

# Icatibant: 24 month predicted versus actual analysis

## Drug utilisation sub-committee (DUSC)

*June 2015*

### **Abstract**

#### ***Purpose***

To compare the predicted and actual utilisation of icatibant during the first 24 months of PBS listing (1 August 2012 to 31 July 2014). At its February 2015 meeting, the DUSC requested that the report include analysis of the number of prescriptions per patient, as the number of attacks per patient and the proportion of these that are of a high enough severity to justify the use of icatibant was considered to be highly variable and unpredictable at the time of listing.

#### ***Date of listing on the Pharmaceutical Benefits Scheme (PBS)***

Icatibant was listed on the PBS on 1 August 2012.

#### ***Data Source / methodology***

- PBS pharmacy claims data from the Department of Human Services (DHS) prescription database.

#### ***Key Findings***

- The number of patients supplied icatibant has been much lower than expected (■ % of expected). This is probably due to an overestimate of number of people with hereditary angioedema (HAE) as epidemiological data was limited at the time of listing. Alternatively, uptake may be lower than expected, but this is unlikely as clinicians advised that all patients diagnosed with HAE should be supplied icatibant.
- The number of injections supplied per patient is higher than predicted, at approximately ■ that predicted in year 2. This could be due to;
  - use for cutaneous attacks;
  - use for mild symptoms of non-cutaneous attacks;
  - patients having supplies on hand;
  - expiry of icatibant for patients with infrequent attacks;
  - patients experiencing more attacks with moderate to severe symptoms than anticipated;
  - a higher than expected rate of treatment of moderate to severe attacks; and/ or
  - on average, a higher number of injections per attack;

- The base case economic model accepted by the PBAC included 3.25 treated attacks per year (ICER of \$45,000 to \$75,000/QALY) with a sensitivity analysis of [REDACTED] treated attacks per year (ICER of \$75,000 to \$105,000 /QALY, includes treatment of [REDACTED] % of cutaneous attacks).

## Purpose of analysis

To compare the predicted and actual utilisation of icatibant during the first 24 months of PBS listing (1 August 2012 to 31 July 2014). At its February 2015 meeting, the DUSC requested that the report include analysis of the number of prescriptions per patient, as the number of attacks per patient and the proportion of these that are of a high enough severity to justify the use of icatibant was considered to be highly variable and unpredictable at the time of listing.

## Background

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

## Pharmacology<sup>1</sup>

Hereditary Angioedema (HAE) attacks are accompanied by an increased release of bradykinin; the key mediator in the development of clinical symptoms and oedema formation. Icatibant is a selective competitive antagonist at the bradykinin type 2 (B2) receptor. It is a synthetic decapeptide with a structure similar to bradykinin.

## Therapeutic Goods Administration (TGA) approved indications<sup>1</sup>

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

## Dosage and administration<sup>1,2</sup>

*Abridged – see Product Information and Consumer Medicines Information for full details<sup>1,2</sup>*

Patients can self-administer icatibant upon recognition of symptoms of an HAE attack, where their doctor has determined this is appropriate and provided adequate training.

The recommended dose of icatibant is one subcutaneous injection of 30 mg preferably in the abdominal area, for the treatment of a HAE attack. Injection should be given slowly due to the large volume to be administered (3 mL).

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<sup>1</sup> Icatibant (Firazyr) Product Information. Available from <https://www.ebs.tga.gov.au>, Accessed 2 Mar 2015

<sup>2</sup> Icatibant (Firazyr) Consumer Medicines Information, Available from <https://www.ebs.tga.gov.au>, Accessed 2 Mar 2015

Patients who self-inject should be advised to seek urgent medical attention if there is no evidence of resolution of the HAE attack within 2 hours of self-injection, or immediately should the HAE attack progress to involve the face, lips or pharyngolaryngeal area. Patients whose initial HAE attack involves the face, lips or pharyngolaryngeal area should seek urgent medical attention, regardless of their response to icatibant following self-injection.

In the majority of cases a single injection of icatibant is sufficient to treat an attack. In case of insufficient relief or recurrence of symptoms, a second injection of icatibant can be administered after 6 hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection of icatibant can be administered after a further 6 hours. Second and subsequent injections, if required, should be given by or in consultation with a doctor. No more than 3 injections of icatibant should be administered in a 24-hour period.

In clinical trials, not more than 8 injections of icatibant per month were administered.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

## **Clinical situation**

Icatibant is prescribed and supplied in anticipation of a future HAE attack. Patients may hold their own icatibant supply either for self-administration or for administration by a trained companion or a medical professional at a clinic or hospital.<sup>3</sup> PBS subsidised medicines are available for patients treated in a community setting, in private hospitals, and in public hospital outpatient and discharge settings. PBS subsidy is not available for public hospital inpatients.

PBS data in this report relates to the supply of the medicine; not its administration.

