



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1394 – C1 Esterase Inhibitor concentrate for hereditary angioedema

Applicant: Health Services Division

Date of MSAC consideration: MSAC 64th Meeting, 30-31 July 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

Two applications were received by the National Blood Authority (NBA) for the inclusion of C1 esterase inhibitor (C1-INH) concentrate in the National Product and Services List (NPSL) for the management of hereditary angioedema (HAE).

2. MSAC's advice to the Minister

After considering the strength of the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of C1 esterase inhibitor concentrate, MSAC advised the Minister and the Jurisdictional Blood Committee (JBC) that it supported listing C1 esterase inhibitor concentrate in the National Products and Services List (NPSL) under the National Blood Agreement (NBA) for the treatment of acute attacks of Types I or II hereditary angioedema, with pricing determined on a cost-minimisation basis against icatibant.

MSAC further advised that C1 esterase inhibitor concentrate should also be listed in the NPSL for pre-procedural and routine prophylaxis of Types I and II hereditary angioedema at this reduced price. Consistent with the TGA approvals, this advice in relation to prophylaxis only applies to the Cinryze product. MSAC also advised that guidance should be given to prescribers that pre-procedural prophylaxis should be limited to at-risk surgery and that routine prophylaxis is only justified in terms of cost-effectiveness beyond a pre-prophylaxis rate of 8 acute attacks per month. MSAC suggested that consideration should be given to introducing a rebating arrangement such that any expenditure on C1 esterase inhibitor concentrate beyond the financial projections are borne by Shire.

MSAC recommended that the JBC/NBA work with the Australasian Society of Clinical Immunology and Allergy (ASCIA) to develop guidelines and governance arrangements for use of C1 esterase inhibitor concentrate for the clinical circumstances which reflect MSAC's advice.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that hereditary angioedema is a rare disorder that has a prevalent pool of about 500 individuals in Australia with around 100 individuals requiring treatment annually. It was also noted that, although there is a variable spectrum of disease, the involvement of the airways can be life threatening. MSAC also noted that C1 esterase inhibitor concentrate is currently available to be injected in a hospital setting.

MSAC noted that the clinical need appears evident because it is already in use as a first-line alternative to subcutaneous icatibant for acute attacks, and as a second-line option for pre-procedural and routine prophylaxis of hereditary angioedema. MSAC accepted that, although icatibant is not effective for pre-procedural or routine prophylaxis due to its short half-life, icatibant is the appropriate comparator for acute attacks.

MSAC noted that the C1 esterase inhibitor concentrates are derived from human plasma with similar safety to icatibant, noting that no cases of blood borne disease have been reported following use of the concentrate despite the theoretical risk.

MSAC concluded that it had moderate confidence that the use of C1 esterase inhibitor concentrates offered clinically important improvements over placebo for the treatment of acute attacks of hereditary angioedema. MSAC noted that the comparative effectiveness against icatibant is uncertain due to the small trials involved in the indirect comparisons, with varying baseline characteristics of participants and varying outcome measures. MSAC noted that there is a view that the mode of action of C1 esterase inhibitor concentrate is more physiological than that of icatibant.

MSAC concluded that it had low confidence that the use of C1 esterase inhibitor concentrates offered clinically important improvements for pre-procedural and routine prophylaxis of hereditary angioedema. MSAC noted the small studies without an active comparator and only retrospective observational studies in pre-procedural prophylaxis.

In relation to claims that C1 esterase inhibitor concentrates might be more suitable than its alternatives in paediatric, pregnant and lactating populations, MSAC noted that they relied on the TGA-approved product information documents, for which the most notable feature is the absence of clinical data for any of the alternatives in these populations.

MSAC noted that despite training in intravenous self-administration for C1 esterase inhibitor concentrate, icatibant would still be more conveniently given by subcutaneous injection for acute attacks in remote and emergency situations.

MSAC was concerned with the issue of patients stockpiling both C1 esterase inhibitor and icatibant at home to treat attacks, possibly using different treatments for different types of attacks. MSAC noted that this would add to the expense due to the increased risk of wastage if the dispensed product expires before it can be used, and therefore recommended that the NBA take this into account when negotiating the pricing agreement with the sponsor.

MSAC noted that the main source of uncertainty for the proposed cost-minimisation analysis against icatibant for acute attacks was frequency of acute angioedema episodes.

The economic evaluation for pre-procedural prophylaxis was less relevant because it compared NPSL-funded C1 esterase inhibitor (including community use) against the current arrangements (not including community use) rather than against not using pre-procedural

prophylaxis. However it provided reassurance, that at the reduced price to match icaltiban in the cost-minimisation for acute attacks, the incremental costs for this small volume of second-line use applying to Cinryze only would not be excessive. Noting that the intention is to reserve this use to high risk procedures of dental work, head or neck surgery, or surgery requiring intubation, MSAC recommended that the JBC/NBA work with the Australasian Society of Clinical Immunology and Allergy (ASCIA) to develop guidelines and governance arrangements for second-line use of C1 esterase inhibitor as pre-procedural prophylaxis that reflects this intention.

