

**4.01 ICATIBANT,
Injection, 3 mg in 3 mL (as acetate), single use pre-filled
syringe,
Firazyr®,
Shire Australia Pty Ltd.**

1 Purpose of Application

- 1.1 The submission presented a revised economic evaluation to support the cost effectiveness of the higher than expected number of icatibant injections per patient as reported by DUSC to the July 2015 PBAC meeting. No new clinical data were presented in the submission. The submission included a new economic evaluation and updated financial impact analysis in the context of the revised treatment algorithm. The submission also requested a re-negotiation of the current risk sharing arrangement (RSA) applied to the funding of icatibant.

2 Requested listing

- 2.1 The submission did not request any change to the current PBS listing.
- 2.2 The current listing does not specify either the site (i.e. cutaneous, abdominal or laryngeal) or the severity of HAE attacks to be treated. The intent of the listing is that appropriate use is covered by the 'Note' section of the PBS listing which recommends treatment according to the Australasian Society of Clinical Immunology and Allergy (ASCIA) Emergency Action Plan.
- 2.3 At the March 2012 PBAC meeting, listing was recommended on the basis of high but acceptable cost effectiveness in the context of high clinical need, compared to placebo which was used as a proxy for best supportive care (BSC), with delayed use of C1-INH if required. The current submission also claimed cost effectiveness in the context of a comparison with delayed use of C1-INH.

3 Background

- 3.1 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).
- 3.2 Icatibant was listed on the PBS for HAE treatment in August 2012 following two major (re)submissions considered at the July 2010 and July 2011 PBAC meetings, and two minor re-submissions considered at the November 2011 and March 2012 PBAC meetings. The ESC recalled that, at that time, a 5-year, single-tiered subsidisation cap RSA was negotiated to mitigate the risk of use of icatibant beyond the intended PBS restriction.
- 3.3 At the July 2015 meeting, the PBAC considered the DUSC report for the 24 months predicted versus actual (PvA) use of icatibant as a PBS item. The PvA report showed

that the number of patients dispensed icatibant was lower than expected (■% of predicted). However, the number of injections supplied per patient was higher than predicted (■% more in year 1 and ■% more in year 2) but within the upper bound of the range considered by the PBAC. In July 2015, the PBAC noted that while an RSA was in place to mitigate the risk to Government of higher overall expenditure, it may not ensure cost effective use. The PBAC recommended that the Department may wish to revise the subsidisation caps in the corresponding Deed of Agreement. The PBAC also considered that a major submission would be required to assess the cost effectiveness of icatibant in the context of an updated treatment algorithm and to support any proposed change in the PBS restriction.

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Summary of the previous submissions and current submission

	Icatibant July 2011 and March 2012 re-submission	Current submission
Current PBS listing	Authority required listing for Anticipated emergency treatment of an acute attack of hereditary angioedema.	Unchanged
Current price	DPMQ: \$ [REDACTED]	Unchanged
Main comparator	Placebo as proxy for best supportive care (BSC), with delayed use of C1-INH if required PBAC accepted	Unchanged
Clinical evidence and clinical claim	In total six randomised trials were considered by the PBAC. Icatibant is described as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo. This is unchanged. PBAC comment: accepted but noted that applicability of the clinical results to the requested PBS population remains uncertain and some uncertainty remained regarding the safety of the self-administration of icatibant.	No additional evidence presented
Economic evaluation	Using July 2011 model and the reduced price proposed in March 2012 minor submission: Cost-utility model with cost/QALY \$45,000/QALY - \$75,000/QALY PBAC Comment: The ICER is very sensitive to the proportion of use in lower risk episodes. The base case estimate included 3.25 treated attacks per year with 0% cutaneous attacks being treated. If [REDACTED]% of cutaneous attacks are treated the ICER is \$75,000/QALY - \$105,000/QALY. <i>The incremental benefits over BSC were almost entirely due to elements not relating to an attack (e.g. convenience and reduction of anxiety)</i>	Cost-utility model with cost/QALY: \$45,000/QALY - \$75,000/QALY (Microsimulation analysis with an average of 6.33 treated attacks/year) \$45,000/QALY - \$75,000/QALY (Cohort analysis with an average of 5.49 treated attacks/year)
Number of patients	Less than 10,000 in Year 1 (2012) increasing to less than 10,000 in Year 5 (2016)	3Less than 10,000 in Year 1 (Aug 2016-July 2017) increasing to less than 10,000 in Year 5. Not used to estimate cost to PBS. Estimates of use and financial impact prepared during the evaluation using a patient estimates approach based on the DUSC data were lower than those provided in the submission.
Estimated cost to PBS	Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of \$10 - \$20 million over the first 5 years of listing. PBAC Comment: considered the proposed RSA options were sufficient to reassure the Committee regarding its concerns about the potential use for treatment of less severe attacks.	Less than \$10 million in Year 1 (Aug 2016-July 2017) increasing to less than \$10 million in Year 5 for a total of \$30 - \$60 million over the first 5 years of listing.
PBAC decision	The PBAC rejected the July 2011 major re-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. There were two minor re-submissions following this rejection in which reduced prices were offered without other change. The PBAC recommended the listing at March 2012 meeting.	

