| A.33 | Tacrolimus - for prevention and treatment of graft rejection following transplantation in adults and children |
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| Does the application adequately address the issue of the public health need for the medicine? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: The application assumes while transplants are not performed around the world transplant recipients are being managed around the world |
| Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market. | • As part of an immunosuppressive regimen, immediate-release tacrolimus is recommended as an initial treatment option to prevent organ rejection.<br>• Compared to other immunosuppressive treatments tacrolimus has been shown to be superior for the most important outcomes such as graft loss and acute rejection, and has been used in both children and adults following organ transplantation as a first-line treatment<br>• Recommendations for improving graft survival and preventing acute rejection in solid organ transplants consist of combination therapy comprised of tacrolimus with mycophenolate and steroids, in conjunction with either basiliximab or anti-thymocyte globulin as an induction agent<br>• Prolonged-release tacrolimus is recommended as an option only for restricted use for the prophylaxis of transplant rejection and may be used as an option for maintenance immunosuppression as second-line agent for patients who suffer intolerable side effects related to peak dose toxicity.<br>• Tacrolimus is effective in kidney transplants. In the setting of a heart and lung transplant, tacrolimus is recommended over cyclosporine as the preferred calcineurin inhibitor (CNI). For optimizing maintenance in after lung transplantation, a switch from cyclosporine to tacrolimus-based immunosuppression is recommended. In adult liver transplantation tacrolimus is used as a treatment option with or without corticosteroids. Evidence from RCTs is also pointing out the superiority of tacrolimus in patients receiving simultaneous kidney-pancreas transplants.<br>• Therapeutic levels of tacrolimus can be maintained throughout pregnancy, with good pregnancy outcomes. |
| Have all important studies and all relevant evidence been included in the application? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>See below for a summary of the exhaustive search for data. |
| Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication? | ☒ Yes<br>☐ No<br>☐ Not applicable |
| Does the application provide adequate evidence of the safety and adverse effects associated with the medicine? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>The submission was exhaustive in its search for data. This included:<br>1. A search for systematic reviews<br><u>KIDNEY TRANSPLANT</u><br>ꕤ Kidney transplant; adults, tacrolimus versus cyclosporine - Comparison of Tacrolimus and Cyclosporine for Immunosuppression after Renal Transplantation: An Updated Systematic Review and Meta-Analysis<br>ꕤ Kidney transplant; adults; Sirolimus + Tacrolimus vs Mycophenolate Mofetil + Tacrolimus - Comparison of Sirolimus Combined with Tacrolimus and Mycophenolate Mofetil Combined with Tacrolimus in Kidney Transplantation Recipients: A Meta-Analysis<br>ꕤ Kidney transplant; adults; belatacept vs tacrolimus; tacrolimus vs. ciclosporin - Indirect treatment comparison of belatacept versus tacrolimus from a |

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| | systematic review of immunosuppressive therapies for kidney transplant patients<br>- Kidney transplant; adults; tacrolimus vs cyclosporine (MetS and CV risk factors) - Effects of tacrolimus and cyclosporine treatment on metabolic syndrome and cardiovascular risk factors after renal transplantation: a meta-analysis<br>- Kidney transplant; adult; belatacept vs cyclosporine vs tacrolimus - A network meta-analysis of the efficacy of belatacept, cyclosporine and tacrolimus for immunosuppression therapy in adult renal transplant recipients [84]<br>- Kidney transplant; patients over age 16; immunosuppressive drugs for maintenance - Safety of Immunosuppressive Drugs Used as Maintenance Therapy in Kidney Transplantation: A Systematic Review and Meta-Analysis<br>- Kidney transplant; children, tacrolimus versus cyclosporine - A Comparison Between Tacrolimus and Cyclosporine as Immunosuppression after Renal Transplantation in Children, A