Clinical Commissioning Policy:

Icatibant for treatment of moderate to severe acute swellings due to bradykinin-mediated angioedema with normal C1 inhibitor (adults) [2315]

Summary

Icatibant is recommended to be available as a routine commissioning treatment option for moderate to severe acute swellings due to bradykinin-mediated angioedema with normal C1 inhibitor within the criteria set out in this document.

The policy is restricted to adults[1] in line with the findings from the evidence review. Note that icatibant is not licensed for treatment of moderate to severe acute swellings due to bradykinin-mediated angioedema with normal C1 inhibitor and therefore this is an off-label use.

Committee discussion

Clinical Panel recommended that this policy should proceed as a routine commissioning clinical policy. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed here:(Link to be added at publication).

What we have decided

NHS England has carefully reviewed the evidence to treat moderate to severe acute swellings due to bradykinin-mediated angioedema with normal C1 inhibitor with icatibant. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed here: [Link to be added at publication].

Plain language summary

About angioedema

Patients with angioedema have uncontrolled and spontaneous swellings, which can occur episodically and result in a build-up of fluid in various parts of the body. These swellings vary by types and locations, including swellings in the:

- Airway - this is particularly dangerous and can lead to death if the patient is not able to breathe properly.

[1] Icatibant may be used in children aged two years and older via NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children).

- Gut - this can cause severe pain in the stomach area, feeling sick (nausea) and being sick (vomiting).
- Deep tissues of the skin - this can cause significant disability for example if the hands, feet or genitals are affected.

Swellings can be spontaneous or occur during times of physiological and psychological stress. They develop as a result of deficiency or improper functioning of certain proteins that help to maintain the normal movement of fluids in and out of blood vessels.

Angioedema can be grouped into different types based on which inflammatory chemicals are triggering them in the body. The two known chemicals involved are histamine and bradykinin. When bradykinin is involved, the condition is referred to as bradykinin-mediated and when histamine is involved, the condition is referred to as histamine-mediated.

About bradykinin-mediated angioedema with normal C1-esterase inhibitor (C1)

Bradykinin-mediated angioedema cannot be treated with anti-histamines, steroids or adrenaline which are used to treat histamine-mediated angioedema.

There are different ways to classify bradykinin-mediated angioedema (see Appendix 1, Table 1). These classifications are grouped into hereditary (passed down from parents to their offspring) and acquired (contracted after birth) and also by whether they have a normal or abnormal C1 inhibitor. The C1-inhibitor is a protein that regulates the immune system, preventing unnecessary immune responses and maintaining harmony in the immune system.

Bradykinin-mediated angioedema with normal C1 inhibitor is extremely rare, and diagnosing these conditions can be challenging. Diagnosis may involve showing a lack of response to high-dose antihistamines, functional/laboratory studies of bradykinin mediators or, in patients with hereditary angioedema with normal C1-inhibitor (HAE-nC1-INH), a family history or genetic mutations that are associated with bradykinin mediated angioedema with normal C1 inhibitor level. A visual diagram is included to show a broad overview (Appendix 1, Figure 1).

This policy applies to patients with recurrent, or long-term, symptoms in two subgroups of bradykinin-mediated angioedema with normal C1 inhibitor:

- HAE-nC1-INH
- Idiopathic non-histaminergic angioedema with normal C1-inhibitor (INHA)

This policy does not cover angioedema associated with C-1 inhibitor deficiency or drug induced angioedema.

About current treatment

Current treatment during acute swellings involves observation and if the airway is involved then intensive care admission may be required for intubation (insertion of a tube into the airway). Intubation prevents complete obstruction of the airway, which otherwise would mean the patient is unable to take in oxygen. Even when the airway is not involved, acute episodes often still require hospital admission for observation. There are no licensed treatments for managing angioedema in patients with HAE-nC1-INH or INHA.

About icatibant

The proposed intervention is icatibant, a bradykinin-2 receptor antagonist. After sufficient training, patients can give the treatment themselves, or carers/parents can give the treatment. The treatment can therefore be delivered at home, for patients to self-administer when they start to feel symptoms of swelling developing. Icatibant is currently licensed for symptomatic treatment of acute attacks of hereditary angioedema with C1 deficiency (types 1 and 2) in adults, adolescents and children aged two years and older.

Epidemiology and needs assessment

HAE with normal C1 inhibitor levels (HAE-n-C1INH) was first described in 2000 (Vitrat-Hincky et al., 2010). It is a rare condition and reliable data on prevalence is scant. Most sources concur that angioedema with normal C1 inhibitor is rarer than hereditary angioedema types 1 and 2 with abnormal C1 inhibitor (Table 1, Column A, Row A), itself estimated to be prevalent in 1:50,000-100,000 (Lumry et al., 2020). A recent survey of all UK centres which specialise in hereditary angioedema identified only 22 patients with HAE-nC1-INH (Yong et al, 2023). INHA is estimated to be even less prevalent than HAE-nC1-INH, estimated at one-tenth of that group, i.e. 2 or 3 patients in UK.

