Draft protocol to guide the assessment of C1 esterase inhibitor for hereditary angioedema

National Blood Agreement
Schedule 4

03 October 2014

Table of Contents

National Blood Arrangements

The national blood arrangements established by the National Blood Agreement provide a specific-purpose scheme for nationally funded supply of blood products under centralised contract arrangements administered by the National Blood Authority. The blood products funded and supplied under the scheme are specified on the National Product and Services List (NPSL) approved by all Health Ministers, and proposals for changes to the list are dealt with through a process specified in Schedule 4 to the Agreement. A framework for consideration has been developed by the Jurisdictional Blood Committee (JBC) involving a Multi-Criteria Analysis template.

A proposal for a new blood product that is not already on the approved NPSL may require a Cycle 1 and/or Cycle 2 MCA assessment:

> Cycle 1 – The Cycle 1 assessment is a high-level evaluation that relies on the information contained in an initiating proposal, together with other desk-top research, information held by the NBA and other information gathered from relevant stakeholders. The main objective of a Cycle 1 assessment is to identify for the JBC whether there is sufficient evidence in which the NBA has adequate confidence for JBC to make a decision or recommendation.
>
> Cycle 2 - If JBC determines at Cycle 1 that one or more criteria requires more detailed evaluation, then it will provide guidance for a Cycle 2 evaluation. JBC will provide direction on the particular Criteria and questions requiring further evaluation.

Schedule 4 of the National Blood Agreement recognises the Medical Services Advisory Committee (MSAC – see below) as a body to undertake evaluation of proposals for changes to the NPSL, in order to support decision making under the National Blood Agreement.

Once a product is decided to be added to the NPSL, the NBA then undertakes an appropriate procurement (tendering or direct negotiation, depending on the situation) within Commonwealth government procurement rules.

Under the funding arrangements for products supplied through NBA contracts established in the National Blood Agreement, the cost of products supplied is shared 63% Commonwealth and 37% States/Territories (by usage).

MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advices the Commonwealth Minister for Health on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a protocol that will be used to guide the assessment of human C1 esterase inhibitor for the management of hereditary angioedema. The protocol will be finalised after inviting relevant stakeholders to provide input and will provide the basis for the assessment of the intervention.

This protocol has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Population – specification of the characteristics of the people in whom the intervention is to be considered for use;

Intervention – specification of the proposed investigative service;

Comparator – specification of the investigative service most likely to be replaced, or supplemented by the proposed investigative service; and

Outcomes – specification of the health outcomes likely to be affected by the introduction of the proposed investigative service.

Purpose of application

Two proposals were received by the National Blood Authority (NBA) requesting the inclusion of purified human C1 esterase inhibitor (C1-INH concentrate) for the management of hereditary angioedema (HAE) on the National Products and Services List (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. Both Cinryze and Berinert are highly purified concentrates of C1-INH derived from human plasma; however, the proposals for inclusion on the NPSL differed in terms of the proposed indications and the approach to the clinical evaluation, economic evaluation and financial analysis.

The proposals for C1-INH concentrate were originally intended to be evaluated according to the Schedule 4 Cycle 1 Multi-Criteria Analysis (MCA). However, after a briefing on the two proposals on 16 June 2014, the Jurisdictional Blood Committee 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. The Jurisdictional Blood Committee agreed with this recommendation at their September 2014 meeting.

On behalf of the NBA, HealthConsult drafted this protocol to guide the assessment of the safety, effectiveness and cost-effectiveness of C1-INH concentrate in order to inform MSAC's evaluation and recommendations regarding public funding of this proposed service through the addition of C1-INH to the National Product and Services List under the National Blood Agreement.

Regulatory status and current arrangements for public reimbursement

Both Cinryze and Berinert are approved by the TGA. Berinert gained orphan drug designation in April 2008 and then TGA registration in January 2010. Cinryze gained orphan drug designation in October 2010 and TGA registration in April 2012. Berinert became available on the Special Access Scheme in 2004. Cinryze became available in Australia in early 2013.

C1-INH concentrate is currently funded directly by individual hospitals and is included in some hospital formularies. This funding arrangement creates inequity of access as the decision to fund such an infrequently used treatment is not broadly taken. Listing on the NPSL would ensure national equity of access to a government-funded therapy.

Clinical condition

Description of clinical condition

HAE is an autosomal dominant disorder characterised by recurrent subcutaneous and submucosal oedema without urticaria (Katelaris et al, 2012). One or more of various peripheral or central areas can be affected during an acute HAE attack, including limbs, trunk, face and sometimes genitals. Abdominal pain, vomiting and hypotension can result from visceral swelling of the gastrointestinal tract. Laryngeal swelling is the most serious manifestation as it can result in fatal asphyxiation.

Attacks can be spontaneous or due to physical or psychological stress. Recognised triggers include dental procedures, mechanical trauma (e.g. a surgical procedure involving the head and neck area), mental stress, hormonal changes, infections and medicinal products (e.g. angiotensin-converting

enzyme (ACE) inhibitors, oral contraceptive pill). Attacks may be preceded by symptoms such as tingling or a non-itchy rash anywhere on the body, and typically take 24 hours to peak and 48 to 72 hours to resolve. The mean age of symptom onset is 8 to 12 years, but HAE diagnosis does not usually occur until the second or third decade of life (Katelaris et al, 2012). Frequency of attacks can vary between patients, from years apart to many times per year.

Patients tend to have typical, but not invariable, patterns of attack locations and frequency. Although less than 1% of episodes are laryngeal, greater than 50% of patients report at least one such attack as some stage (Katelaris et al, 2012). Prior to effective prophylaxis, mortality from laryngeal swelling was 30% (Katelaris et al, 2012). Therefore, regardless of history, the risk of laryngeal attacks must be managed for all patients.

Types and pathogenesis of HAE

There are three types of HAE: types I, II and III. Patients with types I or II have insufficient levels of functional C1-INH, a serine protease inhibitor that acts on a number of complement proteases and contact system proteases. Failure to inhibit these pathways triggers a proteolytic cascade that releases vasoactive mediators leading to oedema. The pathogenesis of HAE type III has not been established, but patients have normal levels of functional C1-INH. Consequently C1-INH replacement therapy is indicated for patients with type I or type II HAE only.

HAE type I constitutes 85% of patients while 15% have HAE type II. The type III form is extremely rare (Craig et al, 2012).

Acquired C1-INH deficiency

In acquired angioedema (AAE), also referred to as acquired C1 esterase inhibitor deficiency or acquired C1-INH deficiency, patients have low levels of serum C1-INH. C1-INH protein function and rate of production is normal in these patients but it is catabolised at an increased rate. AAE is distinguished from HAE by low serum C1q levels, an absence of family history and late onset of symptoms, typically in middle age. AAE is commonly associated with lymphoma or other haematological malignancies.

Diagnosis of HAE

The position paper on HAE by the Australasian Society of Clinical Immunology and Allergy (ASCIA) (Katelaris et al, 2012) lists two indications for diagnostic testing for HAE:

- testing for HAE should be carried out if there is a clinical suspicion in any age group;
- testing should also be carried out if there is a positive family history.

Quantitative and functional protein assays are usually used to confirm a suspected diagnosis from clinical history. Serum levels of C4 may be sufficient to rule out HAE where clinical suspicion is low, while both C4 levels and C1-INH levels and function should be tested where the clinical suspicion is high. C1-INH levels and function are generally 50% below normal in HAE patients.

Genetic testing

According to the evidence-based HAE guidelines published by the World Allergy Association (Craig et al, 2012), genetic testing for the diagnosis of HAE can prove helpful but is rarely necessary or suggested. The ASCIA position paper on HAE (Katelaris et al, 2012) notes specific situations where

diagnostic genetic testing may be appropriate. Genetic testing is rarely required to confirm a diagnosis of HAE type I as low levels of C1-INH are readily assessed from serum assays. The functional assays of C1-INH are less reliable than the quantitative assays, so where the C1-INH functional assay has been inconclusive, genetic testing is warranted. Genetic testing is also useful to clarify the status of adults with less severe angioedema and borderline C1-INH, to distinguish late-onset acquired angioedema from HAE, and to re-evaluate patients on androgenic therapy (which masks the usual, non-medicated levels of C1-INH). In addition, C1-INH levels can be normal or near-normal in very young children with HAE, so genetic testing is the only way to establish the status of young children from affected families.

Epidemiology in Australia

HAE is classified as a primary immunodeficiency (PID), although no increase in risk of infection is observed. There are no known ethnic or gender differences for HAE Types I or II. HAE Type III mainly affects females.

The PID Register established by ASCIA included 66 HAE patients in 2012, which is understood to be under-representative (Katelaris et al, 2012). Based on prevalence estimates from other countries, ASCIA estimates there may be up to 480 cases in Australia, but this is likely to include people with very mild or no symptoms who do not seek healthcare for their condition.

The number of patients with AAE is extremely low, with currently only three patients in South Australia, and none requiring treatment (ASCIA correspondence 22 August 2014).

Management of HAE in Australia

There are three main indications for the management of HAE:

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

Treatment options differ for each of these separate indications, and for various sub-populations of HAE patients (e.g. paediatric patients, pregnant women). This section provides a brief description of the interventions available in Australia and an overview of the indications for which they are TGA-approved.

Description of HAE interventions

Attenuated androgens and anti-fibrinolytics

Attenuated androgens such as danazol (Azol®) increase synthesis of C1-INH protein from the normal C1-INH gene and have long been used for routine and pre-procedural prophylaxis. According to the Product Information (PI), tolerance is an issue with this approach, with side effects including virilisation in females, depression and weight gain, as well as transaminase elevations, liver adenoma and carcinoma. For patients on routine danazol, the oral contraceptive pill is contra-indicated. Danazol is not recommended for routine prophylaxis in children although, depending on the seriousness and frequency of attacks, it is sometimes considered preferable to no prophylaxis (Katelaris et al, 2012). Danazol cannot be used during pregnancy due to risk of foetal virilisation and

is ceased once a pregnancy is planned. It is usually avoided during breastfeeding as evidence of safety is lacking.

Tranexamic acid (Cyklokapron®) is the only anti-fibrinolytic agent currently available in Australia. There are fewer side effects than observed with danazol and, although it can be used for routine prophylaxis, it is less effective than danazol (Katelaris et al, 2012). Tranexamic acid is rated by the Australian categorisation system for medicines for use during pregnancy as Category B1, and is considered reasonably safe in children over the age of 2 years. While not preferred for pre-procedural prophylaxis, it can be used where danazol is contraindicated or not tolerated.

Both danazol and tranexamic acid are taken orally, and are subsidised by the PBS on the General Schedule; danazol is a Streamlined Authority item and tranexamic acid is not restricted. Further PBS information is shown in Table 3.

Icatibant

Icatibant (Firazyr®) is a synthetic antagonist of the bradykinin 2 receptor, the primary mediator of oedema in HAE types I and II. It is indicated for acute HAE attacks only: it has a short half-life of 1-2 hours, making it unsuitable for prophylactic use. Icatibant is administered by subcutaneous injection and is subsidised on the PBS as an Authority Required item. Patients can keep a supply for administration at the onset of symptoms by an out-of-hospital health practitioner or nurse, or self/home-administered. This use of icatibant is referred to as 'on-demand' therapy. The PBS Authority Required restriction for icatibant is shown in Table 1 (also see Table 3 for PBS subsidy details).