Source: Compiled during the evaluation

- 3.4 The submission presented a new economic evaluation to support the cost effectiveness of the higher than expected number of icatibant injections per patient as reported by DUSC to the July 2015 PBAC meeting. The updated Australasian Society of Clinical Immunology and Allergy (ASCI) Emergency Action Plan recommends icatibant treatment in moderate to severe peripheral (cutaneous) swelling, and the submission assumed the reason for the higher than predicted average utilisation per patient was solely due to use in moderate to severe cutaneous attacks. Other potential reasons for the increased use noted by DUSC such as the treatment of mild attacks, a higher number of injections per attack, and possible stockpiling and wastage were not addressed in the submission or the economic evaluation. The PSCR stated that as the model included the costs of all injections irrespective of how the injections were used, the derived Incremental Cost Effectiveness Ratios (ICERs) capture the costs of potential 'inappropriate' use with 'leakage' incorporated into the base case. The PSCR further stated that the model assumed all use of icatibant is at the discretion of the patient, and by definition, so-called 'mild' attacks are those attacks which the patient decides do not require treatment. The ESC considered the types of attacks treated would potentially impact on the benefits of treatment.
- 3.5 HAE attacks are relatively short in duration. In the model the cost effectiveness of icatibant is driven by difference in quality of life outside of the acute attack period which can be attributed to access to self-administration with icatibant. Hence the number of attacks treated affects the incremental costs but has little effect on the incremental effectiveness, and increasing the number of attacks treated reduces the cost effectiveness of icatibant. The ESC noted the model essentially assumed that the quality of life benefit of icatibant treatment is independent of the number of attacks treated (and in fact the overall benefit actually reduces with more attacks due to a reduced period between attacks). This was considered implausible, and an increase in the quality of life benefits would be expected with an increase in the number of attacks. This meant that the model did not appropriately assess the impact of changing the number of attacks per patient.
- 3.6 This approach was consistent with the model in previous submissions, however, the current model included additional benefits for each attack treated with icatibant that were not previously accounted for, stating: "The original modelling may have been overly simplistic by not considering the severity of an attack, and the persistence of attack disutility between HAE attacks. Recent published evidence has shown both factors to be important determinants of health utility between attacks". (p2, Executive Summary of Icatibant submission). The ESC noted the cost per QALY gained increased with an increase in the number of attacks treated and that additional benefits modelled in the current submission versus the previous submission countered this increase.
- 3.7 With regard to the RSA, at their July 2015 meeting the PBAC recommended that the Department may wish to revise the subsidisation cap to reflect the actual number of people treated with icatibant, and the number of injections per patient accepted as cost effective by the PBAC at the time of recommending listing. The ESC noted that this would mean a reduction in the subsidisation cap (since fewer patients are being treated than estimated as the basis of the current RSA). The submission, however, proposed increasing the cap for the years 2015-2021 based on the predicted icatibant expenditure estimated in Section E. The estimates were based on the real

world utilisation data from the DUSC dataset and the Medicare Statistics PBS item report.

4 Clinical place for the proposed therapy

- 4.1 HAE is a rare, potentially fatal autosomal dominant disease caused by deficiency of the 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. Symptoms worsen in the first 12-36 hours as the oedema develops then gradually subside with untreated attacks usually lasting for 2-5 days.
- 4.2 The clinical algorithm is set out in the ASCIA treatment Action Plan (2013) and is based on the revised ASCIA Position Paper on HAE (2012). Icatibant or C1-INH concentrate is not recommended for use in mild attacks. The current Action Plan recommends icatibant or C1-INH treatment for:
- Moderate to severe peripheral swelling. Cutaneous swelling regardless of severity was not eligible for treatment in the previous Action Plan. The PBAC recommended the listing of icatibant based on an economic model that excluded treatment of cutaneous attacks (March 2012 PSD);
 - Moderate to severe abdominal symptoms. If symptoms worsen or last longer than 2 hours, patients need to seek urgent hospital treatment; and
 - Moderate to severe airway swelling, for which patients need to seek urgent hospital treatment immediately.