In the literature, the mean age of first attack is 27 years but patients as young as 12 years have been described. Oestrogen has been identified as a trigger factor for acute swellings; consequently, the condition particularly affects women; one French study identified that over 80% of patients with HAE-nC1-INH were female (Vitrat-Hincky et al, 2010, Bouillet et al, 2017).

Implementation

Inclusion criteria

All adult patients who fulfil the following criteria will be eligible for treatment with icatibant:

A diagnosis of **either**

- HAE-nC1-INH which may or may not include demonstration of specific mutations on gene testing

OR

- bradykinin-mediated angioedema with normal C1 inhibitor[2] and no family history or documented presence of specific gene mutation, including INHA

AND

- patient has been discussed at a multidisciplinary team (MDT) meeting with relevant specialist involvement and they agree with the proposed treatment. Consideration is given to whether self-administration of the medication is possible (if appropriate).

[2] Recognising that terminology around angioedema definitions and subpopulations is changing. Clinical teams are advised to consult the World Allergy Organisation guidelines for the most up-to-date terminologies.

Diagnosis should be made by an immunologist or allergist within a commissioned specialised immunology or specialised allergy centre.

Exclusion criteria

Patients with any of the below features are not eligible for treatment:

- Patients where angioedema with normal C1 inhibitor is secondary to a documented cause, e.g. medication-induced angioedema with normal C1 inhibitor
- Patients with contraindications to therapy with icatibant as outlined in the summary of product characteristics (SmPC).

Starting criteria

Patients that meet the inclusion criteria and do not meet any of the exclusion criteria should be supplied with a minimum of 2 doses. Patients may be supplied with a higher number of doses if their attack frequency at baseline is high.

This drug should be used only for acute treatment and is recommended to be given as soon as a patient is aware of symptoms of an acute swelling. The first dose for any attack may be administered in hospital or in the community, depending on local practice and patient-related factors.

Each individual with angioedema must have an individualised management plan with a strategy to manage life threatening attacks, to manage other clinically significant attacks, and to prevent/reduce attacks.

The prescribing clinician should be aware of the special warnings and precautions, including pregnancy and breast-feeding, for use of icatibant as detailed in the SmPC.

Dose and administration

Icatibant is administered via subcutaneous injection. It can be self-administered, or healthcare professional administered. Repeated administrations of icatibant may be required at a frequency of 6 hourly up to a maximum of 3 doses in 24 hours. The dose is 30mg. See the summary of product characteristics for comprehensive dose and administration information, including sliding scale dosing for those under 18 years old. Standard assessment and training procedures for patients and carers to self administer subcutaneous medications should be followed.

Stopping criteria

Once commenced, patients should remain on treatment until the below stopping criteria are met:

- Resolution of angioedema
  OR

- Patient experiencing adverse effects secondary to icatibant

OR

- No response to treatment as assessed by the clinical team treating the patient, using objective measures or scores for example the Angioedema Control Test (AECT), assessment of time to resolution, assessment of time to onset of symptom regression, severity of attacks before and after icatibant treatment.

