Integrated Impact Assessment Report for Clinical Commissioning Policies

Policy Reference Number	A10X05		
Policy Title	Everolimus for prevention of organ rejection following heart transplant		
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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 to set out a **non-routine commissioning** position for everolimus for immune suppression for the prevention or reduction of organ rejection and kidney dysfunction in patients at risk following heart transplant. The **patient population** would refer to those who have received a heart transplant. In 2014/15, there were 181 adult heart transplants and 37 paediatric heart transplants, 218 heart transplants in total.[i]	

	K1.2 What is the number of patients currently eligible for the treatment under the proposed policy?	K1.2 Patients may be suitable for everolimus in the following indications: 1. **Severe renal failure** - approximately 5% and 9% of patients at three and five years respectively may develop severe renal failure.[ii] 2. **Cardiac allograft vasculopathy (CAV)** - CAV occurs in over 40% of heart transplant patients within 5 years of surgery.[iii] Therefore c. 49% of heart transplants undertaken may be suitable for everolimus within 5 years of surgery.
	K1.3 What age group is the treatment indicated for?	K1.3 The policy is indicated for adults and paediatrics (all ages).[iv]
	K1.4 Describe the age distribution of the patient population taking up treatment?	K1.4 In 2014/15 the median age of adult heart transplant patients was 51 years of age, and 6 years of age for paediatrics. [v]
	K1.5 What is the current activity associated with currently routinely commissioned care for this group?	K1.5 It is estimated that currently no patients receive everolimus for immune suppression for the prevention or reduction of organ rejection and kidney dysfunction in patients at risk following heart transplant.[vi] Everolimus may be used in combination with: [vii] • calcineurin inhibitors (CNI) e.g. cyclosporine or tacrolimus; • corticosteroids; or • metabolic inhibitors e.g. mycophenolate mofetil (MMg) or azathioprine. Patients who show adverse effects or are contraindicated to

		everolimus may discontinue and restart CNI treatment; whereas patients who do not show any adverse effects are titrated and eventually weaned off CNI.[viii] Patients who do not current receive everolimus may instead receive: • an alternative second line therapy, sirolimus. This is the 'sister' drug of everolimus.[ix] Patients may be treated with sirolimus in a similar way to everolimus and in combination with the standard first line drugs: CNI, corticosteroids, metabolic inhibitors.[x]
	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 Data from the NHS Blood and Transplant (2015) register has shown an increase in the number of cardiac transplants over the last c. 10 years. If this trend were to continue, the future number of heart transplants could be[xi]: • ~ 230 in 2016/17 (year 1) • ~ 235 in 2017/18 (year 2) • ~ 255 in 2020/21 (year 5)
	K1.7 What is the associated projected growth in activity (prior to applying the new policy) in 2,5 and 10 years?	K1.7 In the 'do-nothing' it is estimated that activity would remain equal to that identified in K1.5.
	K1.8 How is the population currently distributed geographically?	K1.8 There are five heart transplant centres in England; centres are located in Newcastle, Manchester, Birmingham, London and Cambridge.[xii] However, it is not known how the patient group is geographically distributed as there are a number of indications that may result in heart transplant and these may follow differing regional

		distributions.
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 The policy proposes that everolimus is **not-routinely commissioned** for immune suppression post cardiac transplant.
	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 factors that may affect the growth in the number of heart transplants may include: • The size of the heart donor pool[xiii] • Incidence and prevalence of heart disease and heart failure – heart transplants are used in response to these indications amongst others.[xiv]
	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 No evidence of changes has been identified in this review.
	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 The proposed policy establishes a 'not routinely commissioned' proposal for the relevant population (the specific cohort set out in K1.2). The number of patients who fall outside of the cohort covered by the proposed policy, or for whom exceptionality might be demonstrated is likely to be very small.