Table 1 Authority Required PBS restriction for icatibant

	Authority Required PBS restriction
Initial supply	Initial supply for anticipated emergency treatment of an acute attack of hereditary angioedema in a patient with confirmed diagnosis of C1-esterase inhibitor deficiency who has been assessed to be at significant risk of an acute attack of hereditary angioedema by or in consultation with a clinical immunologist, respiratory physician, specialist allergist or general physician experienced in the management of patients with hereditary angioedema. The name of the specialist consulted must be provided at the time of application for initial supply. The name of the Approved Pathology Authority and date of the diagnosing pathology test must be included in the authority application.
Continuing supply	Continuing supply for anticipated emergency treatment of an acute attack of hereditary angioedema, where the patient has previously been issued with an authority prescription for this drug

Source: Pharmaceutical Benefits Scheme, Department of Health, accessed online 12 August 2014
Abbreviations: PBS, Pharmaceutical Benefits Scheme

Other HAE treatments not yet available in Australia include ecallantide and conestat alfa. Ecallantide (Kalbitor®) is a specific inhibitor of plasma kallikrein (which produces the vasodilator, bradykinin), by-passing the C1-INH pathway to inhibit oedema. It is delivered by subcutaneous injection and has been FDA-approved in the US for the treatment of acute HAE attacks in adults (Katelaris et al, 2012). Due to a short half-life, it is not suitable for prophylactic use.

Conestat alfa (Ruconest®) is a recombinant analogue of human C1-INH that is administered via intravenous (I.V.) injection. It has been approved by the FDA for the treatment of acute HAE attacks

in adults and adolescents. Due to a short half-life of 2.5 hours, conestat alfa is not appropriate for prophylactic use. It is produced by the Pharming Group in the Netherlands.

C1-INH concentrate (Cinryze and Berinert)

C1-INH concentrate is a serine protease inhibitor purified from pooled human donated plasma. Both Cinryze and Berinert are TGA-approved for the treatment of acute HAE attacks, but Cinryze is also TGA-approved for prophylactic use, both pre-procedural and routine. Both treatments are administered by I.V. injection (see following section for more information about the interventions).

TGA-approval status of HAE interventions for various indications

The TGA-approval status of interventions for various HAE indications and administration regimes are shown in Table 2. Cinryze is approved for all HAE indications. Berinert approval is limited to treatment of acute HAE attacks. Icantibant is also indicated for acute attacks only, based on a short half-life. Danazol is indicated for prophylaxis only, consistent with its mode of action[1], while tranexamic acid can be used for acute attacks but is normally used for prophylaxis.

In Appendix A, Table A.1 shows the ASCIA recommendations for specific indications within particular sub-populations. The use of danazol in children is normally limited to pre-procedural prophylaxis, but in some instances the benefits of treatment outweighs the risks. Icatibant is not approved for use in children due to a lack of clinical data. Similarly, Cinryze is not indicated for treatment of acute attacks in children under the age of 12 years[2].

Paediatric, pregnant and lactating patients with HAE require special consideration, especially with regard to danazol which is potentially virilising. It is contraindicated during pregnancy and lactation. The ASCIA Position Paper (Katelaris et al, 2012) states that either on-demand IRT or routine use of C1-INH concentrate is now considered optimal therapy in the pregnant woman with HAE and must be available at parturition in the event of labour triggering oedema.

[1] Danazol increases expression of the normal C1-INH gene, thereby increasing levels of normal C1-INH.
[2] The TGA indication is restricted to patients at least 12 years of age due to insufficient pharmacokinetic data in younger patients and the lack of a rationale for using the same dosing regimen in adults and children. According to the AusPAR for Cinryze, 'the lowest efficacious dose should be elicited in order to increase any margin of safety'.

Table 2 TGA-approval status for various indications in the treatment of HAE

Route of administration	I.V. injection		subcutaneous injection	Oral	
Indication	C1-INH Cinryze	C1-INH Berinert	icatibant	attenuated androgens (danazol)	anti-fibrinolytics (tranexamic acid)
acute angioedema attack	✓	✓	✓[a]		✓[b]
pre-procedural prophylaxis	✓			✓	✓[c]
routine prophylaxis	✓			✓	✓[c]
self-admin – acute attack	✓	✓	✓		✓[b]
self-admin – routine	✓			✓	✓
Subpopulation					
paediatric	≥12 y	✓		✓[d]	✓
pregnancy	✓	✓	?		✓
lactation	✓	✓	?		✓

Abbreviations: ASCIA, Australasian Society of Clinical Immunology and Allergy; C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; I.V., intravenous; TGA, Therapeutic Goods Administration; y, year.
a Not approved for use in children.
b To be used at first sign of an attack. Severity and site of acute attack can impact choice of intervention (as described in ASCIA Position Paper, Katelaris et al, 2012).
c Not preferred for prophylaxis but could be introduced where danazol is contraindicated or unacceptable (ASCIA Position Paper, Katelaris et al, 2012).
d Not normally for routine use in children. Can be used for pre-procedural prophylaxis.

PBS status of HAE interventions

Table 3 shows that icatibant, danazol and tranexamic acid are available on the PBS for the treatment of HAE.

Table 3 PBS details for icatibant, danazol and tranexamic acid

Comparator	Icatibant (Firazyr)	Danazol	Tranexamic acid
PBS code	1976B	1285P; 1287R	2180R
Source	General Schedule	General Schedule	General Schedule
Name, form & strength and pack size	ICATIBANT Injection 30 mg (as acetate) in 3 mL single use pre-filled syringe, 1	danazol 100 mg capsule, 100; danazol 200 mg capsule, 100	tranexamic acid 500 mg tablet, 100
Max qty units	1	1	1
DPMQ	$2571.70	$58.92; $87.31	$52.02
Max price to consumer	$36.90	$36.90	$36.90
Authority Required?	Yes (see Table 1 for wording of restriction)	Yes (Streamlined for 'hereditary angioedema')	No
Note	Icatibant should be provided in the framework of a comprehensive hereditary angioedema prophylaxis program and an emergency Action Plan including training in recognition of the symptoms of hereditary angioedema and the self-administration of icatibant. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au)	Caution: Pregnancy must be excluded prior to administration of this drug.	Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Source: Pharmaceutical Benefits Scheme, Department of Health, accessed online 12 August 2014
Abbreviations: DPMQ, dispensed price maximum quantity; PBS, Pharmaceutical Benefits Scheme

Intervention for proposed inclusion on the NPSL

Description of intervention

Both Cinryze and Berinert are highly purified C1-INH concentrates derived from human plasma. While both products are purified to reduce the risk of pathogen contamination, there are differences in the manufacturing process and formulation (including concentration and excipients).

TGA indications

Table 4 shows the TGA-approved indications for Cinryze and Berinert. Both 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.

Table 4 Indications approved by TGA for Cinryze and Berinert

Indication	Cinryze	Berinert
Treatment of angioedema attacks	Treatment of angioedema attacks in adults and adolescents with C1 inhibitor deficiency.	Berinert is indicated for the treatment of acute attacks in patients with hereditary angioedema (HAE).
Pre-procedure prevention of angioedema attacks	Pre-procedure prevention of angioedema attacks in adults and adolescents with C1 inhibitor deficiency.	Not approved for this indication.
Routine prevention of angioedema attacks	Routine prevention of angioedema attacks in adults and adolescents with frequent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral therapy.	Not approved for this indication.

The TGA may be unwilling to approve Berinert for prophylactic use on the basis of the limited evidence available for this indication.

Dosage and frequency of use

Table 5 summarises the dosing regimens for each product. Berinert uses weight-based dosing whereas Cinryze is administered as a fixed dose. The PI for Cinryze states that the dose of 1000 units can be repeated after one hour if an adequate response is not achieved.

The frequency of acute HAE attacks is highly variable between patients. A survey of 58 Australian patients with HAE found an average of 1.57 attacks per patient per month or 18.9 attacks per year (King and Katelaris, 2012). However, as survey participants were initially recruited by specialists (ASCIA members), they may represent a subset of patients with more severe manifestations of HAE. Lower estimates are available from clinical studies that prospectively documented moderate to severe HAE attacks treated with C1-INH over time. Based on such data, the CSL Behring proposal estimated an average of eight moderate to severe attacks per patient per year that would be recommended for treatment with C1-INH or icatibant according to ASCIA guidelines.

The frequency of use for pre-procedural prophylaxis could vary extensively depending on patient circumstances, but is likely to be occasional. According to ASCIA (correspondence 22 August 2014), routine prophylaxis involves long-term administration of C1-INH concentrate; however, prophylaxis is not necessarily lifelong, as the activity of the condition can change over time. In the case of pregnancy, 'routine' prophylaxis may be used for the term of the pregnancy and then ceased postpartum.

Table 5 TGA-approved dosage regimens for Cinryze and Berinert

Indication	Cinryze	Berinert
Treatment of angioedema attacks	• 1000 Units of CINRYZE at the first sign of the onset of an acute attack. • A second dose of 1000 Units should be administered if the patient has not responded adequately after 60 minutes. A second dose of 1000 Units is more likely to be required in patients experiencing severe attacks, laryngeal attacks or if initiation of treatment is delayed.	The recommended dose is 20 IU per kg body weight.
Pre-procedure prevention of angioedema attacks	1000 Units of CINRYZE within 24 hours before a medical, dental, or surgical procedure.	Not approved for this indication.
Routine prevention of angioedema attacks	1000 Units of CINRYZE every 3 or 4 days for routine prevention against angioedema attacks. The dosing interval may need to be adjusted according to individual response. The continued need for regular prophylaxis with CINRYZE should be reviewed on a regular basis.	Not approved for this indication.

Source: Australian Product Information for Cinryze and for Berinert
Abbreviations: IU, international units

Delivery of the intervention

Both Cinryze and Berinert are provided as powders to be reconstituted in water and administered intravenously. The Schedule 4 proposals report the following presentations for their products:

- Cinryze is supplied as a complete product offering, including product vials, water for injection, reconstitution device, alcohol swabs, treatment mat, a syringe and venepuncture set.
- Each Berinert carton includes one Berinert 500 IU vial, a 10mL water for injections vial, and a Mix2Vial reconstitution and filter transfer device. Each carton is shrink wrapped together with a separate administration kit.

While these products can be administered in the hospital setting when a patient presents with an attack, they are both TGA-approved for self-administration at home or in the community setting. This can be especially useful to patients in remote and rural areas.

Current C1-INH administration is generally limited to hospital or medical facility settings; however, ASCIA advises that home or community use may be possible with appropriate training and facilities (Katelaris et al, 2012). It is the responsibility of the treating physician to identify patients suitable for self/home injection, and to ensure they receive training on I.V. administration (see the health care resources section for more information on proposed provision of training by sponsors). The Cinryze and Berinert PIs provide detailed administration instructions for reconstitution, injection and storage of reconstituted product.

The self/home-administration of C1-INH concentrate at the first sign of an attack is referred to as on-demand individual replacement therapy (IRT). IRT with Cinryze may also be self/home-administered for pre-procedural prophylaxis and routine prophylaxis. The latter use, according to the ASCIA

Position Paper on HAE (Katelaris et al, 2012), would be appropriate for those with frequent attacks and contraindications to other drug therapy[3].

Prerequisites

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

Both Cinryze and Berinert are supplied as a complete administration kit, but patients wishing to self/home-administer C1-INH concentrate will require guidance and training. Table 6 shows the PI information regarding home administration for Cinryze and Berinert.

Table 6 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.

Abbreviations: PI, Product Information

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

Co-administered and associated interventions

There are no interventions that require co-administration with C1-INH concentrate. As discussed earlier, it is necessary to establish a diagnosis of HAE types I or II prior to C1-INH replacement therapy. Such diagnosis is carried out using quantitative and functional C1-INH assays, as part of standard management of patients displaying symptoms or in families with a positive history. Genetic testing is rarely necessary to establish a diagnosis, but may be indicated prior to C1-INH replacement therapy if the form of HAE has not already been confidently established.

Listing proposed for C1-INH

Proposed NPSL listing

C1-INH concentrate is proposed for listing on the NPSL for the management of patients with a confirmed diagnosis of HAE type I or II. The proposal from Cedarglen Investments seeks listing on the NPSL for all registered indications for Cinryze. The CSL Behring proposal requests inclusion of Berinert on the NPSL for treatment of acute HAE attacks, including attacks in pregnancy and in children, and for short-term prophylaxis prior to major dental or surgical procedures or intubation.