The Australasian Society of Clinical Immunology and Allergy (ASCIA) position paper on HAE<sup>3</sup> recommends that treatment should be in consultation with a specialist. The PBS Authority listing requires that a clinical immunologist, respiratory physician, specialist allergist or general physician experienced in the management of patients with hereditary angioedema is consulted. The ASCIA recommends that an emergency Action Plan including training in recognition of the symptoms of HAE and the self-administration of icatibant is produced for all patients in consultation with their specialist.<sup>3</sup>

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<sup>3</sup> Australasian Society of Clinical Immunology and Allergy, Position Paper on Hereditary Angioedema, 2012

## PBS listing details (as at March 2015)

**Table 1: PBS listing of icatibant**

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
1976B	Icatibant injection 30mg (as acetate) in 3mL single use pre-filled syringe	1	1	\$2571.70	Firazyr, Shire Australia Pty. Limited

Source: March 2015 PBS Schedule

### **Restriction**

#### **Authority required**

- Initial supply for anticipated emergency treatment of an acute attack of hereditary angioedema in a patient with confirmed diagnosis of C1-esterase inhibitor deficiency who has been assessed to be at significant risk of an acute attack of hereditary angioedema by or in consultation with a clinical immunologist, respiratory physician, specialist allergist or general physician experienced in the management of patients with hereditary angioedema.
- Continuing supply for anticipated emergency treatment of an attack of hereditary angioedema, where the patient has previously been issued with an authority prescription for this drug.
- Note: icatibant should be provided in the framework of a comprehensive hereditary angioedema prophylaxis program and an emergency Action Plan including training in recognition of the symptoms of hereditary angioedema and the self-administration of icatibant. (For further information see the Australasian Society of Clinical Immunology and Allergy website at [www.allergy.org.au](http://www.allergy.org.au))

For details of the current PBS listing refer to the [PBS website](#).

### **Date of listing on PBS**

Icatibant was listed on the PBS on 1 August 2012.

### **Risk Sharing Agreement**

Icatibant for the treatment of HAE has a Risk Sharing Agreement (RSA) with the Government.

### **Relevant aspects of PBAC consideration**

Icatibant was first considered at the July 2010 PBAC meeting, where the decision was made not to recommend it for PBS listing due to insufficient evidence in the proposed setting to support the clinical place of the therapy and uncertain cost-effectiveness. The PBAC considered that there was a clinical need for effective treatment of HAE outside the emergency setting, but noted that there was uncertainty regarding the appropriate setting for icatibant on the PBS.

The PBAC also noted that the requested restriction was narrower than the ACPM recommendation and the ASCIA position paper; they considered that this may result in considerable potential for utilisation outside the intended restriction of laryngeal/oro-pharyngeal and severe abdominal attacks.

For further details refer to the Public Summary Document from the July 2010 PBAC meeting.

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. It was considered that access to icatibant should be based on a diagnosis of HAE and not the severity of disease, but that the drug should only be used to treat severe attacks. The ACSIA agreed to review the Position Paper on HAE to promote concordance between the intended PBS population (patients with severe attacks) and the HAE guidelines. At the July 2011 PBAC meeting the PBAC rejected a submission to list icatibant based on uncertainty over the extent of clinical benefit in the self-administration setting. The PBAC noted that patients who self-administer were to be 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 PBAC considered that some uncertainty remained regarding the safety of the self-administration of icatibant. However, they recognised that there was a high clinical need for an effective treatment in this patient population.

For further details refer to the Public Summary Document from the July 2011 PBAC meeting.

A minor submission was presented at the November 2011 PBAC meeting, where the PBAC deferred its decision pending further negotiation with the sponsor as the cost effectiveness ratio remained unacceptably high and uncertain.

At the March 2012 meeting, the PBAC recommended the listing of icatibant on the PBS on the basis of high but acceptable cost-effectiveness in the context of high clinical need, compared with placebo as proxy for best supportive care, with delayed use of C1-INH concentrate if required.

The PBAC accepted a base case ICER of \$45,000 to \$75,000/QALY which included 3.25 attacks treated per year. The number of treated attacks per year was based on 0% of cutaneous attacks being treated. The ICER calculation also assumed an average of 1.12 injections of icatibant per treated attack, giving an average of 3.64 injections per patient per year. The PBAC noted that the ICER is very sensitive to the proportion of use in lower risk episodes. If ■■■% of cutaneous attacks are treated the ICER is \$75,000 - \$105,000/QALY. This scenario includes an average of ■■■ (i.e. ■■■ non-cutaneous + ■■■ cutaneous) treated attacks per patient per year. It also assumed ■■■ injections per treated attack, giving an average of ■■■ injections per patient per year.

In addition to the price reduction, the PBAC considered that the proposed risk share agreement options were sufficient to reassure the Committee regarding its concerns about the potential for the Commonwealth to subsidise icatibant for treatment of less severe attacks.

### **Approach taken to estimate utilisation**

The submission took an epidemiological approach to estimate the eligible population for icatibant. The submission applied the prevalence of HAE in Australia, assumed to be 1 in 50,000 (based on the prevalence reported in Fay et al (2002)<sup>4</sup>, Bowen et al (2008)<sup>5</sup> and the 2009 ASCIA Position Paper on Hereditary Angioedema), to population projection figures from the Australian Bureau of Statistics (ABS).

The submission assumed that all patients with existing HAE were already diagnosed and that the number of patients would not increase substantially due to an increased awareness of the disease.

The expected uptake of icatibant was assumed to be ■■■% of patients in the first year, increasing to ■■■% over the first five years of the listing. The uptake rates were assumed to be high due to the lack of alternative treatments.

