Position Paper on Hereditary Angioedema (HAE)

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This is an updated version of the original ASCIA Position Paper on Hereditary Angioedema (HAE) developed by the ASCIA HAE Working Party in 2010 and revised in 2012. A list of ASCIA HAE Working Party members is available on the ASCIA website: www.allergy.org.au/members/committees#wp

This document has been compiled as a Position Paper for ASCIA. It has not been formulated as a formal Guideline. As such, it aims to provide:
- Background education on various aspects of HAE;
- Treatment algorithms for the Australian and New Zealand environments; and
- Statements regarding the Global Guidelines on HAE to which ASCIA is a signatory.

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ABBREVIATIONS USED IN DOCUMENT

ACE angiotensin converting enzyme
ASCIA Australasian Society of Clinical Immunology and Allergy
C1-INH C1 inhibitor
ED emergency department
HAE hereditary angioedema
HRT hormone replacement therapy
NBA National Blood Authority
OCP oral contraceptive pill
PBS Pharmaceutical Benefits Scheme
PID primary immunodeficiency
TA tranexamic acid
TGA Therapeutic Goods Administration
SAS Special Access Scheme

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1.0 INTRODUCTION

1.1 Classification and definitions

Angioedema may result from mast cell activation with release of histamine and other mediators (histamine-mediated) or it may be mediated by bradykinin. Bradykinin-mediated angioedema may be the result of an acquired or hereditary abnormality, the latter due to a deficiency/defect of C1 inhibitor (C1-INH).

Three forms of HAE have been defined:

1. HAE due to C1-INH deficiency (type 1 HAE) - Individuals with this condition have low antigenic and functional C1-INH levels;
2. HAE due to C1-INH dysfunction (type 2 HAE) - Normal (or elevated) antigenic but low functional C1-INH levels define this condition;
3. HAE with normal C1-INH antigenic and functional levels (type 3 HAE) - This is a very rare condition where symptoms are very similar to HAE types 1 and 2. A subset of type 3 HAE patients have mutations in factor XII but there are other yet to be defined genetic abnormalities. This subtype will not be discussed in this document.

Acquired C1-INH deficiency (AAE) may cause angioedema in adults and must be distinguished from HAE (section 4.3).

1.2 Historical facts

The first description of HAE has been attributed to Robert Graves, who in 1843 described a patient with “a tumor rising on the forehead in the space of half an hour” and then later “sometimes the lips, inside of the mouth, palate, and uvula are attacked giving rise to a very considerable inconvenience” ¹. The superseded term angioneurotic edema (a synonym for angioedema) is derived from Heinrich Quincke’s original explanation that swelling arose from increased vascular permeability that could affect not only the face and larynx, but also the
gastrointestinal tract. The autosomal dominant nature of this disorder was described by William Osler, who reported the disorder in each of five family generations. The biological basis for this disorder remained unclear until 1962, when Landerman suggested that HAE might result from dysregulation in kinin generation and that there might be an inherited defect in an inhibitor to a permeability factor such as kallikrein. While investigating the properties of a newly discovered protein shown to inhibit complement factor 1, Donaldson reported low circulating levels of this protein in patients with HAE. Further studies by Rosen found that 85% of patients with HAE had low circulating levels of C1-INH (Type 1 HAE), with the remainder producing a dysfunctional inhibitor (Type 2).

1.3 Epidemiology

Estimates of prevalence of HAE range from 1/10,000 to 1/150,000 individuals. There are no known ethnic or sex differences in HAE types 1 and 2 (unlike HAE Type 3).

1.3.1 HAE in Australia

No formal epidemiological research into this condition has been conducted in Australia. ASCIA established a Primary Immunodeficiency (PID) Register in 1994 with the aim of collecting and analysing data on all patients with PID in Australasia to facilitate diagnosis, treatment, research, education and quality assurance for patients with PID. HAE is defined by the World Health Organisation (WHO) as a PID. However these patients are not prone to increased infection risk. Results from the database were first published in 1997. At that time complement deficiencies accounted for 7.4% of PID cases in the Australian register, with HAE being the most common, accounting for 6.4% of cases, giving a national rate of 0.18/100,000 in the general population. Currently, there are 66 HAE patients registered in the database (representing 5% of all PID registrations in database), which is undoubtedly affected by under-reporting. If the currently quoted number of cases in other populations holds for Australia, then up to 480 cases could be expected to exist. The patient support organisation HAE Australasia has 102 registered members with HAE in their database.
2.0 PATHOGENESIS

C1-INH is a serine protease inhibitor whose major activity is inhibition of a number of complement proteases (C1r, C1s and mannose binding lectin associated-serine protease <MASP>) and contact system proteases (plasma kallikrein and coagulation factor X11a). During attacks of HAE, these plasma proteolytic cascades are activated and several vasoactive substances are released. Studies have shown that bradykinin is the predominant mediator of enhanced vascular permeability. Bradykinin is generated by activation of the contact system and binds to its cognate receptor (the bradykinin B2 receptor) on vascular endothelial cells. It is the primary mediator of swelling in HAE. It is important for normal homeostasis, normal immune responses, inflammation, vascular tone and vascular permeability. Angioedema is primarily mediated through the B2 bradykinin receptor causing increased permeability.

In HAE Type 1 there is low C1-INH protein level and function. This pattern represents 85% of all cases of HAE. Typically the C1-INH level is 5-30% of normal levels even though only one allele is affected. There is both decreased protein production and increased catabolism of the protein in these cases.

In HAE Type 2 there is normal C1-INH protein level but impaired C1-INH function, usually caused by mutations of the active site of the protein.
3.0 CLINICAL PRESENTATION

Summary

In the absence of adequate levels of C1-INH, subcutaneous and submucosal oedema result from the uninhibited action of vasoactive mediators, of which bradykinin is considered the most important. HAE is characterised by recurrent oedema of the limbs, trunk, face and genitals without urticaria, typically taking 24 hours to peak and resolving over 48-72 hours. Importantly it is neither itchy nor pitting. Visceral swelling of the gastrointestinal tract may result in abdominal pain, vomiting and hypotension. The most serious manifestation is laryngeal swelling, which was reported in older cohort studies to result in fatal asphyxiation in up to a third of patients. Attacks may be preceded by a prodrome of tingling, or a non-itchy rash (erythema marginatum) anywhere on the body. Affected patients also have higher than expected rates of autoimmune disease.

3.1 The acute attack

HAE is characterised by episodic swelling of subcutaneous tissues, gut and upper respiratory tract. Clinical episodes may occur frequently or may be years apart. Fifty percent of patients experience their first manifestation of the disease before the age of 10.

HAE attacks in any one individual follow a typical but not invariable pattern. There may be prodromal symptoms such as fatigue, flu-like symptoms, indigestion, tingling, and sometimes, a non-urticarial, non-pruritic macular serpiginous erythema (erythema marginatum) preceding the onset of swelling. This is most often observed on the chest and may not be adjacent to the area of swelling. The swelling usually worsens gradually over 24 hours and may last three to four days or longer and may spread to other sites, thereby prolonging the episode. It does not respond to antihistamines, corticosteroids or adrenaline.

