National Essential Drug List
Tertiary/Quaternary Medication Review Process

TITLE: Extended release tacrolimus in kidney transplant recipients

Date: June 2023

Key findings

- A meta-analysis and systematic review, found no significant differences between extended and immediate release tacrolimus formulations in terms of patient survival, graft survival, biopsy-proven acute rejection rate (BPAR), estimated glomerular filtration rate (eGFR), creatinine Clearance (CrCl), serum creatinine (Scr).[5]
- Once daily dosing has the potential to improve adherence.
- Current costs of extended release tacrolimus far exceeds that of immediate release tacrolimus.

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
			X		

Rationale:
Extended release tacrolimus has been shown to be equivalent to immediate release tacrolimus, and interchangeable on an mg per mg basis (therapeutic level monitoring required). The current price of extended release tacrolimus is unaffordable however, it can be considered if pricing becomes similar to the immediate release tacrolimus (within 15%).

Level of Evidence: moderate to low.

(Refer to appendix 1 for the evidence to decision framework)

BACKGROUND

Tacrolimus has been approved on the Tertiary and Quaternary Essential Medicines List for the following indications (NEMLC: 27 June 2017):

- Primary therapy in high immunological risk renal allograft recipients.
- Renal allograft recipients on ciclosporin who experience steroid resistant acute allograft rejection.

At the time of review only immediate release tacrolimus was available and registered in South Africa, and thus extended release formulations were not considered. Subsequently extended release tacrolimus formulations have become available.

Extended-release formulation allow for once-daily dosing, with the potential to improve adherence. Phase I pharmacokinetic trials have demonstrated a decreased maximum absorption (C_{max}) and a delayed time to maximum concentration (t_{max}) with the extended release formulation, however the area under the plasma concentration-time curve over the last 24-h dosing interval (AUC_{0-24}) was comparable between the extended release and immediate release formulations (C_{max} and t_{max} differences consistent with prolonged release formulations). Phase II and III studies have also shown comparable AUC_{0-24} from day 3 or 4 (reductions in AUC_{0-24} seen on initial doses of extended release formulations in *de novo* transplant patients – may necessitate increased initial dose).[1]

Conversion studies from immediate to extended release tacrolimus on a milligram for milligram basis have showed that similar steady state pharmacokinetics are achieved between the formulations in stable kidney transplant recipients. [2,3] There have however been studies in various solid organ recipients showing the need for dose escalations in up to 50% of recipients, thus therapeutic drug monitoring following conversions between formulations is warranted.[1]

This limited review explores the efficacy and estimated budget impact of extended-release tacrolimus release formulation compared to the immediate release formulation in transplant recipient patients.

Purpose/Objective i.e. PICO

-P *(patient/population):* Transplant recipient patients (particularly kidney)

-I *(intervention):* Tacrolimus extended release formulations

-C *(comparator):* Immediate release formulations

-O *(outcome):*

- Patient survival
- Graft survival
- Biopsy-proven acute rejection rate (BPAR)
- Estimated glomerular filtration rate (eGFR)
- Creatinine Clearance (CrCl)
- Serum creatinine (Scr)

-S *(study type):* Systematic reviews and meta-analysis

Methods

Data sources: PubMed, Cochrane

Search strategy:

((tacrolimus[MeSH Terms]) OR (tacrolimus[Title/Abstract])) AND ((extended release[MeSH Terms]) OR (extended release[Title/Abstract])) *Filters:* ***Meta-Analysis, Systematic Review***

- 5 Results (see table below)

