A.33	Tacrolimus – organ transplant rejection
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The unmet public health need is immunosuppression for prevention and treatment of rejection in organ transplantation.
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.	The EML currently lists Azathioprine and Ciclosporin as well as steroids (eg methyl prednisolone) as immunomodulators. Tacrolimus has been studied for 25 years as an immunosuppressant specifically focussed on reducing grant rejection after transplantation. Originally studied in liver transplants, a series of trials have expanded its use into a wide range of other transplants, including kidney, heart and lung, pancreas, intestinal It is licensed for use in children and adults, with FDA approval for liver, kidney and heart transplants. While it has significant toxicity concerns, some of the toxicity seen with ciclosporin and azathioprine are not seen with tacrolimus. The application focusses on the immediate release oral tacrolimus where there is the most evidence, including granules for children (iv and prolonged release once daily formulations are available).
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: This is a very thorough and well conducted evaluation, with a very clear search strategy and an evidence based review of the primary evidence, systematic reviews and practice guidelines.
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). A SR from 2018 of 21 RCTs concluded that tacrolimus is superior to ciclosporin for graft loss. And acute rejection, but not mortality. Older Cochrane reviews have reported that tacrolimus is superior to ciclosporin for the prevention of rejection in both renal and liver transplants, although rates of new onset diabetes appeared to be higher.

	Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? There is reasonable evidence of efficacy in children, across the different types of organ transplant and there are child appropriate formulations. The great majority of the studies are from the HIC setting.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The toxicities are well recognised and therapeutic drug monitoring is routine during therapy.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: New Onset Diabetes Mellitus is a recognised concern and routinely monitored for during therapy. Renal and neurological complications are also reported.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	There is reasonable evidence from multiple trials that tacrolimus is superior to ciclosporin for prevention of rejection in renal, liver and heart transplants, with an overall a favourable efficacy and toxicity profile.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The level of evidence is overall high, given the numbers of transplants that occur. There have been multiple trials, SR and MA and Cochrane's.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Therapeutic drug monitoring is recommended, but this is well established and the appropriate levels for adults and children are well defined.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: Licensed by the FDA for the principal indications.

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 ☒ No ☐ Not applicable Comments: But the 63rd WHA has called for new guidelines on human organ and tissue transplantation to improve safety quality and efficacy.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	There a number of major generic producers of tacrolimus and the IR is cheaper than PR formulations. However the costs are still very significant at thousands of dollars per year.
Any additional comments	
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.	The proposed recommendation is to add Immediate Release Tacrolimus to the EML. The evidence base for its inclusion is robust for its enhanced efficacy and safety compared to ciclosporin that is already on the EML. It's indication is for organ transplantation and it would therefore only be used in settings where this is available and affordable. The formulations are 0,5 mg, 0,75 mg, 1 mg, 2 mg, 5 mg capsules 0,2 mg and 1mg granules 5mg/ml solution.
References (if required)	