[3] The only other prophylactic drug therapy is attenuated androgens (danazol) or, less frequently, tranexamic acid.

Consideration should be given as to whether acquired C1 esterase inhibitor deficiency is also a legitimate indication for NPSL-funded C1-INH concentrate. According to ASCIA (communication 22 August 2014), C1-INH concentrate is clinically indicated in these patients, although larger doses are sometimes required due to rapid consumption. Icatibant is effective at normal doses and may be preferred. Long-term prophylaxis with C1-INH concentrate is extremely rare, with AAE patients usually responding to treatment of the underlying disease.

Acute HAE attacks

For the treatment of acute HAE attacks, neither the PIs nor the Schedule 4 Proposals for either Cinryze or Berinert suggest C1-INH concentrate use be restricted based on attack characteristics. According to the ASCIA Position Paper on HAE (Katelaris et al, 2012) and as shown in the clinical management algorithm in Figure 1, C1-INH concentrate or icatibant are to be administered either in hospital or by the patient, carer or community health worker at the onset of an HAE attack that occurs in the following locations:

- oropharangeal, laryngeal or accompanied by a change in voice;
- moderate to severe abdominal pain; or
- head, neck, hands, feet or urogenital.

Where a patient is not responsive to the first dose of C1-INH concentrate, a second dose is recommended after 1 hour. The availability of on-demand IRT with C1-INH concentrate would potentially reduce the need for re-dosing, the likelihood of which is increased by delays in administration of the first dose.

Pre-procedural prophylaxis

Cinryze has TGA approval for dosing within 24 hours before a medical, dental, or surgical procedure. Neither the PI nor Schedule 4 Proposal for Cinryze suggest restriction of C1-INH concentrate use for pre-procedure prophylaxis based on procedure type. According to the ASCIA Position Paper on HAE (Katelaris et al, 2012), pre-procedural prophylaxis with C1-INH concentrate is appropriate for any high risk dental procedures, such as tooth extraction or extensive dental work, any head or neck surgery, or any surgery requiring intubation.

Berinert is not TGA-approved for pre-procedure prophylaxis. However, the Schedule 4 Proposal for Berinert proposes that it be included on the NPSL for short term prophylaxis prior to major dental or surgical procedures or intubation, to reflect the recommendations in the ASCIA Position Paper (Katelaris et al, 2012).

A single dose 1 to 6 hours prior to the procedure is recommended, with further doses readily available. The occasional use of pre-procedural prophylaxis would be expected for most patients, but could vary extensively depending on patient circumstances.

Routine prophylaxis

The TGA-approved indication for routine prophylaxis with Cinryze restricts use to patients with frequent HAE attacks who are intolerant to or insufficiently protected by oral therapy. The ASCIA Position Paper on HAE (Katelaris et al, 2012) does not make a specific recommendation regarding the appropriate restriction of C1-INH concentrate for routine prophylaxis, and notes that uniform criteria directing the use of prophylactic therapies in general for HAE have not been established. However,

the Cinryze Schedule 4 Proposal includes written support from ASCIA for the listing of Cinryze on the NSPL for this indication (in fact, for all TGA-approved indications).

Berinert is not TGA-approved for routine prophylaxis, nor has the Berinert Schedule 4 Proposal suggested this indication. It is possible, however, that Berinert will be used for routine prophylaxis if listed on the NPSL.

The dosage regimen for routine prophylaxis is one dose every three to four days, although the Cinryze PI notes the dosing interval may need to be adjusted according to an individual's response. In addition, the PI notes that the continued need for regular prophylaxis with Cinryze should be reviewed on a regular basis. As noted earlier, ASCIA has indicated that long-term prophylaxis does not necessarily mean lifelong prophylaxis, as a patient's condition is subject to variability and the need for routine prophylaxis is expected to be periodically reviewed.

Routine prophylactic use has the potential to form the greatest proportion of C1-INH concentrate use, especially if prescribed to patients outside the populations indicated by the TGA (adults and adolescents with frequent attacks of HAE, who are intolerant to or insufficiently protected by oral therapy).

Utilisation and access considerations upon NPSL listing

Individual hospital pharmacy or emergency departments make funding decisions and set criteria for C1-INH concentrate use based on budgetary circumstances. Consequently, in Australia the use of C1-INH concentrate both within and outside the hospital setting has been limited by local variations in availability and by cost (as hospitals currently pay for C1-INH concentrate, prescribers would experience pressure to limit its use). The current funding arrangements have led to inequity of access.[4] Listing on the NPSL would address this issue and provide equitable access to a government-funded therapy, which in some instances will free patients to travel or even live in locations that are currently impractical.

If C1-INH concentrate becomes available on the NPSL, utilisation is expected to increase in both the hospital setting (price signals may change if the funding is dissociated from the hospital) and, more so, in the out-of-hospital setting (treatment at home or in the community is acknowledged as an option, but is currently limited by cost). Of course, some offset of hospital presentations might be expected after the introduction of community administration as patients that previously presented to an emergency department may manage many, if not all, of their own attacks.

Home/community administration of C1-INH concentrate would require specific management arrangements to be put in place by the NBA and health services to ensure:

- appropriate selection, consenting and supervision of patients who are suitable for home/community administration of C1-INH concentrate;
- provision of patient training and appropriate medical support; and
- effective supervision of product supply, management, use and data recording.

Examples of such management arrangements already exist within supply arrangements administered by the NBA, including for clotting factor products for haemophilia and similar bleeding disorders, and subcutaneous immunoglobulin for certain specified conditions.

[4] Reported in the Cinryze proposal, quoting personal contact: Interviews and correspondence with 13 Clinical Immunology and 1 Pharmacy specialist across Australia from 4 June 2012 to 7 September 2012.

Clinical place

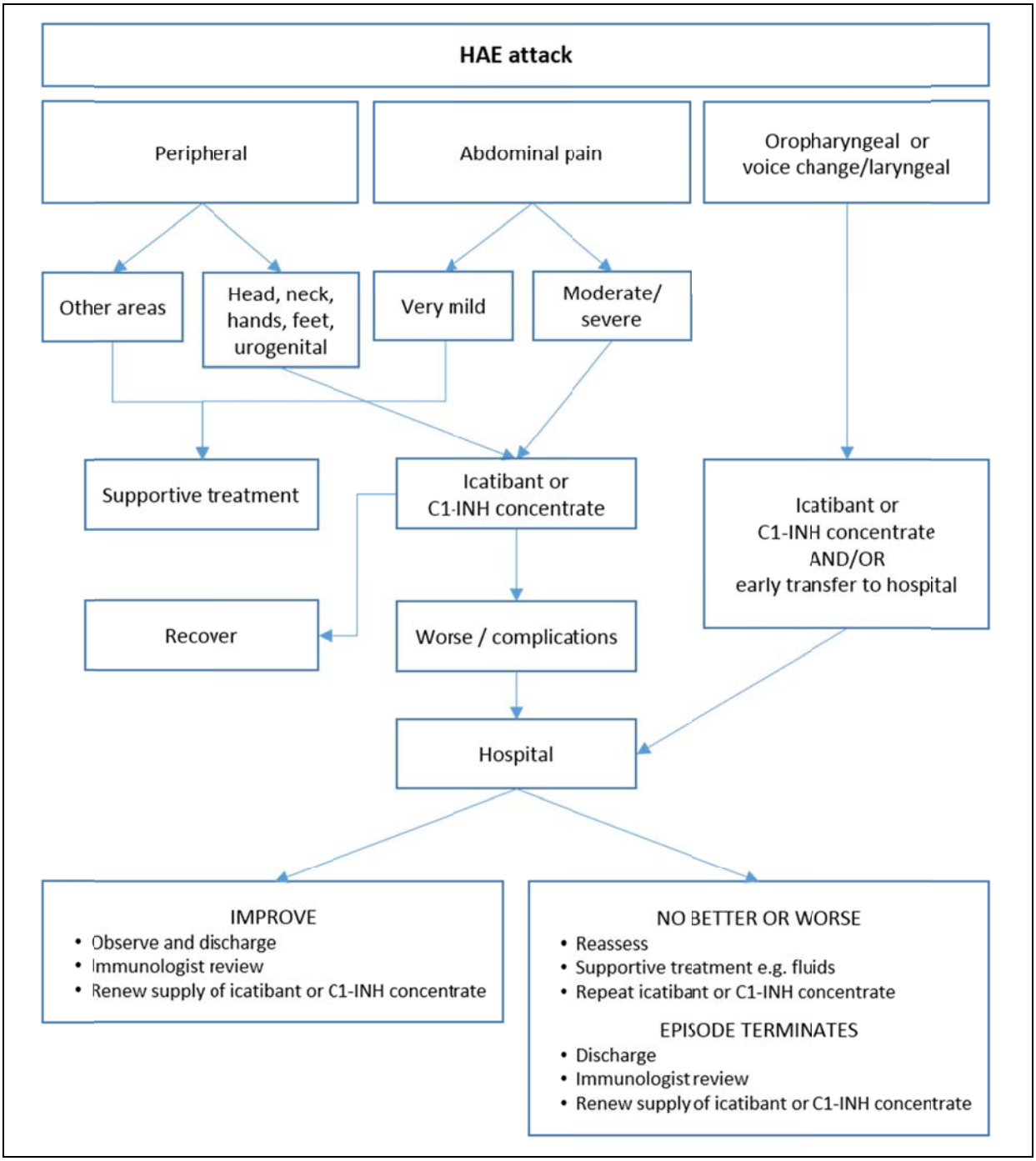
Acute HAE attacks – current Australian management algorithm

Figure 1 shows a representation of the ASCIA clinical management algorithm for HAE attacks (Katelaris et al, 2012). An HAE attack is characterised first by location: if oropharyngeal or laryngeal, or if there is a change in the voice, the risk of asphyxiation is sufficient to warrant immediate transfer to hospital for administration of icatibant or C1-INH concentrate, with administration of these interventions prior to arrival at hospital if the patient has them in their possession.

If the attack is either peripheral or abdominal, transfer to hospital is not necessary. Supportive treatment is considered sufficient if abdominal pain is mild, or if attack is at a peripheral site other than head, neck, hands, feet or urogenital. Otherwise, administration of icatibant or C1-INH concentrate is recommended. If resolution is not achieved, transfer to hospital is recommended.

This algorithm describes the option of self-administration of either icatibant or C1-INH concentrate prior to presentation at hospital, if they are at hand. Icatibant is currently available for such use, and has reduced the number of emergency presentations in recent years (ASCIA, communication 22 August 2014). However, as previously mentioned, current C1-INH administration is generally limited to hospital or medical facility settings, although home or community use may be possible with appropriate training and facilities (Katelaris et al, 2012).

Figure 1 ASCIA 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.

