Integrated Impact Assessment Report for Clinical Commissioning Policies

Policy Reference Number	A13X07		
Policy Title	Rituximab for immunoglobulin G4-related disease (IgG4-RD)		
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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 proposes a **routine commissioning** position for the use of rituximab for immunoglobulin G4-related disease (**IgG4-RD**). As awareness of IgG4-RD is relatively recent, there are limited studies on its epidemiology, and it is therefore difficult to estimate prevalence. The prevalence in England is estimated at around 1000 in 2014/15.[i] However, this estimate varies internationally, for example, in Japan, the **prevalence** of IgG4-RD is estimated at 63 to 79 persons per million (pmp).[ii] **Incidence** in the same Japanese study has been found to be 2.8 to 10.8, pmp.[iii]	

	K1.2 What is the number of patients currently eligible for the treatment under the proposed policy?	K1.2 Under the proposed policy, rituximab would be used as a third line treatment after corticosteroids (first line treatment) and second line treatment (methotrexate, azathioprine, or mycophenolate mofetil) if patients showed incomplete response, experienced significant adverse events, or were contraindicated.[iv] It is estimated that approximately 10% of the patients, or c. 100 patients, may be eligible to receive rituximab.[v]
	K1.3 What age group is the treatment indicated for?	K1.3 The treatment is indicated for adults (age 18 and above).
	K1.4 Describe the age distribution of the patient population taking up treatment?	K1.4 A study has found the average age at onset of the disease to be 59 years; the male to female ratio of persons with IgG4-RD has been estimated to be 1:0.77.[vi] Life expectancy after diagnosis was calculated to be approximately 20 years.[vii]
	K1.5 What is the current activity associated with currently routinely commissioned care for this group?	K1.5 Patients within the target population may be receiving first and second line treatment with **glucocorticoids** as monotherapy or in combination with steroid-sparing **immunosupressive** treatments (as set out in K1.2). In addition, as the target population comprises those refractory to these earlier lines of treatment, patients require additional treatment. Currently, there are **no further pharmacological treatments** following first and second line therapy.[viii] Current **treatment** for this group is **targeted at the affected organ**, e.g. or operations in relation to the salivary glands, treatment of acute pancreatitis,[ix] dialysis if IgG4-RD presents in the renal system.[x]

		Multiple organs are affected in 60% to 90% of patients.[xi] A total of c. 15 individual funding requests (IFRs) were submitted for **rituximab** for IgG4-RD from FY 2013/14 to September 2015/16.[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 No disease-specific growth rate has been identified, although diagnosis rates may increase as the disease becomes better known.[xiii] As such, it is estimated that the prevalence would grow at least in line with the population. Future prevalence of the condition could be c. 1,000 in the next five years.[xiv] Of this, the number needing rituximab is estimated at 10% of the population or around c.100.
	K1.7 What is the associated projected growth in activity (prior to applying the new policy) in 2,5 and 10 years?	K1.7 Under a "do nothing" scenario, current activity is assumed to be 'steady state' in future years. Based on this, the activity set out in K1.5 is expected to grow in line with population growth.[xv]
	K1.8 How is the population currently distributed geographically?	K1.8 Across England – no significant geographical differences in the disease have been identified.[xvi]
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 This policy proposes to routinely commission rituximab for IgG4-RD and adds a further line in the treatment pathway for patients who do not tolerate, experience side-effects or no longer respond to other treatments.[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 The understanding of IgG4-RD is emerging, and as such it may currently be underdiagnosed. If diagnosis rates increase, this could affect the number eligible for rituximab, however it was not possible to estimate this growth given the limited information.
	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 It is estimated that there are currently few or no patients receiving rituximab. As such, any new activity represents a net increase in the number who will access the treatment. Assuming 75% part year effect in year one, the **total number of patients** taking rituximab is estimated at: [xviii] • c. 75 in 2016/17 (year 1, 75% part year effect) • c. 100 in 2017/18 (year 2) • c. 105 in 2020/21 (year 5). These figures are based on the prevalent population, and so the figure represents an increase as compared to the base case rather than a year-on-year increase. The number of new patients starting treatment (and patients leaving it) will be small.
K3 Activity	K3.1 What is the current annual activity for the target population covered under the new policy? Please provide details in accompanying excel sheet.	K3.1 The current activity for the target population is set out in question K1.5; it is estimated that patients would be on first and second line treatments, with treatments targeted at organs affected by the disease.