3.2 Manifestations

**Abdominal pain**, frequently accompanied by nausea, vomiting, abdominal distention, dehydration, diarrhoea or constipation, is the most frequent clinical manifestation of HAE. Acute
attacks may mimic surgical emergencies and result in unnecessary appendectomy or exploratory laparotomy.\(^1\)\(^2\)

**Cutaneous angioedema**, a non-pitting, non-pruritic swelling, usually affects the face, limbs or genitals.

**Upper airway swelling** is a much less frequent manifestation and may affect the oropharynx (tongue, soft palate) or the larynx. Laryngeal swelling can cause death from asphyxiation. Even though it accounts for fewer than 1% of episodes, more than 50% of patients report at least one occurrence of laryngeal angioedema at some stage in life.\(^1\) Historical data suggest that mortality from laryngeal swelling was 30% prior to the introduction of effective treatment\(^2\).

### 3.3 Other features

Urticaria is **not** a feature of HAE or other kinin-related forms of angioedema.\(^21\) Erythema marginatum may mimic urticaria but it is flat and not pruritic. Although a family history is usual, about 25% of newly diagnosed patients report no known affected family members.\(^22\) In these patients a de novo mutation is presumed.\(^23\) Members of the same kindred (with presumably the same genetic variant) may differ greatly in their expression of the disease (age of onset and frequency, severity and location of manifestations).\(^24\) There is an increased frequency of autoimmune disorders in patients with HAE, such as glomerulonephritis, systemic lupus erythematosis (SLE), thyroiditis and inflammatory bowel disease.\(^25\)

### 3.4 Trigger factors

Recognised exacerbating factors include stress, infection, injury, dental and other surgery, oestrogens (oestrogen-oral contraceptives, hormone replacement therapy and pregnancy) and angiotensin converting enzyme inhibitors.\(^28\) Often no precipitating factor can be discerned.

<table>
<thead>
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<th>Table 1. Classification of angioedema</th>
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<tr>
<td><strong>Bradykinin Induced</strong></td>
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<tr>
<td>• HAE type 1 (C1-INH deficiency),</td>
</tr>
<tr>
<td>• HAE type 2 (C1INH dysfunctional),</td>
</tr>
<tr>
<td>• HAE type 3 (HAE with normal C1INH),</td>
</tr>
<tr>
<td>• AAE (acquired C1INH deficiency),</td>
</tr>
<tr>
<td>• ACE-I induced</td>
</tr>
<tr>
<td>• Idiopathic bradykinin induced angioedema</td>
</tr>
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</table>
Histamine Induced (Mast cell dependent) – majority of cases
- Idiopathic histamine induced angioedema
- Allergic angioedema (e.g. IgE-mediated food or drug allergy)
- Drug induced histamine dependent angioedema (e.g. NSAID intolerance)

Suspect mast cell dependent when
- Angioedema coexists with urticaria or other features of anaphylaxis
- Obvious trigger (e.g. drug, food)
- Response to antihistamines (either for treatment or prevention)

A trial of antihistamines and corticosteroids is indicated until diagnosis is confirmed.

Table 2. Features distinguishing HAE from other forms of Angioedema

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>HAE</th>
<th>Acquired</th>
<th>Allergic/IgE Mediated</th>
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<tbody>
<tr>
<td>Angioedema</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Urticaria</td>
<td>No</td>
<td>No</td>
<td>Usually</td>
</tr>
<tr>
<td>Age of onset (most frequent)</td>
<td>6-20</td>
<td>&gt; 50</td>
<td>Anytime</td>
</tr>
<tr>
<td>Family history</td>
<td>Usually</td>
<td>No</td>
<td>Variable</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Location of swelling</td>
<td>All</td>
<td>All</td>
<td>Especially face, lips</td>
</tr>
<tr>
<td>Precipitation by trauma</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Duration of swelling, hr</td>
<td>48-72</td>
<td>48-72</td>
<td>2-48</td>
</tr>
<tr>
<td>Response to treatment with</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>adrenaline, antihistamine,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticosteroids</td>
<td></td>
<td></td>
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</table>
3.5 Special circumstances

In a number of circumstances individuals with HAE require special measures to protect them from the risk of swelling.

3.5.1 Pregnancy

The published experience regarding the effect of pregnancy on HAE has yielded conflicting results. The most substantial study on clinical manifestations of HAE to date has been a case series of 30 patients by Frank et al looking at the clinical characteristics of HAE. In this series there were 10 patients in whom the effect of HAE on pregnancy was evaluated. Among the 10 women with a total of 25 pregnancies more than 80% of the pregnancies were associated with a decreased incidence of attacks in the second and third trimester. In the two patients who had an increase in the frequency of attacks at this time, the attacks were not related to the delivery. Trauma is recognised as a frequent trigger for acute HAE attacks, so it is somewhat surprising that angioedema attacks are rare at the time of delivery despite the associated injury to the birth canal. However, it has been suggested that the physical trauma associated with normal labour can precipitate airway difficulties, presumably as a result of straining. Similarly, the same mechanism may result in mucosal swelling in the genital tract, for example vulval oedema 29.

Chinniah and Katelaris 30 have recently published the results of a retrospective study reviewing the outcomes of 16 pregnancies in seven HAE patients in Australia. In 15/16 pregnancies, women had greatly reduced or no attacks in the last two trimesters compared with attacks occurring in the first trimester. No woman experienced angioedema at time of delivery. During the post-partum period, four women experienced increased frequency and severity of attacks when compared to the pre-pregnancy state (baseline). For two women, this impacted on their breast feeding routine due to the need for commencement of danazol, the only prophylactic therapy available at the time of the study. Since danazol has the theoretical potential for androgenic effects in breast-fed infants, infants were weaned off breast milk before initiation of treatment with danazol.
3.5.2 Perioperative period

Surgical procedures may pose a special risk to patients with HAE and when possible, require planning and consultation between the immunologist, anaesthetist and surgical teams. Some procedures such as those involving laryngopharyngeal manipulation or instrumentation carry a much greater risk of triggering potentially life-threatening episodes. Postoperative complications such as sepsis increase the risk of attacks during this period.

Regimens to protect individuals from acute attacks during interventions are based on uncontrolled studies and are aimed at increasing temporarily the plasma C1-INH levels (see 6.2).

3.5.3 Dental procedures

Triggering of attacks following dental work is unpredictable. Extensive dental work may be carried out without complication and conversely, minor work may occasionally precipitate an attack. Fatal laryngeal attacks have been documented following tooth extraction and episodes have been triggered by the administration of local anaesthetics. All patients undergoing any dental procedure should be warned of the risk of an acute attack in the 36 hours following the intervention and should have prompt access to emergency treatment such as C1-INH concentrate or icatibant whether or not they have received prophylaxis. Given the difficulties with exact predictions of the likelihood of an attack a management plan for dental interventions should include the following:-

- If minor work is planned no prophylaxis is given but ready access to emergency treatment such as C1-INH concentrate or icatibant should be assured.
- More complex manipulations may be covered by the use of danazol 10mg/kg/day for 5 days before and 2 days after the event. C1-INH concentrate or icatibant should be readily available.
- For any procedure requiring intubation, or for tooth extraction, C1-INH concentrate 1-6 hours before the procedure with further doses readily available.
Evidence of efficacy of pre-procedural prophylaxis is shown in a study by Jurado-Palomo et al (Jurado-Palomo et al. Management of Dental-Oral Procedures in Patients with Hereditary Angioedema due to C1 Inhibitor Deficiency (J Investig Allergol Clin Immunol 2013; Vol. 23(1): 1-6) which examined outcomes in 24 HAE patients undergoing dental procedures. Increasing danazol or pre-procedural C1-INH administration protected from swellings. Nine patients were given no prophylaxis and 3 of 9 had swelling post-dental procedure.

