, on the basis of insufficient evidence in the proposed setting to support the clinical place of the therapy and uncertain cost-effectiveness.

The PBAC noted that there was no evidence demonstrating the effectiveness or safety of icatibant actually undertaken in the self-administration setting i.e. effectiveness and safety were 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 was 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 was made on the basis of a naïve 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 that the data presented in the submission were insufficient to support a claim of non-inferiority against the comparator, C1-INH, and that the cost-minimisation approach was therefore not adequately supported. Further, the cost-minimisation approach against C1-INH assumed that all use of icatibant would be in a hospital setting and was therefore not appropriate given the potential for self-administration. 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.

A Stakeholder Meeting was held in September 2010 with the aim of defining the clinical place of icatibant. At this meeting, it was agreed that a major re-submission to the PBAC would be required to demonstrate cost-effectiveness of icatibant followed by standard care (C1-INH) over the agreed comparator of standard care alone.

A copy of the Public Summary Document (PSD) from the July 2010 meeting is available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Icatibant-july10.

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 an acute attack of hereditary angioedema in a patient with confirmed diagnosis of C1-esterase inhibitor deficiency with treatment initiated by or in consultation with an immunologist or other relevant specialist.

Supply for anticipated emergency treatment of an acute attack of hereditary angioedema, where the patient has previously been issued with an authority prescription for this drug.

A treatment action plan should be issued to the patient to ensure appropriate use in the self-administration setting.

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. Long-term prophylactic treatment is with danazol or tranexamic acid, with short-term prophylaxis and potentially life-threatening acute episodes being treated with intravenous C1-INH concentrate.

The submission proposed that the place in therapy of icatibant is as an alternative treatment for HAE that can be self-administered in the home setting.

6. Comparator

The submission nominated placebo as proxy for "best supportive care (BSC), with delayed use of C1-INH concentrate if required" as the comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The re-submission presented six trials (FAST-1, FAST-2, FAST-3, IMPACT-1, Kunschak and Zuraw). All but FAST-3 were also presented in the July 2010 submission.

FAST-3 (unpublished) is a randomised, double-blind, placebo-controlled trial of icatibant in a hospital setting.

As was the case in the previous submission, no randomised evidence of the use of icatibant in the self-administration setting was available.

Publications details of the trials presented in the submission and not previously reported in the July 2010 PSD are in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Trials including comparisons of icatibant versus placebo		
FAST-1		
Banerji A	Clinical efficacy and safety of icatibant: Results from the controlled and open-label extension phases of the FAST-1 trial.	J Allergy Clin Immunol 2010; 125(2):AB166
Cicardi M et al	Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema.	New Engl J Med 2010; 363(6):532-541
Trials including comparisons of icatibant versus tranexamic acid		
FAST-2		
Cicardi M et al	Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema	New Engl J Med 2010; 363(6):532-541
Trials including comparisons of C1-INH concentrate versus placebo		
IMPACT-1		
Krassilnikova S et al	Summary of the International Multicenter Prospective Angioedema C1-inhibitor Trials 1 and 2 (IMPACT1 and 2)	Expert Rev Clin Immunol 2010; 6(3):327-334
Zuraw 2010		
Zuraw BL et al	Nanofiltered C1-INHibitor concentrate for treatment of hereditary angioedema	New Engl J Med 2010; 363(6):513-522
Kalfus I et al	Angioedema: Therapeutic options to suit the pathophysiology: An update on hereditary angioedema (HAE)	Chest 2009; 136(4)

8. Results of Trials

The submission presented the results of the FAST-1 and FAST-3 trials of icatibant versus placebo as pivotal evidence.

The key results from FAST-1 and FAST-3 are summarised below:

	Median [IQR] hours	**Median [IQR] hours**	
Trial ID	**Icatibant TOR30+**	**Placebo TOR30+**	**p-value[a]**
FAST-1	2.5 [1.1, 6.0]	4.6 [1.8, 10.2]	0.142
FAST-3	1.5 [1.0, 3.5]	18.5 [2.0, 30.9]	<0.001
	Icatibant TOR50+	**Placebo TOR50+**	**p-value**
FAST-1	-	-	-
FAST-3	2 [1.0, 5.0]	19.8 [3.5, 37]	<0.001
	Icatibant TOR90+	**Placebo TOR90+**	**p-value**
FAST-1	8.5 [2.5, 31.5]	19.4 [10.2, 55.7]	0.079
FAST-3	8.0 [2.5, 50.1]	36.0 [29.0, 50.9]	0.012

TOR30+ = time in hours to onset of relief for the primary symptom; relief measured by a reduction in the VAS to less than six-sevenths of the baseline VAS minus 16mm (VAS = visual analogue scale).
TOR50+ = time in hours to onset of relief for all symptoms measured in the composite score (cutaneous swelling, cutaneous pain and abdominal pain) by at least 50% of the baseline VAS.
TOR90+ = time to almost complete relief for all symptoms measured in the composite score (cutaneous swelling, cutaneous pain and abdominal pain) which occurs once the score for all symptoms drops to or below 10mm on a VAS.
[a] Analyses of FAST-1 use the Wilcoxon log-rank test, analyses of FAST-3 use the Peto-Peto Wilcoxon test.