	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 The new activity is estimated to be c. 75 patients in year 1. The **total number of patients taking rituximab** is estimated at • c. 75 in 2016/17 (year 1) • c. 100 in 2017/18 (year 2) • c . 100 in 2020/21 (year 5).[xix]
	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 In the do nothing scenario, current activity is assumed to be the 'steady state' which would be expected to roll forward in future years. The future activity levels are therefore estimated to grow in line with the population, 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 Once diagnosis is confirmed, corticosteroids is a first line treatment, unless the treatment is contra-indicated or the patient is corticosteroid dependent. If the patient shows incomplete response, methotrexate is prescribed second line unless contraindicated; azathioprine or mycophenolate mofetil are alternative second line agents.
	K4.2. What are the current treatment access criteria?	K4.2 Patients with a confirmed diagnosis of IgG4-RD, based on: 1. Tissue diagnosis 2. Imaging to define the extent of organ involvement 3. Serology 4. Clinical symptoms
	K4.3 What are the current treatment stopping points?	K4.3 If corticosteroids are contra-indicated, patient shows incomplete response or is corticosteroid dependent, treatment should be stopped.

		If methotrexate is contraindicated or patient shows incomplete response, treatment should be stopped. If azathioprine or mycophenolate mofetil are contraindicated or patient shows incomplete response, treatment should be stopped.
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. K5.2 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.	K5.1 There is no other routinely commissioned pathway for patients who have failed first and second-line treatments, apart from managing organ specific disease. 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 policy. K6.2 Where there are different stopping	K6.1 If the patient shows incomplete response to second line treatments and/or has significant associated adverse effects such as infection, diabetes, osteoporosis or cardiovascular disease, rituximab is proposed as third line treatment. K6.2 Rituximab should be stopped if the patient has serious adverse

	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.	events (e.g. anaphylaxis); is non-adherent; or has no response or incomplete response on regular monitoring and a 12 months assessment, following one course of treatment with the option to re-treat within a year in case of partial or late responders
K7 Treatment Setting	K7.1 How is this treatment delivered to the patient? ○ Acute Trust: Inpatient/Daycase/ Outpatient ○ Mental Health Provider: Inpatient/Outpatient ○ Community setting ○ Homecare delivery	K7.1 Rituximab is delivered in a day case setting.[xx]
	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 Rituximab is a high cost drug excluded from tariff, so it should be captured in the high cost drug dataset for routine commissioning.[xxi] Delivery in a day case setting would be recorded in the SUS data set.

	K8.2 How will this activity related to the new patient pathway be identified?(e.g. ICD10 codes/procedure codes)	K8.2 The activity could be identified using OPCS codes in combination with ICD, but difficult to uniquely identify.[xxii]
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 Information on the following outcomes should be collected following the administration of a course of two infusions two weeks apart:- Time to defined clinical response;- Time to clinical remission;- Duration of effect;- Timing of re-treatment;- Reduction/Discontinuation in steroids/immunosuppressants;- Frequency of re-treatment;- Total immunoglobulin levels pre-, and post-treatment; and- Serious adverse effects.
	K9.3 What analytical information /monitoring/ reporting is required?	K9.3 A specific IgG4-RD registry should be set up to ethically and robustly create a database of patients with IgG4-RD, their clinical course and outcomes at various centres across the UK. It is proposed this is modelled on the national registry for biologic therapy in systemic lupus erythematous (BILAG-BR) (A13/PS/a). Specific audit reports on the use of rituximab and specific outcomes in this patient group will be requested by the commissioner.
	K9.4 What contract monitoring is required by supplier managers? What changes	K9.4 None.

	need to be in place?	
	K9.5 Is there linked information required to complete quality dashboards and if so is it being incorporated into routine performance monitoring?	K9.5 No.
	K9.6 Are there any directly applicable NICE quality standards that need to be monitored in association with the new policy?	K9.6 No.
	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 Use of prior approval software platform could be anticipated.
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 IgG4-RD is a recently discovered condition with no formalised service support. At present, treatment is delivered in specialised tertiary centres with clinicians who have an interest in, and knowledge of, IgG4-RD. Typically, these sit within the rheumatology and gastroenterology/hepatology and other specialities.

	L1.2 How will the proposed policy change the way the commissioned service is organised?	L1.2 No change expected.
L2 Geography & Access	L2.1 Where do current referrals come from?	L2.1 Patients are mainly referred by specialists for where the disease presents. However, this is largely based on individual awareness of IgG4-RD and their knowledge of specialist clinicians.
	L2.2 Will the new policy change / restrict / expand the sources of referral?	L2.2 It is expected that a policy will expand the sources of referral, as it will increase awareness of IgG4-RD in the healthcare system.
	L2.3 Is the new policy likely to improve equity of access?	L2.3 Yes, by commissioning appropriate treatments for which sufficient clinical evidence exists to a well-defined population group
	L2.4 Is the new policy likely to improve equality of access / outcomes?	L2.4 Yes, through a consistent commissioning position across the country
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 anticipated time for implementation. The drug is available for prescription.
	L3.2 Is there a change in provider physical infrastructure required?	L3.2 No change in provider physical infrastructure.