3.6 Paediatric presentations

When a child has a parent or other family member with diagnosed HAE, there is a strong clinical suspicion about the diagnosis if the child presents with recurrent abdominal pain or swelling. There is typically, difficulty and delay with diagnosis if no such family history exists.

3.6.1 Delayed diagnosis

More than 50% of those with HAE have their first attack before the age of 10 years, the mean age being 8 to 12 years. Occasionally episodes occur in the first year of life (7%) and another 35% present in the second decade. The diagnosis, however, is usually not made until the second or third decade of life. Studies have documented an average delay to diagnosis of 13 to 21 years despite improvements in screening and general awareness of HAE.

3.6.2 Implications of paediatric presentation

Angioedema with urticaria is common in children and in most cases is associated with allergy or recent infection. Thus there may be a greater chance that the significance of angioedema without urticaria may be missed than occurs in adults.

There is an inverse correlation between age at onset and severity of disease. In a cohort of 209 patients, the 64 individuals whose symptoms commenced under 5 years had an average of 31.4 episodes per year whilst the 68 patients who first developed symptoms aged over 15 years averaged 17.8 episodes a year, a statistically significant difference.
3.6.3 Special clinical features

It is important to recognise that although episodes of severe swelling are less common in children, they nevertheless can occur and may need acute intervention.

**Laryngeal oedema**, more frequently reported in patients in their mid-20’s, is less common in children. However when it does occur, usually in the context of swelling of the face and neck progressing to involve the uvula, soft palate and larynx, the small calibre of the airways increases the risk of rapid onset of obstruction from relatively mild swelling. A nine year old boy reportedly died of asphyxia 20 minutes after onset of swelling. In comparison, severe laryngeal swelling in adults usually develops over 8 to 12 hours.

**Epiglottic swelling** has also been reported as an unusual manifestation in a 12 year old boy, diagnosed with HAE at age 7. No precipitating factors were identified but early recognition leading to intubation and treatment with ε-aminocaproic acid lead to rapid resolution and discharge without complications.

Children presenting with *episodic abdominal pain* can be a difficult diagnostic dilemma since such episodes are usually secondary to causes other than HAE. Isolated abdominal pain can sometimes be the first and only manifestation of HAE. In 43 of 153 (28.1%) patients in a recent series, abdominal pain preceded subcutaneous swelling by a mean interval of 8.4 years (range 1–33 yr). Manifestations can range from diffuse abdominal pain to episodes mimicking an acute surgical emergency with ileus and hypovolaemic shock. Vomiting and diarrhoea are also common. A rare complication of severe swelling is intussusception.

In general however, symptoms in children consist of *recurrent episodes of soft tissue swelling* involving the extremities, predominantly involving fingers and toes (45%), sometimes also involving subcutaneous angioedema of face, neck, genitals and trunk. These usually resolve spontaneously within 2 to 4 days. Mechanical trauma and infection are common precipitating factors.
4.0 DIAGNOSIS

When there is a suspicion of the diagnosis of HAE, patients must be screened and if the diagnosis is confirmed, family members must be screened as well.

4.1 Indications for testing

Testing for HAE should be carried out if there is a clinical suspicion in any age group (see box). Testing should also be carried out if there is a positive family history.

Tests of C1-INH level, function and C4 may not be reliable in patients younger than one year of age and therefore testing performed in patients before the age of one year should be confirmed after the age of one year.

4.2 Testing for HAE

The tests available for screening and diagnosis of HAE include C4 (screening), C1-INH level and C1-INH functional assay. In an untreated patient a normal C4 level makes the diagnosis of HAE unlikely. Serum C4 levels are invariably low during attacks however in approximately 2% of cases, the serum C4 level is normal in between attacks

In patients with isolated angioedema where clinical suspicion of HAE is low, screening with C4 levels may be adequate. If HAE is strongly suspected, serum C4 and serum C1-INH level and function should be measured. In general, C1-INH level and functional assay measurements are 50% below the normal range in HAE.

Results should be confirmed by repeat testing before making a definitive diagnosis of HAE since delay in processing or refrigeration can result in artifactually low results especially in the C1-INH functional assay.
4.3 Acquired C1 INH deficiency (AAE)

A detailed discussion of acquired forms of angioedema (AAE) is beyond the scope of this paper. AAE usually has its onset in middle age with those affected experiencing attacks similar to HAE. There is an absence of a family history. The attacks do not respond to antihistamines or corticosteroids. AAE results from increased destruction or metabolism of C1-INH.

Two types are described:

**Type 1 AAE** typically occurs in association with B cell lymphoproliferative and rheumatologic disorders. Such patients have circulating anti-idiotypic antibodies to immunoglobulins on the surface of B cells. Complexes between these are formed with continuous activation of C1-INH which is consumed in this process and levels decline below normal as synthesis cannot keep up with consumption.

**Type 2 AAE** is characterised by formation of autoantibodies directed against C1-INH. Binding of these to C1-INH results in inactivation of C1-INH.

A reduced serum C4 and C1-INH protein level should be followed up by measurement of serum C1q. 75% of patients with acquired C1-INH deficiency have reduced serum C1q whereas C1q level is normal in HAE.
5.0 GENETIC DIAGNOSIS OF HAE

Three forms of HAE have been described. Mutations in the *SERPING1* gene that encode the C1-INH protein result in HAE Types 1 and 2 (OMIM 106100). Sequencing of multiple exons is required since the reported mutations are scattered throughout the gene. The causative role of these mutations has allowed the categorisation of the disease into either a truncating deletional or non-sense mutation leading to a quantitative reduction in levels (Type 1) or missense mutations producing a dysfunctional protein (Type 2). The inheritance pattern is autosomal dominant. Haploinsufficiency of the C1-INH protein due to inadequate level of expression of C1-INH from the normal haplotype results in the disease. Medications such as attenuated androgens increase expression from the normal allele and reduce attack frequency.

HAE Type 3 is not caused by C1-INH deficiency and describes a rare form of angioedema mainly affecting females. Diagnosis requires a strong family history as the genetics are not well defined. A subset of patients have a mutation in the Factor XII gene (OMIM610618). Factor XII levels in HAE Type 3 are normal and affected females do not exhibit abnormal clotting.

Confirmation of the genetic basis for the diagnosis of HAE Type I has limited clinical utility but may be useful for confirming the status of young children who manifest normal or near-normal C1-INH levels when they come from affected families. Genetic testing may also be useful in clarifying the status of adults with less severe angioedema and borderline C1-INH as well as for re-evaluation of patients on androgenic therapy.

Genetic testing for confirmation of a diagnosis of HAE Type 2 has more clinical utility than for HAE Type I. The clinical laboratory assays of C1-INH function are less robust than the quantitative assays. Genetic testing may therefore be useful for distinguishing late onset acquired angioedema from HAE or when the laboratory tests for HAE have been inconclusive. Genetic testing is the only method to confirm the diagnosis of Type 3 HAE due to factor XII mutation. Genetic testing also enables prenatal diagnosis.
6.0 MANAGEMENT

Summary

Australia

There are several treatment options for acute HAE attacks all of which are in the high cost category. Long term prophylaxis has been limited to danazol and tranexamic acid until recently.