	Systematic review and meta-analysis	Recommendation
1	Effects of CPY3A5 Genetic Polymorphisms on the Pharmacokinetics of Extended release and Immediate-release Tacrolimus Formulations in Renal Transplant Recipients: A Systematic Review and Meta-analysis. Xie Q, Xiang Q, Liu Z, Mu G, Zhou S, Zhang Z, Ma L, Cui Y.Curr Drug Metab. 2021;22(10):758-771.	Does not meet PICO
2	Once-Daily versus Twice-Daily Tacrolimus in Kidney Transplantation: A Systematic Review and Meta-analysis of Observational Studies. Vadcharavivad S, Saengram W, Phupradit A, Poolsup N, Chancharoenthana W.Drugs. 2019 Dec;79(18):1947-1962.	Include
3	Extended release versus immediate release tacrolimus in kidney transplant recipients: a systematic review and meta-analysis. Saengram W, Vadcharavivad S, Poolsup N, Chancharoenthana W.Eur J Clin Pharmacol. 2018 Oct;74(10):1249-1260	Include
4	Once-daily extended-release versus twice-daily standard-release tacrolimus in kidney transplant recipients: a systematic review. Ho ET, Wong G, Craig JC, Chapman JR.Transplantation. 2013 May 15;95(9):1120-8.	Include
5	Definition and Prospective Assessment of Functional Recovery After Liver Transplantation: A New Objective Consensus-Based Metric for Safe Discharge. Brustia R, Boleslawski E, Monsel A, Barbier L, Dharancy S, Adam R, Dumortier J, Lesurtel M, Conti F, Scatton O; Groupe de Recherche Français en Greffe de Foie (GReF²) and the Association de Chirurgie Hépato-Pancréato-Biliaire et Transplantation (ACHBT) Collaborative Group.Liver Transpl. 2020 Oct;26(10):1241-1253.	Does not meet PICO

Evidence synthesis:

Three potential systematic reviews identified:

- Vadcharavivad et.al. 2019[4] – Systematic review and meta-analysis of observational studies (10 studies).
- Saengram et.al. 2018[5] – Systematic review and meta-analysis of 11 randomised trials in kidney transplant recipients.
- Ho et.al. 2013[6] – Systematic review of six randomised trials in kidney transplant recipients.

Inclusion/Exclusion:

Excluded: Ho.et.al. - All RCTs besides one phase II RCT included in Saengram et.al. Excluded phase II study does not add anything extra.

Inclusion:

- Saengram et.al. 2018
- Vadcharavivad et.al. 2019 (observational, but included for completeness)

Citation	Study design	Population (n)	Treatment	Main findings *(details below in efficacy discussion)*	Risk of bias
Saengram et.al. 2018[5]	Systematic review and meta-analysis of randomised trials	11 RCTs: Adult kidney transplant recipients	Extended release once daily versus immediate release formulation tacrolimus	Impact on allograft function comparable between formulations	Cochrane risk of bias tool used. Low risk of in 2 RCTs, however most trial not blinded, and majority did not provide information on random sequence generation and/or allocation concealment.
Vadcharavivad et.al. 2019[4]	Systematic review and meta-analysis of observational studies	10 observational studies: Adult kidney transplant recipients		Extended release formulation associated with a 30% lower risk of BPAR at 12 months post kidney transplant. No significant difference at other time points. No difference in graft/patient survival rates.	ROBINS-I tool used. One assessed as moderate quality and remaining 9 studies assessed as serious overall risk of bias.

COMPARATIVE ISSUES RELATING TO TACROLIMUS FORMULATIONS:

Efficacy

Patient survival

» The pooled relative risk (RR) for patient survival in the first 6 months post kidney transplant was 1.00 (95% CI 1.00 to 1.01; p = 0.31; 8 RCTs n = 2252) and 1.00 at 12 months (95% CI 0.99 to 1.02; p = 0.63; 4 RCTs n = 1738). The difference in survival rate post 12 months was not significant (RR 1.01; 95% 0.98 to 1.04; p = 0.68; 2 RCTs n = 969).[5]

» No significant difference in patient survival found in observational studies. At 6 months and 1 year post kidney transplant, patient survival RR 0.99 (95% CI 0.94 to 1.04; p = 0.75; 2 studies, n = 153) and 1.00 (95% CI 0.97 to 1.03; p = 0.94; 4 studies, n = 426).[4]

Graft survival

» The pooled RR for graft survival rate within 6 months was 1.00 (95% CI 0.98 to 1.02; p = 0.89; 7 RCTS n = 1709) and 1.01 at 12 months (95% CI 0.99 to 1.03; p = 0.47; 4 RCTS n = 1738). The pooled RR for graft survival rate after 12 months post kidney transplant was 1.02 (95% CI 0.98 to 1.05; p = 0.29; 2 RCTs n = 969).[5]

