Integrated Impact Assessment Report for Clinical Commissioning Policies

Policy Reference Number	F06X04		
Policy Title	Plasma-derived C1-esterase inhibitor for Prophylactic treatment of hereditary angioedema (HAE) types I and II		
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Section K - Activity Impact			
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)	
K1 Current Patient Population & Demography / Growth	K 1.1 What is the prevalence of the disease/condition?	K1.1 This policy is to **routinely commission** long-term prophylactic use of C1 esterase inhibitors in certain patients with hereditary angioedema (HAE).[i] In England, the prevalence of HAE is estimated to be around 1:100,000 to 1:50,000,[ii] or around 550 to 1,100 individuals in 2014/15.[iii]	
	K1.2 What is the number of patients	K1.2 The policy is intended for a minority of HAE patients that	

	currently eligible for the treatment under the proposed policy?	experience clinically significant acute attacks of swelling at least twice a week,[iv] and for whom oral prophylaxis is ineffective or not tolerated. The number of patients estimated to fall within this group in 2014/15 is c. 50 to 100, or around 5% to 20% of the prevalent population.[v]
	K1.3 What age group is the treatment indicated for?	K1.3 This treatment is indicated for all ages.[vi]
	K1.4 Describe the age distribution of the patient population taking up treatment?	K1.4 HAE is a hereditary condition, and affects all ages. The condition may have a younger patient population than the general population because of earlier mortality.[vii]
	K1.5 What is the current activity associated with currently routinely commissioned care for this group?	K1.5 The current activity for the group eligible for prophylactic C1 esterase inhibitor as set out in K1.2 is estimated in the region of 5,200 to 15,600 **clinically significant attacks per year for 2014/15**.[viii] These attacks may be treated in a hospital setting or through use of medication at home.[ix] In relation to attacks **treated in a hospital setting**, a Secondary Uses Services (SUS) data extract identified around 300 non-elective admissions in 2014/15 that could relate to the target population.[x] It is unclear how many of these admissions relate to the target population described in K1.2 (i.e. those with two or more acute attacks per week), which is a subset of those with HAE. In addition, the number of A&E attendances for the group was not identifiable in the data. Attacks may also be **treated at home with medications** such as C1 esterase inhibitor and icatibant.[xi]

		In view of the relatively limited number of admissions associated with the condition as compared to the estimated yearly attacks for the relevant population, it is inferred that the **majority of clinically relevant attacks would be treated without a hospital admission**. This is supported by the estimate that 90% of patients in the eligible population defined in K1.2 would be able to self-administer medication, and hence would not be reliant on the hospital setting for managing many of their cases.[xii]
	K1.6 What is the projected growth of the disease/condition prevalence (prior to applying the new policy) in 2, 5, and 10 years?	K1.6 Specific factors described in K2.2 that could affect the prevalence rate have not been quantified. The **overall prevalent population** is still expected to grow because of demographic factors. In line with this, future prevalence of HAE is estimated to be in the region of: [xiii] • 550 to 1,100 in 2016/17 • 555 to 1,110 in 2017/18 • 570 to 1,130 in 2020/21 • 600 to 1,200 in 2025/26 Of the above, the **target population** (as described in K1.2) would be in the region of:[xiv] • ~50 to 100 in 2016/17 • ~50 to 100 in 2017/18 • ~50 to 105 in 2020/21 • ~55 to 110 in 2025/26
	K1.7 What is the associated projected growth in activity (prior to applying the new policy) in 2,5 and 10 years	K1.7 Each patient with HAE has an individualised management plan with a strategy for managing and reducing attacks.[xv] Activity for patients with HAE could therefore remain relatively constant once a management plan has been established, and so would grow in line