Icatibant (Firazy)

Icatibant is listed on the Pharmaceutical Benefits Scheme (PBS) for emergency treatment of acute angioedema in patients 18 years and over with known HAE. It is provided in a pre-filled syringe with allowance for two (1 plus 1 repeat) syringes to be dispensed. Provision of an authority script must be accompanied by education and training for self-injection by the individual in the community, sparing visits to the emergency department and ensuring prompt treatment of an attack and therefore faster resolution. A prescription must be accompanied by provision of an HAE management plan.

Purified C1-INH concentrate (Berinert, Cinryze) is available for intravenous use in the hospital setting or may be used by the patient at home after adequate training.

Cinryze (Shire) is registered for use in acute attacks, pre-procedural prophylaxis and for long term prophylaxis in adults and in children older than 6 years;

Berinert (purified C1-INH, CSL Behring) is registered for acute attacks in all age groups.

C1-INH concentrate supply is managed by the National Blood Authority. Recently, a decision was taken regarding funding arrangements of C1-INH concentrate in Australia. Governments will now fund C1-INH concentrate (Berinert) for the following indications for HAE Type 1 or 2:

- treatment of acute attacks
- pre-procedural (short term) prophylaxis for high risk procedures such as dental work, head or neck surgery, or surgery requiring intubation
- second line as routine (long term) prophylaxis for patients who experience the equivalent of eight or more acute attacks per month (for ordering see Appendix 10.3).

Danazol and tranexamic acid are used for prophylaxis, however are limited by side effects and relative lack of efficacy, respectively. Danazol is currently a streamlined authority item for
hereditary angioedema. It is available as 100mg and 200mg capsules in quantities of 100 capsules with up to 5 repeats.

Tranexamic acid is available on the PBS as a 500mg tablet and also in injectable form. The dose is 30-50mg/kg daily divided into 2 or 3 doses (this can result in up to 10 large tablets per day).

**New Zealand**

Icatibant is funded for use in acute attacks of HAE.

C1-INH concentrate (Berinert) is funded for on demand treatment, accessed and regulated through a national blood service, the New Zealand Blood Service.

For long term prophylaxis, danazol is available and funded for HAE; stanzolol is also used but requires a funding application and Tranexamic acid is funded generically.

Section 6 describes the current practices in terms of management of acute episodes and long term prophylaxis. For a detailed description of individual treatments, see Appendix 10.1.

Section 7 details specific therapies and recommendations for optimal management.

### 6.1 Treatment of acute attacks of angioedema

Acute angioedema in patients with HAE do not respond to antihistamines, corticosteroids or adrenaline. Minor peripheral attacks may not require active treatment and will settle after a few days.

The current treatments available in Australia and New Zealand for acute attacks of HAE are replacement purified C1-INH concentrate (Berinert is funded in both countries; Cinryze is available in Australia for acute attacks but not funded) or the bradykinin antagonist icatibant (Firazyr). Both are safe, well-tolerated and effective for all attacks of angioedema in any location.

C1-INH concentrate is administered by IV injection and is therefore generally limited to use in a hospital or medical facility, although home or community use may be possible with appropriate training and facilities. While in Australia, the NBA has agreed to the funding of Berinert for treatment of acute attacks, in practice icatibant, supplied in a pre-filled syringe and given by subcutaneous injection, will be the preferred first line treatment once patients are trained in its administration. There are a number of specific circumstances where C1-INH concentrate is the preferred option for acute attack management, including:
Pregnancy and lactation

Children under 18 yrs

When icatibant is contraindicated or not tolerated

When icatibant is not effective

Icatibant is administered subcutaneously and is suited to self-administration in and out of hospital settings or administration in hospital. Treatment options are not determined by the location, severity or duration of angioedema.

**Cutaneous angioedema:** Episodes of peripheral or truncal angioedema causing only mild or moderate discomfort and little or no disability may not require treatment. Symptomatic treatment with analgesics (paracetamol, NSAID, opiates) can be used. Some attacks of peripheral angioedema may be severe and cause pain and significant disability. Oedema of the face or genitalia may cause major discomfort and functional impairment. Treatment with icatibant or C1-INH is warranted in these cases to reduce the severity and shorten the duration of the attack.

**Abdominal pain:** Some minor attacks of gastrointestinal angioedema resolve with rest and simple analgesia. Attacks causing severe abdominal pain, distention and vomiting may require treatment in hospital with opiate analgesia and fluid replacement. Abdominal attacks which cause significant discomfort and disability warrant treatment with icatibant; early treatment may result in rapid resolution of discomfort, return to normal activities and avoid the need for hospitalisation. Treatment at home or in the community with C1-INH concentrate is also an option. C1-INH concentrate is the treatment of choice for attacks of abdominal angioedema in pregnancy, lactating women and childhood.

**Laryngeal/airway oedema:** Airway angioedema in HAE is dangerous and a medical emergency, and fatalities occur. Swelling can occur in the larynx or posterior pharynx. It should be noted that swelling of the tongue on its own seldom affects respiration but patients with tongue swelling should be monitored in case of progression to the airway. Laryngeal swelling is not visible externally and may present as an isolated phenomenon in a patient who appears normal externally and even on examination of the oropharynx. Symptoms that suggest laryngeal oedema are the sensation of a lump or fullness in the throat, voice change, dysphagia and of course stridor in a patient with known HAE. Indirect laryngoscopy is desirable for confirmation...
but not necessary in a patient with known HAE; direct laryngoscopy may aggravate swelling if traumatic.

Symptoms of upper airway angioedema in a patient with known HAE are an absolute indication for icatibant or C1-INH concentrate. Treatment should commence at home if possible, by self-administration of subcutaneous icatibant or intravenous C1-INH concentrate. Treatment should be administered urgently even if respiration does not seem to be threatened since oedema may sometimes progress rapidly and icatibant or C1-INH concentrate may take 30-60 minutes to begin to act. Lack of response after 60 minutes is an indication for a further dose. If treatment is commenced out of hospital or if home or community treatment is not available, urgent transfer to hospital by ambulance is indicated in all cases. Facilities and expertise for intubation should always be made available and because laryngeal oedema can make intubation difficult, tracheostomy or emergency cricothyrotomy may be required in extreme situations. These measures are seldom required when definitive treatment is given early in the attack.

Historically, fresh frozen plasma has been used as a treatment modality for C1-INH replacement but with access to more specific treatment it has been superseded. It carries the risk of blood borne infection, worsening the severity of the attack because of the inclusion of other biologically active molecules, and the risk of reaction to it as a blood product. Historically, fresh frozen plasma has been used as a treatment modality for C1-INH replacement but with access to more specific treatment it has been superseded. It carries the risk of blood borne infection, worsening the severity of the attack because of the inclusion of other biologically active molecules, and the risk of reaction to it as a blood product. It should be considered as a last resort and is probably preferable to no treatment in emergency cases where no alternatives are available.

6.2 Short-term prophylaxis

Short term prophylaxis is required to prepare patients for elective dental and surgical procedures involving the head and neck area.

For minor dental and medical procedures danazol may be used, either by introduction in a patient not already on it, or by increasing the dose prior to the procedure (box 1). Danazol can be used for short-term prophylaxis in children since virilisation is only likely to occur with long-term treatment. Dental procedures should be undertaken in or near hospitals with facilities for emergency management and icatibant or C1-INH concentrate should be immediately available. It must be emphasised that attacks are not always predictable and do not always follow a consistent pattern so patients and their doctors should not become complacent about the risk.
Although the major focus of attention is on procedures on the head and neck area, because danazol prophylaxis is inexpensive and usually well-tolerated it can be used for other procedures.