5 Comparator

- 5.1 Placebo as proxy for best supportive care (BSC), with delayed use of C1-INH if required. This is as previously accepted by the PBAC.
- 5.2 Currently, C1-INH is not reimbursed by the Commonwealth Government. In July 2015, MSAC recommended listing of C1-INH through the National Products and Services List (NPSL) under the National Blood Agreement (NBA) for the treatment of acute attacks of HAE, with the recommended price determined on a cost-minimisation basis against icatibant. The MSAC recommendation included the possibility of intravenous self-administration with C1-INH, but considered icatibant given by the subcutaneous route would be more common in remote and emergency situations.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from one (1) individual, and one (1) organisation via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with icatibant including the sense of security provided to patients by having the treatment on hand should attacks occur. The comments also noted that the availability of icatibant can help patients recover from attacks to carry out normal daily functions, and gives patients the ability to travel away from their local hospital as they can take their treatment with them. The comments from HAE Australia stated that icatibant has minimal side effects, and reduces the need for patients to be treated in hospital.

Clinical trials

- 6.3 The submission did not present new clinical evidence on the efficacy and safety of icatibant for HAE on the basis that it had been previously assessed by the PBAC. A literature search conducted as part of the evaluation did not identify any further studies of direct interest.

Comparative effectiveness

- 6.4 In total, there were six randomised controlled trials considered by the PBAC previously:
- 1) FAST-1: Icatibant (30 mg) vs placebo (patients were given delayed rescue, as required, after 8-9 hours of placebo treatment).
 - 2) FAST-2: Icatibant (30 mg) vs tranexamic acid (2x500 mg capsules).
 - 3) FAST-3: Icatibant (30 mg) vs placebo.
 - 4) IMPACT 1: Compared two doses of C1-INH (10U/kg and 20U/kg) vs placebo (delayed rescue after 4 hours of intervention therapy).
 - 5) Kunschak (1998): C1-INH (25U/kg) v placebo (rescue therapy allowed under certain conditions).
 - 6) Zurow (2008): C1-INH (dose and form of administration were not specified in the published abstract) vs placebo (rescue allowed after 4 hours of therapy)
- 6.5 The key results are summarised in Table 1:

Table 1: Time in hours to onset of relief following icatibant or placebo across the direct randomised trials

	Median [IQR] hours		
Trial ID	Icatibant TOR30+	Comparator TOR30+	p-value
FAST-1	2.5 [1.1, 6.0]	4.6 [1.8, 10.2]	0.142
FAST-2	2.0 [1.0, 3.5]	12.0 [3.5, 25.4]	<0.001
FAST-3	1.5 [1.0, 3.5]	18.5 [2.0, 30.9]	<0.001
	Median [IQR] hours		
	Icatibant TOR90+	Comparator TOR90+	p-value
FAST-1	8.5 [2.5, 31.5]	19.4 [10.2, 55.7]	0.079
FAST-2	10.0 [2.8, 23.2]	51.0 [12.0, 79.5]	≤0.001
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).

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.

- 6.6 Issues that were previously raised by the PBAC and remain applicable to the updated economic and financial analyses in this submission include:
- the data describe the clinical benefits in terms of time to the resolution of symptoms, and there was no evidence that treatment with icatibant reduces the intensity or severity of a HAE attack;
 - the treatment effect among laryngeal attacks is not sufficiently supported by the trial data as there were only 5 patients with laryngeal attacks randomised to either placebo or icatibant; and
 - difficulty in estimating the treatment effect for self-administered icatibant. All the randomised trials were conducted in the hospital setting. It is not possible to determine an estimate of the relative treatment effect of self-administered icatibant, followed by hospital treatment if needed, compared with delayed administration (in the hospital setting) of best supportive care, including rescue medications.
- 6.7 The probability of an attack treated with icatibant or placebo being mild, moderate or severe 4 and 12 hours post treatment is presented in Table 2. These probabilities are based on the pooled data from the FAST-1 and FAST-2 trials and are used to support the current submission’s claim that icatibant reduces the severity of HAE attacks.

