Clinical commissioning policy

Intravenous (6 years and above) and subcutaneous (adolescents and adults) C1-esterase inhibitor injections for routine prophylaxis of hereditary angioedema (HAE) type I and II or acquired angioedema (AAE) [16045/P]

Summary

C1-esterase inhibitor is recommended to be available as a routinely commissioned treatment option for hereditary angioedema (HAE) types I and II, and the related presentation of acquired angioedema (AAE), within the criteria set out in this document.

The policy is restricted to certain age groups as there is insufficient evidence to confirm safety, and it is not recommended through the licence authorisation process to be used in those age groups not included in the policy.

What we have decided

NHS England has carefully reviewed the evidence to treat HAE types I and II, and the related presentation of AAE, with C1-esterase inhibitor. We have concluded that there is enough evidence to make the treatment available at this time.

Links and updates to other policies

This document updates:

- Algorithms for hereditary and acquired angioedema secondary to C1 esterase inhibitor deficiency

This document links to:

- Lanadelumab for preventing recurrent attacks of hereditary angioedema (NICE TA606)
- Berotralstat for preventing recurrent attacks of hereditary angioedema (NICE TA738)
- Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over (NICE TA1101)

Plain language summary

About hereditary and acquired angioedema

Hereditary angioedema (HAE) is a very rare inherited illness where the C1-esterase inhibitor does not work as it should. The mutated C1-inhibitor gene is passed down through

families, and people with HAE have a 50% chance of passing it onto each of their children. There are two main types of HAE. In type I HAE, there is not enough C1-inhibitor. In type II HAE, there are normal levels of C1-inhibitor, but it does not function normally. Rarer types of HAE are linked to specific gene mutations and hormone (oestrogen) related, and are out of scope of this policy. Both types of HAE can be life threatening.

As well as HAE, more rarely, patients can have acquired angioedema (AAE). AAE typically develops later in life and is often due to an autoimmune process or blood-cell cancer, rather than a genetic mutation. Like HAE, it results in reduced levels of C1-inhibitor and therefore it is included in this policy as the underlying mechanism of oedema in HAE and AAE are the same. It is important to note that, as per the NHS England treatment algorithm for acquired angioedema secondary to C1 esterase inhibitor deficiency, the underlying cause of C1-Inh deficiency in AAE is treated as this will usually resolve the AAE. Only AAE refractory or resistant to primary treatment, and where the AAE attack frequency meets the threshold in the algorithm, are within the scope of this policy.

Without normal C1-inhibitor protein in HAE or AAE, patients have uncontrolled and spontaneous swellings caused by a build-up of fluid in various parts of the body. These swellings are called ‘angioedema’ and may appear as:

- Swelling in the airway - this is particularly dangerous and can lead to death if the patient is not able to breathe properly
- Swelling in the gut - this can cause severe pain in the stomach area, feeling sick (nausea) and being sick (vomiting)
- Swellings in the deep tissues of the skin - this can cause significant disability, for example if the hands, feet or genitals are affected

When angioedema is either potentially life-threatening because it affects the head or neck **or** causes pain/disability such that the patient cannot continue their normal activities (e.g. severe abdominal pain that does not respond to analgesia), it is classified as a ‘clinically significant attack.’ Varying treatment pathways do not imply that an attack requiring hospital treatment is necessarily more significant than one which can be treated with self-administered therapies.

About current treatment

Acute attacks:

Each individual with HAE or AAE will have an individualised management plan with a strategy to manage acute attacks (life threatening attacks and clinically significant attacks) and to prevent/reduce attacks where possible.

For potentially life-threatening attacks involving the airway, the patient would require management in an emergency setting where they would be treated for acute symptoms as required. Individuals may have treatment doses of C1-inhibitor or icatibant at home which can (with appropriate training from the specialist centres) be self-administered for clinically significant attacks.