MSAC advised that, at a base case ICER per QALY of more than \$500,000 for routine prophylaxis, the cost-utility analysis did not support funding of this indication without further targeting. MSAC noted that this analysis was particularly sensitive to the incremental attack rate per month. Noting the caveats with the corresponding sensitivity analysis, MSAC considered that routine prophylaxis would be likely to be acceptably cost-effective if limited to those individuals who suffer from at least 8 attacks per month without routine prophylaxis. In the absence of clear arrangements to reinforce such a limitation, MSAC recommended that the JBC/NBA work with ASCIA to develop guidelines and governance arrangements for second-line use of C1 esterase inhibitor as routine prophylaxis (see Figure 2 on page 13), that reflects this limitation. Noting that the source of evidence for this analysis (Zuraw et al, 2012) reported 19 of a total of 146 participants in the CHANGE 3 study who suffered from at least 8 attacks per month without routine prophylaxis, MSAC anticipated that the population eligible for routine prophylaxis could be reduced by up to 87%, whilst also ensuring that the extent of reduction in the number of attacks per person for this smaller eligible population would be greater than for the larger eligible population in the initial base case analysis.

In view of these uncertainties and caveats particularly relating to the extent of use as prophylaxis, and in the context of moderate financial implications for a rare condition, MSAC suggested that consideration should be given to introducing a rebating arrangement such that any expenditure on C1 esterase inhibitor concentrate beyond these financial projections are borne by Shire given that use as prophylaxis should apply to Cinryze only. Such arrangements are now a routine aspect of new listings in the Schedule of Pharmaceutical Benefits.

4. Background

Two proposals were received by the NBA requesting the inclusion of purified human C1 esterase inhibitor (C1-INH) concentrate for the management of hereditary angioedema (HAE) in the NPSL; one from Cedarglen Investments (on behalf of ViroPharma SPRL, now Shire Australia) for Cinryze[®] in December 2012 and the other from CSL Behring for Berinert[®] in May 2013. Listing in the NPSL would allow full government subsidy of the product in Australia, through cost shared arrangements between the Commonwealth and State and Territory governments. The mechanism for the subsidy is centralised tendering and supply contracting by the NBA.

The JBC assesses and endorses new listings in the NPSL under Schedule 4 of the National Blood Agreement through a Multi-Criteria Analysis (MCA) process. The proposals for C1-INH concentrate were originally intended to be evaluated according to the Schedule 4 Cycle 1 MCA. However, after a briefing on the two proposals on 16 June 2014, the JBC Working Group advised that the evaluation of C1-INH concentrate is more complex than would typically constitute a Cycle 1 MCA and recommended that the assessment be referred to MSAC for advice to supplement the initial MCA process. At its 5 September 2014 meeting, the JBC agreed to this referral via the Commonwealth member of the JBC.

On behalf of the NBA, HealthConsult drafted a Protocol that was considered by PASC in December 2014. The Protocol (finalised on 6 February 2015) outlines the framework for this assessment of the safety, effectiveness and cost-effectiveness of C1-INH concentrate for three indications:

- treatment of acute angioedema attacks;
- pre-procedural (short-term) prophylaxis against angioedema attacks; and
- routine (long-term) prophylaxis against angioedema attacks.

An Assessment Report was prepared to inform MSAC’s evaluation and advice regarding public funding of C1-INH concentrate under the National Blood Agreement.

5. Prerequisites to implementation of any funding advice

Both C1 esterase inhibitor concentrate products are TGA-approved for administration in the following settings:

- in hospital;
- out-of-hospital by a health practitioner or nurse (community administration); and
- self/home-administered.

6. Proposal for public funding

Cinryze is TGA-approved for routine prophylaxis, but approval is restricted to patients 12 years of age and older. The ASCIA does not specify age restrictions on the use of C1-INH concentrate for routine prophylaxis, however if listed on the NPSL, it is possible that Cinryze will be used in paediatric patients for routine prophylaxis.

The supply of C1-INH concentrate will need to be managed by, or be in consultation with, a clinical immunologist, a respiratory physician, specialist allergist or general physician experienced in the management of patients with HAE.

Cinryze and Berinert are both supplied as a complete administration kit, however patients wishing to self/ home administer will require guidance and training. Product information instructions for the self/ home administration kit are as follows:

Table 1 Product Information instructions for the self/home-administration of Cinryze and Berinert

Instructions from PI	Cinryze	Berinert
Self/home-administration	It is the responsibility of the prescribing physician to determine which patients may be suitable for self-administration of Cinryze and to provide training.	If deemed appropriate by the treating physician, Berinert may be self-administered by the patient (or carer) following adequate training. This includes its administration in the home or other appropriate setting. If self-administration/home treatment is deemed appropriate, ensure that the patient/carer receives clear instructions, adequate training on intravenous administration and has demonstrated the ability to perform intravenous infusions.

Patients who are unable to self-administer, and do not have the option of administration by another person such as a family member or a carer, can access on demand administration using the service of a community nurse, GP or other out-of-hospital health professional.