Clinical place for C1-INH concentrate for acute HAE attacks

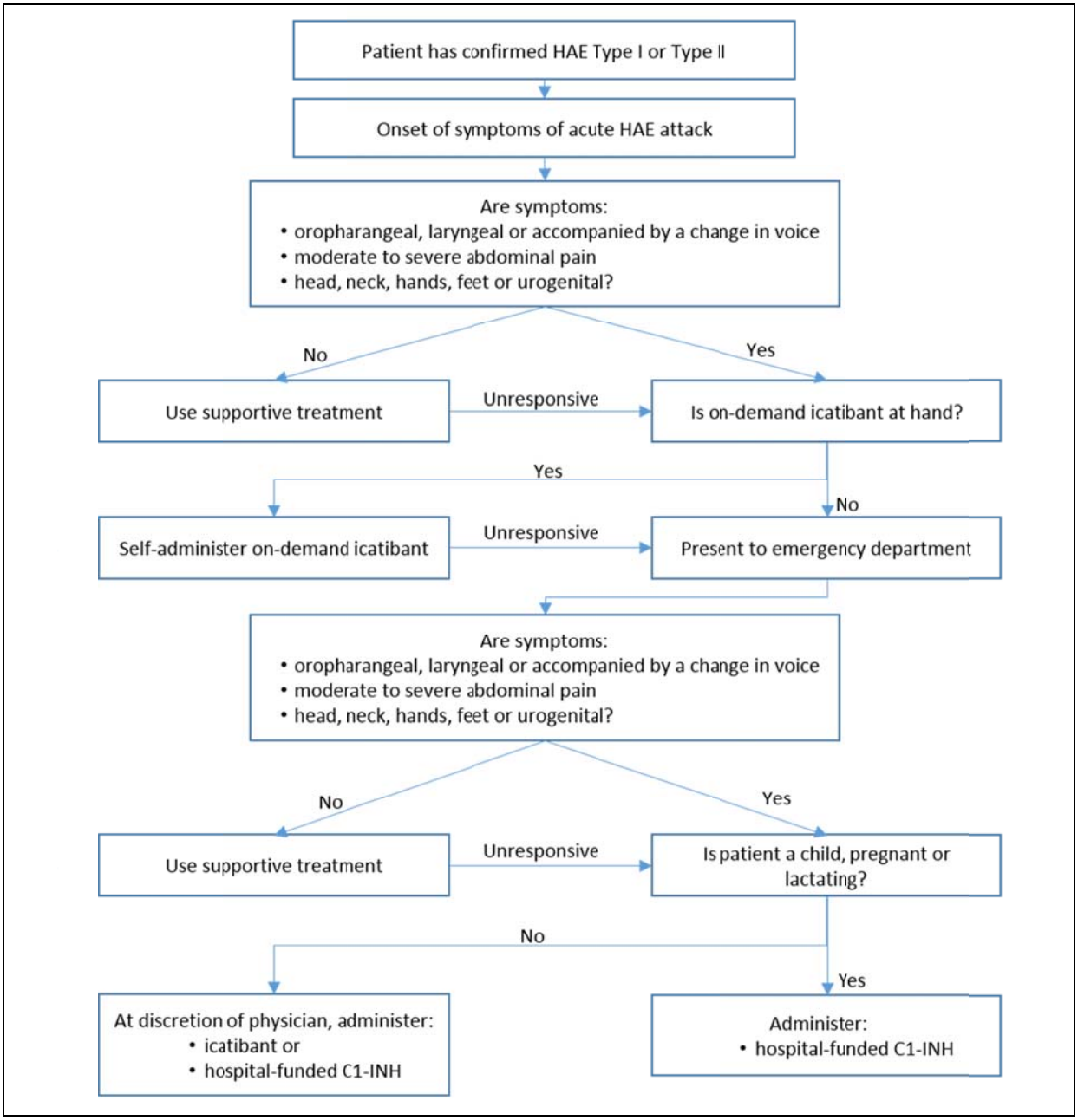
Figure 2 shows the current management algorithm for acute HAE attacks, and is based on the ASCIA management algorithm (Katelaris et al, 2012) represented above in Figure 1. Treatment decisions are initially guided by factors such as location of oedema and severity of attack to determine whether a patient requires treatment with either icatibant or C1-INH concentrate. For those patients who do require such treatment, a choice is then made between the hospital-funded C1-INH concentrate and the PBS-subsidised icatibant. In some instances this choice will be guided by treatment history

(tolerance and response), as well as age (children) and pregnancy. Otherwise, C1-INH concentrate occupies the same clinical position as icatibant: there is no head-to-head clinical evidence to suggest that one of these interventions is more effective than the other, so neither is generally indicated as a first line option[5] (although perceptions of superiority of one or the other may exist among clinicians). However, the high cost of C1-INH concentrate has applied a significant pressure against its use, in both the hospital setting and as 'on-demand' IRT out of hospital. Therefore, unlike the ASCIA algorithm, the clinical management algorithm of current practice shown in Figure 2 does not include on-demand IRT with C1-INH concentrate because it is currently not funded for this use.

Therefore, if listed on the NPSL, the clinical place of C1-INH concentrate for treating acute attacks in hospital will be no different to the current scenario. However, as the decision to use either icatibant or C1-INH concentrate would be less influenced by cost and availability, the existing downward pressure on the use of C1-INH concentrate would be lifted. The financial constraints on the use of C1-INH concentrate for 'on-demand' IRT would also be lifted (as shown in red in Figure 3), although the challenges of I.V. administration could continue to present a constraint for some patients. There is also the possibility that C1-INH concentrate would be used to treat presentations for which the ASCIA Position Paper recommends supportive care, both by the patient/carer and in hospitals (Katelaris et al, 2012).

[5] There are significant precautions for the use of icatibant in children and during pregnancy and lactation, and these presentations are likely to precipitate the choice of C1-INH concentrate.

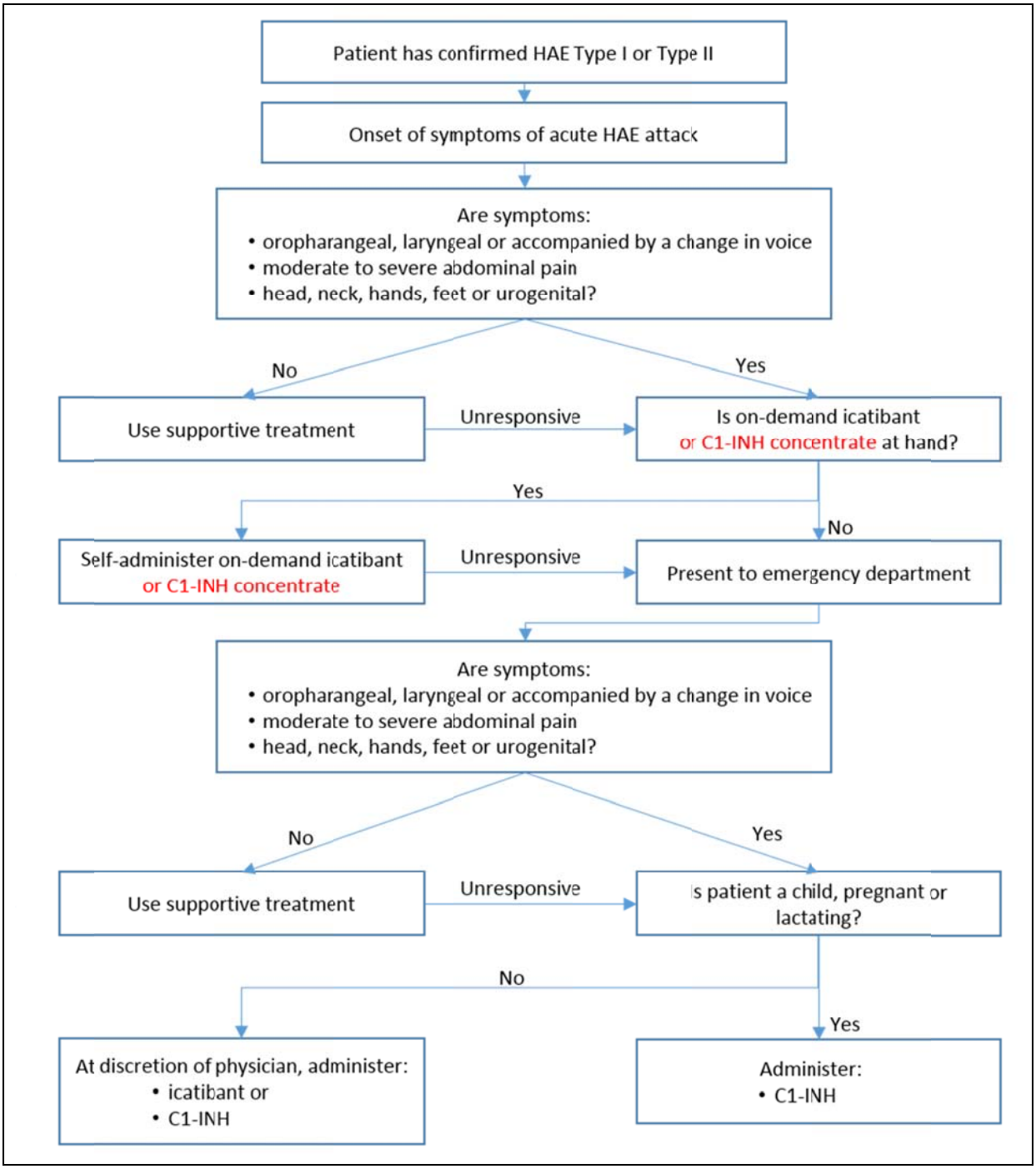
Figure 2 Current clinical management algorithm for acute HAE attacks



Source: based on the current Australian clinical management algorithm for an acute attack of HAE from ASCIA Position Paper (Katelaris et al, 2012).
Abbreviations: C1-INH, C1 esterase inhibitor concentrate

Figure 3 shows the proposed management algorithm with NPSL-funded on-demand IRT with C1-INH concentrate.

Figure 3 Proposed clinical management algorithm for acute HAE attacks



Source: based on the current Australian clinical management algorithm for an acute attack of HAE from ASCIA Position Paper (Katelaris et al, 2012).
Abbreviations: C1-INH, C1 esterase inhibitor concentrate

Clinical place for C1-INH concentrate for prophylaxis

The ASCIA Position Paper states that the clinical need for prophylaxis should be balanced against the cost and potential morbidity of prophylactic agents (Katelaris et al, 2012). The benefits of lower morbidity are currently largely outweighed by the high cost of C1-INH concentrate. If the cost to the patient or hospital is reduced by listing C1-INH concentrate on the NPSL, this equation will shift towards increased use of C1-INH concentrate for prophylaxis. Administration by I.V. injection would

continue to place a constraint on use for some patients. The potential changes in the clinical place of C1-INH concentrate for prophylaxis are explored in this section.

Clinical place for pre-procedural prophylaxis

Figure 4 shows the current management algorithm for pre-procedural prophylaxis, based on the recommendations and opinions expressed in the ASCIA Position Paper for HAE (Katelaris et al, 2012). C1-INH concentrate is appropriate for use as a pre-procedure prophylactic but cost and access are currently limiting prophylactic use. Due to the short half-life of icatibant, it is not suitable for use as a prophylactic.