Table 2: Transition probability between severity states during attack (Pooled results from FAST-1 and FAST-2)

		4 hours post treatment			12 hours post treatment		
		Mild	Moderate	Severe	Mild	Moderate	Severe
Icatibant	Moderate	■	■	■	■	■	■
	Severe	■	■	■	■	■	■
Placebo/TA	Moderate	■	■	■	■	■	■
	Severe	■	■	■	■	■	■

Source: Table C.3.6 of the Commentary.
TA=Tranexamic acid

Comparative harms

- 6.8 A summary of the adverse events from FAST-1, FAST-2 and FAST-3 is presented in Table 3. The most commonly reported adverse drug reaction was injection site reactions.

Table 3: Summary of clinical adverse events

Trial ID Dose group	N	Symptoms at injection site n (%)	Any adverse event n (%) ^a	Serious event n (%)	Severe adverse event n (%)	Discontinuations due to adverse events n (%)	Death n (%)
FAST-1							
Icatibant	27	26 (96.3)	11 (40.7)	0	2 (7.4)	0	0
PBO	29	8 (27.6)	18 (62.1)	0	4 (13.8)	0	0
FAST-3							
Icatibant	46	46 (100)	19 (41.3)	0	2 (4.3)	0	0
PBO	46	19 (41.3)	24 (52.2)	3 (6.5)	10 (21.7)	0	1 (2.2)
FAST-2							
Icatibant	36	35 (97.2)	18 (50.0)	3 (8.3)	3 (8.3)	0	0

Source: July 2011 PBAC meeting Public Summary Document

PBO = placebo

^a Symptoms at injection site are not included in the adverse event categories. An adverse event is counted in the controlled phase if the start date of the event was between the first treatment dose (dose given at the first attack) and the second treatment dose (dose given at the second attack).

Clinical claim

- 6.9 Icatibant is described as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo. This is unchanged from the July 2011 submission.
- 6.10 The PBAC previously recommended that, on the basis of the clinical trials, icatibant was superior in terms of efficacy over placebo (July 2011). However, at that time the PBAC noted that the applicability of the trial results to the requested PBAC population remained uncertain.
- 6.11 The PBAC previously accepted the claim that icatibant was inferior in terms of comparative safety compared to placebo.

Re-analysis of DUSC estimates for model input

- 6.12 The estimate of treated attack frequency used in the economic evaluation was derived from the DUSC data. The number of initiators in the first 16 months of listing was 152, and the number of injections per year was used to calculate the treated attack frequency. Using the same cohort and using the mean number of prescriptions (adjusted for initial supply), rather than the number of injections as used in the submission, the DUSC calculated 4.1 treated attacks per patient per year, which is lower than the number of treated attacks used in the model (6.33 treated attacks in the microsimulation analysis, 5.49 treated attacks in the cohort analysis). The ESC considered that the approach taken in the DUSC analysis was more appropriate given the possibility of re-dosing and stockpiling.

Economic analysis

- 6.13 The submission presented an updated cost-utility analysis and conducted two analyses of the economic model: a Markov cohort analysis and a microsimulation analysis.

Table 4: Summary of model structure and rationale

Time horizon	One year
Outcomes	QALY gained; utility values were attached to time with an attack, recovering from an attack, and the between attack period (to capture the benefit from the availability of self-administered treatment and reduced severity of an attack).
Methods used to generate results	Cohort expected value analysis. Microsimulation with distribution of treated attack frequency. The inclusion of the microsimulation analysis is purely to allow an estimate of the effect on the incremental cost effectiveness of varying attack frequency. This could have been achieved within the cohort model structure.
Cycle length	One day No half-cycle correction was applied. This is reasonable given the short cycle length.
Transition probabilities	The distribution of treated attacks is derived from the DUSC data and compared with data from the FAST trials. In the model, the distribution of treated attacks was translated to overall attack frequency. The transition probabilities between severity levels during attacks were derived from a pooled analysis of data from FAST-1 and FAST-2.
Discount rate	Not applied as the time horizon is only one year.

Source: compiled during the evaluation

- 6.14 The key differences between the July 2011 economic model and the updated economic model are summarised in Table 5. This was a new model not previously assessed by the PBAC.