7. Summary of Public Consultation Feedback/Consumer Issues

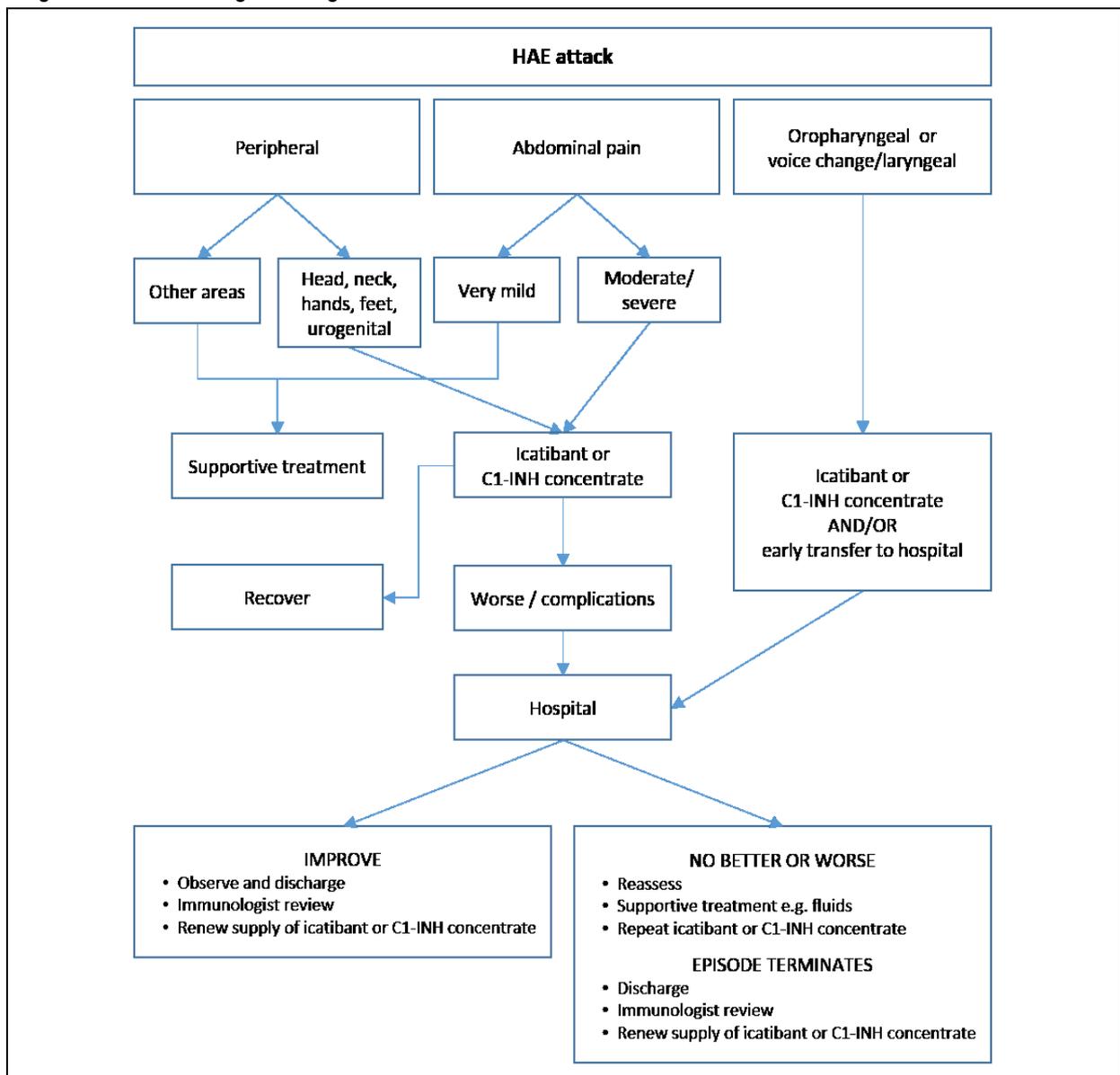
PASC received eighteen public responses including one general practitioner, eleven consumers and 6 peak organisations. The feedback received confirmed the potential positive

impact for treatment and quality of life of the small number of relevant patients with HAE and associated conditions, particularly for whom currently available therapies are not adequate (such as: children, pregnant and lactating women).

8. Proposed intervention's place in clinical management

The clinical management algorithm below describes the options of self-administration of either icatibant or C1-INH concentrate for an acute attack of HAE prior to presentation at hospital, if they are at hand. Corresponding clinical management algorithms for pre-procedural prophylaxis and routine prophylaxis, which do not involve a comparison with icatibant and reserve C1-INH concentrate to second-line therapy, are available in the Protocol.

Figure 1 Clinical management algorithm for an acute attack of HAE



Source: ASCIA Position Paper on Hereditary Angioedema (Katelaris et al, 2012).

Abbreviations: ASCIA, Australasian Society of Clinical Immunology and Allergy; C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema.

9. Comparator

The comparators for each of the indications and populations of interest are as follows:

Table 2 Comparator treatments for C1-INH concentrate for various HAE indications and populations

Population Indication	Comparator	Is C1-INH concentrate currently used? ^a	Comments
Adults /adolescents			
Acute attack	Icatibant	Yes	Recommended alongside C1-INH concentrate.
Pre-procedural prophylaxis, major procedures	No prophylaxis in patients who are intolerant to, or insufficiently protected by, oral therapy	Yes	PASC has advised that C1-INH concentrate (Cinryze) should be positioned after oral therapy for this indication due to lack of evidence.
Routine prophylaxis	No prophylaxis in patients who are intolerant to, or insufficiently protected by, oral therapy	No ^b	C1-INH concentrate (Cinryze) is recommended second line, after failure of oral therapy such as danazol.
Children			
Acute attack	No treatment ^c	Yes	-
Pre-procedural prophylaxis, major procedures	No prophylaxis in patients who are intolerant to or insufficiently protected by oral therapy	Yes	Cinryze is not TGA-approved for children <12 years.
Routine prophylaxis	No prophylaxis in patients who are intolerant to or insufficiently protected by oral therapy ^d	No ^b	Cinryze is not TGA-approved for children <12 years.
Pregnancy /lactation			
Acute attack	No treatment ^c	Yes	-
Pre-procedural prophylaxis, major procedures	No prophylaxis in patients who are intolerant to or insufficiently protected by oral therapy	Yes	TA may be used in pregnancy, but is a Category B1 pharmaceutical and caution is advised in lactating women. ^e PASC has advised that C1-INH concentrate (Cinryze) should be positioned after oral therapy for this indication due to lack of evidence.
Routine prophylaxis	No prophylaxis in patients who are intolerant to or insufficiently protected by oral therapy	No ^b	TA may be used in pregnancy, but is a Category B1 pharmaceutical and caution is advised in lactating women. ^e