Meta-Analysis and Systematic Review<br>- Kidney transplant: population age not reported, tacrolimus vs sirolimus - Sirolimus Versus Tacrolimus as Primary Immunosuppressant After Renal Transplantation: A Meta-Analysis and Economics Evaluation<br>- Kidney transplant; adults and children; tacrolimus vs cyclosporin - Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients<br><u>LIVER TRANSPLANT</u><br>- Liver transplant; adults; maintenance immunosuppression - Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis<br>- Liver transplant; adults, tacrolimus versus cyclosporine - Systematic Review and Meta-Analysis of Tacrolimus versus Ciclosporin as Primary Immunosuppression After Liver Transplant<br>- Liver transplant; adults; immunosuppression monotherapy - Efficacy of immunosuppression monotherapy after liver transplantation: A meta-analysis<br>- Liver transplant; adults and children, tacrolimus versus cyclosporine - Cyclosporin versus tacrolimus for liver transplanted patients<br>- Liver transplant; adults and children; tacrolimus vs cyclosporin - Cyclosporin versus Tacrolimus as Primary Immunosuppressant After Liver Transplantation: A Meta-Analysis<br><u>LUNG TRANSPLANT</u><br>- Lung transplant; adults; tacrolimus vs cyclosporin - Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients<br>- Lung transplant; adults; tacrolimus vs cyclosporine - Tacrolimus Versus Cyclosporine for Adult Lung Transplant Recipients: A Meta-Analysis<br><u>HEART TRANSPLANT</u><br>- Heart transplant; adults and children, tacrolimus vs cyclosporine - Tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials<br>- Heart transplant; adults and children; tacrolimus versus cyclosporine microemulsion - Tacrolimus Versus Cyclosporine Microemulsion for Heart Transplant Recipients: A Meta-analysis<br><u>DIABETES MELLITUS</u><br>- Diabetes mellitus onset; adults; tacrolimus vs cyclosporine - New Onset Diabetes Mellitus in Patients Receiving Calcineurin Inhibitors: A Systematic Review and Meta-Analysis<br>2. A search for randomized controlled trials (RCTs) – many included in Systematic Reviews<br><u>EVIDENCE FROM RCTS NOT INCLUDED IN PRESENTED SYSTEMATIC REVIEWS</u> |

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| | KIDNEY TRANSPLANTATION<br>ꕥ Miller et al, 2000<br>ꕥ Chang et al, 2001<br>ꕥ Pascual et al, 2002<br>ꕥ Jarzembowski et al, 2003<br>ꕥ Abou-Jaoude et al, 2003<br>ꕥ Viko et al, 2005<br>ꕥ Kumar et al, 2005<br>ꕥ Rostaing et al, 2005<br>ꕥ Gallon et al, 2006<br>ꕥ Vacher-Coponat et al, 2012<br>ꕥ Asher et al, 2014<br>ꕥ Ciancio et al, 2016<br>ꕥ Huh et al, 2017<br>ꕥ de Graav et al., 2017<br>ꕥ Kojima et al, 2018<br>LIVER TRANSPLANTATION<br>ꕥ Boillot et al, 2001<br>ꕥ Martin et al, 2004<br>ꕥ Gonzalez et al, 2005<br>ꕥ Spada et al, 2006<br>ꕥ Becker et al, 2008<br>ꕥ Lerut et al, 2008<br>ꕥ Otero et al, 2009<br>ꕥ Klintmalm et al, 2011<br>ꕥ Neumann et al, 2012<br>ꕥ Takada et al, 2013<br>ꕥ Levy et al, 2014<br>ꕥ Asrani et al, 2014<br>LUNG TRANSPLANTATION<br>ꕥ Treede et al, 2001<br>HEART TRANSPLANTATION<br>ꕥ Baran et al, 2011<br>ꕥ Sanchez-Lazaro et al, 2011<br>ꕥ Kaczmarek et al, 2013<br>SIMULTANEOUS PANCREAS AND KIDNEY (SPK) TRANSPLANTATION<br>ꕥ Woeste et al, 2002<br>ꕥ Bechstein et al, 2004<br>ꕥ Boggi et al, 2005<br>ꕥ Ciancio et al, 2015<br>3. A search for GUIDELINES – including<br>ꕥ 2017 guidelines of the National Institute for Health and Care Excellence (NICE) for a **kidney** transplant in **adults**, as well as in **children and young adults**<br>ꕥ 2020 Clinical Practice Guidelines - Standardisation of immunosuppressive and anti-infective drug regimens in UK **Paediatric Renal** transplantation: The Harmonisation Programme<br>ꕥ European Association of Urology (EAU) Guidelines on **Renal** Transplantation updated in 2018<br>ꕥ 2010 KDIGO clinical practice guideline for the care of **kidney** transplant recipients, by the International Society of Nephrology<br>ꕥ 2017 Renal association clinical practice guideline in post-operative care in the kidney transplant recipient<br>ꕥ 2020 guidelines of the Canadian Cardiovascular Society/Canadian Cardiac Transplant Network for **heart** transplantation<br>ꕥ 2015 Antibody-Mediated Rejection in **Cardiac** Transplantation: Emerging Knowledge in Diagnosis and Management - A Scientific Statement from the |