Table 5: Key differences between the July 2011 economic model and the updated economic model

	Previous submissions (July 2011 and March 2012)	Current submission (November 2016)
Model structure	The model comprised 4 health states to describe attack free and within attacks states by site (cutaneous, abdominal, laryngeal).	The model comprised 9 health states to describe attack-free, within attack, and post attack (recovery period) states by severity levels (mild, moderate and severe).
	Attacks defined by site (cutaneous, abdominal, laryngeal).	Attacks defined by severity (mild, moderate, severe).
	One year model with weekly cycles.	One year model with daily cycles.
Circumstance of uses	Abdominal and laryngeal attacks were treated; cutaneous attacks were not treated. Base case: 3.25 treated attacks per patient per year.	Moderate and severe attacks were treated regardless of the site of the attack; mild attacks were not treated. Base case: 6.33 in microsimulation analysis and 5.49 treated attacks per patient per year in cohort analysis (Table D.5.1).
Treatment outcome	Treatment outcome applied in the model is the median time to almost complete relief (TOR 90+).	Treatment outcome applied in the model is the transition probability between severity levels after receiving treatment from the pooled analysis of the FAST trials.
Transition probabilities	Probability of experiencing an attack is based on FAST trials.	Probability of experiencing an attack is based on the DUSC data and FAST trials.
Utilities values	Utility values based on the scenario-based utility valuation study with standard gamble method.	Utility values based on EQ-5D measured in Nordenfelt 2014 and the utility study with standard gamble method.
	Attack-free states: utility is independent of attack severity, site or frequency.	Attack-free states: utility is dependent on severity of previous attack and availability of self-administered treatment.
	A nominal 0.5 utility decrement for within attack states for both arms.	Utility within attack is determined by severity of attack and treatment.
	No recovery period considered.	Time to restore utility to pre-attack levels in recovery period is assumed to be 9 days.
Proportion of attacks with hospital emergency department visit	Icatibant arm: ABD 11.9%, LAR: 11.9% Comparator arm: ABD 22.0%, LAR: 11.9%	Icatibant arm: no hospital service. C1-INH: severe attacks (43%, 20/47 sourced from Nordenfelt 2014)

Source: Adapted from Table 43, pp.106-107 and relevant section in Section D of the submission; July 2011 icatibant Commentary.

ABD = abdominal attacks; CUT = cutaneous attacks; HAE=hereditary angioedema; LAR = laryngeal attacks; BSC = best supportive care

6.15 The key model drivers are summarised in Table 6 below.

Table 6: Key drivers of the model

Description	Method/Value	Impact
Distribution of treated attacks	The model used evidence on the number of treated attacks that was estimated from a cohort analysis of the DUSC data and was compared with the pooled patient level data of the number of treated attacks from the FAST trials. In the cohort model, it was calculated that 5.49 attacks were treated per year, while in the microsimulation model, it was assumed that 6.33 attacks were treated per year.	High, unknown
Utility difference for the attack free health states between the treatment arms	A utility difference of [REDACTED] based on an online scenario utility valuation study was applied to account for the benefits of self-administration with icatibant during 'attack free' health states. There is considerable potential for bias in the utility weights sourced from the literature and the utility valuation study. The resulting utility values for between attack health states are higher than population norms for Australia. The ESC noted the utility difference between attacks was due to the severity of the previous attack as well as the availability of icatibant for self-administration, and as icatibant was assumed to reduce attack severity, the average utility difference between attacks was > [REDACTED].	High, favours icatibant
Cost of treatment	Icatibant: \$ [REDACTED] per attack treated, drug cost only (1.12 injections per attack), moderate and severe attacks are treated Delayed C1-INH: \$ [REDACTED] per attack treated, drug cost ([REDACTED] injections per attack) plus emergency department attendance for each administration. Assume all severe attacks received C1-INH (42.5% of all treated attacks, sourced from Nordenfelt 2014)	High, favours icatibant

Source: compiled during the evaluation

6.16 The results of the economic evaluation are presented in Table 7 below.

Table 7: Results of the economic evaluation

Component	Icatibant	BSC±C1-INH	Increment cost/QALY
Cohort analysis: 5.49 treated attacks			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Microsimulation analysis: 6.33 treated attacks			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Model estimates in March 2012 minor submission (PBAC accepted)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Table 51 & Table 52, pp123-124 of the resubmission; March 2012 PSD.