		with population growth. For the eligible population, the number of acute attacks per year is estimated to be in the range of:[xvi] • 5,300 to 15,800 (relating to ~50 to 100 patients) in 2016/17 • 5,300 to 15,900 (relating to ~50 to 100 patients) in 2017/18 • 5,400 to 16,300 (relating to ~50 to 105 patients) in 2020/21 • 5,600 to 16,800 (relating to ~55 to 110 patients) in 2025/26 As set out in K1.5, it is not possible to determine how many of these attacks required treatment through a hospital admission. However, it is estimated that most of these attacks would translate into home usage of C1 inhibitors and icatibant.
	K1.8 How is the population currently distributed geographically?	K1.8 Across England, no evidence of differences in geographical distribution was identified. However, it was noted by the policy working group that HAE is clustered in families.
K2 Future Patient Population & Demography	K2.1 Does the new policy: move to a non-routine commissioning position / substitute a currently routinely commissioned treatment / expand or restrict an existing treatment threshold / add an additional line / stage of treatment / other?	K2.1 Currently C1 esterase inhibitors are approved to treat acute attacks of swelling in HAE. This policy would extend to cover the use of the medication for prophylaxis. There is currently one C1 esterase inhibitor licenced for prophylaxis.[xvii]
	K2.2 Please describe any factors likely to affect growth in the patient population for this intervention (e.g. increased disease prevalence, increased survival)	K2.2 As a hereditary condition, fertility rates for the current cohort of patients could affect growth. Improvements in management of the condition could also affect the overall prevalence, as patients live longer. It was not, however, possible to quantify the impact of these factors on the prevalence rate.

	K 2.3 Are there likely to be changes in geography/demography of the patient population and would this impact on activity/outcomes? If yes, provide details	K2.3 None identified.
	K2.4 What is the resulting expected net increase or decrease in the number of patients who will access the treatment per year in year 2, 5 and 10?	K2.4 Under the policy there would be a **net increase in the number of patients accessing the prophylactic treatment (and associated number of patients experiencing a reduction in acute attacks), compared to the 'do nothing' position.** As the policy is to commission for the eligible population, the entire target population set out in K1.2 would be expected to access the treatment. Overall, as compared to the 'do nothing' case where the policy is not implemented and the current activity is rolled forward as a steady state, the number of patients accessing the treatment each year would be the target population (described in K1.6) adjusted for 75% of full year effect in 2016/17. This is estimated to be in the range of: [xviii] • ~40 to 75 more patients than the 'do nothing' in 2016/17 • ~50 to 100 more patients than the 'do nothing' in 2017/18 • ~50 to 105 more patients than the 'do nothing' in 2020/21 • ~55 to 110 more patients than the 'do nothing' in 2020/21 As set out above, once the treatment becomes available and is prescribed to existing patients, the number of patients on the treatment is estimated to stay relatively constant, growing with demographic factors set out in K1.6.
K3 Activity	K3.1 What is the current annual activity for the target population covered under the new policy? Please provide details in	K3.1 The current activity is set out in K1.5.

	accompanying excel sheet	
	K3.2 What will be the new activity should the new / revised policy be implemented in the target population? Please provide details in accompanying excel sheet	K3.2 It is estimated that there would be between c. 5,300 and 10,600 **doses of prophylactic C1 inhibitor needed** in the first year of 'full year effect' (2017/18) to treat the target population.[xix] For around 90% of patients, prophylaxis would be **self-administered** at home.[xx] However, for a minority of patients, treatment could be administered with family support or via alternative arrangements. Based on the evidence review, prophylactic use of C1 esterase inhibitor could **reduce the number of acute attacks requiring acute treatment** by around 80%.[xxi] On this basis, the estimated clinically relevant acute attacks for the eligible population would be between c. 1,050 and c. 3,150 under the policy.[xxii]
	K3.3 What will be the comparative activity for the 'Next Best Alternative' or 'Do Nothing' comparator if policy is not adopted? Please details in accompanying excel sheet	K3.3 If the policy were not implemented, activity figures would be as set out in K1.7.
K4 Existing Patient Pathway	K4.1 If there is a relevant currently routinely commissioned treatment, what is the current patient pathway? Describe or include a figure to outline associated activity	K4.1 Patients currently have a number of options depending on the severity and frequency of the swelling attacks that they are prone to. Some may achieve adequate control with oral prophylaxis, others may need to additionally treat acute attacks with C1-inhibitor injections. All patients may need short-term prophylactic interventions before known triggers such as surgery or dental work..