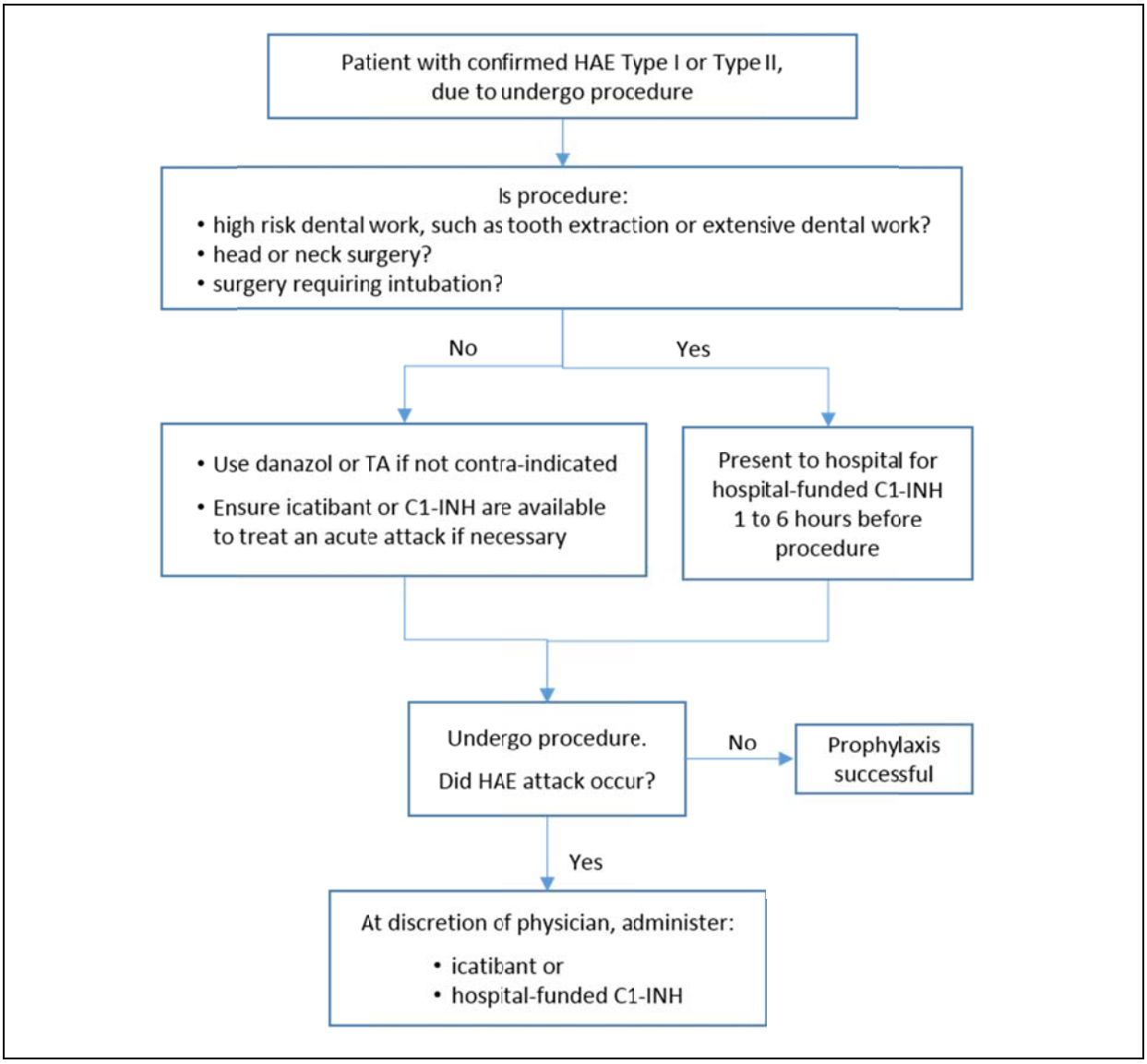
The use of C1-INH concentrate for pre-procedural prophylaxis is likely to be uncommon under the current funding arrangements, although clinical need may result in hospital-administered C1-INH prior to major procedures in some instances. The most accessible, current options for pre-procedural prophylaxis are danazol and, where that is contraindicated, tranexamic acid. In a number of patients these oral interventions are either ineffective, contraindicated or not tolerated, leaving many without an option for pre-procedure prophylaxis. Thus, there is a clinical need for wider access to C1-INH concentrate, especially for children and pregnant/lactating women.

Figure 5 shows the proposed clinical management algorithm if C1-INH concentrate became available on the NPSL. It is expected that a higher number of patients would access pre-procedural prophylaxis using C1-INH concentrate, both in hospitals and self/home-administered, with the latter limited by the challenges of self/home I.V. administration.

CSL Behring is requesting that Berinert is listed on the NPSL for prophylaxis prior to major dental or surgical procedures or intubation. While there is a clinical need for pre-procedural prophylactic options for children, Berinert is not TGA-approved for pre-procedural prophylaxis in any patients[6] and Cinryze is not TGA-approved for pre-procedure prophylaxis in patients under 12 years of age[7]. Use of either Cinryze or Berinert for pre-procedural prophylaxis in children under 12 years would therefore be 'off-label'. The ASCIA Position Paper does not stipulate an age restriction for C1-INH for any indication, nor does it distinguish between Cinryze and Berinert with respect to indications.

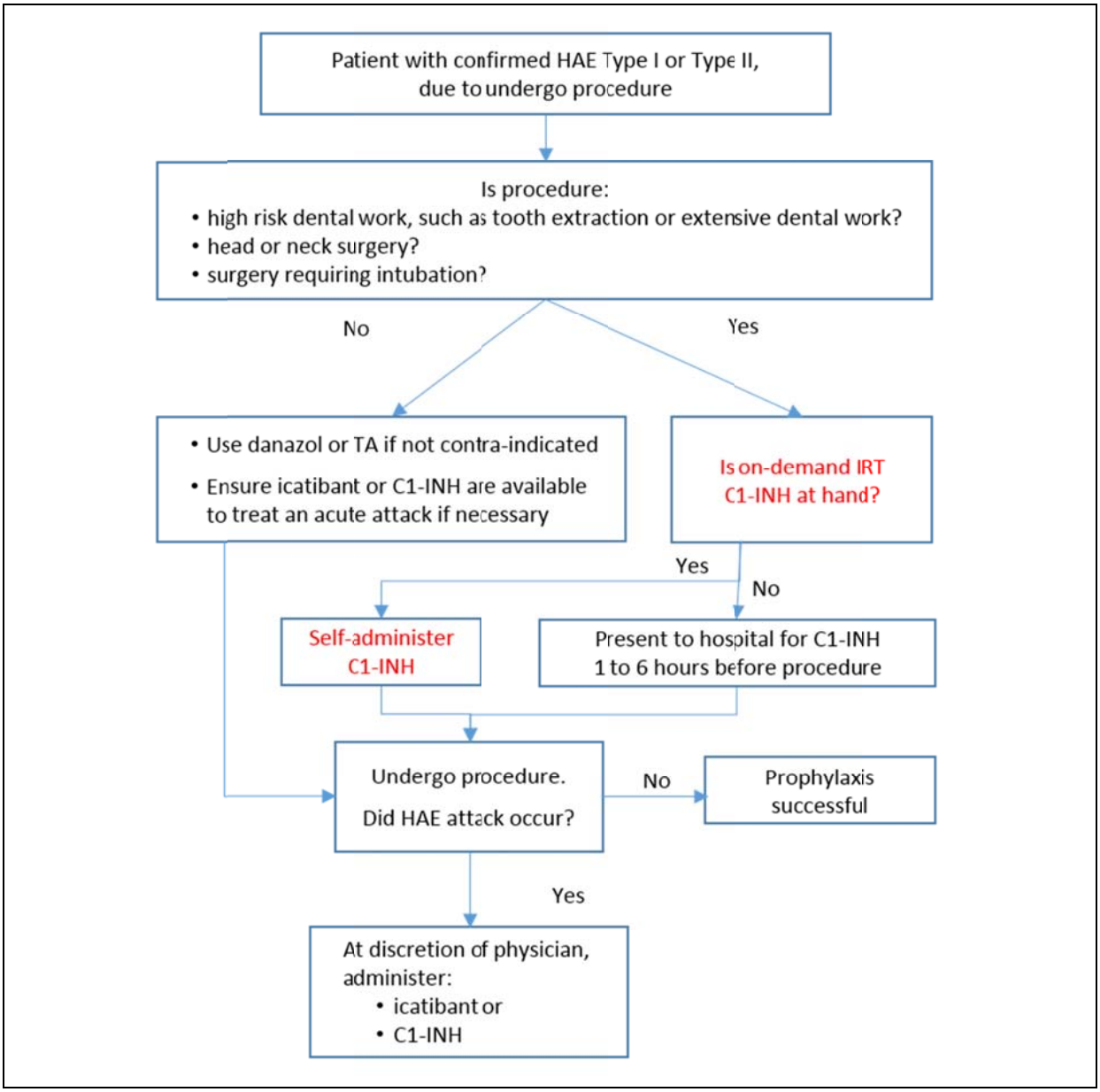
[6] Due to a lack of evidence of efficacy for this indication.
[7] Due to a lack of pharmacokinetic data and dosing rationale in children.

Figure 4 Current clinical management algorithm for pre-procedural prophylaxis



Source: based on recommendations from the ASCIA Position Paper (Katelaris et al, 2012).
Abbreviations: C1-INH, C1 esterase inhibitor concentrate; TA, tranexamic acid

Figure 5 Proposed clinical management algorithm for pre-procedural prophylaxis



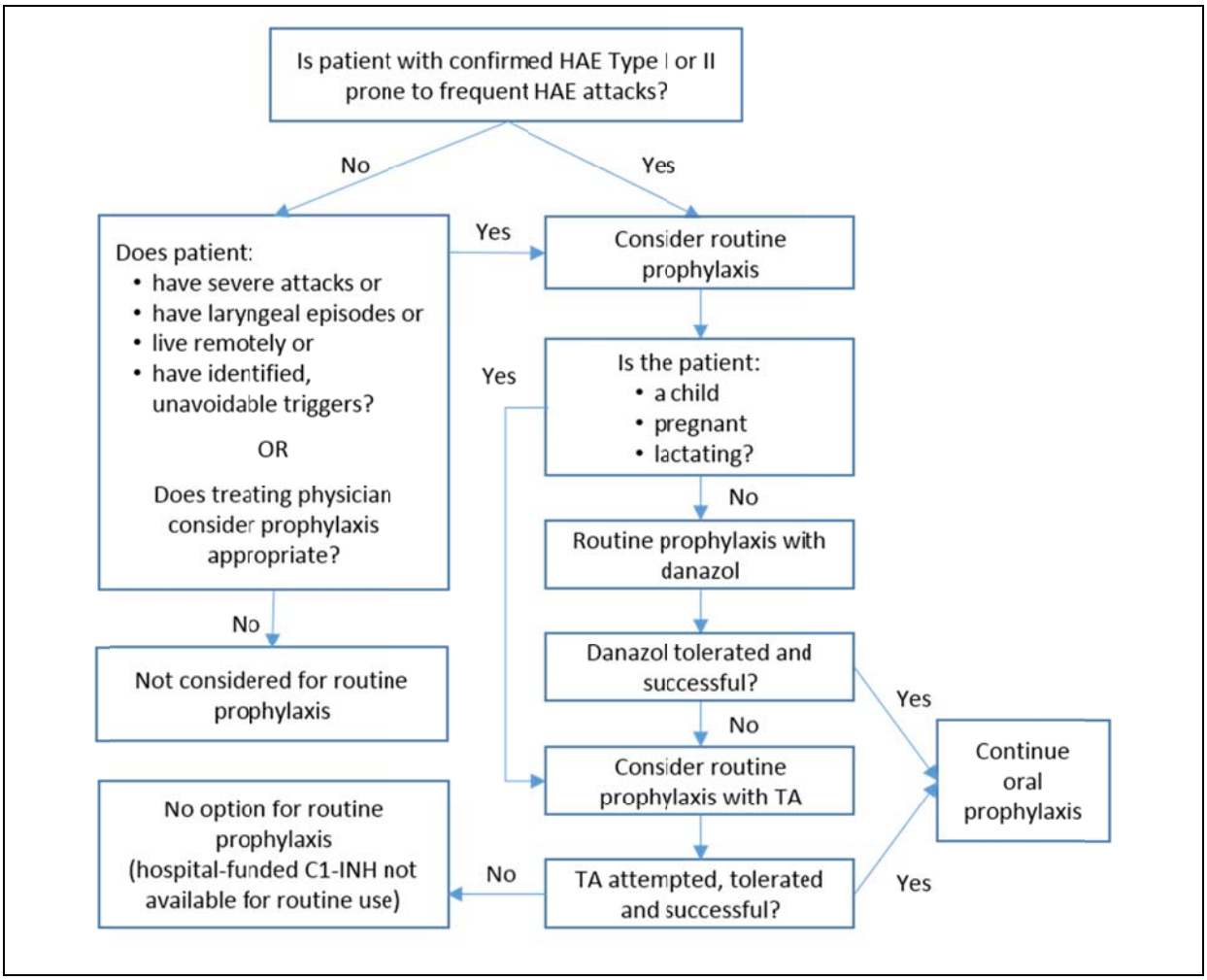
Source: based on recommendations from the ASCIA Position Paper (Katelaris et al, 2012).
Abbreviations: C1-INH, C1 esterase inhibitor concentrate; TA, tranexamic acid

Clinical place for routine prophylaxis

Figure 6 depicts the main features of the ASCIA guidance (Katelaris et al, 2012) for routine prophylaxis under the current funding arrangements. ASCIA states that uniform criteria directing the use of prophylactic therapy have not been established, but recommends that routine prophylaxis is considered if certain patient criteria are met (frequent attacks, severe attacks, remote or rural location of patient, etc.). Danazol is the most commonly administered option for routine prophylaxis, but where this is contraindicated, not tolerated or ineffective, tranexamic acid can be used. The ASCIA Position Paper (Katelaris et al, 2012) states that danazol and tranexamic acid are the only options for routine prophylaxis. However, routine prophylaxis using C1-INH concentrate is discussed as an option: the implication is that as hospital-funded C1-INH concentrate is not currently available for routine prophylaxis, it is considered not to be a currently accessible option for this indication.