Abbreviations: C1-INH, C1 esterase inhibitor; conc., concentrate; HAE, hereditary angioedema; TA, tranexamic acid

a Indicates where hospital-funded C1-INH concentrate currently may be used.

b This is an assumption. It is possible that some patients are using C1-INH concentrate routinely but it seems highly unlikely given the financial burden it would place on either the patient or the hospital. Comments made in the ASCIA Position Paper (Katelaris et al, 2012) are consistent with this assumption.

c While TA is not contraindicated in these populations, it is of very limited benefit for acute attacks and the ASCIA Position Paper makes no mention of its use for this indication.

d Oral therapy in children would usually be TA but the ASCIA Position Paper states 'In some cases the benefits of routine danazol in children outweigh the risks', so danazol may be used routinely in some children.

e The PI for TA states that caution should be exercised when administered to a nursing woman. Not for 12 hours prior to breastfeeding.

10. Comparative safety

In a study by Farkas et al (2012), patients presented no adverse side effects with the administration of Berinert and neither viral transmission or development of anti-C1-INH antibodies. Similarly, in a study by Bork et al (2011), patients showed no drug-related side effects.

The three studies that investigated the safety of Cinryze found no evidence of viral transmission related to Cinryze exposure or detection of clinically relevant antibodies to

Cinryze. None of the studies reported serious adverse events (AEs) that were related to the use of Cinryze as prophylaxis.

In the study by Baker et al (2013), the most commonly reported AEs were infection, gastrointestinal disorders, headache, and rash. However, none of the AEs was considered by the investigators to be related to the use of Cinryze.

In the study by Lumry et al (2013), there were no serious or severe AEs that were associated with Cinryze. Further, there was no evidence of HIV or viral hepatitis transmission or development of clinically relevant antibodies to Cinryze.

In the study by Grant et al (2012), of the 41 subjects who received pre-procedural Cinryze, a total of 12 AEs in seven subjects were reported within seven days after dosing. There were three AEs that were considered serious (procedural pain, intestinal perforation, and B-cell lymphoma). Other events included single reports of coronary artery disease, back pain, adenoidal hypertrophy, increased blood glucose, herpes simplex virus, upper abdominal pain, and renal transplant. However, most of these events were caused by the condition for which the procedure was being performed or were the result of other pre-existing conditions; none of the AEs were considered by the investigators to be related to Cinryze and none was associated with an HAE attack.

Overall, the pre-procedural use of C1-INH concentrate as prophylaxis appeared to be safe, with no HIV or viral hepatitis transmission or detection of clinically relevant anti-C1-INH antibodies.

11. Comparative effectiveness

Randomised trial evidence for the two C1-INH products and icatibant is limited to placebo-controlled trials for the treatment of acute attacks. There were no randomised trials comparing the two C1-INH products with each other or with icatibant. Indirect comparisons across randomised trials were hindered by the trials assessing different outcomes and recruiting different study populations. There were no randomised trials of any C1-INH concentrate in pre-procedural prophylaxis. There was one randomised placebo-controlled trial of Cinryze for routine prophylaxis.

Treatment of acute attacks

Individual trial results show that Cinryze, Berinert and icatibant significantly reduce the median time to onset of relief of acute HAE attacks (Table 3) and the median time to attack resolution (Table 4). However, there are large differences between placebo arms across the trials, which may reflect differences between the studies in the type/location of attacks, the way in which rescue medication was used, and the differences in how the outcomes were defined and measured. Given the heterogeneity among the three sets of trials, a robust comparative assessment of their effectiveness and toxicity profiles is difficult and therefore a claim of non-inferiority across the three products, although seemingly reasonable, cannot be confirmed.

Table 3 Time to onset of relief outcomes from the pivotal RCTs for acute attacks

Trial ID	Analogous outcome	Study group	N	Median time-to-event (h)	P-value
CHANGE Part A	Median time to onset of unequivocal relief of symptoms at defining site	Cinryze	35	2 ^a	0.02
		Placebo	33	>4 ^{a,b}	
IMPACT 1	Median (range) time to onset of symptom relief	Beriner	43	0.5 (0.17 – 24.00)	0.0025
		Placebo	42	1.5 (0.20 – 24.00)	
FAST 1	Median [IQR] time to first improvement of the index symptom according to the patient ^c	Icatibant	27	0.8 [0.5, 2.0]	<0.001
		Placebo	29	16.9 [3.2, NA]	
FAST 3	Median (95% CI) time to initial symptom relief according to the patient ^c	Icatibant	43	0.8 (0.5, 1.0)	<0.001
		Placebo	45	3.5 (1.9, 5.4)	

Source: Table B.6.2 of the Assessment Report (Zuraw et al, 2010; Craig et al, 2009; Cicardi et al, 2010; Lumry et al, 2011)

Note: Detailed outcome definitions are provided in Section B.5.1 of the Assessment Report.