Long-term treatment (prophylaxis):

For the majority of people with HAE or AAE their attacks do not occur frequently and consequently most patients do not need medication to prevent attacks, they can instead manage them as they occur 'on demand'. However, for some patients medication needs to be taken to prevent attacks (called 'prophylactic' treatment) together with a plan to treat acute attacks. Treatments taken to prevent attacks are taken long-term, thereby reducing the need for treatment of acute attacks.

Treatment options available to prevent attacks differ for HAE and AAE. With AAE, the only commissioned treatment to prevent attacks is C1-esterase inhibitor (C1-INH) given through a vein (intravenous). For HAE, there are more options available. Currently, berotralstat is the only licenced oral medication used in HAE to prevent attacks. The National Institute for Health and Care Excellence (NICE) recommends that berotralstat is an option in patients aged 12 years and older if they have at least 2 attacks per month, and it is stopped if the number of attacks per month does not reduce by at least 50% after 3 months (NICE, 2021).

Other preventative treatments for HAE are given as injections. Garadacimab and lanadelumab are given as injections under the skin (subcutaneous injections). Garadacimab (TA1101) is recommended by NICE for use at the same attack threshold frequency, 2 attacks per month, as berotralstat. Lanadelumab (TA606) has been recommended at a higher attack threshold, 2 per week, which is the same as NHS England has historically commissioned C1-Inh prophylaxis. In common with berotralstat, garadacimab and lanadelumab are recommended by NICE for patients aged from 12 years old. However, lanadelumab has subsequently been licensed for patients from age 2 years and is commissioned for this younger group through the NHS England Commissioning Medicines for Children in Specialised Services policy (NICE, 2019; NHS England, 2017).

About C1-esterase inhibitor

A minority of people with HAE or AAE may have more frequent attacks of swelling and, for HAE, it may not be possible to control these attacks with berotralstat, garadacimab or lanadelumab. In these cases, long-term C1-esterase inhibitor (C1-INH) injections can be used instead to prevent attacks for both HAE and AAE.

Licensed products of C1-INH contain C1-INH extracted from donated plasma which is then purified to eliminate the risk of contamination with pathogens. In respect of prophylaxis, there are differences across the licenses and routes of administration although all products and formulations are established in UK practice. Both products are licensed for the management of HAE as outlined in Table 1 but none are licensed for AAE.

C1-INH:

- Cinryze:
  - Cinryze 500 IU powder and solvent for solution for injection - Summary of Product Characteristics (SmPC) - (emc) | 2808
- Berinert:
  - Berinert 500 IU Powder and solvent for solution for injection / infusion - Summary of Product Characteristics (SmPC) - (emc) | 6523

- Berinert 1500 IU Powder and solvent for solution for injection - Summary of Product Characteristics (SmPC) - (emc) | 7043
- Berinert 2000 IU Powder and solvent for solution for injection - Summary of Product Characteristics (SmPC) - (emc) | 13819
- Berinert 3000 IU Powder and solvent for solution for injection - Summary of Product Characteristics (SmPC) - (emc) | 13820

Table 1: Summary of licensed indications for C1-INH products

Product name	Treatment of acute attacks	Pre-procedure prevention	Routine prevention
Cinryze (intravenous)	Adults, adolescents and children (2 years old and above)	Adults, adolescents and children (2 years old and above)	Adults, adolescents and children (6 years and above)
Berinert (intravenous)	Adults and children	Adults and children	
Berinert (subcutaneous)			Adults and adolescents (only high dose formulations, 2000IU and 3000IU, are licensed for subcutaneous use)

Cinryze is licensed for the treatment and pre-procedure prevention of angioedema attacks from 2 years old and above, and for routine prevention from 6 years and above. It is licensed for intravenous use only.