Median TOR30+ (time to onset of relief - time point of ≥30% symptom relief) was similar for the icatibant arms of FAST-1 and FAST-3. However, the PBAC noted the median TOR30+ between the placebo arms was very different. Similarly, median TOR90+ (time to onset of relief - time point of ~90% symptom relief) was similar for the icatibant arms, while there was a large difference between the placebo arms. The PBAC noted the sponsor's claim that the difference was due to the way in which rescue medication was used (earlier and more often in FAST-1 than FAST-3).

The re-submission presented new toxicity data from FAST-3. Comparative toxicity with C1-INH concentrate has not changed from the previous submission.

A summary of adverse events from FAST-1, and FAST-2 has been previously reported in the July 2010 PSD.

Two additional periodic safety update reports were available for the re-submission (PSUR, 12 JUL 2009 to 11 JAN 2010; and PSUR, 12 JAN 2010 to 11 JUL 2010). The most commonly reported adverse drug reaction reported was injection site reactions. A causal relationship between icatibant and one occasion of myocardial infarction cannot be ruled out due to the temporal relationship of the treatment.

9. Clinical Claim

The submission described icatibant as superior in terms of efficacy and inferior in terms of comparative safety over placebo.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

An updated modelled economic evaluation was presented in the re-submission to reflect the changes to the requested restriction in terms of the proposed setting for use of icatibant on the PBS i.e. self-administration compared to administration in the hospital setting in the previous submission.

The submission presented an economic evaluation based on the utility benefits reported in the scenario-based utility valuation study. The time horizon of the model is one year, with a cycle length of one week. The model compared self-administered icatibant for emergency treatment of all laryngeal attacks and moderate-severe abdominal attacks, with best supportive care plus delayed administration of C1-INH if indicated.

There are four health states: attack-free, a week with a cutaneous HAE attack, a week with an abdominal attack, and a week with a laryngeal attack. The model did not include a death state. From the attack-free health state, patients may transition to any of the three attack health states or may remain in the attack-free health state. All patients in the attack states transition back to the attack-free health state after a week with an attack; they cannot have two attacks in two consecutive weeks.

The model did not include costs associated with patients who are admitted to hospital for observation and/or emergency treatment.

The incremental cost per quality adjusted life year (QALY) gained was between $45,000 and $75,000.

The incremental benefits of icatibant over best supportive care are almost entirely due to elements not directly relating to an attack (i.e. convenience and reduction of anxiety in the asymptomatic phase), rather than the incremental gain in clinical effectiveness.

The base case economic evaluation did not incorporate potential use of icatibant beyond the intended PBS restriction.

The results of sensitivity analyses indicated that the model is most sensitive to the number of attacks likely to be treated per patient per year, the difference in the utility weight for the attack-free health state between the treatment arms, and the proportion of cutaneous attacks that may inappropriately, be treated with icatibant.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at a net cost to the PBS per year of less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC noted that the revised requested PBS restriction no longer specifies either the site (i.e. cutaneous, abdominal or laryngeal) or the severity of an attack to be treated with icatibant. Patients who self-administer icatibant are provided with a treatment action plan to ensure appropriate use. Despite acknowledging the good intent of the proposed emergency action plan, the PBAC considered that there would be a high risk that patients would use icatibant where symptoms are milder than in the intended population. The Committee also noted, as with the previous submission, that the proposed clinical management algorithm with icatibant is more restrictive than that published in the Australian Society of Clinical Immunology and Allergy (ASCIA) position paper on hereditary angioedema (Katelaris 2010). Thus, there was considerable doubt whether icatibant would be used in practice according to the requested restriction and the proposed clinical management algorithm.

The Committee accepted the proposed comparator of best supportive care and C1-INH concentrate if required. It was noted however, that the trials were placebo controlled and thus placebo was nominated as a proxy for best supportive care (BSC). BSC differs depending on the nature of the HAE attack:

- For laryngeal - BSC includes admission and C1-INH as soon as possible
- For severe or progressive (abdominal) - admission and C1-INH
- For other attacks, including abdominal - analgesia, rest and observation.

The PBAC noted that use of pain medication in the trials was restricted for 8-9 hours which is not reflective of Australian clinical practice. Thus, the use of placebo as a proxy for best supportive care was considered uncertain and would likely overestimate the benefit of icatibant.