The average number of treated attacks per patient per year was based on the data from the FAST-1 and FAST-2 studies.<sup>6</sup> The submission base case assumed that on average each patient would only be treated for 3.25 non-cutaneous attacks per year. Table 2 summarises how this figure was calculated.

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<sup>4</sup> Fay A, M Abinun M. Current management of hereditary angio-oedema (C'1 esterase inhibitor deficiency). J Clin Pathol. 2002 April; 55(4): 266–270.

<sup>5</sup> Bowen et al. Hereditary angiodema; a current state of the art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol. 2008; 100(Suppl 2): S30-S40

<sup>6</sup> Report JE049-5121 Additional Efficacy Analyses For Studies JE049 #2103 (FAST-1) and JE049 #2102 (FAST-2)

**Table 2: Parameters derived from FAST trials**

Site of Attack	Cutaneous	Abdominal	Abdominal & Cutaneous	Laryngeal	All
Number of attacks	1,980	1,202	603	121	3,906
Distribution of attacks	50.7%	30.8%	15.4%	3.1%	100.0%
Number of attacks per patient per follow up year*	10.50	6.37	3.20	0.64	20.71
Number of treated attacks	623	406	159	48	1,236
Distribution of treated attacks	50.4%	32.8%	12.9%	3.9%	100.0%
Number of treated attacks per patient per follow up year*	3.30	2.15	0.84	0.25	6.55
Economic model base case (0% of trial treated cutaneous attacks PBS treated, ICER = \$45,000 to \$75,000 per QALY)	0.00	3.25			3.25
Economic model sensitivity analysis (█% of trial treated cutaneous attacks PBS treated, ICER = \$75,000 - \$105,000 per QALY)	█	█			█

Source: Section E spreadsheet for March 2012 submission to PBAC.

\* The follow up start date and last visit date for each patient in the trials was known and so the follow time for the recorded attacks was known for each patient

Using the icatibant administration data from the open label phase of the FAST-1 and FAST-2 trials it was estimated that each HAE attack would require an average of 1.12 icatibant doses.

The submission assumed that each prescription would have a quantity of 1 (i.e. one 30 mg injection) and that the average attack requires 1.12 injections. Neither the economic model nor the utilisation estimates took into account that patients need to have a supply of icatibant on hand sufficient to treat an attack.

A summary of the predicted number of patients treated and utilisation of icatibant is presented in Table 3.

**Table 3: Expected utilisation of icatibant in the first 5 years of PBS listing**

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients with HAE in Australia	█	█	█	█	█
Expected uptake of icatibant	█	█	█	█	█
Number of patients using icatibant	█	█	█	█	█
Average number of attacks per patient per year treated with icatibant	█	█	█	█	█
Total number of attacks treated with icatibant each year	█	█	█	█	█
Number of icatibant injections per attack (assume same for all sites)	█	█	█	█	█
Total number of icatibant PBS items dispensed each year	█	█	█	█	█

Source: Section E spreadsheet for March 2012 submission to PBAC.

## Methods

PBS & RPBS (R/PBS) prescription data for icatibant were extracted from the Department of Human Services (DHS) Prescription database for the period from August 2012 to December 2014 inclusive, based on the date that the prescription was supplied.

The number of prevalent patients was determined by counting the number of people supplied at least one PBS prescription of icatibant using person specific numbers (non-identifying) in the data for the specified time periods.

Patient initiation date was defined as the date of supply of the first prescription.

Data analysis was undertaken using SAS.

## Results

### Analysis of drug utilisation

Figure 1 shows the number of prescriptions and number of injections of icatibant supplied since PBS listing on 1 August 2012. The PBS listing allows for a quantity of one 30mg injection and one repeat. Increased maximum quantities and repeats may be authorised by the Department of Human Services.