Monitoring

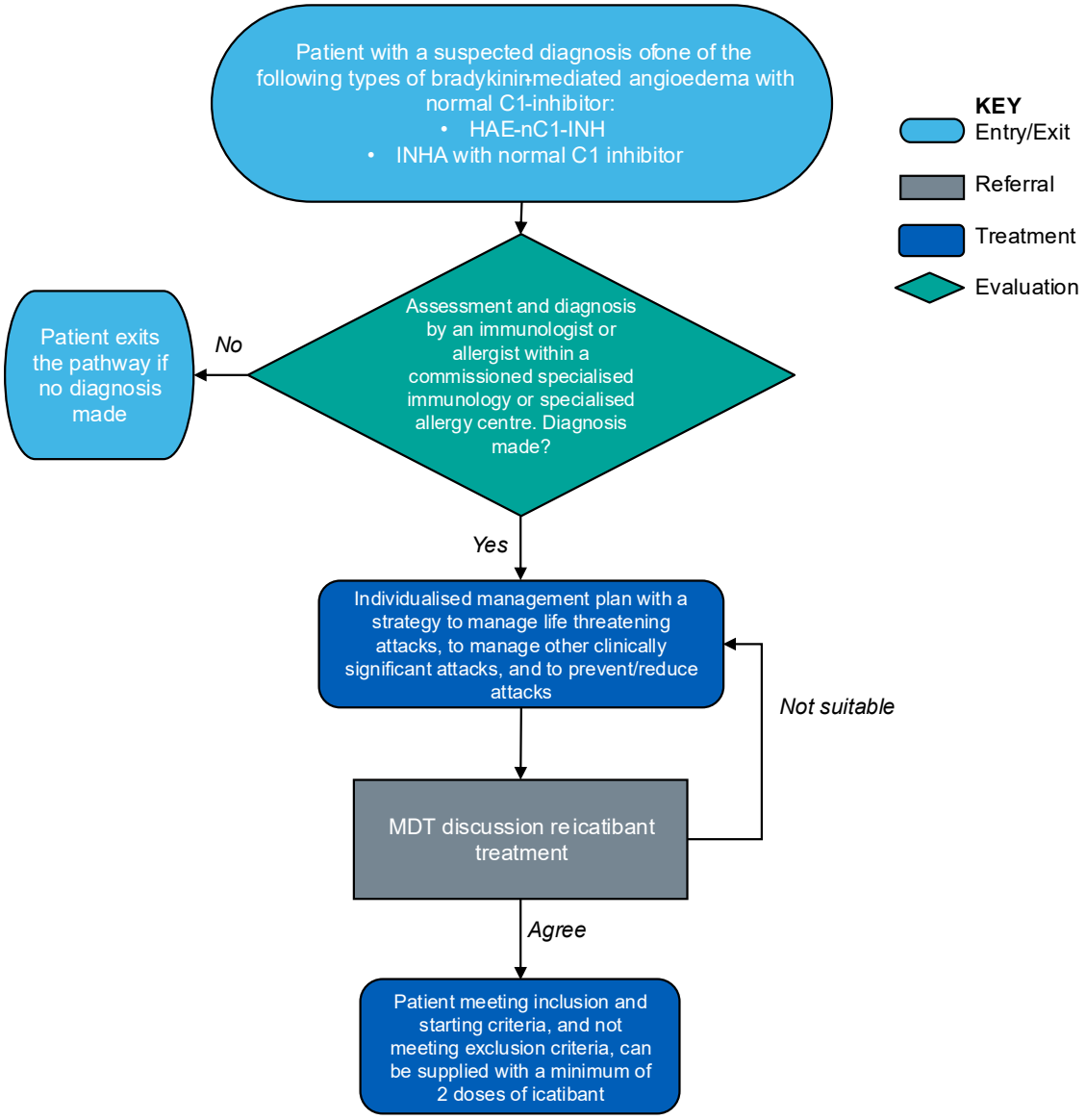
Each individual with angioedema must have an individualised management plan with a strategy to manage life threatening attacks, other clinically significant attacks, and to prevent/reduce attacks where possible, of which pharmacological treatments represent one part. For potentially life-threatening attacks involving the airway, the patient must call for emergency care or visit emergency care settings for monitoring and ongoing management, even if icatibant has been administered. Where blood tests/radiology are needed to monitor side effects associated with treatments for this condition these are sometimes organised through shared care with primary care.

Patients should be followed up virtually or in person by the specialised immunology or specialised allergy service that initiated the treatment. Frequency of follow up should be determined by frequency of attacks but should be a minimum of annually. Patient initiated follow up should be encouraged, and patients should be encouraged by clinical teams to initiate first follow up after first use of treatment.

Follow up must include assessment of clinical response, which should include objective measures or scores, for example AECT, assessment of time to resolution, assessment of time to onset of symptom regression, severity of attacks before and after icatibant treatment.

Patient pathway

Patients should be under the care of commissioned specialised immunology or specialised allergy centres. Treatment initiation and follow up should remain with these centres.



Governance arrangements

This policy should be used in conjunction with the following Service Specification for Specialised Immunology B09/S/a

The use of icatibant in the context of this policy is off-label. Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics Committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

Icatibant within the criteria set out in this document will be commissioned and funded by NHS England under existing arrangements for the provision of specialised services.

Audit requirements

A prior approval software will be used to support monitoring patients data on dose and frequency. Clinical audit should be conducted periodically as part of the providers audit cycle.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Angioedema	The rapid swelling of the dermis. Symptoms are caused by a collection of fluid in the deep layers of the skin, which most often affects the hands, feet, eyes, lips, or genitals

References

Bouillet, L., Boccon-Gibod, I., Launay, D., Gompel, A., Kanny, G., Fabien, V., Fain, O. and IOS Study Group, 2017. Hereditary angioedema with normal C1 inhibitor in a French cohort: clinical characteristics and response to treatment with icatibant. Immunity, Inflammation and Disease, 5(1), pp.29-36.