	K4.2. What are the current treatment access criteria?	K4.2 Existing approved treatments are provided based on severity of the disorder and clinical and cost-effectiveness as determined by a specialist. Long-term prophylactic C1-inhibitor injections would not be available unless the patient went through the IFR route for exceptional cases.
	K4.3 What are the current treatment stopping points?	K4.3 Stopping points include lack of tolerance or lack of efficacy in preventing frequency and severity of attacks.
K5 Comparator (next best alternative treatment) Patient Pathway	K5.1 If there is a 'next best' alternative routinely commissioned treatment what is the current patient pathway? Describe or include a figure to outline associated activity.	K5.1 The patient pathway outlined in K4.1 includes the current alternatives including oral prophylaxis with treatment of acute attacks as required. For some patients, this will not achieve adequate control and they may require emergency treatment or suffer negative impacts on their QoL.
	K5.2 Where there are different stopping points on the pathway please indicate how many patients out of the number starting the pathway would be expected to finish at each point (e.g. expected number dropping out due to side effects of drug, or number who don't continue to treatment after having test to determine likely success). If possible please indicate likely outcome for patient at each stopping point.	K5.2 Not applicable.
K6 New Patient Pathway	K6.1 Describe or include a figure to outline associated activity with the patient pathway for the proposed new	K6.1 The proposed pathway remains as current with the addition of long-term C1-inhibitor injections for those patients who cannot achieve adequate control (defined as two or more clinically significant

	policy	attacks per week). There may be some reduction in the need to treat acute attacks, as set out in K2.4 and K3.2
	K6.2 Where there are different stopping points on the pathway please indicate how many patients out of the number starting the pathway would be expected to finish at each point (e.g. expected number dropping out due to side effects of drug, or number who don't continue to treatment after having test to determine likely success). If possible please indicate likely outcome for patient at each stopping point.	K6.2 Following six months of treatment, the dosing interval should be gradually increased. If symptoms have decreased to fewer than 2.0 clinically significant attacks per week once treatment discontinued, treatment should be discontinued. If breakthrough attacks present, the dosing interval 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.
K7 Treatment Setting	K7.1 How is this treatment delivered to the patient? o Acute Trust: Inpatient/Daycase/ Outpatient o Mental Health Provider: Inpatient /Outpatient o Community setting o Homecare delivery	K7.1 The treatment would be delivered through homecare. The treatment would be managed under the existing structure of specialist centres for HAE. There might be one or two additional day case episodes for training as patients would already be trained to self-administer for acute attacks.[xxiii]
	K7.2 Is there likely to be a change in delivery setting or capacity requirements, if so what? *e.g. service capacity*	K7.2 No

K8 Coding	K8.1 In which datasets (e.g. SUS/central data collections etc.) will activity related to the new patient pathway be recorded?	K8.1 The use of prophylactic C1 esterase inhibitor could be recorded through a prior approval software platform.[xxiv]
	K8.2 How will this activity related to the new patient pathway be identified?(e.g. ICD10 codes/procedure codes)	K8.2 This will be identified using a prior approval software platform.
K9 Monitoring	K9.1 Do any new or revised requirements need to be included in the NHS Standard Contract Information Schedule?	K9.1 No
	K9.2 If this treatment is a drug, what pharmacy monitoring is required?	K9.2-K9.4 Clinicians would be required to record both short-term and long-term outcomes of patients with HAE who receive long-term prophylactic C1-inhibitor injections. Trusts will be expected to audit the use of these agents as outlined in the service specification.
	K9.3 What analytical information /monitoring/ reporting is required?	
	K9.4 What contract monitoring is required by supplier managers? What changes need to be in place?	