- Funded supply of C1-INH concentrate (Berinert) under the NBA is indicated for pre-procedural (short term) prophylaxis for high risk procedures such as dental work, head or neck surgery, or surgery requiring intubation (box 2). C1-INH concentrate can be used at short notice for urgent procedures. If C1-INH concentrate is unavailable then danazol prophylaxis should be used and the procedure undertaken with great caution and with emergency facilities immediately available.

**Box 1 - Minor dental and medical procedures**

**Short term prophylaxis with danazol:**
- For those already on danazol - double the dose
- For those not on long-term prophylaxis - introduce danazol 600mg/day (100-300mg in children) for 5 days prior to procedure and 2 days afterwards:
- C1-INH concentrate or icatibant should be available in case of failure of prophylaxis

**Box 2 - Major dental procedures and intubation**

**Prophylaxis with C1-INH concentrate:**
- 20U/kg Berinert (funded by NBA) or 1,000U Cinryze 1 to 6 hours prior to the procedure

### 6.3 Long-term prophylaxis

#### 6.3.1 General

Long-term prophylaxis refers to the use of regular medication to prevent attacks of angioedema in those with confirmed HAE. The decision to institute long-term prophylaxis depends on individual factors such as impact on the patient's quality of life determined by the frequency of attacks, the severity and location of previous attacks, the presence or absence of known triggers.
and their ability to be modified, and the balance of these factors against the acceptability, cost and potential morbidity of prophylactic agents.

6.3.2 Avoidance of triggers

Avoidance of triggers is important for prevention of angioedema attacks. Angiotensin converting enzyme (ACE) inhibitors are contraindicated in HAE. Angiotensin receptor antagonists have also been shown to increase bradykinin levels and should be avoided or used with caution. Oestrogen-containing oral contraceptives increase attacks in many patients but not all. The progesterone-only contraceptive pill may be associated with reduced attack frequency and is generally recommended for women with HAE.

6.3.3 Attenuated androgens

Androgens increase hepatic synthesis of C1-INH protein from the remaining normal C1 gene. The response is dose-related but the dose required to suppress angioedema and/or normalise C4 and/or C1-INH levels varies widely between individuals. Side effects (box 3) are also dose related but again highly variable, with some patients unable to tolerate even low doses whereas others including females tolerate surprisingly high doses for many years without apparent problems. In a recent survey, 79% of patients experienced adverse effects from danazol, but only 25% discontinued treatment because of these; the benefits were great with >90% reduction in episode frequency in >70% of patients, and a 95% reduction in the frequency of laryngeal episodes..

Recommended dosage regimens vary. It is reasonable to commence with a modest dose (for example 100-200mg daily) and then increase or decrease on a monthly basis depending on the frequency of episodes until satisfactory control is reached (Budapest protocol). The maintenance dose required to suppress or substantially reduce angioedema varies between 100mg second daily and 800mg daily. However, for minimising long term detrimental side effects, global guidelines suggest that a dose in excess of 200mg daily should not be used long term. The aim of treatment is to minimise the frequency and severity of attacks and not to normalise the biochemical parameters. Monitoring of patients on long-term danazol is essential (box 4). As in many chronic conditions patient autonomy is an issue and some patients vary the dosage without consultation depending on the activity of their condition, balanced against adverse effects. Non-adherence to regular dosage is often associated with breakthrough episodes. Conversely some
patients experience prodromal symptoms or recognise trigger exposures (for example infection or stress) and may be advised to temporarily increase the dose of danazol.

Danazol may inhibit ovulation but cannot be relied upon to prevent pregnancy. Patients receiving danazol must be counselled to use contraception. The oestrogen-containing oral contraceptive pill is contraindicated. Danazol must not be taken during pregnancy because of the risk of virilisation of the foetus and is ceased to allow planned pregnancy. The safety of danazol during breastfeeding has not been established so it is usually avoided.

Danazol is not recommended for long term prophylaxis in children but its long term use in children has been reported and in some cases the benefits outweigh the risks (see Paediatric section).

**Box 3 - Potential side-effects of androgenic drugs e.g. danazol**

- General: headaches, nausea, fatigue, constipation, myalgias or muscle cramps, weight gain
- Virilisation in females: hirsutism, acne, voice changes, decreased breast size, altered libido, menstrual irregularities, clitoromegaly
- Hepatic: abnormal liver enzymes, hepatic necrosis, cholestasis, adenoma, adenocarcinoma
- Metabolic: hypertension, dyslipidaemia (but not hypercholesterolaemia)\(^45\), atherogenesis, polycythaemia, hyperglycaemia

**Box 4 - Monitoring on long-term danazol**

- 6 monthly- BP, Hb, glucose, lipids, liver enzymes, CK
- 12 monthly- alpha-fetoprotein, hepatic ultrasound

**6.3.4 Antifibrinolytic agents**

Antifibrinolytic drugs act by inhibiting plasmin which may partially inhibit the bradykinin pathway. They have no effect on C1-INH or C4 levels.

The only currently available antifibrinolytic drug is tranexamic acid (Cyklokapron). It has some benefit for long term prophylaxis of angioedema in HAE but is less effective than attenuated androgens\(^46\).
Side effects include minor GI upsets, myalgia/CK elevation and a theoretical risk of thrombosis; it is contraindicated in the presence of thrombophilia or situations of increased thrombotic risk. There is little experience with tranexamic acid in pregnancy so it is rated category B1, but it is not contraindicated during breastfeeding. It may have a place in the management of prepubertal children when attenuated androgens are contraindicated; it is considered reasonably safe in children greater than 2 years of age.

6.3.5 C1-INH concentrate prophylaxis

In Australia, funded supply of C1 inhibitor concentrate (Berinert) for longterm prophylaxis under the NBA has become available recently. The stated indication is as second line therapy for long term prophylaxis for patients who experience the equivalent of eight or more acute attacks per month.

The recommended dose is 1,000 U twice weekly. With appropriate training, patients can learn to self-administer it intravenously at home. In the future, a subcutaneous preparation may become available resulting in greater ease of administration.

6.3.6 Monitoring treatment

**C1-INH replacement:** Both available C1-INH products are manufactured with a nanofiltration step to remove viral particles. However haemovigilance (bloodborne pathogen surveillance) and baseline biochemical analysis and viral studies (such as Hepatitis B, C and HIV screening) should be collected and stored at diagnosis and annually or biannually.

**Attenuated androgens and antifibrinolytics:** Attenuated androgens and antifibrinolytics may predispose patients to atherogenesis and liver disorders. Serum lipid profile should be obtained before androgen administration. Liver function studies, including alanine aminotransferase, total bilirubin, alkaline phosphatase, creatine kinase, lactic dehydrogenase, blood urea nitrogen, creatinine, complete and differential blood cell count, and urinalysis should be performed at diagnosis. Blood pressure should be monitored. Abdominal liver and spleen ultrasonography can be considered before continuous androgen administration and performed every year if receiving regular androgen therapy and annually even after ceasing treatment if treated for more than 10 years (box 4).
7.0 MANAGEMENT RECOMMENDATIONS FOR AUSTRALIA

7.1 General advice

An individualised care plan giving indications of what to treat, when to treat and how to treat attacks should be produced for all patients. This may be accompanied by a letter from the specialist so it may be given to any treating physician unfamiliar with the individual and the condition. Ideally, a patient’s local emergency department will have an alert system in place to fast track patients when they need to present there, outlining the proposed management plan for each presentation such as abdominal pain or laryngeal attacks.