	L3.3 Is there a change in provider staffing required?	L3.3 There is a need to develop multidisciplinary teams in a few specialised centres in England who have developed expertise in assessing and managing patients with IgG4-RD.
	L3.4 Are there new clinical dependency / adjacency requirements that would need to be in place?	L3.4 No new requirements.
	L3.5 Are there changes in the support services that need to be in place?	L3.5 No change in support services.
	L3.6 Is there a change in provider / inter-provider governance required? (e.g. ODN arrangements / prime contractor)	L3.6 No change in governance required.
	L3.7 Is there likely to be either an increase or decrease in the number of commissioned providers?	L3.7 No
	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 This drug is 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 Rituximab would be negotiated under local arrangements. The list price for MabThera is £873.15 for 500mg/50ml.[xxiii] The annual cost per patient (including VAT) is set out in M2.1.
	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 VAT would be payable as it is envisaged the drug would be administered in a day case setting.[xxiv]
	M1.6 Do you envisage a prior approval / funding authorisation being required to support implementation of the new policy?	M1.6 Not applicable.
M2 Average Cost per Patient	M2.1 What is the revenue cost per patient in year 1?	M2.1 Patients would receive one course of **rituximab** in the first year, at an approximate cost of £5,830. This is based on: • An initial dose of two infusions of rituximab of 1g each (at a total of £4,190 for rituximab)[xxv] • delivered over two day case visits (at £820 each)[xxvi] Hence the cost of the drug is estimated at c. £4,190 (incl. of VAT)[xxvii] in the first year and £1,640 for the day case administrations. Patients on rituximab would be able to **discontinue first and second line treatments**, however the cost savings of these are likely to be small.[xxviii] Note that some patients may need another course of rituximab after 6 months.[xxix] The cost for these patients is estimated to be £11,660.
	M2.2 What is the revenue cost per patient in future years (including follow up)?	M2.2 In future years, patients are estimated to need **rituximab to treat relapses** from a low frequency estimated at once every 2 years,[xxx] to twice per year.[xxxi] At these frequencies, the future cost of rituximab per patient could be £2,910 to £11,660 on average per year.
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 Cost pressure. This policy is estimated to be cost pressure. The pressure may be in the region of:[xxxii] • c. £0.2m - £0.9m in 2016/17 (year 1)

		• c. £0.3m - £1.2m in 2017/18 (year 2) • c. £0.3m - £1.2m in 2020/21 (year 5)[xxxiii] These figures take an average of the low and high frequency of use of rituximab.[xxxiv] If rituximab is instrumental in arresting the progression of organ damage, there could be substantial savings. For example, some patients with IgG4 may require renal dialysis, liver transplantation, or other costly interventions as a result of organ damage caused by the disease. However it has not been possible to estimate these savings based on existing evidence.[xxxv]
	M3.2 Where this has not been identified, set out the reasons why this cannot be measured.	M3.2 Not applicable.
M4 Overall cost impact of this policy to the NHS as a whole	M4.1 Indicate whether this is cost saving, neutral, or cost pressure for other parts of the NHS (e.g. providers, CCGs).	M4.1 Cost neutral.
	M4.2 Indicate whether this is cost saving, neutral, or cost pressure to the NHS as a whole.	M4.2 Cost pressure. In the region of c. £0.3m to £1.2m from the first year of full year effect (see M3.1).
	M4.3 Where this has not been identified, set out the reasons why this cannot be measured.	M4.3 Not applicable.

	M4.4 Are there likely to be any costs or savings for non NHS commissioners / public sector funders?	M4.4 No evidence of costs or savings beyond the NHS has been identified.
M5 Funding	M5.1 Where a cost pressure is indicated, state known source of funds for investment, where identified. *e.g. decommissioning less clinically or cost-effective services*	M5.1 For consideration at CPAG.
M6 Financial Risks Associated with Implementing this Policy	M6.1 What are the material financial risks to implementing this policy?	M6.1 The estimates are based on the current levels of diagnosis, which are not expected to rise dramatically. However, future increases in awareness could impact the cost under the policy.
	M6.2 Can these be mitigated, if so how?	M6.2 None identified.
	M6.3 What scenarios (differential assumptions) have been explicitly tested to generate best case, worst case and most likely total cost scenarios?	M6.3 A high cost scenario was tested, in which c. 200 patients started treatment with rituximab instead of the estimated 100 patients in the base case set out in M3.1. Under this scenario, the cost pressure would be double, or c. £0.6m to £2.4m in 2017/18.[xxxvi]
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*	M7.1 and M7.2 There were no information on the cost effectiveness in the studies reviewed.