» No significant difference in graft survival found in observational studies. Six months and 1 year graft survival RR 1.01 (95% CI 0.96 to 1.07; p = 0.68; 3 studies, n = 161) and 1.01 (95% CI 0.98 to 1.04; p = 0.50; 4 studies, n = 426) respectively. [4]

Biopsy-proven acute rejection rate (BPAR)

» The pooled RR for BPAR 6 months post kidney transplant was 1.03 (95% CI 0.82 to 1.28; p=0.81; 7 RCTs n=2452), and 1.11 twelve months post kidney transplant (95% CI 0.88 to 1.40; p = 0.40; 4 RCTs n = 1738).[5]

» In 5 observational studies, reported BPAR incidence between formulations was 15.7% in extended release group and 23.7% in immediate release group, absolute risk difference of 8%. A significantly lower BPAR found with use of the extended release formulations 12 months post kidney transplant (RR 0.69, 95% CI 0.51 to 0.95; p = 0.02; 5 observational studies, n = 659). No significant findings at other points.[4]

Estimated glomerular filtration rate (eGFR) at 12 months

» No significant difference in eGFR between extended release and immediate release formulations at 12 months post kidney transplant (Mean difference: -0.77 mL/min/1.73m^2; 95% CI: -2.41 to 0.87; p = 0.36) *[4 Randomised Controlled Trials, n=1738].*[5]

» No significant difference found in eGFR at 12 months post kidney transplant in observational studies. Pooled results at 12 months should mean difference of -1.37 mL/min/1.73m^2 (95% CI -4.80 to 2.07; p = 0.44; 2 studies, n = 307). [4]

Estimated glomerular filtration rate (eGFR) at 6 months

» No significant difference in eGFR between extended release and immediate release formulations at 6 months post kidney transplant (Mean difference: -0.42 mL/min/1.73m^2; 95% CI: -1.82 to 0.98; p = 0.56) *[6 Randomised Controlled Trials, n=1768].*[5]

» No significant difference found in eGFR at 6 months in observational studies.[4]

Creatinine Clearance (CrCl)

There was no significant difference shown in CrCl at 6 and 12 months post kidney transplant (Mean difference: -0.90 mL/min; 95% CI -3.27 to 1.47; p = 0.46; 3 RCTs) and (Mean difference: 0.24 mL/min; 95% CI -2.08 to 2.55; p = 0.84; 2 RCTs) respectively.[5]

Serum creatinine (Scr)

» There was no significant pooled difference in Scr at 6 months (Mean difference: 0.04 mg/dL; 95% CI – 0.05 to 0.13; p = 0.42; 2 RCTS) and 12 months after kidney transplant (Mean difference: -0.01 mg/dL; 95% CI – 0.07 to 0.05; p = 0.85; 2 RCTS).[5]

» No significant difference in Scr found in observational studies. At 6 post kidney transplant, mean difference in Scr – 0.05 mg/dL (95% CI -0.25 to 0.15; p = 0.62; 3 studies, n = 246).[4]

Adherence versus patient satisfaction

Once daily dosing has the potential to improve adherence. Non-adherence has been shown to be common in adult renal transplant recipients, and have a large impact on transplant survival.[7] Studies have shown that generally prescribed number of doses per day is inversely related to adherence, with less frequent dosing resulting in better compliance.[8] A prospective observational study conducted to determine the efficacy, safety and immunosuppressant adherence in liver transplant patients found a statistically significant reduction in non-adherence from 66% at study entry to 30.9% at 12 months post conversion from tacrolimus twice daily

to extended release tacrolimus p < 0.001, (using basal assessment adherence scale to immunosuppressives.[9]
(Also see EtDF: values, preferences, acceptabilities)

Cost comparison

The equivalent dosing of immediate and extended release tacrolimus is 1:1 ratio.