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Appendix 1

Supplementary material

The table below details the bradykinin-mediated angioedema types grouped by classification:

Bradykinin-mediated Angioedema *(also referred to as Non-Histaminergic Angioedema)*	**Column A:** Abnormal C1- inhibitor	**Column B:** Normal C1-inhibitor
Row A: Hereditary	Not included in this policy: Hereditary angioedema (HAE) type 1 and 2 secondary to abnormal C1 esterase inhibitor (HAE-C1-INH)	Included in this policy: Hereditary angioedema with normal C1 esterase inhibitor (HAE-nC1-INH) *[includes other single gene defects i.e. Factor 12 (FX11) and Plasminogen (PLG)]*
Row B: Acquired	Not included in this policy: Acquired angioedema secondary to C1 esterase inhibitor deficiency. (C1-INH-AAE)	Included in this policy: Idiopathic non-histaminergic angioedema (INHA) with normal C1 inhibitor *[has previously been included as part of the wider term Idiopathic Angioedema]* Not included in this policy: Drug induced angioedema

Table 1

A broad overview of how recurrent angioedema is differentiated in clinical practice is outlined below:

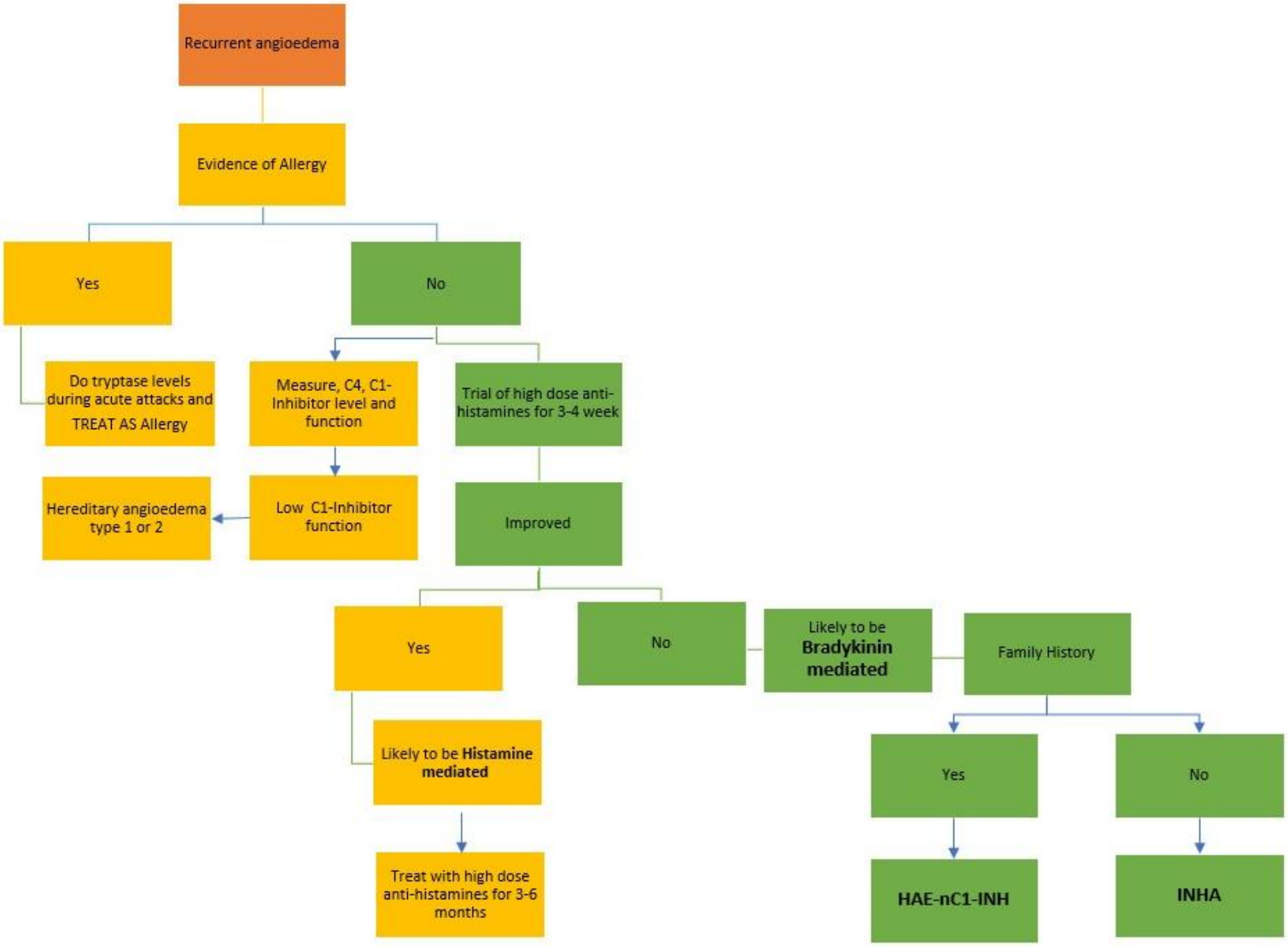

Figure 1