Abbreviations: CI, confidence interval; h, hours; IQR, interquartile range; NA, not applicable

a Variance not reported

b All patients not achieving onset of symptom relief at 4 hours were censored at 4 hours for the primary outcome.

c Data are shown for patient-selected pre-defined measures of improvement. This outcome was also assessed using a Visual Analog Scale.

Table 4 Time to attack resolution outcomes from the pivotal RCTs for acute attacks

Trial ID	Analogous outcome	Study group	N	Median time-to-event (h)	P-value
CHANGE Part A	Median time to complete resolution of the attack	Cinryze	35	12.3 ^a	0.004
		Placebo	33	25.0 ^a	
IMPACT 1	Median (range) time to complete resolution of all symptoms ^b	Beriner	43	4.92 (0.47 – 1486.17)	0.0237
		Placebo	42	7.79 (0.33 – 1486.17)	
FAST 1	Median [IQR] time to almost complete relief of all symptoms	Icatibant	27	8.5 [2.5, 31.5]	0.08
		Placebo	29	19.4 [10.2, 55.7]	
FAST 3	Median (95% CI) time to almost complete symptom relief	Icatibant	43	8.0 (5.0, 42.5)	0.012
		Placebo	45	36.0 (29.0, 50.9)	

Source: Table B.6.4 of the Assessment Report (Zuraw et al, 2010; Craig et al, 2009; Cicardi et al, 2010; Lumry et al, 2011)

Note: Detailed outcome definitions are provided in Section B.5.1 of the Assessment Report.

Abbreviations: CI, confidence interval; h, hours; IQR, interquartile range; RCT, randomised controlled trial

a Variance not reported

b Described as an exploratory variable, and includes resolution of pain

Pre-procedural prophylaxis

There were two retrospective observational studies that evaluated the pre-procedural use of Beriner in the prevention of HAE attacks (Table 5). Based on the available evidence, pre-procedural prophylaxis with Beriner significantly reduced the frequency of HAE attacks compared to no prophylaxis.

Table 5 Post-procedural oedema attacks with and without the use of Beriner

Study Population	Outcome	Prophylaxis with Beriner 500 U	Prophylaxis with Beriner 1000 U	Without prophylaxis	P-value
Bork et al (2011) - Adults	HAE attacks per tooth extraction procedure, n/N (%)	12/75 (16)	4/53 (8)	124/577 (21)	NR
Farkas et al (2012) - Adults	HAE attacks per surgical/ diagnostic intervention, n/N (%)	4/51 (8)	-	39/89 (44) ^a	NR
Farkas et al (2012) - Children	HAE attacks per surgical/ diagnostic intervention, n/N (%)	1/36 (3)	-		

Source: Section B.6.2 of the Assessment Report

Abbreviations: HAE, hereditary angioedema; NR, not reported

a Retrospective data in a broader population informed the rate of attacks without prophylaxis. Breakdown for children/adults not reported.

No comparative evidence is available for the pre-procedural use of Cinryze, but *post-hoc* analyses of open-label use in the pivotal studies shows low rates of post-procedure attacks: 2 attacks in 91 procedures in CHANGE 2; 1 attack in 40 procedures in children in CHANGE Part A and CHANGE 2.

Routine prophylaxis

One randomised, placebo-controlled crossover clinical trial (CHANGE Part B) compared the effectiveness and safety of Cinryze with no prophylaxis for the overall prevention of attacks

in patients with HAE. The efficacy results, summarised in Table 6, show that subjects experienced a significant reduction in attack frequency, severity and duration when treated with Cinryze compared with placebo.

Table 6 Summary of efficacy results from CHANGE Part B – crossover RCT routine prophylaxis

Key efficacy outcomes (N=26)	Cinryze	Placebo	P-value
Attacks per 12-week period, mean ±SD	6.26 ±NR	12.73 ±NR	P<0.001
Severity of attacks ^a , mean ±SD	1.3 ±0.85	1.9 ±0.36	P<0.001
Duration of attacks (days), mean ±SD	2.1 ±1.13	3.4 ±1.39	P=0.002
Open-label rescue therapy, n/N (%)	11/22 (50)	22/22 (100)	NR

Source: Table B.6.16 of the Assessment Report (Zuraw et al, 2010)

Abbreviations: C1-INH, C1 esterase inhibitor; NR, not reported; RCT, randomised controlled trials; SD, standard deviation

Note: There was no evidence of a significant sequence effect (P=0.54) or period effect (P=0.42).

^a Measured on a 3-point scale with 1 indicating mild, 2 moderate, and 3 severe

12. Economic evaluation

The economic evaluation consisted of three discrete analyses:

- C1-INH concentrate versus icatibant to treat acute HAE attacks in adults and adolescents (the ‘acute attack model’).
- Pre-procedural prophylaxis with C1-INH concentrate with the option of community- (or self-) administration versus hospital-administered C1-INH concentrate in patients who are intolerant to, or insufficiently protected by, oral therapy (the ‘pre-procedural prophylaxis model’).
- Routine prophylaxis with C1-INH concentrate versus no prophylaxis in patients who are intolerant to, or insufficiently protected by, oral therapy (the ‘routine prophylaxis model’).

Treatment of acute attacks model (cost-minimisation analysis)

The results of the acute attack analyses are presented in Table 7. The analyses took into consideration the average number of vials required to treat an acute attack plus the need for re-dosing in a proportion of patients as well as other health care resources depending on attack severity. The base case analysis assumed that the average cost of an initial dose of Cinryze is \$redacted (2 x 500 U vials at \$redacted/vial), or \$redacted with re-dosing in 30.9% of patients. The total average cost of an initial dose of Berinert is \$redacted (3.1370 x 500 IU vials at \$redacted /vial), or \$redacted with re-dosing in 1% of patients.