Table 1: Price comparison Immediate and extended release tacrolimus formulations
(Only generic item on contact included – all generics included on supplementary spreadsheet)

	Company	Medicine Proprietary Name	Formulation type	Price per pack	Price per capsule	Price per mg
CONTRACT*	Accord Healthcare (Pty) Ltd	Tacrolimus 0.5mg capsules, 30s	Immediate	R91.08	R3.04	R6.07
CONTRACT	Accord Healthcare (Pty) Ltd	Tacrolimus 1mg capsules, 30s	Immediate	R180.78	R6.03	R6.03
CONTRACT	Accord Healthcare (Pty) Ltd	Tacrolimus 5mg capsules, 30s	Immediate	R892.86	R29.76	R5.95
SEP**	Accord Healthcare (Pty) Ltd	Tacrolimus 5mg capsules, 100s *(Tarograf 5*)	Immediate	R10,667.92	R106.68	R21.34
SEP	Accord Healthcare (Pty) Ltd	Tacrolimus 1mg capsules, 100s *(Tarograf 1)*	Immediate	R2,205.82	R22.06	R22.06
SEP	Accord Healthcare (Pty) Ltd	Tacrolimus 0.5mg capsules, 30s *(Tarograf 0.5)*	Immediate	R1,199.66	R12.00	R24.00
SEP	Astellas Pharma (Pty) Ltd	Advagraf 0,5 mg	Extended	R711.69	R23.72	R47.44
SEP	Astellas Pharma (Pty) Ltd	Advagraf 5 mg	Extended	R6,310.33	R210.34	R42.07
SEP	Astellas Pharma (Pty) Ltd	Advagraf 1 mg	Extended	R1,296.86	R43.23	R43.23

**Master Health Product List: April 2023*
***Database of Single Exit Prices: December 2022*

Table 2: Price comparison based on average dose in average patient

(Dose: 0.2mg/kg/day; Patient: 70kg)

	Company	Medicine Proprietary Name	Active Ingredients	Daily Price per average daily dose/patient	Monthly price per average daily dose/patient	Annual price per average daily dose/patient
CONTRACT	Accord Healthcare (Pty) Ltd	Tarograf products	Tacrolimus *(immediate)*	**R83.63**	**R2,341.58**	**R28,099.01**
SEP	Accord Healthcare (Pty) Ltd	Tarograf products	Tacrolimus *(immediate)*	**R301.60**	**R8,444.80**	**R101,337.60**
SEP	Cipla Medpro (Pty) Ltd	TACRUM products	Tacrolimus *(immediate)*	**R487.48**	**R13,649.44**	**R163,793.28**
SEP	Strides Pharma SA (Pty) Ltd	Talomune products	Tacrolimus *(immediate)*	**R479.88**	**R13,436.64**	**R161,239.68**
SEP	Astellas Pharma (Pty) Ltd	Prograf products	Tacrolimus *(immediate)*	**R556.56**	**R15,583.68**	**R187,004.16**
SEP	Astellas Pharma (Pty) Ltd	Advagraf products	Tacrolimus ***(extended release)***	**R593.60**	**R16,620.80**	**R199,449.60**

Table 3: Sensitivity analysis (estimated contract price of extended release tacrolimus)

		Estimated Contract Price (per mg)							
	Current SEP/mg	**70%**	**60%**	**50%**	**40%**	**30%**	**20%**	**15%**	**10%**
Extended release tacrolimus 0,5 mg	R47.44	R33.21	R28.46	R23.72	R18.98	R14.23	R9.49	**R7.12**	**R4.74**
Extended release tacrolimus 5 mg	R42.07	R29.45	R25.24	R21.03	R16.83	R12.62	R8.41	**R6.31**	**R4.21**
Extended release tacrolimus 1 mg	R43.23	R30.26	R25.94	R21.62	R17.29	R12.97	R8.65	**R6.48**	**R4.32**

Current National Contract Price for tacrolimus immediate release capsules ranges from R5.95 to R6.07 per milligram. Table 3 shows sensitivity analysis of estimated contract price. To be comparable to the currently available tacrolimus formulation, the cost of extended release tacrolimus would need to be 10-15% of the current price.