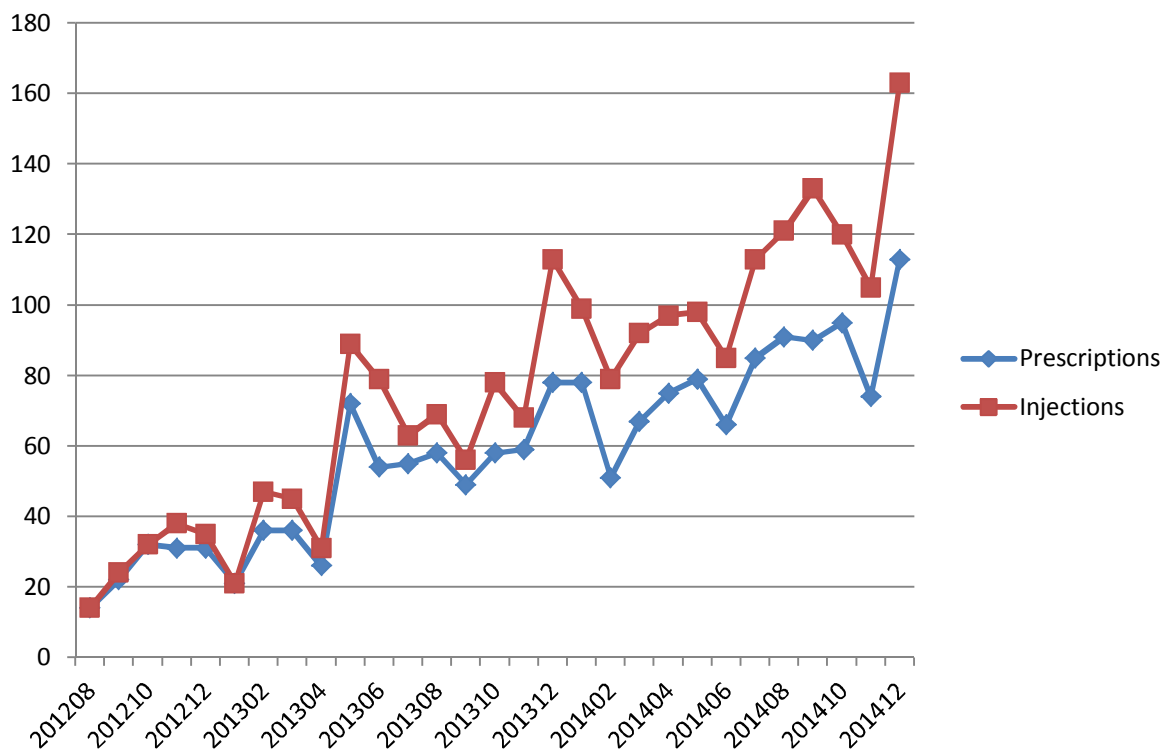


Figure 1: Icatibant prescriptions and injections (Item code 1976B) by month of supply

In the first 2 years of listing, 17.5% of prescriptions supplied were for an increased maximum quantity. Where an increased maximum quantity was supplied, 12.6% were for 2 injections, 1.1% for 3 injections and 3.8% for more than 3 injections.

The weighted average number of injections per prescription, calculated from the data in Figure 1, was 1.21, 1.32 and 1.42 in Years 1, 2 and 3 YTD (i.e. September to December 2014) of listing, respectively.

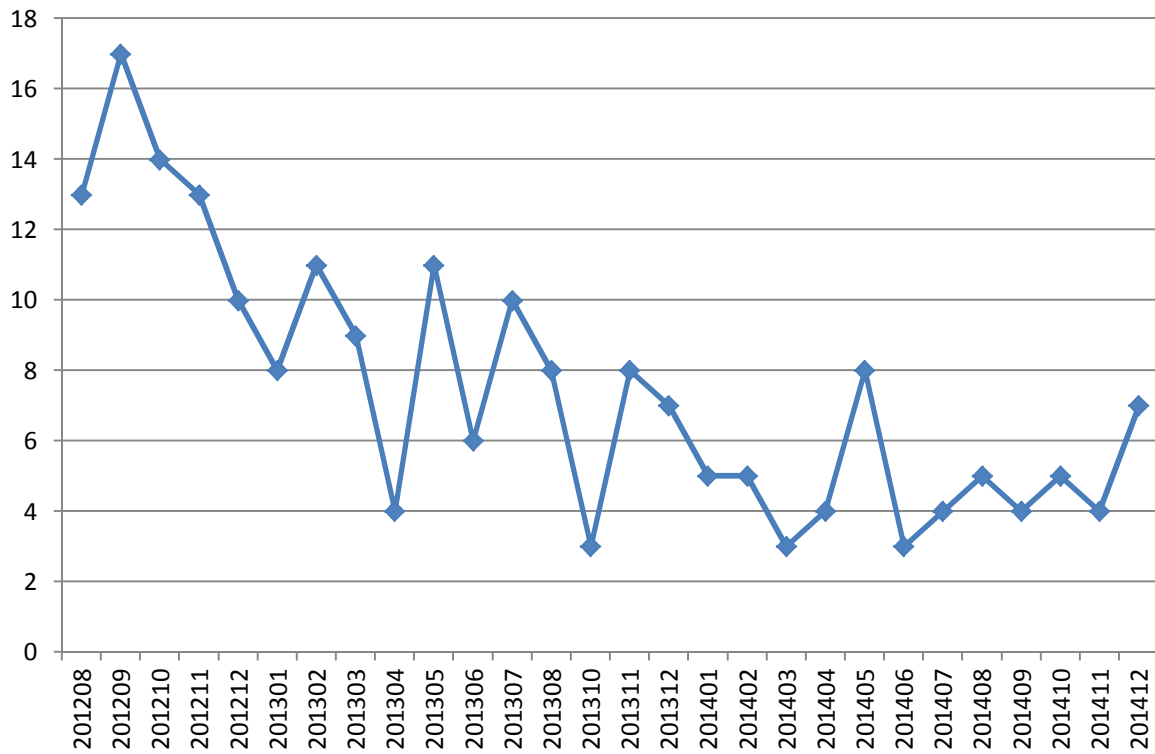
19.5 % of original prescriptions were authorised to have increased maximum number of repeats (i.e. more than 1 repeat). Table 4 shows the distribution of the number of approved repeats on original prescriptions.

**Table 4: Distribution of approved repeats**

Approved Repeats	Original prescriptions	% Distribution	Total Injections if all repeats were filled	% Distribution
0	61	7.8%	90	3.4%
1	571	72.7%	1,208	45.6%
2	39	5.0%	228	8.6%
3	55	7.0%	440	16.6%
4	4	0.5%	25	0.9%
5	52	6.6%	636	24.0%
7	3	0.4%	24	0.9%
Total	785	100.0%	2,651	3.4%

Source: Original prescriptions in the DHS Prescription database for the supply period from August 2012 to December 2014 inclusive.