The re-submission presented one additional trial, FAST-3 which is a randomised, double-blind, placebo-controlled trial of icatibant in a hospital setting. As was the case in the previous submission, no randomised evidence of the use of icatibant in the self-administration setting is available. The re-submission identifies the applicability of hospital setting data to the self-administration setting as an issue and addresses this with the presentation of an open-label, single-arm study of self-administered icatibant, Study JEO49. The submission claimed that the nature and severity of attacks treated and the clinical outcomes in patients self-administering icatibant are comparable to those in the FAST trials. Therefore, the submission concluded that the clinical outcomes from the FAST trials are applicable to the self-administration setting and, to the proposed use of icatibant on the PBS. Given the paucity of evidence for the use of icatibant in the self-administration setting, and the potential confounding due to differential use of C1-INH and icatibant as rescue medications between the three trials and Study JE049-3101, the PBAC agreed that this conclusion was not adequately justified.

The PBAC accepted that on the basis of the clinical trials, icatibant is superior in terms of efficacy over placebo. However, the applicability of these results to the requested PBS population remains uncertain for the following reasons:

- The reported treatment effect appears to be heavily influenced by cutaneous symptoms, which are not intended to be treated in the PBS population;
- The lack of evidence of the effectiveness of icatibant relative to the use of pain and symptom reducing medication restrict the use of these medications;
- No treatment effect among laryngeal attacks can be estimated as there are insufficient data as only 5 patients with laryngeal attacks were randomised to either placebo or icatibant;
- Difficulty in estimating the treatment effect for self-administered icatibant, which will allow patients to treat an attack at an earlier stage than in the hospital setting. It is unclear whether earlier treatment will change clinical outcomes;
- No evidence that treatment with icatibant reduces the intensity or severity of a HAE attack.

The PBAC accepted the claim that icatibant is inferior in terms of comparative safety over placebo, and the submission's claims that the differences in adverse events between the placebo and icatibant arms were minimal and that the only identified safety concern is injection site reactions (which occur in nearly all patients prescribed icatibant and were generally mild and quick to resolve). The PBAC considered that some uncertainty remained regarding the safety of the self-administration of icatibant, for example patients may delay attending hospital following self-administration of icatibant in cases that they ordinarily would not.

The Committee noted that the outcome of the economic evaluation is largely dependent on the difference in the utility weight for the attack-free health state between the two treatment arms, as elicited in the scenario-based utility valuation study presented in the submission. There were a number of uncertainties about the results of this study, in particular:

- The results of the study did not show a statistically significant difference between Scenarios A (no effective emergency treatment) and B (effective emergency treatment available in hospital) and approximately 17% of respondents were not deemed to be "rational traders";

- The wording of the scenarios overstates the differences between self-administration and best supportive care in a number of ways that are likely to have influenced the utility values, particularly in a general population sample (for the wording emphasises lack of medical knowledge in the non-self administration setting as a concern, and may over-state the extent to which self-administration provides a normal life etc);
- The on-line administration of the survey to a general population (rather than to HAE patients) may be problematic for this setting, given the difficulties associated with adequately describing a rare disease (compared to a familiar set of health states) to participants.

Overall, the PBAC was of the view that the scenarios used in the utility study are not adequately supported. Further uncertainty arose because attack treatment algorithm variables used in the model are based on the outcomes of trials performed in the hospital setting, the applicability of which to the self-administration setting remains uncertain. Given that the model is driven by the difference between self-administration and best supportive care, the Committee agreed that it is fundamental that there is evidence to support the assumptions about resource use and outcomes in these different settings, that reflects likely usage and outcomes from availability of self-administered icatibant (including differences in timing of treatment, differences in probability of being treated etc).

In view of the uncertainties over the economic model the PBAC considered that the already high ICER of between $45,000 and $75,000 per QALY gained was likely to be even higher.

With respect to estimates of utilisation, there is considerable potential for icatibant to be used outside the intended PBS population, i.e. for cutaneous attacks and mild abdominal attacks, the cost effectiveness of which is unknown. Further, the number of attacks per patient, and the proportion of these that are of a severity to justify the use of icatibant, is highly variable and unpredictable; therefore, the submission's financial estimates are highly uncertain.

The Committee recognised there is a high clinical need for an effective treatment in this patient population. However, the PBAC rejected the submission on the basis that uncertainty remains over the extent of clinical benefit in the self-administration setting and on the basis of the resultant uncertain, as well as unacceptably high, cost effectiveness ratio.

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 appreciates that the PBAC recognises there is a high unmet clinical need for an effective treatment in this patient population. Shire remains committed to making this treatment available to affected patients and remains confident of being able to address the PBAC's needs. Shire thanks the PBAC for their open and ongoing dialogue.