While tranexamic acid may be used during pregnancy, some clinicians may consider it contraindicated for pregnancy due to the Category B1 classification. Similarly, due to the precautions associated with tranexamic acid, it is possible that some patients would opt for no prophylaxis rather than taking it while breastfeeding.

Figure 6 Clinical management algorithm for routine prophylaxis – current funding arrangement

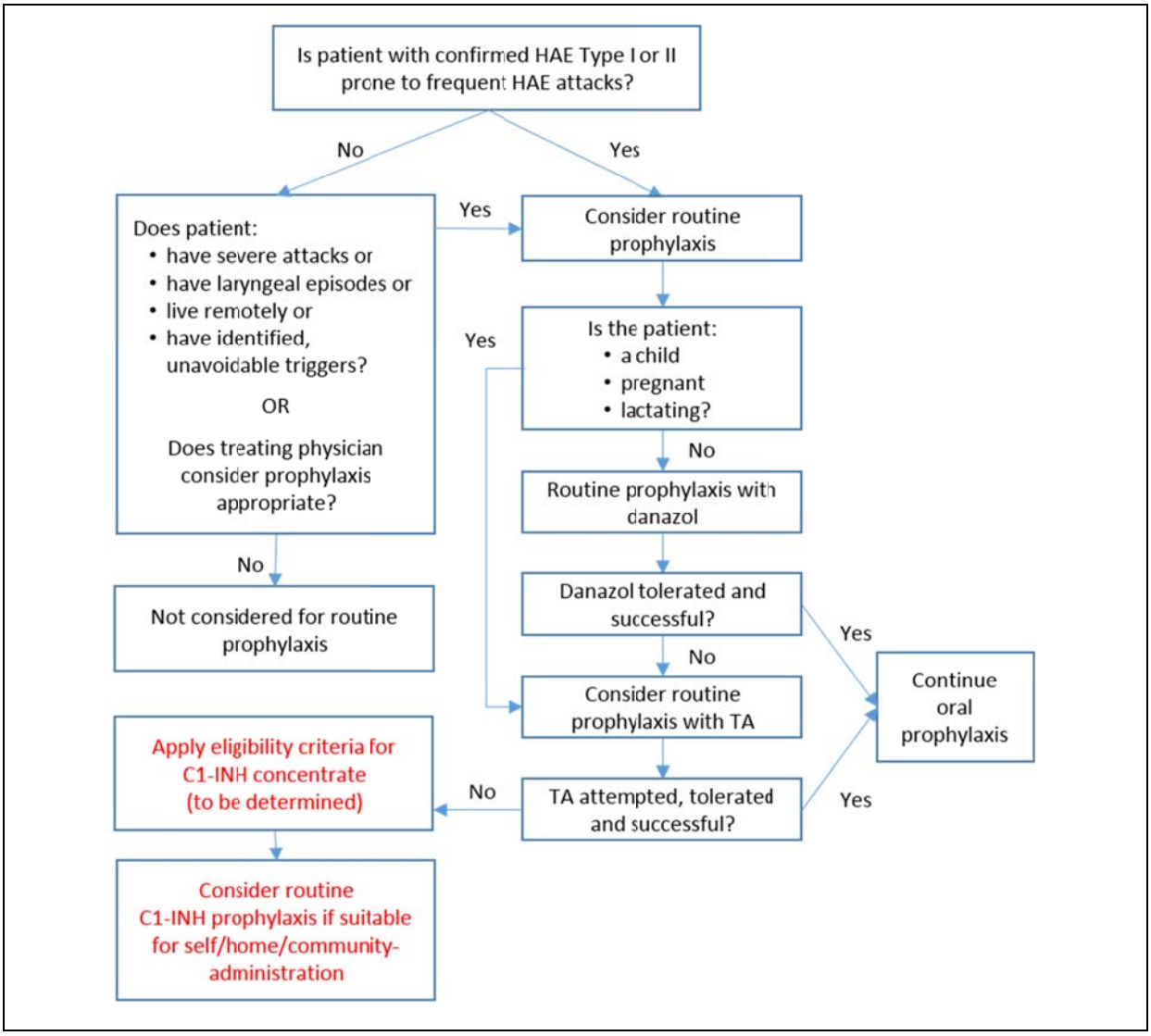


Source: based on recommendations from the ASCIA Position Paper (Katelaris et al, 2012).
Abbreviations: C1-INH, C1 esterase inhibitor concentrate; HAE, hereditary angioedema; TA, tranexamic acid
a Tranexamic acid in pregnancy is rated Category B1
b The ASCIA Position Paper (Katelaris et al, 2012) states that 'The only options for long term prophylaxis are danazol and tranexamic acid'. Long-term prophylaxis using C1-INH concentrate is discussed as an option, but as it is not currently funded, it may be considered to be currently inaccessible to patients.

Figure 7 shows the potential scenario if C1-INH concentrate is listed on the NPSL, making it a viable option for routine prophylaxis after the failure of oral therapy. While uniform criteria are not established for routine prophylaxis with oral therapies, access to C1-INH concentrate for this indication may require specific eligibility criteria. These may align with those indicated for the use of oral therapies shown in Figure 7, or they may be more restrictive, perhaps specifying the history of attack frequency while on oral therapy. Without specific restrictive criteria, it is possible that C1-INH concentrate could replace oral therapies for routine prophylaxis. Given than tranexamic acid is limited by a relative lack of efficacy, for many patients C1-INH concentrate may become a preferred alternative where danazol is contraindicated or not tolerated. In addition, many patients currently

using danazol for routine prophylaxis may switch to C1-INH concentrate as a preferred alternative offering fewer side effects (and greater disease control, either actual or perceived).

Figure 7 Clinical management algorithm for routine prophylaxis – proposed funding arrangement



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

Cinryze and Berinert for routine prophylaxis

Only Cinryze is TGA-approved for routine prophylaxis but that approval is restricted to patients 12 years of age and older (see Table 4). ASCIA does not specify age restrictions on the use of C1-INH concentrate for routine prophylaxis. If listed on the NPSL, it is possible that Cinryze will be used in paediatric patients for routine prophylaxis.

Berinert is not TGA-approved for routine (or pre-procedure) prophylactic use. The CSL Behring application does not propose inclusion of Berinert on the NPSL for routine prophylaxis. However, if listed on the NPSL, it is possible that Berinert will be used for routine prophylaxis.

Comparators

The identification of appropriate comparisons for NPSL-funded C1-INH concentrate is complicated by the current in-hospital use of C1-INH concentrate funded by some hospital formularies. Inclusion on the NPSL may allow for greater community-based administration, which has the potential to provide superior efficacy in treating acute attacks. In addition, broader geographic accessibility may bring improved quality of life to patients who currently need to manage their condition by remaining close to those hospitals that provide C1-INH concentrate. So while the intervention remains the same (hospital-funded vs NPSL-funded C1-INH concentrate), the funding source has the potential to impact on patient-relevant factors.

For these reasons, the assessment of C1-INH concentrate for inclusion on the NPSL requires consideration of three separate issues, as described below.

Treatment comparisons: C1-INH concentrate versus other treatments

This comparison will examine the relative efficacy/effectiveness and safety of C1-INH concentrate and other interventions (or no intervention).

Setting comparisons: community-administered versus hospital-administered

This comparison will examine the relative efficacy/effectiveness and safety of community-administered and hospital-administered C1-INH concentrate.

Funding comparisons: NPSL-funded versus hospital-funded

This comparison will examine the potential impact of listing on the NPSL on availability of C1-INH concentrate resulting from changes in price signals (potentially lifting limits on use) and broader geographical accessibility. While not based on published clinical evidence, a framework for these considerations is appropriate and necessary for a full assessment of whether C1-INH concentrate should be included on the NPSL.

Treatment comparators for C1-INH concentrate

Although C1-INH concentrate is already in use in some hospitals for acute attacks and pre-procedure prophylaxis, the main clinical comparator is the most appropriate alternative treatment.

Table 7 shows the identified main clinical comparators for C1-INH concentrate for each of the three indications, and for the subpopulations of children, pregnancy and lactation. Either icatibant, danazol or tranexamic acid are appropriate main comparators for C1-INH concentrate, depending on the population and the indication.

For acute attacks in adults, icatibant is recommended by ASCIA alongside C1-INH concentrate so it is the main treatment comparator for this indication.

For prophylaxis prior to major procedures such as head, neck and dental surgery, ASCIA recommends C1-INH concentrate and, ‘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'. Therefore danazol is the main comparator for pre-procedure prophylaxis for major surgery[8].

For routine prophylaxis, danazol is recommended first-line and C1-INH concentrate is second line, after failure of oral therapy. As there are no other options for this indication, the appropriate comparator for C1-INH concentrate is no prophylaxis after failed oral therapy.

It should be noted that danazol may continue to be used by some patients with high clinical need for prophylaxis despite it not being well tolerated or providing insufficient protection. For such patients routine prophylaxis with C1-INH concentrate may be indicated, and once it becomes an accessible option they may be deemed to have failed oral therapy.

In children, the main comparator for acute attacks is no treatment as there is no clinical data for icatibant in children (the ASCIA position is that being under 18 years of age is an absolute indication for C1-INH concentrate over icatibant (communication 22 August 2014)). The comparator for prophylaxis prior to major procedures in children is danazol, which can be used short-term in children. For routine prophylaxis the main comparator is no prophylaxis after failed oral therapy. The only option for oral therapy in this population is tranexamic acid, as danazol is contraindicated for long-term use in children.

In pregnant and lactating patients, the main comparator for acute attacks is no treatment, as icatibant is classified as Category C for pregnancy[9], and breastfeeding must cease for 12 hours after treatment. The comparator for pre-procedural prophylaxis prior to major procedures during pregnancy and lactation is tranexamic acid, although it is rated a Category B1 for pregnancy (the safety profile during pregnancy is not well-established) and precautions are advised during breastfeeding. For routine prophylaxis the main comparator is no prophylaxis after failed oral therapy. The only option for oral therapy in pregnant and lactating patients is tranexamic acid, which may be considered contraindicated by some clinicians given the advised precautions in these populations.

[8] Danazol is first line for minor pre-procedure prophylaxis but C1-INH concentrate is not deemed necessary for minor procedures.

[9] According to ASCIA, pregnancy is an absolute indication for C1-INH concentrate over icatibant for acute attacks (communication 22 August 2014).