	M7.2 What issues or risks are associated with this assessment? *e.g. quality or availability of evidence*	
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 None identified.
	M8.2 If so, confirm the source of funds to meet these costs.	M8.2 Not applicable.

[i] Based on clinician consensus.

[ii] This is based on a prevalence of 8,000 to 10,000 in Japan, inferring the rate pmp for Japan (Japan's population was 127m in 2014 according to: Bureau of Statistics, Japan, http://www.stat.go.jp/english/data/jinsui/2014np/index.htm) and then using 2012 ONS estimates of the population in England to estimate the prevalence in England. The prevalence figures are taken from: Uchida, K., et al., "Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey", International Journal of Rheumatology, Volume 2012 (2012), accessed via: http://www.hindawi.com/journals/ijr/2012/358371/. Incidence rates from Japan are used as epidemiological studies are limited, as agreed with the policy working group.

[iii] This is based on an estimated incidence of 2.8 pmp to 10.8 pmp. These figures are taken from: Uchida, K., et al., "Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey", International Journal of Rheumatology, Volume 2012 (2012), accessed via: http://www.hindawi.com/journals/ijr/2012/358371/. Incidence rates from Japan are used as epidemiological studies are limited, as agreed with the policy working group.

[iv] Please see the policy proposition.

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

[vi] Uchida, K., et al., "Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey", International Journal of Rheumatology, Volume 2012 (2012), accessed via: http://www.hindawi.com/journals/ijr/2012/358371/.

[vii] Uchida, K., et al., "Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey", International Journal of Rheumatology, Volume 2012 (2012), accessed via: http://www.hindawi.com/journals/ijr/2012/358371/ and discussed with the policy working group.

[viii] Policy proposition.

[ix] Often associated with pancreatitis. Uchida, K., et al., "Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey", International Journal of Rheumatology, Volume 2012 (2012), accessed via: http://www.hindawi.com/journals/ijr/2012/358371/.

[x] Policy proposition.

[xi] Policy proposition; Moutsopoulos, HM, et. al. (2015). Overview of IgG4-related disease. http://www.uptodate.com/contents/overview-of-igg4-related-disease

[xii] National IFR database.

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

[xiv] The growth rate used is that of the general population, based on 2012 ONS population estimates. Figures are rounded as there is a level of uncertainty.

[xv] Based on discussions with policy working group.

[xvi] As affirmed through discussions with the policy working group.

[xvii] Policy proposition.

[xviii] Figures are rounded. 75% based on the c. 10% of the prevalent population that would likely be eligible for rituximab as set out in K1.2.

[xix] Figures are rounded.

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

[xxi] See K9.

[xxii] In the SUS dataset, the following codes were used to identify activity related to rituximab (OPCS code X892).

[xxiii] Dictionary of medicine, entry for for MabThera is £873.15 for 500mg/50ml, http://dmd.medicines.org.uk/DesktopDefault.aspx?AMPP=7697211000001103&toc=nofloat, last accessed: 13/11/2015.

[xxiv] Based on discussions with NHS England pharmacists and finance leads. Section 3.2, When can goods being provided on prescription be zero-rated for VAT purposes? https://www.gov.uk/government/publications/vat-notice-70157-health-professionals-and-pharmaceutical-products/vat-notice-70157-health-professionals-and-pharmaceutical-products. [Accessed 16/12/11].

[xxv] Based on 4 x doses of 500mg of rituximab (price set out in M1.3).Includes 20% VAT.

[xxvi] Based on analysis of SUS data for 2011/12 to September 2015/16, for OPCS code X892 (Monoclonal antibodies Band 2), for the POD code "DC". The SUS data used for these calculations relates only to spells which include K861 (ICD-10 code for "Other chronic pancreatitis") in the first three positions of ICD-10 codes. As IgG4-RD can affect a whole range of organs/ sites, this average cost has been discussed with the policy working group to check it is representative for IgG4 patients more generally.

[xxvii] Please refer to M2.1 for the underlying price of the drug.

[xxviii] Discussions with the policy working group.

[xxix] Emerging insight based on clinical observation – policy working group.

[xxx] Policy proposition.

[xxxi] Every six months, as discussed with policy working group.

[xxxii] Based on a target population of 100 (75% phasing in year 1), with an estimated frequency of rituximab of once every two years for the low cost impact estimate, and twice per year for the high cost impact estimate.

[xxxiii] Figures are rounded.

[xxxiv] At a high frequency of 2 times per year, and a low frequency of 0.5 times per year (once every two years) the average frequency is estimated at 1.25 times per year.

[xxxv] Discussed with policy working group.

[xxxvi] Figures rounded.