7.2 Special circumstances

7.2.1 Travel

When an individual with HAE wishes to travel, it is advisable to have:

- a MedicAlert bracelet as well as an updated action plan and consultant’s letter, translated into the relevant language if needed.
- Prescriptions for adequate supplies of danazol, if used.
- For those patients using C1-INH concentrate for funded indications, applications for temporary overseas supply of C1-INH concentrate is to be conducted in accordance with NBA temporary overseas supply policy
- Icatibant, at least two syringes, with a letter for customs/airport controls, for the management of acute attacks is ideal although one must investigate the legality of carrying certain medications if unregistered in the destination country.

7.2.2 Pregnancy and delivery

Danazol needs to be ceased prior to conception. Tranexamic acid may be used with caution if frequent attacks occur. C1-INH ncentrate on demand, as individual replacement therapy, or at scheduled regular intervals if frequent attacks are occurring is now considered optimal therapy in the pregnant woman with HAE. There is no data on the use of icatibant in pregnancy. C1-INH concentrate must be available in the delivery room/suite in the event of triggering of oedema at parturition but routine prophylaxis with C1-INH is not usually recommended.
7.3 Acute attacks

If acute episodes are occurring frequently, are particularly severe or if there has been a laryngeal episode, prophylactic therapy must be considered. The patient's quality of life and preferences are important factors in the consideration for prophylaxis and the choice of agent.

7.3.1 Peripheral swellings

Minor – no treatment may be necessary; this decision is made by the patient. Severe - hands and feet where there is loss of function/work/school loss, C1-INH concentrate or icatibant either administered by the patient at home or by a health practitioner in a medical facility. Self treatment allows for earlier, and therefore, more efficient therapy.

7.3.2 Oropharyngeal/facial attacks

Treat early with C1-INH concentrate or icatibant.

7.3.3 Abdominal attacks

Treat early with C1-INH concentrate or icatibant. May still require hospital attendance, analgesics and IV fluids.

7.3.4 Laryngeal attacks

Treat early with C1-INH concentrate or icatibant. If patient has on demand treatment at home, a dose of either agent should be administered at the earliest onset of suspicious symptoms and then the patient is to be transported to the nearest hospital where there is capacity to manage the threatened airway. May be an indication for long term prophylaxis.

7.4 Short term prophylaxis

Generally, for short term prophylaxis, treatment strategies are similar for children and adults. Short term use of danazol in children is safe.
Surgery and dental procedures

*High risk procedures:* C1-INH concentrate 1-6 hrs before the procedure, and available for postoperative use if required. This is now a funded indication for Berinert in Australia. There are no studies on the prophylactic use of icatibant in this setting; because of its short half life, it is not an ideal prophylactic agent.

*Low risk procedures:* No treatment, but have C1-INH concentrate or icatibant available as rescue treatment (there is no data on the use of icatibant in children) OR short term danazol for 5 days before and 2 days after with rescue medication on hand. If already on danazol, double dose for same period.

7.5 Long term prophylaxis

The common options for long term prophylaxis have been discussed in the document. When to institute long term prophylactic therapy requires input from the individual patient and treating Immunologist. Any patient experiencing laryngeal attacks must consider this option as should those with severe episodes. Patients living in rural or remote regions may opt for prophylaxis earlier than city patients because of the lack of readily available services. Options for long term prophylaxis include danazol, tranexamic acid and C1-INH concentrate. In certain circumstances when long term prophylaxis is indicated, such as during pregnancy and breast feeding, when attacks may occur more frequently, or in children, C1-INH concentrate is the treatment of choice. Currently, the funded indication for C1-INH concentrate (Berinert) for long term prophylaxis is as second line therapy (if danazol is not tolerated, not effective or contraindicated) for patients who experience the equivalent of eight or more acute attacks per month. The use of one of the validated tools available for assessment of frequency and severity of attacks may aid the clinician in the decision to prescribe long term prophylaxis. Consultation with an immunologist is strongly recommended before long term prophylaxis is prescribed.

7.6 On demand therapy (ODT)

ODT is the preferred treatment option as patients have rapid access to treatment and autonomy over treatment decisions.
With appropriate training, most patients can be taught to self-administer therapy for acute attacks. Icatibant, provided in a pre-filled syringe and administered by subcutaneous injection, is a very convenient and effective agent for on demand treatment. C1-INH concentrate is given as an intravenous infusion, so it is more complex to administer, however patients and relevant support persons can be trained successfully for home administration. Ideally, on demand therapy is managed by, or in consultation with, an Immunologist and patients will require regular follow up, monitoring of frequency of use and injection technique.

### 7.7 Quality of Life (QOL) issues

As in other areas of medicine, patients’ quality of life is being given the attention it deserves. For those living with HAE, there are complex issues to address. Some of these concern the burden of living with a genetic disorder and the concern that the condition may be passed on to a child. Other concerns centre around the ever present yet unpredictable threat of a painful, debilitating attack or a life-threatening swelling. The advent of availability of effective therapy for acute attacks that can be self-administered at home has made an enormous impact on the quality of life of HAE patients. QoL should be considered when discussing treatment options with HAE patients. Specific tools have been developed to assist in measuring QoL and can be useful in following up the effect of treatment interventions.

### 7.8 Home based therapy

Home based therapy is now standard practice for management of HAE attacks. It is a particularly attractive option for our patient population, particularly those who live a distance from a hospital and those in rural and remote areas. Many other patients with young families and busy lives welcome the possibility of self-management. Specialist Immunology centres offer training in the skills needed for HAE patients to undertake home management of their condition. (see Appendix 10.2).

### 8.0 GLOBAL GUIDELINES

ASCIA is a signatory to the [GALEN/EAACI/WAO](#) Global Guidelines for the management of HAE. The general principles expressed in the evidence-based Guideline document are in line with those expressed in this Position Paper.
9.0 REFERENCES


22. Davis AE. Hereditary angioedema: a current state-of-the-art review, III: mechanisms of hereditary angioedema. Annals of Allergy Asthma and Immunology 2008; 100 (1 Suppl 2)::S7-12.


10.0 APPENDIX

10.1 SPECIFIC THERAPIES

A number of specific therapies are registered in Australia for management of HAE.

10.1.1 Berinert® (Human C1-INH concentrate)

Berinert® (distributed by CSL Behring) was for many years the only available C1-INH product in Australia. Berinert is a highly purified, freeze-dried C1-INH derived from human plasma. It contains 500 units (U) of C1-INH per vial (50 U/mL). One unit is equal to the amount of C1-INH in 1mL of human plasma, which is equivalent to approximately 240 mg/L of plasma. It is a soluble single-chain glycoprotein containing 478 amino acid residues.

Administration of Berinert to patients with C1-INH deficiency replaces the missing or malfunctioning C1-INH protein resulting in relief from the symptoms of HAE. The product is administered intravenously and is immediately available in the plasma with a plasma concentration corresponding to the administered dose.