	K9.5 Is there inked information required to complete quality dashboards and if so is it being incorporated into routine performance monitoring?	K9.5-9.6 No
	K9.6 Are there any directly applicable NICE quality standards that need to be monitored in association with the new policy?	
	K9.7 Do you anticipate using Blueteq or other equivalent system to guide access to treatment? If so, please outline. *See also linked question in M1 below*	K9.7 A prior approval software platform will be used to support audit and monitoring.
Section L - Service Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
L1 Service Organisation	L1.1 How is this service currently organised? (i.e. tertiary centres, networked provision)	L1.1 Long-term prophylactic C1-inhibitor injections may currently be provided by specialist clinicians via IFR.[xxv] There was one application via IFR for prophylactic C1-inhibitor use in 2015/16 (part year to September 2015).[xxvi]
	L1.2 How will the proposed policy change the way the commissioned service is organised?	L1.2 The use of long-term prophylactic C1-inhibitor will only be initiated by consultant immunologists in specialist centres which have a contract for the provision of HAE and in spoke clinics undertaken by those clinicians. 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.
L2 Geography & Access	L2.1 Where do current referrals come from?	L2.1 Initial referrals may have originated from a variety of clinicians. Most of these referrals would be via GPs to secondary care and then onwards to Specialist Immunology or Allergy Centres.
	L2.2 Will the new policy change / restrict / expand the sources of referral?	L2.2 No change anticipated.
	L2.3 Is the new policy likely to improve equity of access	L2.3-2.4 New policy likely to improve equity and equality of access / outcomes due to routinely commission position.
	L2.4 Is the new policy likely to improve equality of access / outcomes?	
L3 Implementation	L3.1 Is there a lead in time required prior to implementation and if so when could implementation be achieved if the policy is agreed?	L3.1 No lead time anticipated.
	L3.2 Is there a change in provider physical infrastructure required?	L3.2-L3.6 No change in current service delivery model anticipated.

	L3.3 Is there a change in provider staffing required?	
	L3.4 Are there new clinical dependency / adjacency requirements that would need to be in place?	
	L3.5 Are there changes in the support services that need to be in place?	
	L3.6 Is there a change in provider / inter-provider governance required? (e.g. ODN arrangements / prime contractor)	
	L3.7 Is there likely to be either an increase or decrease in the number of commissioned providers?	L3.7 No change anticipated.
	L3.8 How will the revised provision be secured by NHS England as the responsible commissioner? (e.g. publication and notification of new policy, competitive selection process to secure revised provider configuration)	L3.8 Publication and notification of new policy.

L4 Collaborative Commissioning	L4.1 Is this service currently subject to or planned for collaborative commissioning arrangements? (e.g. future CCG lead, devolved commissioning arrangements)?	L4.1 No
Section M - Finance Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
M1 Tariff	M1.1 Is this treatment paid under a national prices*, and if so which?	M1.1 No (see M1.2).
	M1.2 Is this treatment excluded from national prices	M1.2 C1 esterase inhibitors are excluded from national prices as a high cost drug.
	M1.3 Is this covered under a local price arrangements (if so state range), and if so are you confident that the costs are not also attributable to other clinical services?	M1.3 This drug is excluded from national prices and would be subject to local negotiation. Based on the Dictionary of Medicines, the price for the only C1 esterase inhibitor currently licenced for prophylactic use is £668 per vial 500unit/10m (exclusive of VAT).[xxvii] Please see M2.1 for information on the estimated yearly cost per patient.
	M1.4 If a new price has been proposed how has this been derived / tested? How will we ensure that associated activity is not additionally / double charged through existing routes	M1.4 Not applicable.
	M1.5 is VAT payable (Y/N) and if so has it been included in the costings?	M1.5 Products for therapeutic purposes derived from human blood

		are exempt from VAT.[xxviii]
	M1.6 Do you envisage a prior approval / funding authorisation being required to support implementation of the new policy?	M1.6 No funding approval is envisaged in order to implement the policy.
M2 Average Cost per Patient	M2.1 What is the revenue cost per patient in year 1?	M2.1 Assuming a dose of two vials for prophylaxis,[xxix] at a cost of £668 per vial (500-unit)[xxx] and a usage of 2 doses per week for prophylaxis,[xxxi] the **annual prophylactic cost of the drug is estimated to be around c. £139,000** (variance £69,500 and £208,000[xxxii]) per person at current prices. In addition to these costs, there is an expected saving due to reductions in acute attacks requiring additional treatment. If these attacks are treated at home with acute administration of treatments such as icatibant or C1 inhibitor,[xxxiii] **the cost saving for treating acute attacks is estimated in the region of c. £110,000 to £190,000**. The costs of treating remaining 'break through' acute attacks are estimated at between c. £30,000 and £50,000 per year.[xxxiv] Homecare is estimated at an additional £300 to £600 per year based on delivery costs of between £50 and £100 per delivery and six deliveries per year.[xxxv] A high-level estimate of £200 - £900 for initial training at the hospital site might be required for patients using self-administration.[xxxvi]