For both Cinryze and Berinert, treatment of acute attacks is associated with a greater cost than treatment with icatibant. To achieve a cost-neutral result, the price per vial of Cinryze would need to be reduced from \$redacted to \$redacted under the current set of assumptions, while the price per vial of Berinert would need to be reduced from \$redacted to \$redacted. Note that these reductions would be smaller if a difference in attack rates or attack severity could be proven. Without such a benefit, the cost difference is driven by the cost of the medication only.

Table 7 C1-INH concentrate (manufacturer’s requested price) versus icatibant: treatment of acute attacks

Total cost per acute HAE attack	C1-INH concentrate	Icatibant
Cinryze	redacted	redacted
Berinert	redacted	redacted

Source: Disaggregated costs are shown in Table B.6.4 and Table B.6.4 of the Assessment Report. The disaggregated costs for the “cost-neutral” pricing analysis are shown in Table D.5.3 and Table D.5.4 of the Assessment Report.

The acute attack model appears to be sensitive to the number of vials required for each treatment, the re-dosing assumptions and the proportion of individuals who use self-administration. It is noted that there are poor data supporting each of these assumptions in the base case and the result of the base case analysis should, therefore, be interpreted with caution. In particular, the uncertainty around the number of vials of Berinert required to adequately treat patients suffering an acute attack could have a profound impact on the conclusions drawn.

Of relevance to considerations of setting, if the proportion of patients that self-administer C1-INH concentrate is reduced from 100% to 25%, the incremental cost of Cinryze over icatibant decreases from **\$redacted** to **\$redacted**, and the incremental cost of Berinert over icatibant decreases from **\$redacted** to **\$redacted**.

Pre-procedural prophylaxis model (cost-minimisation analysis)

This model compared C1-INH concentrate being available in the NPSL for pre-procedural prophylaxis with hospital-funded and administered C1-INH concentrate. In the intervention arm, community use C1-INH concentrate is assumed for 50% of individuals (hospital-administered C1-INH concentrate is assumed for the other 50%), while the comparator arm assumes 100% hospital-administration in the base case. Alternative assumptions regarding community-administered C1-INH concentrate are tested in sensitivity analyses in Section D.6 of the Assessment Report, together with varying assumptions around the proportion of patients not receiving pre-procedural prophylaxis.

The model assumed that major surgical and dental procedures are associated with a risk of HAE attacks, although there is a lower risk in patients who receive prophylaxis. In those who suffer an attack, a mix of medication and other treatment is administered until the attack is resolved. The resources required are a function of the severity of the attack. Individuals costs are tracked within the model until their attack-free procedure or until the attack is resolved.

The results of the pre-procedural prophylaxis analyses are provided in Table 8. Where community use of C1-INH concentrate is available, there is a cost saving of **\$redacted** per breakthrough attack for both products. Cinryze and Berinert are therefore already cost-minimising at the requested price.

Table 8 C1-INH concentrate – community use available versus no community use available (manufacturer’s requested price): pre-procedural prophylaxis

Total cost of prophylaxis per breakthrough attack	With community use available	Without community use available
Cinryze		
- manufacturer’s requested price	redacted	redacted
- cost-neutral price from acute attack model	redacted	redacted
Berinert		
- manufacturer’s requested price	redacted	redacted
- cost-neutral price from acute attack model	redacted	redacted

Source: Table D.5.5 and Table D.5.6 of the Assessment Report

An increase in the proportion of patients that do not use pre-procedural prophylaxis with C1-INH concentrate in the comparator arm brings about an increase in the incremental cost of NPSL-funded (i.e. community use available) Cinryze and Berinert, since the reduction in the cost of prophylaxis in the comparator arm is greater than the increase in the costs associated with acute attacks. If the proportion of patients that do not receive pre-procedural prophylaxis with C1-INH concentrate is increased from 0% to 25% in the comparator arm, the

incremental cost of NPSL-funded Cinryze increases from - \$redacted to \$redacted, and the incremental cost of NPSL-funded Berinert increases from - \$redacted to \$redacted.

Routine prophylaxis model (cost-utility analysis)

This model allocated individuals to receive ongoing (routine) prophylaxis or not. In the case of breakthrough attacks, which occurred with greater frequency in the ‘no prophylaxis’ arm of the model, individuals received treatment to resolve the attack. This included, though is not limited to, medication in the form of either the same treatment they received for prophylaxis or, in the case of those who did not undergo prophylaxis, either Cinryze, Berinert or icanitabant. Once the attack was resolved, individuals in the ‘routine prophylaxis’ arm would resume prophylaxis once more.

The model takes the form of a Markov model using monthly cycles for a period of five years in the base case. Since individuals who did not receive prophylaxis would incur more than one attack per cycle, the model did not apply different health states for each level of attack severity. Instead, the model calculated the average cost and utility impact of attacks in any given cycle.

In the base case analysis, Cinryze costs \$redacted more per monthly cycle compared to no prophylaxis. The estimated incremental cost per quality-adjusted life year (QALY) of routine prophylaxis with Cinryze is presented in Table 9. Using the “cost-neutral” price of Cinryze from the acute attack model, the incremental cost per QALY is \$redacted.