Berinert can be given as a slow intravenous injection or as a subcutaneous injection. Only the Berinert 2000IU and 3000IU vials are licensed for subcutaneous use. Subcutaneous administration is particularly useful for patients who cannot use the intravenous route (e.g. poor access). Intravenous Berinert is licensed for the treatment and pre-procedure prevention of angioedema attacks. No age indication is given in the SmPC and dosing information is available for paediatric populations, with no weight restriction. For subcutaneous Berinert, this is only licensed for the prevention of HAE attacks in adolescent (no age specification given) and adult patients.
When possible, prescribing clinicians should follow the licensed indications for routine prevention of each C1-INH product. For example, children 6 years and above should receive Cinryze when C1-INH product is required as it is licensed for this age group. This policy recommends the off-label use of C1-INH products for routine prevention in the following situations:

- Cinryze: children aged 2-6 years (through the Commissioning Medicines for Children in Specialised Services) with HAE and all patients with AAE
- Berinert (intravenous): adults (Cinryze should be used for routine prophylaxis in children when eligible) for HAE and AAE
- Berinert (subcutaneous): Adults and adolescents with AAE

C1-INH injections may be preferable to lanadelumab as some patients cannot tolerate lanadelumab and some patients may prefer to use C1-INH to prevent attacks, if on demand C1-INH has worked for acute attacks.

Berotralstat, garadacimab and lanadelumab are not recommended for use during pregnancy. The Summary of Product Characteristics (SPC) advises that intravenous C1-INH injections, both Cinryze and Berinert, can be given to pregnant women only if clearly needed. The SPC for subcutaneous Berinert is less equivocal and does not advise against use in pregnancy. No studies of C1-INH concerning fertility have been performed and it is unknown whether C1-INH is transferred into breast milk. In clinical practice, patients who are pregnant or breastfeeding are often switched to subcutaneous C1-INH. It is usually more convenient to train patients to administer a subcutaneous than an intravenous injection, which is especially useful for patients who do not have a current or recent history of using intravenous C1-INH (e.g. if using oral or subcutaneous prophylaxis).

Epidemiology and needs assessment

A national survey across the UK estimated that approximately 1152 patients in the UK have type I or II HAE. Around 45% of patients are on long-term prophylaxis, equating to approximately 518 patients (Yong et al, 2023). Prior approval registrations suggest that approximately 110-200 patients had intravenous C1-INH prophylaxis in 2024/2025. Approximately 10-20% of these patients are expected to use subcutaneous C1-INH. Therefore, clinical need is estimated at about 25 patients for subcutaneous C1-INH prophylaxis and about 130 patients for intravenous C1-INH prophylaxis.

Factors which may play a part in determining the frequency and severity of swellings include variations in mutations of the C1-inhibitor gene, inflammatory stimuli, exposure to infections, low level trauma, variations in concentrations of sex hormones and environmental factors such as emotional stress. Attacks can also be precipitated by angiotensin-converting-enzyme inhibitors, surgery and dental work.

Implementation

Inclusion criteria

Patients 6 years[1] and older with HAE type I or II or AAE are eligible for intravenous C1-INH[2] if **at least ONE of** the following criteria is met:

1. The patient continues to experience two or more clinically significant attacks per week, despite prior prophylaxis, over a period of at least 56 days requiring treatment with C1-INH or icatibant.

OR

2. Prior prophylaxis is contraindicated (for example pregnant women, hypersensitivity to an ingredient, age or not commissioned for AAE), and the patient continues to experience two or more clinically significant attacks per week, over a period of at least 56 days requiring treatment with C1-INH or icatibant, recognising that there are

[1] Children aged 2-5 years old are able to access treatment with Cinryze through the Commissioning Medicines for Children in Specialised Services policy.. Adults are able to access intravenous C1-INH with Cinryze or Berinert (off-label).
[2] In this policy, specific brands of C1-INH are recommended for different age groups and each brand has a specific formulation. Please refer to the dosing section for further information of which brand should be used when.

currently no other prophylactic treatment options during pregnancy and that there is increased risk of rapid deterioration in condition and additional risks to women during pregnancy.

