## 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 ratio > 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**
  - Obtain levels 3-5 days post conversion (NOTE: EVR half-life is shorter than sirolimus)
  - Checking EVR level sooner than 3 days post conversion provides inaccurate information and should not be done
  - EVR level should be a trough level (i.e. patient gets AM lab draw BEFORE taking morning dose of EVR)
  - 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.
  - Once stable EVR level is achieved monitor monthly and then at frequency of regular maintenance labs
### 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 urine (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

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