Figure 2 shows the number of patients initiating PBS icatibant treatment over time.



**Figure 2: Patients initiating PBS icatibant by month of first PBS supply**

The number of patients supplied their first PBS prescription for icatibant started at a high level and then declined to a stable level of about 5 patients per month after 16 months (i.e. by January 2014). The initial high level likely represents the prevalent pool of diagnosed HAE patients receiving their first PBS supply of icatibant, with the plateau representing incident diagnosed patients.

In the first 2 years of listing, 184 patients were supplied at least one PBS prescription of icatibant).

### Analysis of expenditure

**Table 5: R/PBS expenditure (based on date of supply)**

	Year1 Aug12 to July13	Year 2 Aug13 to July14
R/PBS expenditure	\$1,332,970	\$2,691,220

## Analysis of actual versus predicted utilisation

Table 6 shows the predicted and actual use of icatibant in each of the first 2 years of listing.

**Table 6: Predicted vs Actual utilisation**

		Year1 Aug12 to July13	Year 2 Aug13 to July14
Patients	Predicted (P)	█	█
	Actual (A)	126	145
	Difference (A-P)	█	█
	% Difference (A-P)/P	█	█
Prescriptions	Predicted (P)	█	█
	Actual (A)	430	803
	Difference (A-P)	█	█
	% Difference (A-P)/P	█	█
Prescriptions per patient	Predicted (P)	3.64	3.64
	Actual (A)*	3.41	5.54
	Difference (A-P)	-0.21	1.91
	% Difference (A-P)/P	-6%	53%
Injections per patient	Predicted (P)	3.64	3.64
	Actual (A)*	4.11	7.22
	Difference (A-P)	0.48	3.60
	% Difference (A-P)/P	+ 13%	+ 99%
R/PBS expenditure	Predicted (P)	█	█
	Actual (A)	\$1,332,970	\$2,691,220
	Difference (A-P)	█	█
	% Difference (A-P)/P	█	█

\* calculated as number of prescriptions/number of patients with at least one supply in the year  
 Note: Predicted values from final agreed estimates based on March 2012 submission to PBAC

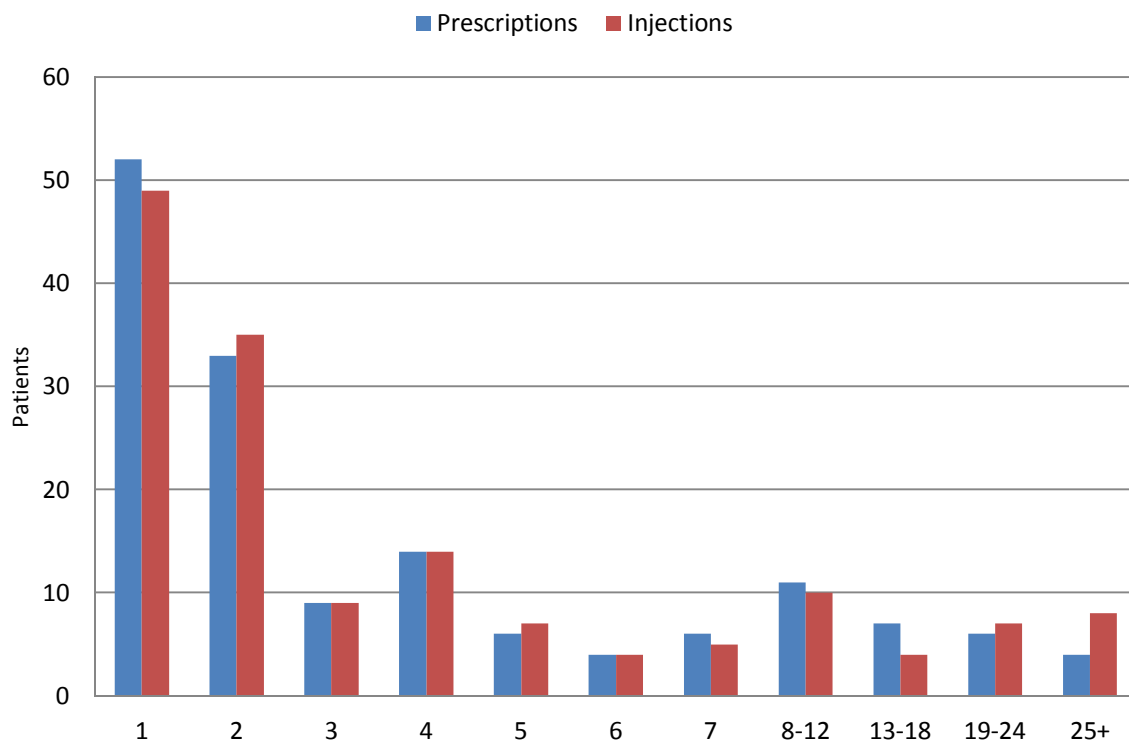
The number of patients supplied icatibant is much lower than expected. The prevalence of HAE was acknowledged as uncertain at the time of listing. Reported prevalence rates ranged from 1/10,000 to 1/150,000. The final estimate of 1/50,000 was based primarily on the Bowen et al (2008)<sup>7</sup> (see “Discussion” section for details).