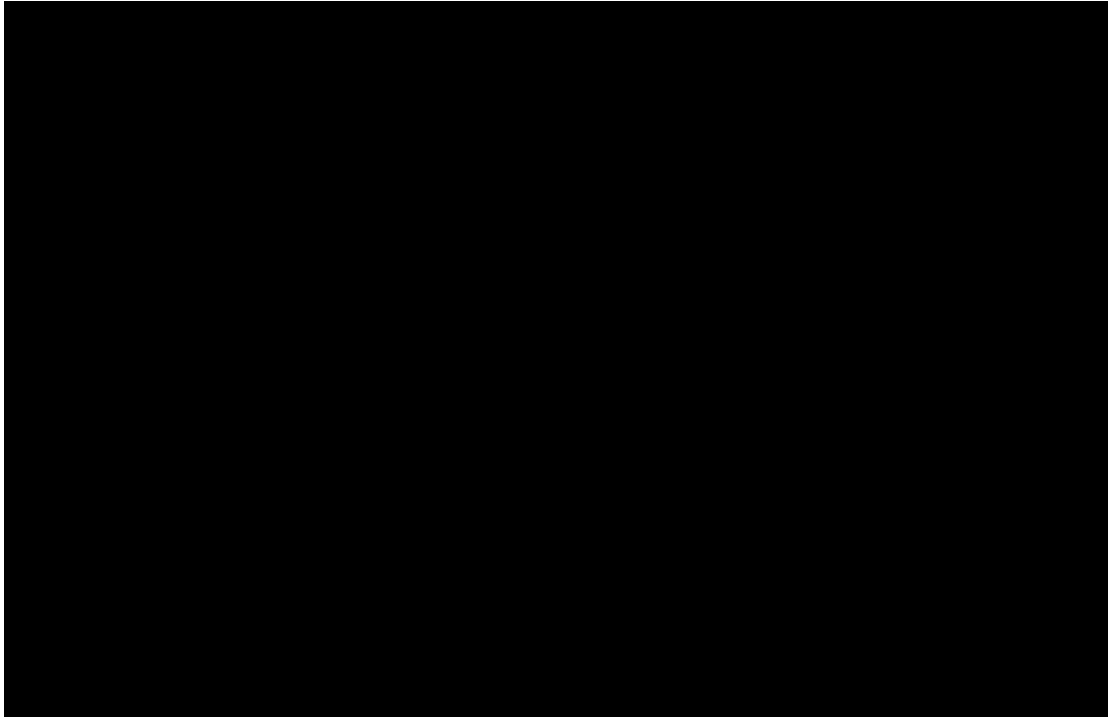
6.17 The structure for the new model is based on changes in attack severity (mild, moderate, severe). The data presented in the submission and previous (re)submissions described the clinical benefits in terms of time to the resolution of symptoms, and the PBAC has previously concluded that there is no evidence that treatment with icatibant reduces the intensity or severity of a HAE attack (July 2011 PSD). The ESC noted the March 2012 model estimated an increase in QALYs of 0.1233 (only slightly more than the [REDACTED] increase assumed for the self-administration

of icatibant). In the current model this increased to [REDACTED] for the cohort analysis and to [REDACTED] for the microsimulation model. The cost offset for C1-INH also increased relative to March 2012 model even when accounting for the increase in the number of attacks treated.