Table 9 Modelled incremental cost per QALY for routine prophylaxis using Cinryze

	Routine prophylaxis	No routine prophylaxis	Incremental value
Average cost over five years	\$redacted	\$redacted	\$redacted
Average QALYs gained over five years	3.7132	2.7349	0.9783
Incremental cost per QALY			\$redacted

Source: Table D.5.9 of the Assessment Report

Abbreviations: QALY, quality-adjusted life year

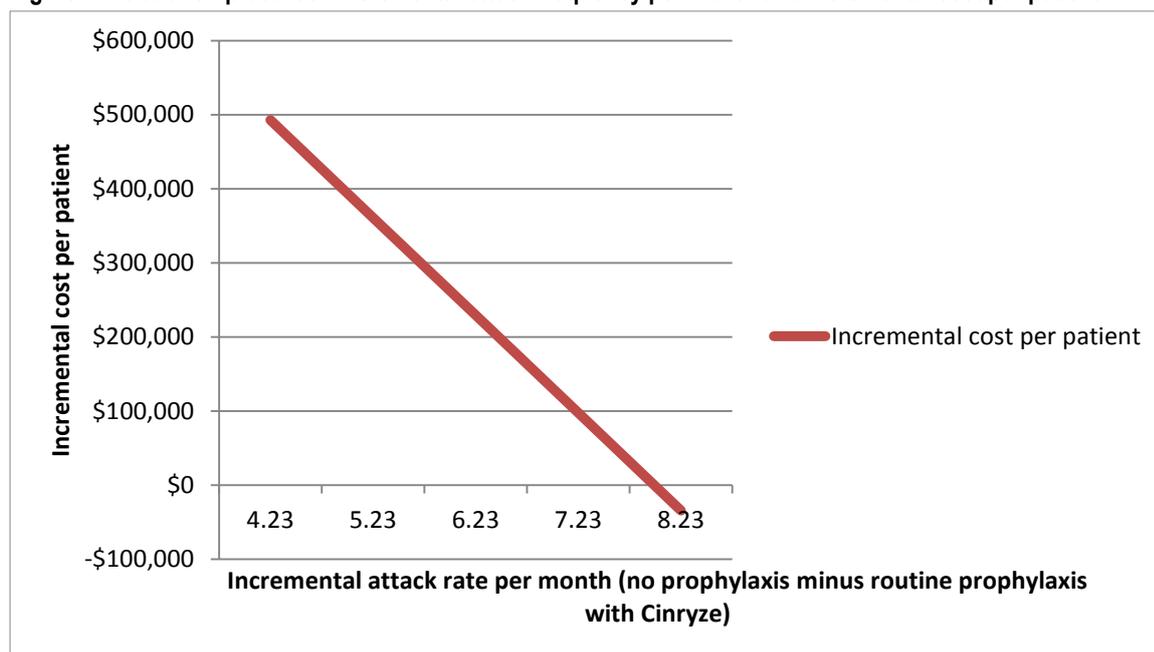
The incremental cost per QALY estimated is substantially higher than what would typically be considered cost-effective. It is noted, however, that it comprises direct healthcare costs only. Inclusion of other indirect costs such as lost productivity or out of pocket expenses could improve the cost-effectiveness considerably, but is outside the remit of the current research question.

The cost-utility estimate associated with the routine prophylaxis model is high for all but one of the modifications made to the base case assumptions. This extends even to reductions in the model duration, which do not lead to changes in the results generated, since costs continue to accrue while offering the same benefit as in the base case. There appears to be little scope within the assumptions applied to the model to reduce the incremental cost sufficiently to generate a reasonable ICER, with the exception of restricting access to only those patients with a very high attack frequency.

In the base case analysis (where all patients regardless of baseline attack rate were included), the incremental attack rate (the difference in attack rates between the two arms of the model) was set to 4.23 per month (4.7 in the case of no prophylaxis and 0.47 in the case of routine prophylaxis). The sensitivity presented in Figure 2 below shows the impact of moderate to severe attack frequency on the incremental cost per patient over five years. The data to populate Figure 2 were generated by varying the incremental attack rate by artificially

keeping the attack rate in the Cinryze arm unchanged at 0.47 attacks per month and increasing the monthly attack rate in the no prophylaxis arm.

Figure 2 Relationship between incremental attack frequency per month and incremental cost per patient



This sensitivity analysis shows how closely the incremental attack rate relates to incremental cost per patient. MSAC used this sensitivity analysis to target the proposed funded use of C1-INH concentrate as routine prophylaxis, noting the following caveats:

- it assumes that the incremental QALYs gained (0.9783 over five years) does not also change as markedly with varying incremental attack rate, so that incremental cost per patient still reasonably reflects incremental cost-effectiveness
- it notes that, despite there being some imprecision about how varying the attack rate in the no prophylaxis arm might predict the attack rate in the Cinryze arm to achieve the modelled incremental attack rate in Figure 2, it is reasonable to base the MSAC advice on a more practically implementable threshold based on the attack rate without routine prophylaxis.

13. Financial/budgetary impacts

Table 10 presents the estimated numbers of Australian patients with HAE who may be eligible for NPSL-funded C1-INH concentrate.