		There is expected to be no net change in the number of patients accessing the treatment under the policy as compared to the 'do nothing' scenario and that activity would remain at 0.
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 Current annual activity is identified in K1.5.
	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 As the policy is to not routinely commission, the activity under the policy would be similar to the 'do nothing' scenario is as described in K1.7.
	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 Under the 'do nothing' scenario, activity would be as set out in K1.5 and K1.7. The activity for everolimus in the patient group is expected to remain at zero in future years under a non-routine commissioning position.
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 First line treatment post cardiac transplant is a standard triple therapy consisting of calcineurin inhibitors (CNI) such as cyclosporine or tacrolimus, steroids, and metabolic inhibitors such as mycophenolate mofetil (MMF) or azathioprine. This is provided in tertiary or quaternary care at transplant centres. Some patients experience adverse effects to first line treatment, such as renal dysfunction. Patients are usually weaned off the steroids if there is no history of rejection. However, CNIs form the backbone of immunosuppression long-term after heart transplant to minimise risk

		of rejection. Second line treatments include sirolimus.
	K4.2. What are the current treatment access criteria?	K4.2 Patient's condition is monitored by physicians who are part of a transplant MDT. Access to second line treatment includes renal impairment following first line treatment post cardiac surgery, or a weaning strategy to replace MMF with sirolimus or tacrolimus. Patients can only start treatment with everolimus a minimum of 4 weeks post cardiac surgery when wounds are healed.
	K4.3 What are the current treatment stopping points?	K4.3 Adverse effects to treatment, comorbidities, ongoing wound healing problems or an acute rejection episode.
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 See K4.1. Sirolimus and tacrolimus are alternative routinely commissioned second line treatment.
	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	K5.2 See K4.3

	indicate likely outcome for patient at each stopping point.	
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 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.	K6.1 The patient pathway does not change as this policy recommends a not routinely commissioned position of everolimus. K6.2 No change as proposed to not routinely commission.
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 Everolimus would be administered between 4-6 weeks after transplant. Patients are prescribed everolimus by a multidisciplinary team through tertiary care at one of the five transplant centres in England.[xv]

	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 change as proposed to not routinely commission.
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 Not applicable as proposed to not routinely commission.
	K8.2 How will this activity related to the new patient pathway be identified?(e.g. ICD10 codes/procedure codes)	K8.2 Not applicable as proposed to not routinely commission.
K9 Monitoring	K9.1 Do any new or revised requirements need to be included in the NHS Standard Contract Information Schedule?	K9.1 No change as proposed to not routinely commission.
	K9.2 If this treatment is a drug, what pharmacy monitoring is required?	K9.2 No change as proposed to not routinely commission.
	K9.3 What analytical information /monitoring/ reporting is required?	K9.3 No change as proposed to not routinely commission.
	K9.4 What contract monitoring is required by supplier managers? What	K9.4 No change as proposed to not routinely commission.

	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 No change as proposed to not routinely commission.
	K9.6 Are there any directly applicable NICE quality standards that need to be monitored in association with the new policy?	K9.6 No change as proposed to not routinely commission.
	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 No change as proposed to not routinely commission.
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 Second line treatment can only be initiated by physicians and ongoing prescribing by an appropriate member of the transplant MDT in a designated heart transplant centre.
	L1.2 How will the proposed policy change the way the commissioned	L1.2 No change as proposed to not routinely commission.

	service is organised?	
L2 Geography & Access	L2.1 Where do current referrals come from?	L2.1 Patient pathway of cardiac transplant patients
	L2.2 Will the new policy change / restrict / expand the sources of referral?	L2.2 No change as proposed to not routinely commission.
	L2.3 Is the new policy likely to improve equity of access?	L2.3 No change as proposed to not routinely commission.
	L2.4 Is the new policy likely to improve equality of access / outcomes?	L2.4 No change as proposed to not routinely commission.
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 change as proposed to not routinely commission.
	L3.2 Is there a change in provider physical infrastructure required?	L3.2 No change as proposed to not routinely commission.
	L3.3 Is there a change in provider	L3.3 No change as proposed to not routinely commission.

	staffing required?	
	L3.4 Are there new clinical dependency / adjacency requirements that would need to be in place?	L3.4 No change as proposed to not routinely commission.
	L3.5 Are there changes in the support services that need to be in place?	L3.5 No change as proposed to not routinely commission.
	L3.6 Is there a change in provider / inter-provider governance required? (e.g. ODN arrangements / prime contractor)	L3.6 No change as proposed to not routinely commission.
	L3.7 Is there likely to be either an increase or decrease in the number of commissioned providers?	L3.7 No change as proposed to not routinely commission.
	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 No change as proposed to not routinely commission.
L4 Collaborative Commissioning	L4.1 Is this service currently subject to or	L4.1 No change as proposed to not routinely commission.