Adolescent[3] and adult patients with C1-INH are **also** eligible for subcutaneous C1-INH, as an alternative to intravenous C1-INH, if:

1. The patient is not able to tolerate the intravenous route of administration (e.g. poor technique, poor access, pregnancy-related compliance[4])

Exclusion criteria

Clinicians should refer to product-specific contraindications under Section 4.3 of the Summary of Product Characteristics (SmPC) for the C1-INH products. At the time of writing, there are two C1-INH products in scope for this policy, Cinryze and Berinert.

Starting criteria

Before starting prophylaxis with C1-INH, each case must be reviewed by a specialist immunology network of at least three consultant immunologists either at a regional network meeting or remote/electronic discussion to ensure that C1-INH prophylaxis is the most appropriate treatment option. At least two of these consultants will be from centres different to the host centre. A host centre which is exclusively staffed by non-immunologists will need to liaise with immunologists locally and from other centres.

Stopping criteria

C1-INH should be stopped if:

- After two months, treatment is ineffective, defined as a lack of reduction in attack frequency despite optimised treatment.

In these circumstances, treatment with prophylactic C1-INH should be discontinued and alternative therapy options considered (see treatment algorithm).

Dosing

There are different C1-INH products available with subtly different dosing instructions. Cinryze is the only intravenous C1-INH licensed for routine prophylaxis. Berinert (intravenous) is not licensed for routine prophylaxis and use in this indication is off-label.

[3] The age range has not been specified in the Berinert SmPC beyond 'adolescents and adults.'. Varying definitions of adolescence exist. The European Medicines Agency (EMA) considers patients aged 12-18 years as adolescent. The World Health Organisation (WHO) considers patients aged 10-19 years as adolescent.

[4] Pregnancy-related compliance refers to isolated situations in pregnant, trying to conceive or breastfeeding patients where patients are not skilled in the use of intravenous injections and compliance can be achieved more easily using the subcutaneous route.

Prescribing clinicians should refer to the relevant product SmPC when prescribing C1-INH. Table 2 provides an overview of the C1-INH products in scope of this policy by age.

Table 2: A summary of C1-INH products referenced in this policy

Product name	Age range:
Cinryze (intravenous)	6 years and above (2 years and above through the Commissioning Medicines for Children in Specialised Services policy)
Berinert (intravenous)	Adults only
Berinert (subcutaneous)	Adolescents and adults

1) Intravenous use:

Adults:

For Cinryze and Berinert, for long-term prophylaxis, 1000IU of C1-INH should be given every 3 to 4 days. This is given as an intravenous injection at a rate of 1ml per minute.

Children and adolescents (Cinryze only):

In children aged 12-17 years, 1000IU of C1-INH should be given every 3 to 4 days. This is given as an intravenous injection at a rate of 1ml per minute.

In children aged 6-11 years, 500IU of C1-INH should be given every 3 to 4 days. This is given as an intravenous injection at a rate of 1ml per minute.

In children aged 2-5 years (Cinryze as per the NHSE Commissioning Medicines for Children in Specialised Services policy), 500IU of C1-INH should be given initially every 3 to 4 days. Higher or more frequent doses should be considered if required with strict monitoring.

2) Subcutaneous use:

In both adults and adolescents[5], the recommended dose of subcutaneous C1-INH is 60IU/kg body weight every 3-4 days[6]. The lowest clinically effective dose should be used and only the higher unit vials of Berinert (2000IU and 3000IU) are licensed for subcutaneous use. The suggested site for subcutaneous injection is the abdominal area.

In the unlikely event that an individual is not able to self-administer, it may be possible to work with carers (family or health care professionals) to administer on their behalf. This would be assessed by the clinical teams on an individual basis with the aim of administering the treatment at home or as near to the patient's home as is practically possible.

[5] The age range has not been specified in the Berinert SmPC beyond 'adolescents and adults.'. Varying definitions of adolescence exist. The European Medicines Agency (EMA) considers patients aged 12-18 years as adolescent. The World Health Organisation (WHO) considers patients aged 10-19 years as adolescent.