Table 10 Estimated number of Australian patients with HAE and eligible for C1-INH concentrate

	2016 Year 1	2017 Year 2	2018 Year 3	2019 Year 4	2020 Year 5
Prevalence of HAE	487	496	504	512	521
HAE patients seeking health care	108	110	112	114	116
Treatment of acute attacks					
Total number of acute HAE attacks that are moderate to severe and not treated with icatibant	377	400	423	446	469
Pre-procedural prophylaxis					
Total number of procedures requiring prophylaxis with C1-INH concentrate	54	55	56	57	58
Routine prophylaxis					

Total number of HAE patients that may receive routine prophylaxis with C1-INH concentrate	4	6	7	8	8
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Source: Table E.2.1 of the Assessment Report

Abbreviations: C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema

Table 11 presents the estimated cost to the NPSL of C1-INH concentrate for each of the three scenarios.

In the first scenario, the cost of treating acute attacks is calculated in the absence of any C1-INH concentrate prophylaxis. As prophylaxis reduces the number of acute attacks, the cost of treating acute attacks is also calculated for scenarios in which pre-procedural prophylaxis, or both pre-procedural and routine prophylaxis, are used.

The cost of providing pre-procedural prophylaxis and routine prophylaxis are shown separately. Finally, the aggregated costs of mixed indications (either acute attacks plus pre-procedural prophylaxis or all three indications) is presented.

The total costs in Table 11 are calculated using the proposed vial prices for Cinryze and Berinert from the sponsors.

Table 11 Estimated base case total cost to the NPSL of C1-INH concentrate

	2016 Year 1	2017 Year 2	2018 Year 3	2019 Year 4	2020 Year 5
Base case 1: Acute attack treatment costs only					
Cinryze	\$ redacted				
Berinert	\$ redacted				
Base case 2: With reduced attacks due to pre-procedural prophylaxis					
Cinryze					
Cost of acute attacks	\$ redacted				
Cost of pre-procedure prophylaxis	\$ redacted				
Total	\$ redacted				
Berinert (off-label)					
Cost of acute attacks	\$ redacted				
Cost of pre-procedure prophylaxis	\$ redacted				
Total	\$ redacted				
Base case 3: With reduced attacks due to pre-procedural and routine prophylaxis					
Cinryze					
Cost of acute attacks	\$ redacted				
Cost of pre-procedure prophylaxis	\$ redacted				
Cost of routine prophylaxis	\$ redacted				
Total	\$ redacted				

Source: Table E.4.1 of the Assessment Report

Abbreviations: C1-INH, C1 esterase inhibitor; NPSL, National Product and Services List

A sensitivity analysis was performed in which the market share of icatibant decreased from 70% of all attacks in Year 1 to 50% by Year 3 and thereafter. For the treatment of acute attacks, the estimated savings to the PBS is \$54,000 in Year 1 increasing to \$620,000 in Year 5. If C1-INH concentrate is listed for all three indications, the estimated savings to the PBS is \$598,000 in Year 1 increasing to \$1,629,000 in Year 5.

14. Key issues from ESC for MSAC

ESC considered that the main benefit of listing of the product would be a potential increase in access resulting from more reliable funding compared with current State mechanisms.

ESC considered that there were a range of translational issues which would limit the reliability of the economic analysis. In particular, ESC noted that the study populations were not entirely consistent with the Australian population, and that the model was sensitive to assumptions based on limited data, including the number of vials, re-dosing requirements, and the proportion of people self-administering.

ESC acknowledged that the rarity of the condition limited the availability of evidence.

ESC questioned:

- whether a formalised set of access criteria would be required, depending on the risk of expanded or inappropriate use of the product, noting that this could be based on the ASCIA guidelines, but is not usual practice for the NPSL;
- whether arrangements should be put in place to facilitate or require a specific data collection on product access, management, use and/or outcomes.

ESC considered that self-administration, particularly for children, was a key access issue, and noted that the two sponsors had offered training to assist patients to learn self-infusion. ESC questioned whether health service staff might be better placed to deliver training, utilising materials provided by sponsors.

ESC had no concerns in relation to safety of C1-INH concentrate.

15. Other significant factors

For each of the three indications (treatment of an acute attack, pre-procedural prophylaxis and routine prophylaxis), a comparison is also presented of setting (hospital-administered versus community-administered) and funding source (current arrangements versus inclusion in the NPSL). ESC noted that there was very limited data for the setting comparison, and the funding comparison emphasised the NPSL as a “reliable, assured and equitable” funding mechanism.

The following issues are relevant to the NBA in terms of supply implementation and ongoing governance and management under the National Blood Arrangements:

- Whether or not a formalised set of access criteria is required, implemented through a structured and arm’s length authorisation process, depending on the risk of expanded or inappropriate use of the product?
- Whether or not arrangements should be put in place to facilitate or require a specific data collection on product access, management, use and/or outcomes?
- The two sponsors have offered training to assist patients to learn self-infusion. The question arises whether such training would be more appropriate to be provided by health service staff, utilising materials provided by the sponsors, rather than directly by sponsor staff to patients?

16. Applicant’s comments on MSAC’s Public Summary Document

Comments from Shire

Shire welcomes the MSAC’s recommendation for C1-esterase inhibitor to be listed on the NPSL under the NBA. Shire will continue to work with the NBA and other stakeholders so that patients with hereditary angioedema have access to treatment options for this rare and spontaneous condition.

Comments from CSL Behring

CSL Behring is pleased at MSAC's recommendation that C1 esterase inhibitor concentrate should be listed on the NPSL for treatment of acute attacks of Types I or II hereditary angioedema (HAE). We welcome working with the NBA to develop an appropriate registry to understand with more accuracy HAE in Australia, as well as with the NBA and JBC to expedite this listing, ultimately to allow patient access under the National blood arrangements of CSL Behring's Berinert.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.