	planned for collaborative commissioning arrangements? (e.g. future CCG lead, devolved commissioning arrangements)	
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 Everolimus is listed as a high cost drug and therefore is not included in national prices.
	M1.2 Is this treatment excluded from national prices?	M1.2 Please refer to M1.1.
	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 As a high cost drug, everolimus may be subject to local price negotiations. The price of everolimus (marketed under the trade name Certican®) varies by dose and is in the region of: • 0.25mg – 6 x 10 tablets = £149 or £178 including VAT[xvi] • 0.50mg – 6 x 10 tablets = £297 or £356 including VAT[xvii] • 0.75mg – 6 x 10 tablets = £446 or £535 including VAT[xviii]
	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 recoverable under certain specific conditions[xix]. It is assumed here that VAT would be not be recoverable and is therefore included in the cost estimates below.
	M1.6 Do you envisage a prior approval / funding authorisation being required to support implementation of the new policy?	M1.6 No.
M2 Average Cost per Patient	M2.1 What is the revenue cost per patient in year 1?	M2.1 The revenue cost per patient per year would be zero under a **non-routine commissioning** policy. The cost per patient per annum, were patients to be treated with everolimus, would vary based on the variance of the dose that may be required. [xx] As such, a broad range of the cost per year per patient has been calculated[xxi]: • c. £2,170 based on two 0.25mg tablets per day • c. £4,440 based on two 0.50mg tablets per day • c. £6,510 based on two 0.75mg tablets per day An initial dose regimen of 0.75mg twice daily is prescribed (for adults) and this will be subsequently modified from day four onwards.[xxii] For paediatric patients, the starting dosage would be in accordance with local protocols.[xxiii] The cost per annum of everolimus is estimated to be greater than sirolimus, the comparator treatment. Under the assumption that patients are prescribed with either 1mg or 2mg tablets per day,[xxiv] the cost per patient per year for sirolimus is estimated to range from

		£1,265 to £2,525. [xxv] [xxvi]
	M2.2 What is the revenue cost per patient in future years (including follow up)?	M2.2 The cost per patient in future years is likely to remain equal to that in M2.1.
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 neutral. As discussed in K1.5, there are currently estimated to be zero patients receiving everolimus and activity is not expected to change under a **non-routine commissioning** position.
	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 neutral.
	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 None 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 Not applicable.
M6 Financial Risks Associated with Implementing this Policy	M6.1 What are the material financial risks to implementing this policy?	M6.1 Not applicable.
	M6.2 Can these be mitigated, if so how?	M6.2 Not applicable.
	M6.3 What scenarios (differential assumptions) have been explicitly tested to generate best case, worst case and most likely total cost scenarios?	M6.3 Not applicable.
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 Two studies were found that looked at the cost effectiveness of everolimus treatments. The first study (Radeva et al., 2005) compared the total cost of everolimus and azathioprine, with both treatments aiming for standard doses of cyclosporine. The study found that everolimus was marginally more expensive, $72,065 vs $70, 815 (£47,910 v £47,079). This difference was primarily due to increased hospitalisation costs and secondarily due to increased concomitant

		medication costs, although there were savings made on the cyclosporine costs. The second study (Annemans et al., 2007) was based on the German health care model and looked at the incremental cost of everolimus and MMF verses azathioprine divided by the reduction in efficacy failure (the incremental cost effectiveness ratio ICER). The study favoured everolimus over MMF with an ICER of 24,457 Euros vs 29,912 Euros (£17,593 v £21,516), although the study doesn't appear to include hospitalisation costs.
	M7.2 What issues or risks are associated with this assessment? *e.g. quality or availability of evidence*	M7.2 Radeva et al. (2005) cannot be regarded as a completely independent study, as the authors received grants from Novartis. This study was based on a 1 year period and costs were estimated according to the costs of the centres where the treatments took place. Annermans et al. (2007) is an independent study. The limitations of the study are, principally, that the included costs only include drug costs and not hospitalisations. Additionally, it is not clear how sensitive the results of the study are to variation in the efficacy (as estimated by primary composite endpoint rates). Only peer-reviewed literature was considered in the assessment.
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] NHS Blood and Transplant. (2015). Annual report on cardiothoracic transplantation: report for 2014/15 (1 April 2005 – 31 March 2015). [Online] available at: http://www.odt.nhs.uk/pdf/organ_specific_report_cardiothoracic_2015.pdf [Accessed 5 Jan. 2016]