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| | American Heart Association<br>ꟷ 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Monitoring of Nonsteroidal Immunosuppressive Drugs in Patients With Lung Disease and **Lung Transplant** Recipients<br>ꟷ 2020 Adult **liver** transplantation: UK clinical guideline - part 2: surgery and post-operation<br>ꟷ 2016 EASL Clinical Practice Guidelines: **Liver** transplantation<br>ꟷ Long-Term Management of the Successful Adult **Liver** Transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation<br>4. A search for Health Technology Assessment (HTA) Reports<br>ꟷ Immunosuppressive therapy for kidney transplantation in adults: a systematic review and economic model. Health Technol Assess 2016;20(62).<br>ꟷ All Wales Medicines Strategy Group Final Appraisal Recommendation – Advice no. 0811, Tacrolimus (Advagraf®) June 2011 v1.3<br>ꟷ All Wales Medicines Strategy Group Final Appraisal Recommendation – Advice no. 2315, Tacrolimus (Envarsus®) July 2015<br>ꟷ Immunosuppressive therapy for kidney transplantation in children and adolescents: systematic review and economic evaluation<br>ꟷ Calcineurin Inhibitors for Renal Transplant: Agency for Healthcare Research and Quality (AHRQ Comparative Effectiveness Reviews) |
| Are there any adverse effects of concern, or that may require special monitoring? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: Transplant rejection requires expertise in its management. It is assumed in the submission that those who would be prescribing these drugs – including tacrolimus – are skilled in the management of transplant rejection and its complications |
| Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.) | A review of the available evidence finds tacrolimus to be effective and while not free of harm, has a well-known and manageable risk profile. It is cost-effective and an important component of a regimen to induce and maintain immunosuppression in most transplant patients |
| Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.) | The submission was exhaustive in its search for data. This is summarized in detail above and included:<br>1. A search for systematic reviews<br>2. A search for randomized controlled trials (RCTs)<br>3. A search for GUIDELINES<br>4. A search for Health Technology Assessment (HTA) Reports |
| Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?**<br>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: As above, transplant rejection requires expertise in its management. It is assumed in the submission that those who would be prescribing these drugs – including tacrolimus – are skilled in the management of transplant rejection and its complications and have access to the needed support. |
| Are you aware of any issues regarding the registration of the medicine by national regulatory authorities?<br>(e.g. accelerated approval, lack of regulatory approval, off-label indication) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: |

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| Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments: |
| Briefly summarize your assessment of any issues regarding access, cost, and affordability of the medicine in different settings. | The cost of tacrolimus is only one component of the cost of the transplant, and the management of a patient in the post-transplant setting. The cost of tacrolimus cannot be divorced from these considerations. It is and has been widely available worldwide and while many formulations have their advocates it would appear there exists sufficient flexibility in the choice of a tacrolimus option. |
| Any additional comments | None |
| Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal. | Tacrolimus is clearly an effective agent and an essential component in the management of patients who have undergone solid organ transplantation. It has been used through to the world for decades and most patients who have been prescribed this drug have had challenging health issues. In effect this drug has been tested in the real world. Despite advocacy for certain formulations, there appears to be sufficient flexibility that finding cost effective options should be possible. The decision as to investment in an individual's health care will have been made by the time a patient needs tacrolimus and the use of tacrolimus in this setting will help that investment have a successful outcome. All of this argues for approval of this application. |
| References (if required) | |