Table 7 Comparator treatments for C1-INH concentrate for various HAE indications and populations

Population Indication	Comparator	C1-INH concentrate is currently used[10]	Comments
Adults and adolescents			
Acute attack	Icatibant	Yes	Recommended alongside C1-INH concentrate.
Pre-procedure prophylaxis, major procedures	Danazol	Yes	C1-INH concentrate is recommended first line (i.e. before danazol).
Routine prophylaxis	No prophylaxis after failed oral therapy	No[11]	C1-INH concentrate is recommended second line, after failure of oral therapy such as danazol.
Children			
Acute attack	No treatment[13]	Yes	
Pre-procedure prophylaxis, major procedures	Danazol	Yes	C1-INH concentrate is recommended first line (i.e. before danazol).
Routine prophylaxis	No prophylaxis after failed oral therapy[12]	No[11]	Berinert is not TGA-approved for prophylaxis and Cinryze is not TGA-approved for children.
Pregnancy /lactation			
Acute attack	No treatment[13]	Yes	
Pre-procedure prophylaxis, major procedures	TA	Yes	TA is pregnancy category B1 and caution is advised in lactating women.[14]
Routine prophylaxis	No prophylaxis after failed oral therapy (TA only)	No[11]	TA is pregnancy category B1 and caution is advised in lactating women.[14]

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

Clinical and economic claim

For each indication, the clinical and economic claims for each of the three comparison categories (treatment, setting and funding) will be discussed.

Claim for acute HAE attacks

Treatment comparison

For the treatment comparison, the clinical claim is that C1-INH concentrate is non-inferior to icatibant in efficacy and safety for acute HAE attacks in adults and adolescents (Table 8). This is based on the ASCIA management algorithm which recommends either icatibant or C1-INH concentrate for acute attacks. The appropriate economic evaluation would be a cost-minimisation analysis. (For children, and during pregnancy and lactation, the appropriate treatment comparison claim would be that C1-INH concentrate is superior in efficacy and safety to no treatment.)

[10] Indicates where hospital-funded C1-INH concentrate currently may be used.
[11] 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 2012) are consistent with this assumption.
[12] Oral therapy in children would usually be tranexamic acid 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.
[13] While TA is not contra-indicated in these populations, it is of very limited benefit for acute attacks (Longhurst et al, 2010) and the ASCIA Position Paper (Katelaris et al, 2012) makes no mention of its use for this indication.
[14] PI for tranexamic acid states that caution should be exercised when administered to a nursing woman. Not for 12 hours prior to breastfeeding.

Table 8 Comparative analysis of C1-INH concentrate for the treatment of acute HAE attacks

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="4">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="6">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: Admin, administration; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; vs, versus
* May be reduced to cost-minimisation analysis.
^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Setting comparison

In all populations, the claim for the setting comparison is that community-administered C1-INH concentrate is superior in terms of efficacy to hospital-administered C1-INH concentrate due to earlier administration, and is non-inferior in terms of safety.

Funding comparison

The claim for the funding comparison is that listing C1-INH concentrate on the NPSL will provide patient benefits associated with greater access to the intervention (note that anticipated changes in use will be explored in the financial impact analysis).

Claim for prophylaxis prior to major procedures

Treatment comparison

The clinical claim for prophylaxis prior to major procedures in adults and children is that C1-INH concentrate is superior to danazol in efficacy and non-inferior to danazol in safety. This is based on ASCIA advice which clearly favours C1-INH concentrate over danazol for this indication. The appropriate economic evaluation would be a cost-effectiveness analysis (Table 9). (For pregnant and lactating women, the appropriate clinical claim would be that C1-INH concentrate is superior in efficacy[15] and safety to tranexamic acid.)

[15] Based on claims made by ASCIA regarding the low efficacy of tranexamic acid (Katelaris et al, 2012).

Table 9 Comparative analysis of C1-INH concentrate for pre-procedural prophylaxis

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="4">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="6">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis
* May be reduced to cost-minimisation analysis.
^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Setting comparison

The clinical claim for the setting comparison is that, for all populations, community-administered C1-INH concentrate is non-inferior to hospital-administered C1-INH concentrate in efficacy and safety.

Funding comparison

The claim for the funding comparison is that listing C1-INH concentrate on the NPSL will provide patient benefits associated with greater access to the intervention for pre-procedure prophylaxis.

Claim for routine prophylaxis

Treatment comparison

The clinical claim for routine prophylaxis is that C1-INH concentrate is superior to no prophylaxis in efficacy, and non-inferior in safety, in adults who have failed oral therapy. The appropriate economic evaluation would be a cost-effectiveness analysis (Table 10). (For children[16], pregnant and lactating women, the appropriate clinical claim would be that C1-INH concentrate is superior in efficacy[17] and safety to tranexamic acid.)

[16] Note that there is currently no TGA-approved C1-INH concentrate for this indication in children: Berinert is not TGA-approved for prophylaxis and Cinryze is not TGA-approved for children.
[17] Based on claims made by ASCIA regarding the low efficacy of tranexamic acid (Katelaris et al, 2012).

Table 10 Comparative analysis of C1-INH concentrate for routine prophylaxis

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="4">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="6">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis
* May be reduced to cost-minimisation analysis.
^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Setting comparison

The clinical claim for the setting comparison is that, for all populations, community-administered C1-INH concentrate is non-inferior to hospital-administered C1-INH concentrate in efficacy and safety.

Funding comparison

There is no clinical or economic claim for the funding comparison, but listing C1-INH concentrate on the NPSL will provide patient benefits associated with gaining access to the intervention for routine prophylaxis, which they currently appear not to have (note that anticipated changes in use will be explored in the financial impact analysis).

Summary of PICO to be used for assessment of C1-INH concentrate

PICO for acute HAE attacks

Assessment of C1-INH concentrate will be guided by three sets of PICO criteria; one for each of the three HAE indications. While this report refers to the assessment of C1-INH concentrate, the evidence should be evaluated for Cinryze and Berinert separately. The efficacy and safety of Cinryze and Berinert should also be compared, either directly or indirectly (depending on the available evidence).

While the bulk of the clinical evidence is likely to relate to adults and adolescents, children and pregnant women should also be considered if evidence is available (noting the differences in comparators shown in Table 7).

Table 11 shows the PICO criteria for the assessment of C1-INH concentrate for the treatment of acute HAE attacks. The research questions to be addressed in the assessment fall into three categories of comparison (as described in the Comparators section on p28):

Treatment comparison

1. ***a)*** *What is the evidence of efficacy/effectiveness and safety of C1-INH concentrate (Cinryze or Berinert) compared with icatibant for the treatment of acute HAE attacks in patients with HAE type I or II?*

   b) *What is the evidence of efficacy/effectiveness and safety of Cinryze compared with Berinert for the treatment of acute HAE attacks in patients with HAE type I or II?*

Setting comparison (early vs late administration)

2. *What is the evidence of efficacy/effectiveness and safety of community-administered C1-INH concentrate (Cinryze or Berinert) compared with hospital-administered C1-INH concentrate for the treatment of acute HAE attacks in patients with HAE type I or II?*

Funding model comparison

3. *What are the likely benefits to patients or the health care system of NPSL-funded C1-INH concentrate compared with hospital-funded C1-INH concentrate for the treatment of acute HAE attacks in patients with HAE type I or II?*

The first category of comparison (treatment) will examine evidence that compares either one of the C1-INH concentrates with icatibant or compares the two C1-INH concentrates with each other.

The second comparison (setting) will examine any evidence (direct or indirect) for early administration in the community setting compared with later administration in the hospital setting.

The third comparison (funding model) will examine the impact of the resultant broader accessibility of the intervention if listed on the NPSL, taking into account the impact of equitable access, increased availability, convenience and adherence.

Table 11 Summary of PICO for assessment of C1-INH concentrate (Cinryze or Berinert) for the treatment of acute HAE attacks

Population	Intervention	Comparator	Outcomes
Patients with confirmed HAE types I or II and an acute HAE attack	1. Treatment C1-INH concentrate 2. Setting Community-administered C1-INH concentrate 3. Funding model NPSL -funded C1-INH concentrate	1. Treatment a. Icatibant; or b. the other C1-INH concentrate (i.e.Cinryze vs Berinert) 2. Setting Hospital-administered C1-INH concentrate[18] 3. Funding model Hospital-funded C1-INH concentrate	Efficacy outcomes • median time from treatment to onset of symptom relief • proportion of patients achieving onset of symptom relief within 4 hours of treatment • median time to complete resolution of attack • use of rescue medication[a] • QoL Safety outcomes • AEs/SAEs • administration-site reactions • antibodies to study drug • virology

Abbreviations: AE, adverse event; C1-INH, C1 esterase inhibitor concentrate; HAE, hereditary angioedema; NPSL, National Products and Services List; QoL, quality of life; SAE, serious adverse event
a rescue medication can be a second dose of study drug or a first dose of an alternative treatment

PICO for prophylaxis with C1-INH concentrate

Table 12 and Table 13 show the PICO criteria for the assessment of C1-INH concentrate for pre-procedure and routine prophylaxis, respectively. For the prophylaxis indications, the frequency of attacks is relevant. Although this outcome may be less impacted by administration setting than the speed of symptom resolution during an attack, the evidence will be considered for each setting separately, where available.

Quality of life (QoL) is a relevant outcome for all three indications, particularly for routine prophylaxis which has the potential to reduce the overall number of attacks a patient will experience. The use of rescue medication is a relevant indicator of the success of treatment for all three indications.

PICO for pre-procedure prophylaxis

The research questions to be addressed as part of the review of the evidence for C1-INH concentrate for pre-procedure prophylaxis fall into the same three comparison categories, although the relevance of the setting category is simply the setting itself, not the timing of administration as a result of the setting. The research questions are:

Treatment comparison

1. ***a)*** *What is the evidence of efficacy/effectiveness and safety of C1-INH concentrate (Cinryze or Berinert) compared with danazol for the prevention of HAE attacks in patients with HAE type I or II who undergo major medical procedures?*

   b) *What is the evidence of efficacy/effectiveness and safety of Cinryze compared with Berinert for the prevention of HAE attacks in patients with HAE type I or II who undergo major medical procedures?*

[18] Self-administered or administered by another person at home or by an out-of-hospital health care professional

Setting comparison

2. *What is the evidence of efficacy/effectiveness and safety of community-administered C1-INH concentrate (Cinryze or Berinert) compared with hospital-administered C1-INH concentrate for the prevention of HAE attacks in patients with HAE type I or II who undergo major medical procedures?*

Funding model comparison

3. *What are the likely benefits to patients or the health care system of NPSL-funded C1-INH concentrate compared with hospital-funded C1-INH concentrate for the prevention of HAE attacks in patients with HAE type I or II who undergo major medical procedures?*

Table 12 Summary of PICO for assessment of pre-procedural C1-INH concentrate for the prevention of HAE attacks

Population	Intervention	Comparator	Outcomes
Patients with confirmed HAE types I or II prior to major medical procedure (i.e. surgeries involving neck, head or dental work or intubation).	1. Treatment C1-INH concentrate 2. Setting Community-administered C1-INH concentrate 3. Funding model NPSL-funded C1-INH concentrate	1. Treatment a. Danazol; or b. the other C1-INH concentrate (i.e.Cinryze vs Berinert) 2. Setting Hospital-administered C1-INH concentrate[19] 3. Funding model Hospital-funded C1-INH concentrate	Efficacy outcomes • proportion of patients without an attack within 72 hours of procedure • use of rescue medication[a] • QoL Safety outcomes • AEs/SAEs • administration-site reactions • antibodies to study drug • virology

Abbreviations: AE, adverse event; C1-INH, C1 esterase inhibitor concentrate; HAE, hereditary angioedema; QoL, quality of life; SAE, serious adverse event
a rescue medication can be a second dose of study drug or a first dose of an alternative treatment

PICO for routine prophylaxis

The research questions to be addressed as part of the review of the evidence for C1-INH concentrate for routine prophylaxis fall into the three comparison categories and, as for pre-procedural prophylaxis, the relevance of the setting category is simply the setting itself, not the timing of administration as a result of the setting. The research questions are:

Treatment comparison

1. ***a)*** *What is the evidence of efficacy/effectiveness and safety of C1-INH concentrate (Cinryze or Berinert) compared with no prophylaxis after failed oral therapy for the overall prevention of HAE attacks in patients with HAE type I or II?*

   b) *What is the evidence of efficacy/effectiveness and safety of Cinryze compared with Berinert for the overall prevention of HAE attacks in patients with HAE type I or II?*