	M2.2 What is the revenue cost per patient in future years (including follow up)?	M2.2 The costs and savings of treatment, as well as the cost of the drug and homecare would be the same in year two as in the first year (see M2.1). The initial training costs would not be incurred in future years. No additional follow up costs are anticipated as patients are currently managed by specialist centres.[xxxvii] The cost of the drug could change in future if further competition is introduced. In particular the patent is anticipated to expire in 2021, and there is no evidence of a supplementary protection certificate to extend patent protection.[xxxviii]
M3 Overall Cost Impact of this Policy to NHS England	M3.1 Indicate whether this is cost saving, neutral, or cost pressure to NHS England	M3.1 The policy could be cost pressure or cost saving. The net cost impact of implementing this policy is estimated at £50k cost saving (variance: £1.4m cost saving to £1.7m cost pressure) in 2016/17 and £60k cost saving (variance: £1.8m cost saving to £2.3m cost pressure) in 2017/18.[xxxix] This includes an increase in costs for prophylactic use, as well as an estimated decrease in the treatment of acute attacks by 80%.[xl] The factors used to estimate this range are set out in M6.3.
	M3.2 Where this has not been identified, set out the reasons why this cannot be measured	M3.2 The policy could be cost saving or cost pressure depending on the average acute attacks experienced by the population taking prophylaxis. Data from Zuraw et. al. (2010) suggest a decrease in the use of acute C1 esterase by 80% following prophylaxis for those in the target population.[xli] If the average number of weekly clinically relevant attacks experienced before prophylaxis is 2.3 to 2.4, the policy is broadly break-even at an 80% reduction in the need to treat

		acute attacks. If the target population experiences a higher average number of attacks pre-treatment, the policy would be cost saving under current assumptions (while a lower number of pre-treatment average attacks in the population as a whole would lead to cost pressure).
M4 Overall cost impact of this policy to the NHS as a whole	M4.1 Indicate whether this is cost saving, neutral, or cost saving for other parts of the NHS (e.g. providers, CCGs)	M4.1 If prophylaxis prevents emergency acute activity, there could be cost savings for CCGs. However, there has not been sufficient evidence to quantify avoided admissions and A&E attendances.[xlii] In addition, there could potentially be cost savings for providers if the length and severity of acute activity is reduced, but the extent of these reductions could not be estimated.[xliii]
	M4.2 Indicate whether this is cost saving, neutral, or cost pressure to the NHS as a whole	M4.2 Cost saving or cost pressure as described in M3.1.
	M4.3 Where this has not been identified, set out the reasons why this cannot be measured	M4.3 Please see M3.2.
	M4.4 Are there likely to be any costs or savings for non NHS commissioners / public sector funders?	M4.4 No cost savings for other funders were identified.
M5 Funding	M5.1 Where a cost pressure is indicated, state known source of funds for	M5.1 To be determined at the CPAG.

	investment, where identified *e.g. decommissioning less clinically or cost-effective services*	
M6 Financial Risks Associated with Implementing this Policy	M6.1 What are the material financial risks to implementing this policy?	M6.1 Risks associated with the policy include the risk that the number of individuals eligible for use could be higher, and that the number of 'break through' attacks could be higher than envisaged under tightly managed use of the drug, or that the target population as a whole experiences under 2.4 clinically relevant attacks per week on average prior to receiving prophylaxis. Break through attacks could include attacks that can be treated at home, as well as attacks that lead to hospital admission. Home treatment has explicitly been factored into scenarios for estimating the cost of this policy.[xliv] In addition, the number of vials of C1 esterase inhibitor used could potentially be higher at up to 4 vials, which would increase the baseline cost for the population for acute attacks. [xlv]
	M6.2 Can these be mitigated, if so how?	M6.2 As set out in the policy proposition, use of prophylactic C1 esterase inhibitor would be monitored for each patient within the existing framework for HAE management; if prophylactic treatment was not effective in reducing the number of acute attacks, the use of prophylaxis or the dosage would be reviewed.[xlvi] Established stopping points within this framework could also mitigate the risk of double payment for high levels of break through attacks.
	M6.3 What scenarios (differential assumptions) have been explicitly tested	M6.3 In the 'low' scenario, the number of patients that use prophylaxis is estimated at the low end (50 patients in 2014/15), and the dosage