Studies of Efficacy

A pivotal Phase III prospective, multinational, randomised, parallel-group, placebo-controlled, dose-finding, three-arm, double-blind clinical study (IMPACT-1) assessed the efficacy and safety of Berinert in 124 adult and paediatric subjects with C1-INH deficiency who were experiencing an acute moderate to severe attack of abdominal or facial HAE. Subjects ranged in age from 6 to 72 years of age. The study objectives were to show that Berinert shortens the time to onset of relief of symptoms of an abdominal or facial attack compared to placebo and to compare the efficacy of two different doses of Berinert. Subjects were randomised to either receive a 10 U/kg body weight dose of Berinert (39 subjects), a 20 U/kg dose of Berinert (43 subjects), or placebo (42 subjects) by slow intravenous infusion (4 mL per minute) within 5 hours of onset of an attack.

Subjects treated with a 20 U/kg dose of Berinert experienced a highly significant reduction (p=0.0025) in the median time to onset of relief from symptoms of an HAE attack (30 minutes) as compared to placebo (90 minutes). The median time to complete resolution of HAE symptoms...
was significantly shorter (p=0.0237) in the Berinert 20 U/kg group (4.9 hours) than in the placebo group (7.8 hours).

The study demonstrated that a 20 U/kg body weight dose of Berinert was significantly more efficacious than a 10 U/kg body weight dose of Berinert or placebo. Additionally, the 10 U/kg body weight dose of Berinert did not show a clinically significant difference compared to placebo.

**Adverse effects**

Berinert has been used for over 30 years in more than 400,000 treatments and has an excellent safety record. In the pivotal Phase III study, the most common adverse effects reported four hours post the 20U/Kg dose were nausea, dysgeusia, abdominal pain and headache; however, no serious adverse events were noted 41.

**Present situation in Australia**

Berinert is now funded in Australia under an agreement with the NBA for specific indications including:

- treatment of acute attacks
- pre-procedural (short term) prophylaxis for high risk procedures such as dental work, head or neck surgery, or surgery requiring intubation
- second line as routine (long term) prophylaxis for patients who experience the equivalent of eight or more acute attacks per month.
10.1.2 Cinryze® (Human nanofiltered C1-INH concentrate)

Cinryze is distributed internationally by Shire, and like Berinert is purified from human plasma. As such it was introduced in Europe in 1972 and was approved in 2008 by the FDA in USA for prophylaxis of HAE. It achieved orphan drug designation in Australia in 2010 “for the treatment, routine prevention and pre-procedure prevention of angioedema attacks in adults, adolescents, and children from 6 years of age with C1-INH deficiency”.

Studies of Efficacy

A single publication (Zuraw 2010) reported 2 randomised trials of Cinryze for the treatment and prophylaxis of hereditary angioedema. In the treatment trial, 68 HAE subjects were randomised to receive Cinryze or placebo within 4 hours of the onset of an episode of moderate to severe nonlaryngeal oedema (laryngeal episodes were treated with open-label Cinryze). Although entry criteria allowed for children down to the age of 6, the majority of subjects were adults. Unlike the Berinert IMPACT-1 trial, a fixed dose of 1,000U of C1-INH was used in all subjects. There was a statistically significant reduction in time to onset of relief in the treatment group (2h) compared with placebo group (>4h, P=0.02) but the proportion of subjects achieving unequivocal relief within 4 hours was still only 60% (42% in the placebo group, P=0.06). 64% of subjects treated with Cinryze required a second dose of the drug at 60 minutes because of inadequate improvement compared with 80% of those treated with placebo. Interestingly in the open-label extension phase of the trial the rate of response to treatment within 4 hours was 93%; the authors commented on psychological factors affecting perception of pain in abdominal attacks.

Cinryze (1,000U twice weekly) was compared with placebo for long-term prophylaxis of angioedema attacks. Episodes were reduced by 50% and were 32% less severe and 38% shorter in duration. Overall swelling days were reduced by 2/3. The use of additional Cinryze for episodes was reduced by 70%. These reductions persisted for beyond a year of treatment. In an open label study Cinryze was administered prior to 91 different medical, surgical and dental procedures with no angioedema attacks reported within 72h of the procedure in 98% of cases.

Children were included in the acute treatment trial (22, age range 2-17), long-term prophylaxis trial (23 subjects, age range 3-17 years) and the open-label short term prophylaxis study (40 subjects). In each case the results were comparable with adult subjects with no adverse effects.
Adverse effects

Adverse reactions in clinical trials and in clinical use have been mild, including nonspecific rash, dizziness and headaches. There is a theoretical risk of thrombosis at high dosage but this has not been observed in HAE patients. Cinryze is a blood product and there is a theoretical risk of transmission of blood-borne pathogens, however the manufacturing process includes 3 viral inactivation/removal steps including nanofiltration at 15nm, smaller than any known viral particles. There is no contraindication to use in children, or in pregnancy or lactation.

Use of Cinryze

Cinryze is indicated for treatment, pre-procedure prophylaxis and long-term prophylaxis of angioedema in adult and paediatric HAE patients. Recommended treatment dose for an acute episode is 1,000U (2 vials) for adults or children, with provision for a second 1,000U dose after 60 minutes if response inadequate. The dose for short-term prophylaxis prior to procedures is 1,000U between 1 and 24h prior to the procedure, with a second dose held in reserve. Dosage for long-term prophylaxis is 1,000U twice weekly in adults and children. Cinryze is supplied as a freeze-dried powder with solvent for reconstitution and can be stored for up to 2 years at room temperature (<25°C). Currently, it is not funded in Australia.
10.1.3 Firazyr® (Icatibant)

Bradykinin is thought to be the final mediator of vascular permeability that causes local tissue oedema in HAE. Its effects are mediated by binding to the constitutive bradykinin 2 receptor (B2R) on vascular endothelial cells. Icatibant is a synthetic peptidomimetic B2R antagonist with high specificity suitable for human subcutaneous administration.

Several studies have examined the efficacy of icatibant in the acute management of angioedema episodes. An initial uncontrolled pilot study reported that the mean time to relief of symptoms after treatment with Icatibant was significantly reduced from 42 hours in historical controls to 1.16 hours. Subcutaneous treatment was well tolerated and relieved symptoms more quickly than intravenous injection.51

Three double-blinded placebo-controlled trials were subsequently carried out; the first two, Fast 1 and 2, were reported in a single publication.

The FAST-1 trial compared subcutaneous injection of icatibant with placebo in 57 subjects presenting acutely with superficial cutaneous or abdominal angioedema episodes. The primary outcome measure was the time to onset of a 30% symptom improvement, but unfortunately the results for the combined group did not meet statistical significance. This result was due to the placebo arm having a higher use of rescue medication including C1-INH, an effective therapy. This would have increased the overall perceived effectiveness of the placebo arm. Subgroup analysis indicated significantly faster time to relief of cutaneous swelling and cutaneous pain in the icatibant group, and a significant difference was seen between the groups at the 4-hour post-treatment time point.

The FAST-2 trial compared subcutaneous icatibant with oral tranexamic acid using a double-blind double-dummy design. In this trial the median time to onset, 30% improvement, and almost complete symptom relief was significantly better in the icatibant group (0.8, 2 and 10 hours) than in the tranexamic acid group (7.9, 12 and 51 hours). No serious adverse events occurred.