- 6.18 There are assumptions and inputs in the model that favour icatibant over BSC±C1-INH :
- The cost of icatibant was underestimated due to not considering the likely use of hospital services for severe laryngeal attacks and unresolved attacks;
 - The cost of C1-INH was overestimated due to overestimating the proportion being treated with C1-INH, 42.6% sourced from Nordenfelt 2014 was high in comparison with the FAST trial results in which 12% in the icatibant arms and 22% in the comparator arms used C1-INH as rescue medicine; and
 - The utility difference ([REDACTED]) sourced from the scenario based utility valuation study rendered the utility values for between attack health states higher than population norms for Australia, which is unreasonable. The PBAC previously noted substantial uncertainties in this scenario based utility valuation study (July 2011 PSD). The ESC considered the utility gain for self-administration ([REDACTED]) appeared large, and resulted in utility values for the time between attacks which were higher than population norms, which lacked face validity. The pre-PBAC response acknowledged that the maximum utility in the model was higher than population norms, but argued that a reduction in the absolute utility values does not impact the ICERs.
- 6.19 The risk of bias for the utility estimates for living with HEA sourced from Nordenfelt 2014 is unclear due to the following reasons:
- Nordenfelt 2014 has a relatively small sample size (n=103);
 - The within-attack utility may be impacted by recall bias as the patients were retrospectively asked to assess their Quality of Life (QoL) in the most recent HAE attack; and
 - The potential heterogeneity of HAE attacks may introduce bias into the between-attack utilities. As stated in the submission, the QoL of patients outside of the attack period is influenced by a number of factors including: time since the last attack, the overall frequency of attacks, and the severity of the last attack (p91 of the submission).
- 6.20 The cost effectiveness estimates were sensitive to the number of treated attacks per year, the difference in the utility weight for the attack free health state between the treatment arms, and the proportion of treated attacks receiving C1-INH treatment. Halving the utility gain applied to the attack free health states ([REDACTED]) increased the ICER to \$75,000 - \$105,000 in the microsimulation analysis. Reducing the proportion of the attacks treated with C1-INH from [REDACTED]% to [REDACTED]% increased the ICER to \$75,000 - \$105,000 in the microsimulation analysis.
- 6.21 The ICER ranged from less than \$15,000 per QALY gained with one treated attack per year to \$105,000 - \$200,000 per QALY gained among patients with 19-24 attacks treated per year (disaggregated results from the microsimulation analysis, see Figure 1). The cost effectiveness of icatibant diminishes as the number of attacks per year increases because of reduced time in attack-free states where patients accrue the benefits from icatibant self-administration, and because the cost of additional treatment is much larger than the QALY benefit associated with treating an attack.

The ESC considered this relationship to be problematic because it is partly driven by the inappropriate assumption of the same (or reduced benefit) when more attacks are treated. The ESC considered that the benefit of self-administration would vary depending on the number and types of attacks treated. The ESC noted that assumed utility gain of 0.12 for self-administration appeared large and resulted in utility values higher than population norms.

Figure 1: Incremental cost per QALY versus number of icatibant injections per annum (microsimulation model)



Source: Figure D.6.1 of the Commentary

- 6.22 During the evaluation, the model previously accepted by the PBAC at the March 2012 meeting was updated assuming a treated attack rate of 4.1/year (based on the DUSC PvA report) and that [REDACTED]% of cutaneous attacks were treated (as per the updated action plan). The resulting ICER was \$75,000 - \$105,000 per QALY gained.

Drug cost/patient/injection: \$ [REDACTED]

- 6.23 The cost of icatibant per injection is \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.24 This submission was not considered by DUSC.
- 6.25 The submission used the DUSC and Medicare statistics PBS item reports to estimate the current use of icatibant and extrapolated the estimates to provide the extent of future use and the financial implications to the PBS. The ESC noted that the number of patients being treated was not used to calculate the cost to the PBS. The previous submissions used an epidemiological approach and the estimates were for the years 2012-2016 so the estimates are not comparable to those in the current submission.

Given the clinical claim and economic model presented in this submission, the ESC considered that an epidemiological approach for estimating appropriate use was warranted. The pre-PBAC response noted that no formal epidemiological research into HAE has been conducted in Australia.

- 6.26 During the evaluation, an alternative approach to estimating the patient numbers was undertaken; the estimates are compared with those from the submission in Table 7. For the submission, the projected prevalent pool was derived from accumulating the predicted number of incident patients in the DUSC dataset each month, without accounting for deaths. This is likely to overestimate patient numbers. The pre-PBAC response acknowledged that the population estimates presented in the budget impact were slightly overestimated given that deaths were not included in the model, but noted that only 1 to 2 patients were likely to die over the five-year period.

The estimated costs were derived from the predicted number of services from the Medicare statistics PBS item reports and the PBS cost per service of icatibant use. During the evaluation, a quasi-epidemiological approach (or patient estimates approach) was taken whereby the projected number of patients was based on a linear extrapolation of the prevalent pool in the DUSC data, and the following inputs adopted from the economic model in the submission:

- 6.33 treated attacks/patient/year;
- 12% re-dosing rate;
- DPMQ of icatibant provided in the submission: \$ [REDACTED]; and
- an average co-payment of \$ [REDACTED] as calculated in the submission .