SUMMARY

- Tacrolimus immediate and extended release formulations have been demonstrated to be equivalent for immunosuppression post kidney transplant.
- Benefits in terms of a once daily dosing (over multiple daily dosing) of extended release tacrolimus may improve adherence.
- The current price of extended release tacrolimus is largely more costly (~80% more) than the available tacrolimus on National Contract.

- The availability of an extended release formulation would be beneficial, however at the current pricing, it is not affordable. If extended release formulation was offered to State at a similar price (within 15%) to that of the immediate release product (on mg/mg basis), this item should be considered for procurement and use.

RECOMMENDATIONS

It was recommended that extended release formulations be considered if they can be procured at a similar price to that of the immediate release tacrolimus.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [x] Low: [ ] Very low: [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Low to moderate: MA and SR of RCT* *Serious bias issues in MA of observational studies*
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: [ ] Moderate: [ ] Small: [ ] None: [X]	*No significant differences*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: [ ] Moderate: [X] Low: [ ] Very low: [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge: [ ] Moderate: [ ] Small: [ ] None: [X]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [ ] Favours control: [ ] Intervention = Control *or* Uncertain: [X]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [ ] No: [ ] Uncertain: [X]	*If costing is similar, and affordability Is not a concern then this should be a feasible recommendation.*

<table>
<tr>
<td>RESOURCE USE</td>
<td>How large are the resource requirements?
More intensive: X
Less intensive:
Uncertain:</td>
<td>Cost of medicines/ month (0.2mg/kg/day, 70kg):
<table>
<tr><th>Medicine</th><th>Cost (ZAR)</th></tr>
<tr><td>Extended Release Tacrolimus</td><td>R16,620.80</td></tr>
<tr><td></td><td></td></tr>
</table>
Additional resources: See Cost section above and costing spreadsheets</td>
</tr>
<tr>
<td>VALUES, PREFERENCES, ACCEPTABILITY</td>
<td>Is there important uncertainty or variability about how much people value the options?
Minor: X
Major:
Uncertain:

Is the option acceptable to key stakeholders?
Yes: X
No:
Uncertain:</td>
<td>Once daily dosing expected to be more acceptable to patients</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Would there be an impact on health inequity?
Yes:
No:
Uncertain: X</td>
<td></td>
</tr>
</table>

References

[1] Patel N, Cook A, Greenhalgh E, Rech MA, Rusinak J, Heinrich L. Overview of extended release tacrolimus in solid organ transplantation. World Journal of Transplantation. 2016, 16(1):144-154.

[2] van Hooff J, Van der Walt I, Kallmeyer J, Miller D, Dawood S, Moosa MR, et.al. Pharmacokinetics in stable kidney transplant recipients after conversion from twice-daily to once-daily tacrolimus formulations. Ther Drug Monit 2012; 34:46-52.

[3] Alloway R, Steinberg S, Khalil K, Gourishankar S, Miller J, Norman D, et.al. Conversion of stable kidney transplant recipients from a twice daily Prograf-based regimen to a once daily modified release tacrolimus-based regimen. Transplant Proc 2005; 37: 867-870.

[4] Vadcharavivid S, Saengram W, Phupradit A, Poolsup N, Chancharoethana W. Once-daily versus twice-daily tacrolimus in kidney transplantation: A Systematic Review and Meta-analysis of Observational Studies. Drugs. 2019, 79: 1947-1962.

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[6] Ho ETL, Wong G, Craig JC, Chapman JR. Once-daily extended-release versus twice-daily standard-release tacrolimus in kidney transplant recipients: a systematic review. Transplantation. 2013, 95: 1120-1128.

[7] Butler JA, Roderick P, Muller M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: A Systematic Review. Transplantation. 2004, 77: 769-789.

[8] Claxton AJ, Cramer J, Pierce C. A systematic review of associations between dose regimens and medication compliance. Clinical Therapeutics. 2001, 23 (8): 1296-1310.

[9] Beckebaum S, Iacob S, Sweid D, Sotiropoulos GC, Saner F, Kaiser G, et.al. Efficacy, safety, and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation. Transpl Int 2011; 24: 666-675.