[19] Self-administered or administered by another person at home or by an out-of-hospital health care professional

Setting comparison

2. *What is the evidence of efficacy/effectiveness and safety of community-administered C1-INH concentrate (Cinryze or Berinert) compared with hospital-administered C1-INH concentrate for the overall prevention of HAE attacks in patients with HAE type I or II?*

Funding model comparison

3. *What are the likely benefits to patients or the health care system of NPSL-funded C1-INH concentrate compared with hospital-funded C1-INH concentrate for the overall prevention of HAE attacks in patients with HAE type I or II?*

Table 13 Summary of PICO for assessment of routine C1-INH concentrate for the prevention of HAE attacks

Population	Intervention	Comparator	Outcomes
Patients with confirmed HAE types I or II who are intolerant to or insufficiently protected by oral therapy	1. Treatment C1-INH concentrate 2. Setting Community-administered C1-INH concentrate 3. Funding model NPSL-funded C1-INH concentrate	1. Treatment a. no prophylaxis after failed oral therapy; or b. the other C1-INH concentrate (i.e.Cinryze vs Berinert) 2. Setting Hospital-administered C1-INH concentrate[20] 3. Funding model Hospital-funded C1-INH concentrate	Efficacy outcomes • median rate of HAE attacks • mean score for the severity of attacks • average duration of attacks • use of rescue medication[b] • QoL Safety outcomes • AEs/SAEs • administration-site reactions • antibodies to study drug • virology

Abbreviations: AE, adverse event; C1-INH, C1 esterase inhibitor concentrate; HAE, hereditary angioedema; QoL, quality of life; SAE, serious adverse event; TA, transexamic acid.
a C1-INH concentrate is clinically indicated where oral therapy provides insufficient protection or is intolerable. Patients successfully using oral therapies would not be appropriate comparators for routine use of C1-INH concentrate.
b rescue medication can be a second dose of study drug or a first dose of an alternative treatment

[20] Self-administered or administered by another person at home or by an out-of-hospital health care professional

Health care resources

Table 14 describes the resources that may be associated with the use of C1-INH, for use in the economic evaluation and/or financial impact analysis.

Table 14 Health care resources for C1-INH concentrate and comparators for the management of HAE

Resource	Treatment of acute attacks	Pre-procedural prophylaxis	Routine prophylaxis
Resources provided to identify eligible population	Eligible patients already have a confirmed diagnosis	Eligible patients already have a confirmed diagnosis	Eligible patients already have a confirmed diagnosis
Resources provided to deliver proposed intervention	• Training costs for patients eligible for on-demand IRT, estimated 3 sessions per patient ($1,000-$2,000), covered by the sponsor. • Cost of C1-INH per administration (supplied as a complete kit) • Emergency department visit for administration of C1-INH if not 'on hand' • Assistance with administration from a healthcare provider (e.g. community nurse, GP) in a proportion of patients who are eligible for on-demand IRT.	• Cost of C1-INH per administration (supplied as a complete kit) • Treatment centre or GP visit for administration of C1-INH if not 'on hand' or if assistance required for injection	• Training costs for patients eligible for self-administered routine prophylaxis, estimated 3 sessions per patient ($1,000-$2,000), covered by the sponsor. • Cost of C1-INH per administration (supplied as a complete kit) • Assistance with administration from a healthcare provider (e.g. community nurse, GP) in a proportion of patients who are eligible for on-demand IRT.
Resources provided in association with proposed intervention	• Ambulance transport, if required • Re-dosing with C1-INH in Emergency Department, if required (non-admitted) • Hospital admission for two-day observation following a severe attack • Intubation and ventilation • Tracheotomy • Other rescue medication to achieve relief	• Re-dosing with C1-INH, if required • Emergency Department visit for breakthrough attack • Hospital admission for two-day observation following a severe attack • Intubation and ventilation • Tracheotomy • Other rescue medication to achieve relief from breakthrough attack	• Ambulance transport, if required • Emergency Department visit for breakthrough attacks • Hospital admission for two-day observation following a severe attack • Intubation and ventilation • Tracheotomy • Other rescue medication to achieve relief from breakthrough attack
Resources provided to deliver the comparator	• Specialist/GP visit for prescription • Cost of icatibant per administration • Emergency department visit for administration of icatibant if not 'on hand' • No administration cost for patients who are eligible for on-demand IRT; however, a proportion of patients will need assistance with SC administration from a healthcare provider (e.g. community nurse, GP).	• Specialist/GP visit for prescription • Cost of oral danazol per administration	

Resource	Treatment of acute attacks	Pre-procedural prophylaxis	Routine prophylaxis
Resources provided in association with comparator	• Ambulance transport, if required • Re-dosing with icatibant in Emergency Department • Hospital admission for two-day observation following a severe attack • Intubation and ventilation • Tracheotomy • Other rescue medication to achieve relief	• Re-dosing with danazol, if required • Emergency Department visit for breakthrough attack • Hospital admission for two-day observation following a severe attack • Intubation and ventilation • Tracheotomy • Other rescue medication to achieve relief from breakthrough attack	• Ambulance transport, if required • Emergency Department visit for breakthrough attack • Hospital admission for two-day observation following a severe attack • Intubation and ventilation • Tracheotomy • Other rescue medication to achieve relief from breakthrough attack

Abbreviations: C1-INH, C1 esterase inhibitor concentrate; GP, general practitioner; IRT, individual replacement therapy; SC, subcutaneous

There are a number of published animal and clinical studies of C1-INH concentrate for indications other than HAE (Singer et al, 2011). In particular, the use of C1-INH concentrate in patients with septic shock has been explored. Being the largest potential alternative population for this intervention, such potential use of C1-INH concentrate will be examined in financial impact sensitivity analyses.

Additional issues identified by JBC Working Group

Table 15 shows a list of additional issues identified by the Schedule 4 JBC Working Group that require consideration in the evaluation of C1-INH concentrate.

Table 15 Issues identified by the MCA Working Group to be considered in the evaluation of C1-INH concentrate

Area	Issue
Comparative dosages	What are the equi-effective doses (i.e. do 2 vials of Cinryze (standard treatment dose) have the same effect as 3.02 vials of Berinert (standard treatment dose))?
Costs	How do Cinryze and Berinert compare in costs to icatibant? Is there potential for governments to spend more on C1-INH through the National Blood Arrangements for the same benefits delivered by icatibant on the PBS? What trends are there in utilisation and cost for icatibant?
Population of consumers	Is the cohort of patients who cannot use icatibant large enough to justify inclusion of these products under the National Blood Arrangements regardless of negative cost comparisons to icatibant?
Wastage comparisons	What is the shelf life for the products compared to icatibant?
Convenience	Icatibant is purchased as a single dose, pre-filled injection administered subcutaneously (similar to an EpiPen) which can be transported at room temperature for emergencies outside of hospital. As Cinryze and Berinert are administered intravenously, are they considered convenient for patients?
Likelihood of uptake	Will patients need additional training and physical requirements, such as good veins and a trained 'infusion partner' to monitor treatment in the home, to appropriately access Cinryze and/or Berinert? Will additional requirements affect rates of uptake?
Governance	Will there be additional costs in setting up a process to regulate and monitor which patients are eligible to receive Cinryze and Berinert? What are these estimated costs?

References

Bork K, Wulff K, Hardt J, Witzke G, Staubach P. (2009) Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. J Allergy Clin Immunol. 124(1):129-34.

Craig T, Aygören-Pürsün E, Bork K, Bowen T, et al (2012) WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J. 5(12):182-99.

Katelaris C, Smith W, Mullins R, Gillis D, et al. Position Paper on Hereditary Angioedema. Australasian Society of Clinical Immunology and Allergy. August 2012.

King N, Katelaris C. (2012) HAE in Australia: the patient experience. European Academy of Allergy and Clinical Immunology (EAACI) 2012 Congress. Poster presentation.

Longhurst HJ (2010) Management of acute attacks of hereditary angioedema: potential role of icatibant. Vasc Health Risk Manag. 6: 795–802

Singer M and Jones AM (2011) Bench-to-bedside review: The role of C1-esterase inhibitor in sepsis and other critical illnesses. Critical Care 2010, 15:203

Appendix A ASCIA treatment recommendations

Table A.1 ASCIA Position Paper recommendations for management of HAE in sub-populations

Route of administration	I.V. injection		subcutaneous injection	oral	
Sub-population	Cinryze	Berinert	icatibant	attenuated androgens (danazol)	anti-fibrinolytics (tranexamic acid)
Paediatric					
acute	✓[a]	✓	X[d]		~[j]
pre-procedural prophylaxis	✓[a]			✓[g]	✓[k]
routine prophylaxis	✓[a]			X[h]	✓[k]
Pregnancy					
acute	✓[b]	✓	X[e]		~[j, l]
pre-procedural prophylaxis	✓[b]			X	✓[k, l]
routine prophylaxis	✓[b]			X	✓[k, l]
Lactation					
acute	✓[c]	✓	~[f]		~[j,m]
pre-procedural prophylaxis	✓[c]			X	✓[k,m]
routine prophylaxis	✓[c]			X[i]	✓[k,m]

Abbreviations: ASCIA, Australasian Society of Clinical Immunology and Allergy; C1-INH, C1 esterase inhibitor; PI, product information.

Note: Shaded cells indicate treatment not effective for that indication in any population (icatibant, danazol) or not TGA-approved for that indication (Berinert). ASCIA Position Paper refers to Katelaris et al (2012).

a PI excludes use in children younger than 12 years old. ASCIA Position Paper states 'there is no contraindication to use in children', and 'is indicated for treatment, pre-procedure prophylaxis and long-term prophylaxis of angioedema in adult and paediatric HAE patients'.

b PI states "may be considered during pregnancy, if necessary". ASCIA Position Paper states there is no contraindication for use during pregnancy.

c PI states it is unknown whether C1-INH is excreted in breast milk and the risk to the infant cannot be excluded. ASCIA Position Paper states there is no contraindication for use during lactation.

d PI restricts use to adults. ASCIA Position Paper states there is no data for use in children, but they do not make a statement to avoid use in children.

e PI states this has an Australian classification for medicines for use during pregnancy of Category C (no clinical data). ASCIA Position Paper offers no opinion regarding use during pregnancy but ASCIA indicated it would not be used in pregnant women due to safety concerns (communication 22 August 2014).

f ASCIA Position Paper makes no statement regarding use during lactation. PI states it is unknown whether icatibant is excreted in human breast milk but it is recommended that breastfeeding women should not breastfeed for 12 hours after treatment.

g PI states 'the safety and efficacy in children has not been established.' ASCIA Position Paper states 'Danazol can be used for short-term prophylaxis in children since virilisation is only likely to occur with long-term treatment.'

h PI states 'the safety and efficacy in children has not been established.' ASCIA Position Paper states 'In some cases the benefits of routine danazol in children outweigh the risks.'

i PI states it is not recommended for use in breastfeeding mothers. ASCIA Position Paper states 'the safety of danazol during breastfeeding has not been established so it is usually avoided'.

j ASCIA Position Paper makes no statement regarding use of tranexamic acid for acute attacks, presumably due to very limited benefit for this indication (Longhurst, 2010).

k ASCIA Position Paper states that tranexamic acid is 'not preferred for prophylaxis but could be introduced where danazol is contraindicated or unacceptable.'

l PI states tranexamic acid has an Australian Pregnancy Categorisation B1. ASCIA Position Paper refers to Category B1 and no further opinion is provided.

m PI states 'While an antifibrinolytic effect in the infant is unlikely at therapeutic doses, caution should be exercised when tranexamic acid is administered to a nursing woman.' ASCIA Position Paper states is not contraindicated.