

**Clinical
Commissioning
Policy: Plasma-
derived C1-esterase
inhibitor for
prophylactic
treatment of
hereditary
angioedema (HAE)
types I and II**

Reference: NHS England: 16045/P



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Clinical Commissioning Policy: Plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II

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Policy Statement

NHS England will commission plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II in accordance with the criteria outlined in this document. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

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

Plain Language Summary

About hereditary angioedema

Hereditary angioedema (HAE) is a very rare inherited illness. People with HAE have a problem with the protein called 'C1-inhibitor' in the body. Their C1-inhibitor protein does not work as it should. HAE can be life-threatening.

Without normal C1-inhibitor protein, 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:

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- swelling in the airway - this is particularly dangerous and can lead to death by 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.

About the current treatment

For the majority of people with HAE, attacks either do not happen often or can be controlled using:

- medicines taken by mouth to prevent attacks (called 'prophylactic' treatment)
- together with a plan to treat acute attacks.

All individuals with HAE should have an emergency plan to treat severe attacks as necessary.

About the new treatment

A minority of people with HAE may have more frequent attacks of swelling. It may not be possible to control these attacks with medicines taken by mouth. Long-term C1-inhibitor injections can be used instead to prevent attacks - this is called 'long-term prophylaxis'.

What we have decided

NHS England has carefully reviewed the evidence for long-term C1-inhibitor injections to prevent hereditary angioedema (HAE). We concluded that there is enough evidence to consider making the treatment available in selected patients with HAE.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission prophylactic C1-inhibitor in selected patients with hereditary angioedema (HAE).

Hereditary angioedema (HAE) is a rare condition arising from a genetic deficiency of C1-esterase inhibitor, also called C1-inhibitor, a regulator of inflammatory pathways. Intravenous administration of reconstituted plasma-derived C1-inhibitor (human) replaces the C1-inhibitor regulatory protein.

In normal individuals, this protein controls enzyme cascade reactions so that uncontrolled swelling of the subcutaneous and submucosal tissues do not normally occur. In HAE, the absence of a functional control protein leads to episodes of uncontrolled swelling. Swellings can be disabling, cause severe pain and can be fatal if occurring in the airways.

Most people with HAE have low concentrations of C1-inhibitor (HAE Type I); around 15% have normal or high concentrations of non-functional C1-inhibitor protein (HAE Type II).

Most patients require C1-inhibitor, or icatibant, as emergency treatment for acute clinically significant attacks and C1-inhibitor for short term (generally single dose) prophylaxis prior to known triggers which include, for example, dental work or surgery. For the majority of people with HAE, attacks are either infrequent or can be controlled adequately using oral prophylactic medications together with a plan to treat acute attacks as above.

A minority of people who experience two or more clinically significant attacks of swelling per week, for whom oral prophylaxis is not tolerated or is ineffective, may benefit from prophylactic C1-inhibitor injections on a regular basis to reduce the frequency of attacks and the need for emergency treatment.

2 Definitions

Angiodema is the 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.

Patients with hereditary angioedema (HAE) have a genetic mutation in the C1 esterase inhibitor (C1-INH) gene which means that the body does not make enough C1-inhibitor protein causing the immune system to trigger the symptoms of angioedema. 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.

Acquired angioedema (AAE) is a form of C1-inhibitor deficiency which has occurs later in life due to an autoimmune process usually triggered by a tumour.

It is included as part of HAE for the purposes of this definition as the symptoms and patient pathway are comparable.

C1-inhibitor is a blood product, extracted from pooled donated plasma, which is then purified to eliminate the risk of contamination with pathogens, especially blood-borne viruses.

A clinically significant attack is one which is i) potentially life threatening because it affects the head or neck or ii) causes pain or disability such that the patient cannot continue their normal activities. This may be due to disabling cutaneous swelling, sufficient to prevent the patient from undertaking normal activities or severe abdominal pain which will not respond to oral analgesia. 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.

Long-term prophylactic describes a medicine or course of action used to routinely prevent symptoms or disease, thereby reducing the need for treatment of acute attacks.

3 Aims and Objectives

The policy aims to confirm NHS England's commissioning policy for long-term, prophylactic C1-inhibitor use for selected people with HAE.