Table 7: Estimated use and financial implications

	Y1 (2016-2017)	Y2 (2017-2018)	Y3 (2018-2019)	Y4 (2019-2020)	Y5 (2020-2021)
Estimated extent of use					
Number of treated patients (submission)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of treated patients (linear extrapolation of DUSC data) (evaluation)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Injections (submission)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Injections- patient estimates approach (evaluation)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS					
Net cost to PBS (submission)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS - patient estimates approach (evaluation)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during the evaluation

The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

- 6.27 The submission did not provide sensitivity analyses for the financial estimates. The DUSC has previously noted ‘the risk of a higher than predicted average utilisation per patient’ and raised a number of concerns regarding the current use of icatibant, such as use for treatment of mild attacks, a higher number of injections per attack, and the issues of patients stockpiling and possible wastage (June 2015 DUSC Meeting

Public Release Document). Thus, predicting service use on the basis of current utilisation might be inappropriate where current use may not fully represent the intended PBS listing or cost effective use of icatibant. Based on prevalence of 1:130,000 indicated in the DUSC report and Australian population provided in the submission (p.136 of the submission), the number of patient in Year 5 is expected to be ■■■.

Quality Use of Medicines

- 6.28 The submission noted that, according to the DUSC data, that the top ■■■% of icatibant prescriptions (in terms of volume of injections accessible to the patient on the prescription, incorporating quantity dispensed and number of repeats) are responsible for ■■■% of the use of icatibant. The submission stated that “to ensure the quality use of icatibant, this submission proposes that the number of injections made available to patients with any given prescription be limited to 12 injections”. The pre-PBAC response noted that limiting any request for increased authority to 12 syringes per request would encourage clinician review for patients experiencing a very high frequency of attacks.

Financial Management – Risk Sharing Arrangements

- 6.29 The sponsor requested a re-negotiation of the current Risk Sharing Arrangement to align with the DUSC utilisation data, the updated treatment algorithm, and the updated economic evaluation. The proposed financial cap is based on the estimates in Section E of the current submission and is higher than the current cap.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC considered that the revised economic evaluation did not adequately support the submission’s claim that the additional use of icatibant reported by DUSC was cost effective. Therefore the Committee recommended that their previous advice on icatibant remained unchanged.
- 7.2 The PBAC agreed that placebo as proxy for best supportive care, with delayed use of C1-INH concentrate if required remained the appropriate comparator.
- 7.3 The PBAC recalled that they had previously accepted that on the basis of the clinical trials, icatibant was superior in terms of efficacy over placebo (July 2011). At that time, the PBAC had considered that the applicability of the trial results to the requested PBS population remained 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;
 - 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.

Subsequent submissions (including the current submission) have not resolved these issues.

- 7.4 The PBAC noted that with both the previous and current model the cost/QALY gained increased as the number of attacks treated per year increased. In the previous submissions it was assumed that 3.25 attacks per year would be treated. This increased to 5.49-6.33 attacks per year in the current submission and hence the cost/QALY gained would be expected to increase. However, the cost/QALY gained was similar to that in the previous submissions and this was because the current model included additional benefits not previously considered. Specifically, (i) the QALYs gained with icatibant treatment increased due to incorporating benefits, both during and between attacks, associated with reduced attack severity in the icatibant arm; and (ii) the cost offsets increased due to increased use of C1-INH in the best supportive care arm. The PBAC did not consider the changes made to the model to be adequately supported. Overall, the PBAC considered that the revised model increased uncertainty around the cost effectiveness estimate, compared to the previous model.
- 7.5 The PBAC noted using the model from the previous submissions and DUSC's estimate of the number of attacks treated per year (4.1) results in a cost/QALY gained of \$75,000 - \$105,000. The PBAC considered this to be acceptable only if the financial risk continued to be managed with a Risk Share Arrangement.
- 7.6 The PBAC noted that the submission assumed that all additional use reported by DUSC was 'appropriate' use, and considered that this assumption was not adequately justified.
- 7.7 The PBAC considered that the approach taken in the submission to estimate the financial impact was unreliable because the number of treated patients in future years appeared to be substantially overestimated.
- 7.8 The PBAC considered that the submission did not provide adequate justification for the requested substantial increase in the financial caps (from \$10 - \$20 million million to \$30 - \$60 million over 5 years). Therefore the PBAC considered it would be appropriate for any new Deed negotiated with the sponsor to be consistent with their previous recommendations with a financial cap extrapolated from the financial estimates presented at the time of the original listing.
- 7.9 The PBAC noted that this submission is not eligible for an Independent Review as it is a change to an existing listing.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Shire will continue to work with the PBAC and the Department of Health on the review of icatibant utilisation.