FAST-3 was a further placebo-controlled randomised double-blind trial in 88 subjects with HAE presenting with acute episodes affecting the abdomen, periphery or airway. The primary endpoint of 50% reduction in symptom scores was significantly different between active treatment (2h) and placebo (19.8h), again without significant adverse events. The time to initial symptom relief was 0.8h versus 3.5h.
The parameters of efficacy of icatibant (time to effect, degree of effect, adverse effects) were broadly similar to those of C1-INH products although direct comparisons have not yet been made. Icatibant has the advantage of the lack of blood-product-associated risks and costs. The possibility of subcutaneous administration will facilitate rapid use in emergency situations, and potentially allow home use and self-administration by patients.

The effectiveness of icatibant in the treatment of HAE demonstrates the importance of the bradykinin pathway in the production of angioedema in HAE. There is additional potential for this agent to treat angioedema caused by acquired C1-INH deficiency and ACE-inhibitors.

Icatibant (distributed in Australia by Shire) was registered in Australia in 2010 and as of 1 August 2012 has been funded by the PBS, as an authority item for patients with proven HAE, 18 years and over. It can be supplied to patients via community pharmacies.

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. It is suitable for storage at room temperature and may be taken when travelling.
10.2 Home Care Program with C1-INH concentrate

Recent consensus documents on the management of HAE have recommended the option of home therapy for HAE patients. This choice should be made available to all HAE patients including children and those who suffer from infrequent attacks, as 50–75% have a life-threatening attack at some time and it is not possible to predict which episodes will deteriorate quickly\textsuperscript{52}. It provides a quick, convenient and probably safe method of dealing with acute attacks of angioedema. This is particularly valuable where access to emergency care is likely to be difficult through reasons of resource or geography. A UK audit has shown that home management could reduce the number of avoidable adverse effects (evidence level 2) and enriches QOL\textsuperscript{50}. In order to be effective a referral to specialist HAE centres, good local links to accident and emergency, and a care management plan are essential.

Below are assessment guidelines (Table 3) and a training program (Table 4). There is also a requirement to maintain competence in the administration of home infusions.

There are a number of important safety considerations. There has to be provision of refrigeration facilities for the storage of the product. Fortunately, the product retains efficacy for many months under less than optimal storage conditions e.g. 6 months at 25°C (evidence level 4). Home therapy programs with intravenous immunoglobulin have demonstrated that it is possible to train patients, with an ‘infusion partner’, to manage infusions and adverse events safely at home. Because C1-INH concentrate is likely to be required when the patient is unwell, 24 hour emergency treatment at the local hospital must remain an option. Patients and carers should be encouraged to use this option where appropriate.

A number of patients may not wish to, be able to or fail to achieve, the self-directed administration of C1-INH concentrate. An alternative in these cases is to have a supply of concentrate held by the patient for his/her use under the supervision of a medical practitioner or other trained healthcare provider. This may involve the general practitioner or a local emergency department.

There is evidence that self-possession reduces the time patients spend awaiting infusions (evidence level 2). Any such programme should be accompanied by appropriate information to be carried with the patient and advice as to strategies for resupply of concentrate.
**Table 3. Assessment guidelines for home infusion of C1-INH**

Criteria to assess the suitability of an individual for entry into home infusion program:

- Proven C1-INH deficiency
- Requiring infusions for acute attacks at least every 3 months (so that infusion skills can be maintained)
- The patient/parent must be motivated to comply with the home therapy programme and all its implications - written consent from patient/parent confirming this must be obtained before the program is commenced
- The patient/parent must have a partner willing to attend the home therapy programme who will be present when therapy is required
- The patient/parent must have access to a telephone when administering therapy
- The patient/parent must have good venous access
- The patient must agree to call for an ambulance if self-cannulation is unsuccessful when concentrate is required
- In most circumstances home therapy is not employed in children (see section 'C1 inhibitor concentrate in children')
Table 4. Home therapy training program

Home therapy training programs should include the following key areas:

- When to use concentrate
- Dose of concentrate
- Supply and storage of concentrate and equipment
- Aseptic techniques
- Preparation of equipment for administration of concentrate
- Product checking procedure, i.e. dosage; expiry date
- Demonstration of the correct technique for reconstitution of solution
- Cannulation with butterfly
- Blood sampling pre-infusion
- Administration of injection/management of infusion
- Management of adverse reactions
- Disposal of equipment
- Documentary evidence of the individual’s training and competence
- Receiving and monitoring infusion logs and other relevant documentation for monitoring appropriate use and technique and keeping the specialist nurse/consultant immunologist informed of any relevant issues regarding care and treatment
- Investigating any adverse reactions/events and taking appropriate action
- Compliance with clinic visits
- Performing an annual review of the individual’s competence to administer injection/infusion
- Liaising with the individual, their G.P, consultant immunologist, pharmacist and other relevant care providers.
10.3 Ordering process for Berinert under NBA Guidelines

Access to Berinert is via an ordering process through CSL Behring:

For order form please refer to the following page or contact CSL Behring Customer Service on 1800 063 892.

Health Providers are to submit orders direct through the CSL Behring customer service, ensuring that use is in compliance with those stated in 6.0 above.

Further information on funding is available from the NBA website:

Further information for patients is available on the HAE Australasia website:
www.haeaustralasia.org.au/
**BERINERT Order Form**

Please send to CSL Behring Customer Service  
Email: customerservice@cslehring.com.au  
Fax: 03 9246 5342  
Phone: 1800 063 892

Supply of BERINERT (C1-esterase inhibitor) funded under the National Blood Arrangement requires mandatory completion of all fields of this Order Form

### Order details

<table>
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<th>Order date:</th>
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BERINERT 500IU Product number: A5532  
Number of vials ordered:  

### Delivery details

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| Contact details:  
Name:  
Phone:  
Email:  |
| Delivery address details:  
(Street no, name, suburb, state, postcode)  |
| Required delivery date:  | /  | / |
| Required delivery time:  
Close of business  
(8am)  
or  
Specify time  
(8am)  |
| Special instructions:  
Products are supplied under the Deed between CSL Behring and the National Blood Authority for the following indications for Type I or II hereditary angioedema:  
- treatment of acute attacks  
- pre-procedural (short term) prophylaxis for high risk procedures such as dental work, head or neck surgery, or surgery requiring intubation  
- second line as routine (long term) prophylaxis for patients who experience the equivalent of eight or more acute attacks per month.  
Authorisation of this order confirms that the product is being ordered for the indications funded by the NBA and is in accordance with the Australasian Society of Clinical Immunology and Allergy (ASCIA) clinical guidance for funded access.  |

### Authorisation

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10.4 Algorithm for modern management of HAE in Australia and New Zealand

**HAE ATTACK**

- **Peripheral**
  - Other areas
  - Supportive treatment
  - RECOVER

- **Abdominal Pain**
  - Head, neck, hands, feet, urogenital
  - Icatibant or C1-INH conc
  - WORSE / COMPLICATIONS

- **Oropharyngeal**
  - Very mild
  - Supportive treatment
  - RECOVER

- **Voice change/ Laryngeal**
  - Moderate / Severe
  - Icatibant or C1-INH conc
  - Early transfer to hospital

**HOSPITAL**

- **IMPROVE**
  - Observe and discharge
  - Immunologist review
  - Renew supply of Icatibant or C1-INH conc

- **NO BETTER OR WORSE**
  - Reassess
  - Supportive treatment e.g. fluids
  - Repeat Icatibant or C1-INH conc
  - Episode terminates
  - Discharge
  - Immunologist review
  - Renew supply of Icatibant or C1-INH conc