The objective is to ensure evidence based commissioning with a view to improving outcomes for patients with HAE.

4 Epidemiology and Needs Assessment

HAE affects around 1 in 50,000 to 100,000 people of any ethnic group and of either gender (NHS England, 2013). Although the deficiency is life-long, attacks rarely occur before two years of age and are less frequent before adolescence. Mean age at onset is between eight and twelve years.

Incidence of swellings varies from more than one per week to less than one per year. In a random sample of 103 patients with HAE, with or without long-term prophylaxis, the mean frequency of angioedema was once every 45 days (Zanichelli et al. 2011).

Death due to asphyxiation is a serious risk in people with previously undiagnosed HAE and in patients who do not receive treatment for a laryngeal attack. Estimates of the frequency of serious adverse events vary widely. A review of HAE published in the 1960s estimated that 25% of HAE patients died from asphyxiation. A later study (Bork et al., 1999) involving a retrospective survey of 58 patients in Germany over the previous 50 years, reported that 28 patients (40%) had died from asphyxiation at an average age of 39 years. The study also found that the risk of asphyxiation had no relationship to the number or frequency of previous episodes of laryngeal oedema.

A Department of Health review determined that the average attack frequency was 12 per year and that 5 patients had died in the UK from angioedema in 2008. Approximately a quarter of swellings are sufficiently severe to require rescue medication like C1-inhibitor or icatibant.

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. Across England, it is estimated that 50-100 people (adults and children) may experience two or more clinically significant attacks per week who may benefit from long-term prophylactic C1-inhibitor injections.

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of C1-esterase inhibitor for long-term prophylactic use in selected patients with HAE. Whilst the evidence is limited, it is recognised that the low number of patients who might be suitable for long-term prophylactic use of C1-esterase inhibitor means that high quality level 1 evidence is unlikely to become available to support the commissioning position.

A summary of the findings of the evidence review are set out below.

Question 1. Is prophylactic C1-esterase inhibitor clinically effective in reducing the severity and frequency of HAE attacks for patients who are not responding, or are intolerant to oral prophylaxis (androgens or fibrinolytics) as evidenced by 2 or more clinically significant attacks per week?

A review of the literature base on long-term prophylaxis with C1INH for HAE was undertaken. There was no RCT or case-control study specifically evaluating C1INH prophylaxis in patients failing oral prophylaxis with 2 or more acute attacks per week. There was one cohort study that investigated C1INH prophylaxis in patients failing or intolerant of oral prophylaxis. Several studies investigated the efficacy of C1INH use in a wider HAE population and lend data supporting the general use of long-term prophylaxis for disease control.

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In the cohort study (Levi et al., 2006) evaluating the effectiveness of C1INH for prophylaxis of angioedema in HAE and AAE patients who had failed or were intolerant to oral prophylaxis, the C1INH dosing was a self-administered 1000 U of IV plasma-derived C1-inhibitor concentrate every 5-7 days (actual mean reported was 6.8 +/- 1 days). 12 patients with HAE or acquired angioedema were included. Patients were eligible for the study if their baseline attack rate despite oral prophylaxis or without prophylaxis due to intolerance was >1 attack per 10 days. The baseline attack rate in the study population was reported as 1 attack per 7.9 (+/- 2.0) days. Of the study participants, 5 were on prophylactic treatment with danazol and tranexamic acid at baseline, 6 were intolerant of danazol, and 1 had a contraindication to danazol use.

The mean age of the subjects reported was 38 +/- 12 years. Study subjects were followed-up for a mean of 3.5 years (range 1.6 - 4.3 years). Results showed a statically significant reduction in the number of angioedema attacks after the start of prophylaxis ($p < 0.001$ for both HAE and acquired angioedema (AAE) patients, analysed separately). In the combined (HAE and AAE) prophylaxis group, the angioedema attack rate decreased from 4.0 to 0.3 attacks per month (no p-value reported). No serious adverse events were reported, and all adverse events were self-limited without the need for medical assistance. Limitations to the study include the small study size limiting the potential power of the study, the lack of reporting on methods for obtaining baseline attack rates (therefore, possibly retrospective patient self-reported which would create concern for potential recall bias), and the methods for obtaining attack rates during the treatment period through patient self-reporting (and therefore increasing the possibility for error and bias in this study).