[6] In some studies, a lower dose of 40IU/kg has been used with varying responses (Craig et al 2019, Levy et al 2020, Longhurst et al 2017)

Training of eligible patients or their infusion partner would take on average two visits to a day-care unit experienced in training patients for self-administration of medication. All specialist immunology centres will have the facilities and appropriately trained nurses to deliver this training in accordance with the Royal College of Physicians Quality in Primary Immunodeficiency Services accreditation scheme. This would need to be assessed by commissioners if the service were to be delivered by non-immunology centres.

Monitoring

Patients should record when they have an HAE or AAE attack or episode, the nature of the attack (e.g. trigger factors, severity, symptoms, duration), and how it was managed (any treatments used, any additional healthcare sought). Patients will ideally be recording this information before commencing prophylaxis so that a fully informed and shared decision can be made about starting prophylaxis and then continued throughout prophylaxis to identify any changes or benefits from treatment and identify as early as possible any loss of control[7].

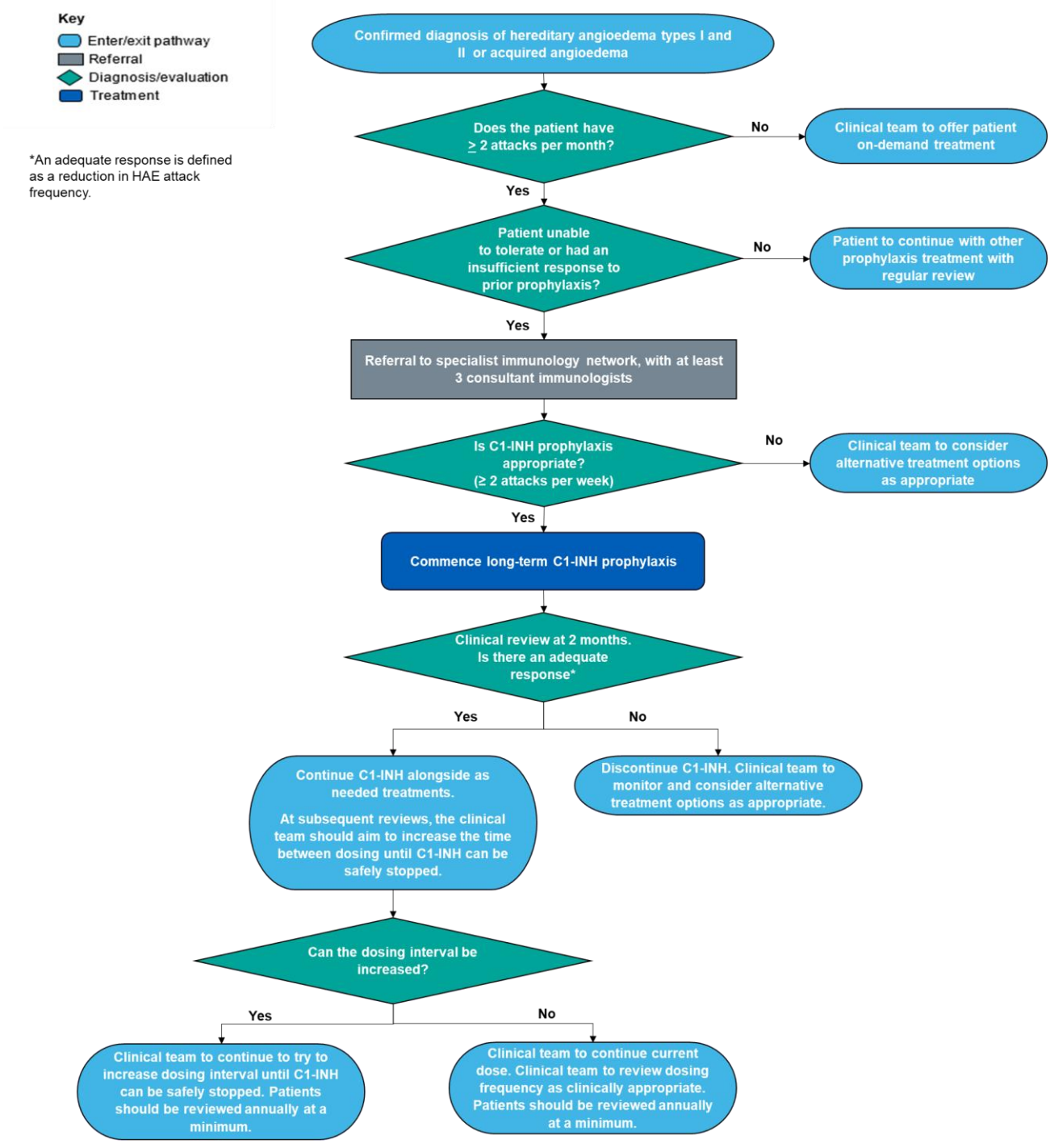
At 2 months after starting on a prophylaxis regimen, a review should be undertaken to determine whether treatment should be continued, i.e. whether C1-INH prophylaxis has been effective in reducing attack frequency.