	to generate best case, worst case and most likely total cost scenarios?	and frequency of use for prophylactic treatment is estimated at twice weekly and two vials per dose. The initial frequency of acute attacks is estimated at 3 per week. [xlvii] The 'high' scenario uses the higher patient estimate of c. 100 (2014/15), with treatment twice a week, 2 vials per dose, and 2 acute attacks per week initially. A 'mid' scenario uses a patient estimate of 75, with dosage twice weekly and 2 vials per dose. The initial frequency of acute attacks is estimated at 2.4[xlviii] per week. Throughout all the scenarios, prophylactic treatment is assumed to reduce the number of acute attacks by 80%.[xlix] An average number of 6 homecare deliveries per year at an average cost of £75 per delivery is assumed.[l] Under this scenario, icatibant use in the do nothing scenario is estimated at c. 1/3 of treatment of acute attacks, compared to c 2/3 for C1 inhibitors.[li] Training costs and costs for patients not able to self-administer are not considered in the calculations as they compose only a small fraction of total costs (see M2.1).
M7 Value for Money	M7.1 What evidence is available that the treatment is cost effective? *e.g. NICE appraisal, clinical trials or peer reviewed literature* M7.2 What issues or risks are associated with this assessment? *e.g. quality or availability of evidence*	M7.1 No studies on the cost-effectiveness of this intervention were identified. M7.2 Not applicable as no studies on cost-effectiveness were identified.

M8 Cost Profile	M8.1 Are there non-recurrent capital or revenue costs associated with this policy? *e.g. Transitional costs, periodical costs*	M8.1 No costs for HAE relate to non-recurrent capital expenditure. There could be non-recurrent expenditure in the first year of a patient's treatment in relation to training, but these costs are estimated to be in the range of one to two training sessions only[lii] In addition, there may be patients that trial prophylaxis for two months under the policy but do not experience a reduction in attacks. There will be a one-off cost pressure (c. £23k per patient for two months of prophylaxis) associated with these patients as they receive prophylaxis without reducing the use of medications for acute attacks.
	M8.2 If so, confirm the source of funds to meet these costs	M8.2 Not applicable.

[i] Please see the policy proposition for further detail.

[ii] NHS Commissioning Board (2013). Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema. NHSCB/B09/P/b https://www.england.nhs.uk/wp-content/uploads/2013/04/b09-p-b.pdf. As discussed in with the policy working group.

[iii] The prevalence estimate uses the stated prevalence rate and multiplies it by the Office for National Statistics (ONS) population estimate for England in 2014/15.

[iv] Please see the policy proposition for further detail.

[v] Based on discussions with the policy working group

[vi] The policy does not specify any specific age. However, HAE does not often manifest until adolescence.

[vii] Studies on deaths from asphyxia may not be applicable to the current population, as some of these studies may not account for current management, or may relate to the undiagnosed population (Bork et al 1999 (as cited in the policy proposition) in Germany cited that 40% of patients had died from the condition at an average age of 39; Bork et al (2012) notes that life expectancy is 31 years lower for undiagnosed HAE patients than for the population without HAE [Source: Bork et al (2012). "Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency". *Journal of Allergy and Clinical Immunology*. 130(3).692-7. [Online] http://www.ncbi.nlm.nih.gov/pubmed/22841766 [Accessed 12/11/15]]. While there may be inference of a shorter life expectancy due to asphyxia from laryngeal swelling events, improvements in treatment may reduce the significance of this. Zanichelli, et. al. (2015) "A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy" *Orphanet Journal of Rare Diseases*, 10 (11). [Online]. http://www.ojrd.com/content/10/1/11 [Accessed 17/11/15].

[viii] 2014/15 Estimate. This estimate is based on the population experiencing an average of between 2 and ~3 attacks per week, with a population of between 50 and 100 patients as noted in K1.2 and 52 weeks per year.

[ix] This includes the acute use of C1 esterase inhibitors and icatibant.

[x] This relates to non-elective activity for patients with the diagnosis code D841 "defects in the complement system" coded within the first ICD-10 position.