The calculated number of prescriptions per patient and injections per patient were similar to expected in Year 1 but was substantially higher than expected in Year 2. The average number of injections per patient in year 2 (7.22) was double that expected (3.64).

<sup>7</sup> Bowen et al. Hereditary angioedema; a current state of the art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol. 2008; 100(Suppl 2): S30-S40

To further understand the patterns of icatibant supply per patient, a deidentified patient level analysis was undertaken. This analysis examined the number of supplies and injections per patient in the 12 months after their first PBS supply of icatibant. This method of measuring prescriptions and injections per patient per year is more comparable with the predicted values which were based on patient level data from the FAST<sup>8</sup> trials. The predicted treated attacks per patient were calculated by dividing the total number of treated attacks by the sum of the follow up periods (which were patient specific).

The cohort analysed for this patient level analysis was those patients (n=152) receiving their first PBS supply of icatibant in the period August 2012 to December 2013 inclusive, as there was insufficient data for the patients who initiated after this to be followed up for 12 months. The distributions of scripts per patient and injections per patient are shown in Figure 3.



**Figure 3: Distribution of prescriptions and injections per patient supplied within 12 months of PBS initiation**

The median number of prescriptions per patient was 2 and the weighted mean was 5.1. The median number of injections supplied per patient was also 2 and the weighted mean was 6.3.

Given that these are all initiators, this implies  $5.1 - 1 = 4.1$  treated attacks per patient in the first 12 months (i.e. allowing for the one supply on-hand). This value is between the

<sup>8</sup> Based on a pooled analysis of FAST-1 and FAST-2; Report JE049-5121 Additional Efficacy Analyses For Studies JE049 #2103 (FAST-1) and JE049 #2102 (FAST-2)

submission base case of 3.25 (excluding cutaneous attacks) and the submission sensitivity case of [REDACTED] (including [REDACTED]% of trial treated cutaneous attacks) attacks per patient predicted. This suggests there may have either been some treatment of cutaneous attacks (approximately [REDACTED]% of the 3.30 treated cutaneous attacks per year, see Table 2) or that the rate of non-cutaneous attacks was under-estimated in the submission.

Whilst the distributions in Figure 3 are strongly right skewed (i.e. there are patients with prescription and injections per patient that are much higher than the median and mean values), this was also true of the data from the FAST trials. In Figure 3 there are 14.5% of patients with more than 10 prescriptions (approximately 9 treated attacks) per year. In the FAST trials data (included in the Section E spreadsheet of the minor submission to the March 2012 PBAC meeting) there were 14.6 % of patients with more than 9 treated non-cutaneous attacks per year.

## Discussion

The number of patients supplied icatibant has been much lower than expected ([REDACTED]% of expected). This is probably due to an overestimate of number of people with HAE as epidemiological data was limited at the time of listing. Alternatively, uptake may be lower than expected, but this is unlikely as clinicians advised that all patients diagnosed with HAE should be supplied icatibant.

The breakdown of the prevalence data relied upon in the submission is as follows:

The 2009 ASCIA Position Paper on Hereditary Angioedema reported a range of 1 in 10,000 to 1 in 150,000. This paper was last updated in August 2012<sup>9</sup> and still reports the same range in prevalence referencing Nzeako et al. (2001)<sup>10</sup> and Frank (2000)<sup>11</sup>.

Fay et al. (2002)<sup>5</sup> quotes an estimate of 1 in 50,000 but does not reference a source.

Bowen et al. (2008)<sup>6</sup> states “The incidence of HAE is estimated at 1:10,000 to 1:150,000, with most authors quoting 1:10,000 to 1:50,000 (with most agreeing that 1:50,000 is the closest estimate), no ethnic group differences have been reported” referencing Zingale et al. (2006)<sup>12</sup> and Roche et al. (2005)<sup>13</sup>. Presumably this statement should be referring to prevalence not incidence.

Zingale et al. (2006) states that “the prevalence of HAE in the population is set at 1:50 000 — a number without solid epidemiological basis, but nevertheless probably fairly accurate” Further investigation of sources for Zingale et al. (2006) did not provide any solid source for the prevalence estimate of 1:50,000.

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<sup>9</sup> [http://www.allergy.org.au/images/stories/pospapers/ASCIA\\_HP\\_Position\\_Paper\\_HAE\\_2012.pdf](http://www.allergy.org.au/images/stories/pospapers/ASCIA_HP_Position_Paper_HAE_2012.pdf)

<sup>10</sup> Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Archives of Internal Medicine 2001; 161:2417-29.

<sup>11</sup> Frank MM Urticaria and angioedema. In: Goldman L, Bennett JC, editor. Cecil Textbook of Medicine. 21 ed. Philadelphia: WB Saunders Co; 2000. p. 1440-5.

<sup>12</sup> Zingale LC, Beltrami L, Zanichelli A, et al. Angioedema without urticaria: a large clinical survey. CMAJ 2006;175:1065-70

<sup>13</sup> Roche et al. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol. 2005 Apr;94(4):498-503.