It should be noted that many of the limitations are inherent to the disease and therefore expected: recruiting large populations for study in rare diseases is unlikely, and a lack of standard, objective criteria for evaluation of attacks lends to better acceptance of self-reported events (especially with consistency in evaluating and reporting of attacks before and after study intervention). Therefore, the results of this study are supportive of prophylactic treatment, but given the quality concerns of the study, this is considered only weak evidence. The authors were based in the Netherlands and reported no conflicts of interest.

In another study (Zuraw et al., 2012), a relatively large (given the rarity of HAE) nonrandomised open-label cohort study, 146 patients were evaluated for response to long-term nano filtered C1INH prophylaxis. Subjects were given long-term prophylaxis with C1INH every 3-7 days for up to 2.6 years. At baseline, almost a third of patients were taking prophylactic androgens. During the study, over half of those patients discontinued the androgen prophylactic therapy. A subgroup analysis of the patients who were able to discontinue androgen use entirely (23 subjects), revealed a reduction in attacks from a median rate of 3.00/month (interquartile range: 1.25-11.00) on androgens to 0.00 (interquartile range: 0.00-0.31) on prophylactic C1INH. Overall results of the entire study population demonstrated a decrease in the mean frequency of attacks from 4.7 +/- 5.2 to 0.47 +/- 0.83 per month ($p < 0.001$). The study therefore concluded that C1INH use is efficacious in long-term prophylaxis of HAE attacks at a dose of 1000 units twice per week. Notably, once a week dosing also showed a positive, though weaker, benefit. Limitations of this study include the nonrandomised and open-label study design, the pre-treatment attack rate being estimated based on the patient's reported history (potential recall bias), and the allowance for variance in administration of the prophylactic doses (protocolled as every 3-7 days). Overall, this is a well conducted prospective cohort study with results that support the policy under review.

In a 2013 systematic review, Bork et al. (2013) noted 2 prospective cohort trials, 1 retrospective survey study, and 5 case reports examining long-term prophylaxis with C1INH. Two of the case studies reported successful long-term prophylactic therapy with C1INH in patients who had failed or had side effects to oral prophylaxis previously. However, it is unclear from these reports how many attacks per week they had before C1INH use or what level of control they had been able to obtain with the previous oral prophylaxis. The retrospective survey reported on two pregnant patients, for which androgen use is contraindicated. One of the prospective cohort studies reported good control of HAE attacks with C1INH use, however it is unclear if they were on an oral prophylactic regimen prior to C1INH use or not. The second prospective cohort study of 19 patients (Bork et al., 2011) contained a subgroup of 10 people who had previously been treated with danazol. However, acute attack severity with danazol use was not reported, nor was this subgroup analysed

separately. Additionally, results were reported for the overall study population, which included patients who had crossed over from on-demand therapy only into the prophylactic group as well as patients who had begun the study in the prophylactic group. This heterogeneity makes interpretation of results difficult, but overall patients reported a decrease in the percentage of severe attacks from 93.3% to 3.8% by the end of the study with C1INH use (which was an average of 9 years). Additionally, 8 of the 14 patients in the prophylactic subgroup, reported a lower number of attacks per month in the final year of the study as compared to the time before C1INH prophylactic use.

In an open-label study (Reshef et al., 2013), the response of a 25 person cohort of HAE patients to long-term prophylaxis with C1INH over 8 weeks was evaluated. The study found that weekly administrations of 50 U/kg C1INH reduced the frequency of HAE attacks in study participants. The baseline attack rate of 0.9 attacks/week decreased to 0.4 attacks per week while on long-term prophylaxis with C1INH, with a 95% CI ranging from 0.28 to 0.56. Unfortunately, prior prophylactic drug use in this cohort of patients was not reported. The drug was also found to be safe and well tolerated. The key limitations of this study were the open-label design and the method of data collection on attack rate prior to study entry (patients' recollection), which create concern for the introduction of bias into the study.