[xi] Based discussions with the policy working group and analysis of the Pharmex database (for the period October 2014 to June 2015). Assuming there are 2 and 3 vials per dose of Cinryze and Berinert respectively (the two C1 inhibitors used to treat acute attacks) and c. 1.1 vials per dose for icatibant (accounting for a 10% uplift for a second dose of icatibant) [Source: NHS England (2013). Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema (B09/P/b) and discussions with the policy working group], this translates to about 2/3 of attacks treated with Cinryze and Berinert and 1/3 treated with icatibant. As Cinryze and Berinert cannot be identified separately, it is assumed that activity is split equally between the two.

[xii] Based on discussions with the policy working group. Please see the policy proposition for further information.

[xiii] The estimated range is based on a prevalence of between 1:50,000 and 1:100,000 and the ONS projected population estimates for 2014/15 to 2025/26. The method used is the same as for K1.1. Figures rounded.

[xiv] These figures are based on growth in the eligible population set out in K1.2, which is based on annual ONS population projections for 2014/15 to 2024/25. Figures rounded.

[xv] As noted in the policy proposition, and as per discussions with the policy working group.

[xvi] The range is based on an estimated 2 to 3 attacks per patient per week, with between 50 and 100 patients in the eligible population in 2014/15 and 52 weeks per year. It assumes newly diagnosed patients have a similar frequency of attacks to the existing population. Growth rates based on ONS population projections are applied to the population to estimate growth in activity from 2014/15. The low estimate is based on 50 patients x 2 attack per week; the high estimate is based on 100 patients x 3 attacks per week (figures rounded).

[xvii] Cinryze. Confirmed in discussions with the policy working group.

[xviii] Based on the assumption that 75% of the effect of the policy will be observed in 2016/17 and 100% effect will be observed in 2017/18.

[xix] This is based on a target population of 50 - 100 in 2014/15 and 2 doses of prophylactic treatment per week as per discussions with the policy working group. The low end of the range is based on 50 2014/15 patients x 2 doses per week x ONS growth rates (see K1.6). The high end is based on 100 2014/15 patients x 2 doses per week x ONS growth rates (see K1.6). Figures rounded.

[xx] Based on discussions with the policy working group.

[xxi] Based on the study: Zuraw BL, Busse PJ, White M, et al. (2010) Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med*. 363(6):513–522. This evidence was classed as Level 1+ evidence as defined as "High-quality meta-analyses, high-quality systematic reviews of clinical trials with very little risk of bias." (please see the Evidence Review for this policy for further information). The study reports a reduction in *acute attacks* from an average of 12.73 over a 12 week period in the placebo group to 6.23 in patients receiving prophylactic treatment with C1 esterase inhibitors. However, treatment of breakthrough attacks is the more relevant measure for estimating a reduction in medical activity as many attacks may not require treatment. In consideration of this, only the breakthrough attacks that required C1 inhibitor and that occurred in the first 80 days of the study have been considered [based on figure 3 in Zuraw et al. (2010)], leading to a reduction in the average number of acute attacks from 11.17 in the placebo group to 2.33 in the treatment group. Based on discussions with the policy working group.

[xxii] This is calculated based on c. 20% of the activity noted in K1.7.

[xxiii] Based on discussions with the policy working group.

[xxiv] Please see the policy proposition for further detail.

[xxv] There was one application noted for prophylactic C1 esterase inhibitor in the last 15 months based on the IFR database.

[xxvi] Based on IFR data from the central database.

[xxvii] Based on the cost for Cinryze 500unit powder and solvent for solution for injection vials (ViroPharma Ltd) 2 vial. NHS Indicative Price. No date listed. Please refer to: http://dmd.medicines.org.uk/ . [Accessed: 03 November 2015]

[xxviii] Based on correspondence with NHS England Pharmacists and HM Revenue & Customs (2014). Section 5.1, VAT Notice 701/31: health institutions. [Online] Available from https://www.gov.uk/government/publications/vat-notice-70131-health-institutions/vat-notice-70131-health-institutions [Accessed: 12/01/2016].

[xxix] Please refer to Annex III: Labelling and Package Leaflet. http://www.cinryze.co.uk/Cinryze_PIL.pdf [Accessed: 03 November 2015].

[xxx] Please see M1.3

[xxxi] Based on a recommended dosage of twice weekly, based on the open label trial (Zuraw, B. L. and I Kalfus, (2012).” Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema”. *The American Journal of Medicine*, 125(9) 1555-7162. A clinician estimate is that this would not reduce over time despite the trial noting that some patients are controlled on less than two doses per week (based on clinician discussions).