Roche et al. (2005)<sup>14</sup> is the first of the above references to actually measure prevalence of HAE. They conclude “The detected minimal prevalence of HAE in Spain is 1.09 per 100,000 inhabitants. Because this is a rare disease and some patients may be misdiagnosed, this prevalence could be higher”.

The actual number of patients in the PBS data may provide a better estimate of the prevalence of HAE in Australia. However, a count of patients in any one year could underestimate prevalence as some patients have very infrequent attacks and the reported shelf-life of icatibant is 2 years. The PBS data shows that 184 individual patients received at least one PBS prescription of icatibant in the first 2 years of listing. Therefore prevalence is more likely to be in the range of 1 in 130,000.

The number of injections supplied per patient is higher than predicted. This could be due to:

- Patients experiencing more attacks with moderate to severe symptoms than anticipated.
- A higher than expected rate of treatment of moderate to severe attacks:  
The treatment rate of HAE attacks in the FAST trials was 31.6%. That is, the annual rate for all HAE attack sites was 20.7 and the rate of treated attacks was 6.55 (which reduced to 3.25 for non-cutaneous attacks). It is possible that the actual treatment rate was higher than 31.6%.
- A higher average number of injections per attack:  
It may be reasonable to assume that the average injections per prescription is a reflection of the average injections per attack. The average number of injections per prescription was 1.21, 1.32 and 1.42 in Years 1, 2 and 3 YTD (i.e. September to December 2014) of listing, respectively. These figures are higher than the 1.12 injections per attack assumed in the submission.
- Use for cutaneous attacks:  
The PBS current restriction does not explicitly exclude use for of cutaneous attacks however appropriate use is covered by the Note section of the PBS listing which recommends an “emergency Action Plan including training in recognition of the symptoms of hereditary angioedema and the self-administration of icatibant”. The ASCIA Action Plan and Position Paper submitted with the major submission to the July 2011 PBAC did not recommend treatment of “peripheral swelling” (i.e. cutaneous attacks) with icatibant. At the PBAC stakeholder meeting it was agreed that the drug should only be used to treated severe attacks. In August 2012 (the month of PBS listing of icatibant) the ASCIA Position Paper was revised to allow the use of icatibant for the treatment of cutaneous attacks. The ASCIA Action Plan was also revised to recommend treatment with icatibant of peripheral swelling with moderate to severe symptoms. This action plan appears to have been updated on the internet in April 2013 (estimated using the website <http://web.archive.org/>). Figure 1 shows that utilisation more than doubled between April and May 2013 which may have been due to the change in the

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<sup>14</sup> Roche et al. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol.* 2005 Apr;94(4):498-503.

ASCIA Action Plan to include treatment of cutaneous attacks with icatibant. As noted in the results section, the greater than expected prescriptions per patient could be accounted for by treatment of █% of cutaneous attacks that were treated in the FAST trials.

- Use for mild symptoms of non-cutaneous attacks:  
The non-treated attacks recorded in the FAST trials are most likely to be pre-attack symptoms. The FAST Patient Trial Guide states “You should inject the study drug only when you develop the symptoms of an HAE attack, not when you have only pre-attack symptoms such as a rash or redness of the skin. You should wait until you feel that your HAE attack symptoms need treatment before you proceed with self-administration of the study drug”. The ASCIA Position Paper on HAE seems to refer to these pre-attack symptoms as a prodrome and the ASCIA Action Plan seems to refer to them as mild HAE symptoms. Thus the non-treated attacks in the FAST data can probably be regarded as pre-attacks, prodromes and mild symptom attacks (these terms being synonymous). Table 2 shows that there was a large difference between the number of attacks and number of treated attacks for each attack site, including the non-cutaneous sites. Thus there are a large number of mild symptom attacks, the treatment of some of which may have contributed to the greater than expected prescriptions and injections per patient.
- Patients having supplies on hand:  
This was not accounted for in the economic or financial modelling, and it is possible that patients may have multiple supplies on hand.
- Expiry of icatibant for patients with infrequent attacks:  
Wastage may also be a factor in the higher than predicted prescriptions per patient. In the submission to the July 2011 PBAC (p. 51) the sponsor agreed to replace, free of charge, any drug that exceeds its expiry date. Any replacement injections would not have appeared in the PBS data and so would not have contributed to the higher than expected prescriptions per patients. Icatibant can be stored at room temperature and has a shelf-life of 24 months<sup>15</sup>. The Sponsor was requested to provide monthly data on the number of injections that have expired and been replaced in their pre-DUSC response. The sponsor reported only 20 syringes have been returned due to expiry since December 2012.

One reason that injections per patient in Year 1 of listing (i.e. 4.11, see Table 6) is less than in Year 2 (i.e. 7.22) is the “half-year” effect. That is, as patients initiate treatment progressively throughout Year 1, they have less than a full year on treatment. If initiations are constant throughout the year, then the average time on treatment would be half a year. This effect is still present in Year 2 for initiators, but is diluted because of the large number of prevalent patients.

