UCMC Liver Transplant mTOR (Everolimus) Conversion Guideline

Preferred mTOR and Initiation Regimen	• Everolimus (EVR) (Zortress®) - available in 0.25, 0.5 and 0.75 mg tablets. To standardize, please use the 0.5mg tablet strength. • Initial dosing (simultaneously initiate EVR while decreasing CNI). EVR - initiate dose at 2mg by mouth TWICE DAILY • CNI (tacrolimus or cyclosporine): decrease total dose by 50% until EVR therapeutic, then discontinue or target appropriate goal
Indications for EVR Conversion	• To minimize or avoid calcineurin inhibitor (CNI) therapy • Chronic Kidney Disease • HIGH RISK for HCC recurrence (initiate POD #31-60 as long as no contraindications) • History of cancer recurrence post-transplantation (HCC or other)
Lab Tests (complete PRIOR to conversion)	• CBC with differential • Renal panel (with eGFR) • Urine protein/creatinine ratio (both must be obtained from same urine collection (same date/time) • Lipid profile (LAB18) - If abnormal adjust/initiate anti-lipid therapy; consider delaying EVR conversion until normal cholesterol levels are achieved
Contraindications to EVR Conversion	• Major open wounds or known impaired wound healing • Anticipated need for surgical intervention • Urine protein/creatinine ration > 1.0 • ANC < 1000
CNI Elimination	**EVR target levels (ng/mL): POD 0-30: 10-12; POD 31-180: 8-10; POD > 180: 6-8** • MMF: maintain or optimize current dose as tolerated • May consider addition of low-dose corticosteroid if history of rejection or inability to tolerate increased MMF dose
CNI Minimization	**EVR target levels (ng/mL): 3-8** and **TAC target levels (ng/mL): 3-5**. *May target combined EVR and TAC levels of 8-10 ng/mL* • MMF: maintain or optimize current dose as tolerated
Monitoring (post conversion)	• *EVR and CNI levels* o Obtain levels 3-5 days post conversion (NOTE: EVR half-life is shorter than sirolimus) o Checking EVR level sooner than 3 days post conversion provides inaccurate information and should not be done o EVR level should be a trough level (i.e. patient gets AM lab draw BEFORE taking morning dose of EVR) o Titrate EVR and CNI doses to achieve EVR target levels as follows: ▪ EVR level at target: continue EVR 2mg by mouth TWICE DAILY and discontinue CNI. Monitor EVR levels every 3-5 days until stable level is achieved. ▪ EVR level sub-therapeutic: increase EVR to 4mg by mouth TWICE DAILY and continue current or increase CNI dose (varies per situation depending on CNI level). Continue to monitor EVR and CNI levels every 3 - 5 days until stable level is achieved for EVR. When therapeutic EVR occurs, then discontinue CNI ▪ EVR level is supra- therapeutic: decrease EVR dose to 1mg by mouth TWICE DAILY and discontinue CNI. Continue to monitor EVR levels every 3 - 5 days until stable dose/level is achieved. o Once stable EVR level is achieved monitor monthly and then at frequency of regular maintenance labs

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Monitoring
(post conversion)
 	
Continued from Pg.1
	• *Lipid profile (LAB18)*
	  ○ Obtain 2 weeks post initiation, then monthly x 2, then every 3 months x 2, then at frequency of regular maintenance labs
	• *Spot u*rine (protein/creatinine ratio (PCR))
	  ○ Obtain every 2 weeks x 2, then monthly x 2, every 3 months x 2, then annually

Common Adverse Events	• In general
	  ○ EVR has fewer, less severe adverse events relative to sirolimus
	  ○ Adverse events are most likely to occur during the initial conversion / dose titration period
	Commonly observed adverse events and recommended therapy:
	• Pulmonary Edema – if radiographically confirmed, then target a lower EVR level
	• Mouth ulcers – initiate therapy (possible options listed below) and may need to target a lower EVR level
	  ○ Chlorhexidine 0.2% (10ml swish and spit two times daily for pain)
	  ○ Benzydamine 0.15% (10-15ml rinsed in mouth every 3 hours for pain)
	  ○ Steroid topical ointment or mouthwash applied twice daily (i.e. hydrocortisone, betamethasone, clobetasol, fluocinolone; consult PharmD for specific doses)
	• Peripheral edema— target a lower EVR level
	• Leukopenia—target a lower EVR level (NOTE: occurs less often compared to MMF and sirolimus)
	• Bone pain – target a lower EVR level (if clinically indicated)
	• Elevated triglycerides (isolated)- TRICOR® 1 tab (145mg) daily (dose adjust for renal dysfunction)
	  ○ Other options: Lovaza® (prescription) or OTC fish oil formulations, statin therapy
	  ○ In those with Type 2 diabetes, check hemoglobin A1C. Elevated A1C may also exacerbate triglyceride levels.

EVR Discontinuation	*Consider discontinuation when:* • Severe adverse events continue despite target level modifications • Triglycerides ≥ 500 despite therapy and strict control of diabetes mellitus • Abnormal LFT's • Proteinuria defined by PCR > 3 (OR) when PCR doubles from baseline

CNI = calcineurin inhibitor; EVR = everolimus; HCC = hepatocellular carcinoma; MMF = mycophenolate mofetil; OTC = over the counter; POD = post-operative day; PCR = protein creatinine ratio