In a 24-week cross over study (Zuraw et al., 2010), C1INH for prophylaxis, given as twice-weekly injections of 1000 units, significantly reduced the frequency of acute attacks (6.26 per 12-week period), as compared with placebo (12.73 per 12-week period). There were 3 patients on baseline androgen therapy in this study, and subjects were not required to discontinue their androgen therapy during the trial. This multi-centre, double-blind, randomised study was designed for 90% power. The primary endpoint results were significant ($p < 0.001$). Secondary endpoints showed the subjects who received the C1- inhibitor concentrate also had significant reductions in both the severity and the duration of attacks, in the need for open-label rescue therapy, and in the total number of days with swelling. There were only 3 AEs and no SAEs considered possibly related to C1INH. This was a well-designed study with low concern for bias, demonstrating the efficacy and safety of prophylactic use of C1INH over a 12 week period. Unfortunately, prior androgen or antifibrinolytics

therapy and characterisation of disease severity on oral prophylaxis was not reported.

In addition to the above studies, two studies of HAE patient subgroups were noted on pregnant and paediatric patients. A small retrospective review (Baker et al., 2013) of outcomes experienced in pregnant women with HAE using C1INH was conducted as androgen therapy is contraindicated in pregnancy. Different sources of data were used (3 studies and 1 compassionate-use program), and some patients only had acute treatment, while others had long-term prophylaxis with acute treatment as needed, and some patients began in an acute treatment only protocol but later transferred into a long-term prophylaxis protocol programme. There was no analysis done across the study patients, no statistical analysis of the results. However, given that androgens are generally contraindicated in pregnancy and concern for safety of antifibrinolytics during pregnancy, the reported safety outcomes in this study are encouraging. As well, efficacy outcomes were generally supportive of long-term prophylaxis with C1INH in pregnancy. Unfortunately, the strength of this evidence is low due to the weaknesses in study design.

In addition, in a post hoc analysis of data on paediatric patients from 4 prospective clinical trials of C1INH (Lumry et al., 2013), 2 trials were relevant to reviewing long-term prophylaxis treatment with C1INH. The placebo-controlled cross-over trial of long-term prophylaxis only contained 4 paediatric patients for inclusion in this article's analysis, while the open-label long-term prophylaxis study included 23 patients. Efficacy and safety results were supportive of long-term prophylaxis use with C1INH. In the cross-over trial, the mean number of attacks per 12 week period was 7.0 while on long-term prophylaxis versus 13.0 while on placebo. Additionally, the number of open-label rescue doses required was less in the long-term prophylaxis group, severity of attacks was unchanged, mean duration of attacks was less while on long-term prophylaxis, and mean duration of swelling was lower while on long-term prophylaxis. In the open-label extension prophylactic study, the median monthly attack rate before enrolment was 3.0 (range, 0.5-28.0) and decreased to 0.39 (range, 0-3.36) with long-term prophylaxis, with 87% reporting 1 or less attacks per month and 22% reporting no attacks during the study period.

The clinical evidence available suggests that the use of C1INH for long-term prophylaxis of acute attacks in hereditary angioedema is effective and safe. There is limited high quality data and a notable lack of comparative data. The evidence base should continue to be reviewed over time, as more data could become available.

Question 2: Is prophylactic C1-esterase inhibitor cost-effective as a prophylaxis to reduce the severity and frequency of HAE attacks for patients who are not responding (or are intolerant) to oral prophylaxis as evidenced by 2 or more clinically significant attacks per week?

The literature search revealed no studies on the cost-effectiveness of this intervention.

6 Criteria for Commissioning

Long-term, prophylactic C1-inhibitor injections should be considered by specialist immunology consultants working in specialists centres, with approval from their respective networks (see Clinical Governance in Immunology Service Specification B09/S/a). Use should be in line with the Marketing Authorisation. Use outside of this will not be funded.

Plasma derived C1-esterase inhibitor will be commissioned for:

- a) Individuals who fail, or are intolerant of oral prophylaxis and who experience two or more clinically significant attacks per week, despite oral prophylaxis (see Definitions), over a period of at least 56 days requiring treatment with c1 esterase inhibitor or icatibant.
- b) Individuals in whom oral prophylaxis is contraindicated for example pregnant women, recognising that there are 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.

Each patient considered for treatment with long-term prophylactic C1-inhibitor injections will have their case assessed by the specialist immunology network to ensure that it is the most appropriate treatment option. Eligibility for treatment will be based on discussion between at least three consultant immunologists either at a regional network meeting or discussion by email or telephone. 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.