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<sup>15</sup> Icatibant submission to the July 2011 PBAC (p. 51)

## DUSC consideration

DUSC considered that the submission to the PBAC:

- Over-estimated the prevalent population.  
This was primarily due to uncertainty in estimating the prevalence of HAE in Australia. This flowed on to an over-estimate of the number of patients that would be treated with icatibant. The DUSC also noted that as there is no data on the use of icatibant in children and it should be used during pregnancy only if the potential benefit justifies the potential risk for the fetus (e.g. for treatment of potentially life threatening laryngeal attacks) that the size of the population who would be treated with icatibant may have been overestimated based on HAE prevalence estimates from the literature. The DUSC suggested that more emphasis be placed on sensitivity analysis of prevalence estimates for rarer diseases.
- Under-estimated prescriptions and injections per patient.  
This was most likely due to the use for mild symptoms or cutaneous attacks, both of which were excluded from the submission to the PBAC base case estimates. An additional factor was the need to have enough injections on-hand to treat an attack, which was not accounted for in the submission estimates.
- Over-estimated R/PBS expenditure.  
This was due to the over-estimated prevalent population.

The DUSC also considered that the RSA was ineffective in protecting against higher than predicted injections per patient because of the lower than expected number of patients.

The DUSC noted that:

- The severity and location of symptoms are not synonymous. The submission assumed that cutaneous attacks treated in the FAST trials only had mild symptoms, so in the Australian population these attacks would not be treated with PBS icatibant and thus were not included in the base-case economic model. The DUSC asked the Secretariat to confirm if the incremental benefits in the base case were calculated on the basis of the entire population across the trial, or on just the non-cutaneous attacks. The secretariat confirmed that the outcomes for the ITT population in the FAST trials, which included cutaneous attacks, were used in the economic evaluation. It was noted from the studies that the treatment effect for icatibant compared with placebo appears to be largely influenced by the time taken for cutaneous symptoms to resolve rather than the abdominal symptoms, which are not intended to be treated in the PBS population. However, this proposed benefit was not the key driver for the cost-effectiveness argument presented. The outcome of the economic evaluation was largely dependent on the difference in the utility weight for the attack-free health state between the two treatment arms, as elicited in a scenario-based utility valuation study.
- The 2012 ASCIA position paper contains the statement “Patients may hold their own icatibant supply (a pack of two syringes) either for self-administration or for

administration by a trained companion or a medical professional at a clinic or hospital". The DUSC noted that the pack available on the PBS only contains a single syringe and multiple syringes can be supplied on a single script if requested by the prescriber via PBS Authority Approval.

- The sponsor reported only 20 syringes have been returned due to expiry since December 2012. The DUSC considered that this figure may increase now that icatibant has been listed for more than 2 years as icatibant has a reported shelf life of 2 years. It is possible that patients will discard expired injections and get a new prescription dispensed rather than having it replaced by the sponsor.

The ASCIA advised that they intend to update their HAE Position Statement, treatment algorithm and action plan by the end of 2015. As the action plan is referenced in the PBS restriction, the PBAC may wish to review the revised Action Plan to see if it is still aligns with cost-effective use of icatibant. The ASCIA also considered it important for the committee to note that a recently published study (Maurer M. et al Allergy and Asthma Proceedings 2014) supports the early use of treatment of HAE with icatibant to shorten attacks more effectively.

The DUSC suggested that the following additional analyses may be informative for any future reviews of icatibant utilisation:

- An analysis by patient location (i.e. rural vs urban) to see if rural patients are likely to have more injections on-hand than urban patients.
- A co-administration / sequential analysis of icatibant with a prophylactic agent (i.e. danazol or tranexamic acid).
- An analysis by patient age to see if children were being treated.

The Secretariat informed DUSC that approximately 20 people aged less than 20 years were dispensed icatibant between August 2012 and December 2014. The vast majority of these were aged between 15 and 19 years.

DUSC considered that the key findings were:

- The number of prevalent icatibant patients was less than [REDACTED] predicted.
- Actual injections per patient has been more than expected.
- The RSA has not achieved the intent of managing risk of greater than expected utilisation per patient because the number of patients was greatly overestimated.
- The changing treatment algorithm may have led to or will lead to in the future, use outside the economic model base-case that the PBAC agreed to when recommending icatibant.

## **Actions undertaken by the Secretariat**

This report was provided to the Sponsor of icatibant (Shire Australia) for comment.

A redacted version of the report was provided to

- Australasian Society of Clinical Immunology and Allergy (ASCIA)
- Medical Services Advisory Committee (MSAC). C1 Esterase Inhibitor (C1-INH) concentrate is proposed for inclusion on the National Products and Services List (NPSL) for the management of patients with a confirmed diagnosis of Hereditary angioedema (HAE) Type I or II<sup>16</sup>. Utilisation of icatibant may inform this consideration.

## **DUSC actions**

The DUSC requested that:

- the report be provided to the PBAC.
- ASCIA and NPS MedicineWise be asked to provide education on appropriate use and wastage minimisation (e.g. how to return expired injections to the sponsor for replacement).
- ASCIA be asked to provide their 2015 revised HAE Action Plan as soon as it is available so that the PBAC can assess any implications for the PBS restriction of icatibant.

## **Context for analysis**

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

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<sup>16</sup> <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1394-public>

## **Sponsors' comments**

- Shire Australia Pty. Limited

The DUSC analysis has clarified the number of patients accessing icatibant in the first two years of listing and provided insights into the patterns of script usage for this rare and spontaneous condition. Shire will continue to work with DUSC and PBAC to ensure appropriate patient access.

## **Disclaimer**

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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