[ii] Policy Proposition

[iii] Policy Proposition

[iv] Policy Proposition

[v] NHS Blood and Transplant. (2014). Annual report on cardiothoracic transplantation: report for 2013/14 (1 April 2004 – 31 March 2014).

[vi] Based on discussion with the policy working group.

[vii] Based on the proposed patient pathway developed by the policy working group.

[viii] Based on the proposed patient pathway developed by the policy working group.

[ix] Based on discussion with the policy working group.

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

[xi] NHS Blood and Transplant (2015). In 2005/06 there were 29 paediatric and 141 adult heart transplants; this increased to 37 paediatric and 181 adult heart transplants in 2014/15. If the total number of patients undergoing heart transplantation each year were to increase at its historic trend CAGR of c.2.8%.

[xii] NHS Blood and Transplant. (2015). Annual report on cardiothoracic transplantation: report for 2014/15 (1 April 2005 – 31 March 2015). [Online] available at: http://www.odt.nhs.uk/pdf/organ_specific_report_cardiothoracic_2015.pdf [Accessed 5 Jan. 2016]

[xiii] Nhsbt.nhs.uk, (2016). Taking Organ Transplantation to 2020 - Increasing the Number of Potential Donors. [online] Available at: http://www.nhsbt.nhs.uk/to2020/the-strategy/strategy/increasing-the-number-of-potential-donors/ [Accessed 5 Jan. 2016].

[xiv] E. Chinnock, R. and L. Bailey, L. (2011). Heart Transplantation for Congenital Heart Disease in the First Year of Life. *CCR*, 7(2), pp.72-84.

[xv] Based on discussion with the policy working group.

[xvi] Dmd.medicines.org.uk, (2016). Dictionary of Medicines and Devices Browser Portal. [online] Available at: http://dmd.medicines.org.uk/DesktopDefault.aspx?AMPP=29699311000001108&toc=nofloat [Accessed 7 Jan. 2016].

[xvii] Dmd.medicines.org.uk, (2016). Dictionary of Medicines and Devices Browser Portal. [online] Available at: http://dmd.medicines.org.uk/DesktopDefault.aspx?AMPP=29699811000001104&toc=nofloat [Accessed 7 Jan. 2016].

[xviii] Dmd.medicines.org.uk, (2016). Dictionary of Medicines and Devices Browser Portal. [online] Available at: http://dmd.medicines.org.uk/DesktopDefault.aspx?AMPP=29699511000001102&toc=nofloat [Accessed 7 Jan. 2016].

[xix] Please refer to Section 3.2 of VAT Notice 701/557 (https://www.gov.uk/government/publications/vat-notice-70157-health-professionals-and-pharmaceutical-products/vat-notice-70157-health-professionals-and-pharmaceutical-products)

[xx] Titrations are highly dependent on the patient. Based on discussions with the policy working group.

[xxi] Please note that these figures are based on the costs in M1.3 and are rounded.

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

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

[xxiv] NHS Papworth Hospital. (2012). DN249 Shared care guideline: Sirolimus (Rapamune®). [Online] available at: http://www.cambsphn.nhs.uk/Libraries/Shared_Care_Guidance/Sirolimus_SCG.sflb.ashx [Accessed 7 Jan. 2016].

[xxv] The price of sirolimus as listed on the Part VIIA tariff: £86.49 (1mg tablets – 30 pack size), £172.98 (2mg tablets – 30 pack size).

[xxvi] The lower estimate assumes that a patient takes one 1mg tablet once a day, while the upper estimate assumes that a patient takes one 2mg tablet once a day.