Subsequent clinical reviews should also include reviewing the dose interval and considering whether this can be safety increased. If, at a dosing interval of one treatment per week, the symptoms remain below two clinically significant attacks per week, a trial of treatment discontinuation should be commenced. If breakthrough attacks present above this level, the time between dosing should be reduced to regain adequate symptom control.

For patients who are well controlled on prophylaxis, an annual review thereafter is recommended.

[7] Smartphone applications are available to assist patients in recording HAE attacks and sharing this information with this clinical team.

Patient pathway



Link to wider HAE patient pathway

C1-Inh prophylaxis in HAE sits alongside other licensed treatment options in the wider HAE patient pathway. NHSE has published a HAE Treatment Algorithm including a section specifically regarding 'Long-term prophylactic treatment'. Clinical teams are requested to review all available treatment options in selecting the most appropriate treatment for their patients. An updated version of NHS England's 'Algorithms for hereditary and acquired angioedema secondary to C1 esterase inhibitor deficiency' can be accessed from https://www.england.nhs.uk/commissioning/spec-services/npc-crg/blood-and-infection-group-f/specialised-immunology-and-allergy-services/

Governance arrangements

Treatment should be directed by specialist immunologists working in a specialist centre, in accordance with the NHS England Service Specification for Specialist immunology services for adults with deficient immune systems: Specialised Immunology Service Specification (all ages)

Specialist centres will be Quality in Primary Immunodeficiency Services (QPIDS) accredited or will be registered as 'working towards QPIDS accreditation'. Other associated specialists (e.g. allergists) with appropriate experience will also be required to demonstrate compliance with the relevant aspects of QPIDS accreditation.

The use of C1-INH prophylaxis in the following scenarios is off-label and Trust policy regarding unlicensed medications should apply:

- Cinryze: children aged 2-6 years (through the Commissioning Medicines for Children in Specialised Services) with HAE and all patients with AAE
- Berinert (intravenous): adults (Cinryze should be used for routine prophylaxis in children when eligible) for HAE and AAE
- Berinert (subcutaneous): adults and adolescents with AAE

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

Initiation and maintenance of C1-INH prophylaxis 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

Trusts will be expected to audit the use of these agents as outlined in the service specification. Blood parameters, symptoms and attack frequency should be regularly monitored as well. A prior approval software platform will be used to support audit and monitoring.

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	Rapid swelling of the dermis. Symptoms include swelling caused by a collection of fluid in the deep layers of the skin, which most often affects the hands, feet, eyes, lips, or genitals. In severe cases, the inside lining of the throat, bowel, urethra bladder and stomach.
Gene	A segment of DNA that contains instructions for making a specific molecule – this is usually a protein.
Prophylactic treatment	A treatment that prevents illness.
Plasma	The liquid part of blood that remains after removing blood cells (red cells, white cells and platelets). It is mostly made up of water.
Pathogen	A biological agent, such as a virus, bacteria or fungus, that can invade the body and cause illness.

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