[xxxii] Based on 1 to 3 doses of prophylactic treatment per week.

[xxxiii] Please see K1.5, K1.7 and K2.4 for further information.

[xxxiv] Based on discussions with the policy working group, the main drugs used to treat acute attacks are *Berinert*, *Cinryze* and icatibant. The cost per dose is in the region of £1,500 depending on the drug used and vials used per dose (see endnote xi). This range estimates a ‘high’ based on frequent pre-treatment attacks (up to 3 attacks per week) and a ‘low’ based on a frequency in the number of attacks of 2 per week for the eligible population. The costing here is based on acute treatment at home, as the relative reliance on hospital admissions is uncertain.

[xxxv] If homecare is used. Frequency of delivery is based on correspondence with the policy working group. The costs of delivery are based on discussions and correspondence with NHS England.

[xxxvi] The policy working group note of perhaps one or two trainings at the hospital site per patient. If the training is conducted in an outpatient setting, it could be in the range of £200 per visit (based on the outpatient first attendance average tariff 2014/15), or around £450 per visit for a day case (based on analysis of SUS data from 2011/12 to H1 2015/16 for day case visits for those with the ICD-10 code D481 in the first three positions, as set out in relation to K1.5).

[xxxvii] If anything, there may be a reduction in the need to access the acute setting if the disease is better managed. Based on discussions with the policy working group.

[xxxviii] Another C1 esterase inhibitor (Berinert) for acute treatment is set to expire in 2021 and the prophylactic version is estimated to have a similar expiry date, as per discussions with pharmacists in NHS England, UKMi.

[xxxix] See question M6.3 for further details on the estimated range.

[xl] Based on the study: Zuraw BL, Busse PJ, White M, et al. (2010) Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *New England Journal of Medicine*. 363(6):513–522.

[xli] Note that four patients were excluded from this calculation as they did not experience a reduction in attacks after the first two months (and therefore would be stopped on the treatment based on the proposed policy criteria (2 patients)), or they did not have 160 days of completed study time (2 patients). Including the patients that ended early does not alter the results. Including the patients that would be stopped under the policy criteria results in a reduction of 70%.

[xlii] Based on discussions with clinicians, patients that would be suitable for treatment would be those who could self-administer (please see K1.5 to K2.4). A patient's management plan would be to seek acute care in extreme attacks (laryngeal swelling) as per discussions with the policy working group. To the extent severe attacks are reduced, there would be a decrease in A&E attendances and acute inpatient admissions, however it has not been possible to quantify this.

[xliii] Zuraw et al. (2010) noted changes to severity and length, but these reductions were not quantified.

[xliv] Please see the analysis and endnotes in relation to K1.5 and K2.4.

[xlv] Based on NHS England (2013). Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema. [NHSCB/B09/P/b]

[xlvi] Based on discussions with the policy working group. Under a successfully managed patient, there might still be break though cases requiring treatment. The evidence review found that prophylactic treatment reduces the number of acute attacks by c. 80%.

[xlvii] The reason the 'low' scenario is obtained when using the high estimate of acute attacks per week is due to the following mechanism: the costs for prophylactic use of C1 inhibitors is constant across scenarios while the cost savings of the policy (due to a reduction in pre-treatment acute attacks by 80%) are larger when the number of acute attacks is higher. The net costs (fixed costs of prophylaxis combined with cost savings from acute attacks) are lowest when the frequency of pre-treatment acute attacks is highest.

[xlviii] Based on clinical experience, this number appears reasonable given the distribution of the frequency of acute attacks.

[xlix] Zuraw et al. (2010).

[l] Please refer to M2.1.

[li] This percentage is derived using Pharmex data on the number of doses of icatibant and C1 esterase inhibitor, and varying the dosage of C1 esterase that would be taken by the population (between 2 and 4 vials).

[lii] These sessions could cost around £200 - £450 per person per training. Clinicians note of perhaps one or two trainings at the hospital site. If the training is conducted in an outpatient setting, it could be in the range of £200 per visit (based on the average tariff for first attendances in 2014/15), or around £450 per visit for a day case (based on analysis of SUS data for day case visits for those with HAE from 2011/12 to 2014/15).