After the first six months of treatment, the time between dosing should be gradually increased. If, at a dosing interval of one treatment per week, the symptoms remain below two or more 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.

If treatment is ineffective after two months (defined as a lack of reduction in attack frequency despite optimised treatment) then treatment with prophylactic C1-inhibitor should be discontinued and alternative therapy options considered.

7 Patient Pathway

Individuals may be diagnosed as suffering from HAE on the basis of a family history, or as a result of referral to a specialist centre with symptoms (typically swellings /abdominal pain). Diagnosis is confirmed with blood tests. Individuals known to have HAE will be managed in specialist centres, with the frequency at which they are reviewed dependent on a range of factors including symptom control and distance to travel.

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.

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Each individual with HAE will have an individualised management plan with a strategy to manage life threatening attacks, to manage other 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.

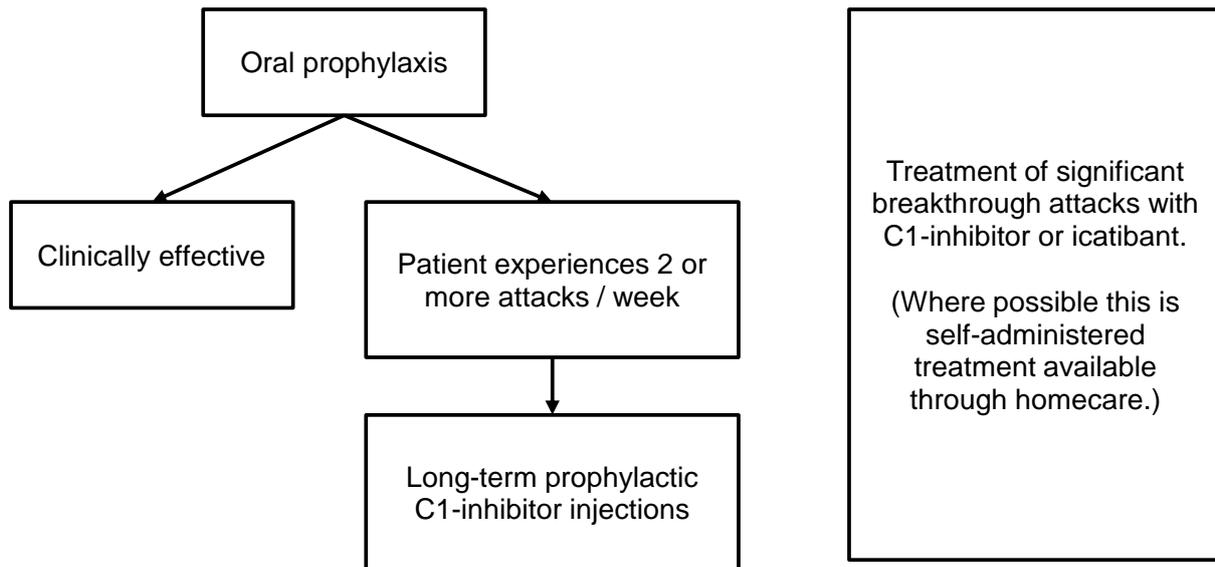
Oral prophylaxis should be the first line of treatment for individuals at risk of attack.

However, for people with HAE who continue to experience two or more clinically significant attacks per week, or who are contraindicated for oral prophylaxis (e.g. pregnant women), and who are under the care of a specialist team, long-term prophylactic C1-inhibitor injections can be considered as an option following discussion within their immunology network multi-disciplinary team.

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 (see Section 10: Proposed Governance Arrangements).

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.

An illustrative patient pathway is included below.



8 Governance Arrangements

Treatment should be directed by specialist immunologists working in a specialist centre, in accordance with the NHS England service specification for commissioned immunology services F06. Specialised and Immunology and Allergy Services. (See Section 8: Criteria for Commissioning for further network detail).

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.

9 Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England specialised commissioning team.

10 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.

11 Documents which have informed this Policy

Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema, April 2013, NHSCB/B09/P/b

European Medicines Agency EPAR Summary for the public, Cinryze (2011)
Specialised Immunology (All Ages) Service Specifications B09/S/a

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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