Informed consent MUST be taken before enoximone is started and documented in the medical notes. Attention should be given to the unlicensed indication for use, age and route and the small risk of arrhythmic complications.

**Indication**
- The main place in therapy of enoximone is for stabilisation of end-stage heart failure patients awaiting cardiac transplantation (“medical bridge”)
- Non-hypertrophic cardiomyopathy
- The inotropic/vasodilatory effects of enoximone have been demonstrated useful in improving cardiac function in patients with congestive heart failure.

**Contra-indications**
- Hypertrophic cardiomyopathy
- Stenotic valvular disease
- Hypersensitivity to enoximone

**Cautions**
Enoximone should be used cautiously in patients with:
- Angina pectoris
- Atrial fibrillation (enoximone may decrease AV nodal conduction and increase ventricular rate)
- Hepatic disease
- Pre-existing ventricular arrhythmias
- Recent myocardial infarction
- Renal disease
- Severe pulmonary disease

**Side-effects/adverse drug reactions**
An increase in ventricular arrhythmias including ventricular ectopy and ventricular tachycardia has been reported in some congestive heart failure patients during oral or intravenous enoximone therapy.

In one study hypotension and syncope were reported in 12 and 10%, respectively, of patients receiving oral enoximone (150 to 450mg/day)

Pruritis has been observed rarely during oral enoximone therapy.
Oral enoximone has been associated with adverse gastrointestinal effects, including nausea, dyspepsia, anorexia and diarrhoea. The incidence of these effects has usually been lower (10% or less) with doses below 3mg/kg/day with the incidence increasing at higher doses (20-40%).

Reversible elevations in serum transaminases have been reported in some patients treated with oral enoximone. These changes were reproducible when rechallenged.

Headache, dizziness and fatigue have accompanied oral enoximone therapy, usually in less than 10% of patients. These effects appear to be more frequent with higher doses of enoximone (3mg/kg/day or greater).

### Mode of action

Enoximone is a phosphodiesterase inhibitor. Similar to other phosphodiesterase inhibitors, enoximone possesses both positive inotropic and vasodilatory activity. Although the exact mechanism of action of enoximone is not completely understood, available evidence suggests that positive inotropic effects are primarily mediated via selective inhibition of cardiac phosphodiesterase. This inhibition results in increases in intracellular levels of cyclic AMP, which facilitate enhanced flux of calcium through sarcolemmal slow channels and increased calcium uptake by the sarcoplasmic reticulum. An increased rate of relaxation of the heart is observed, but contractions are also enhanced as a result of increases in the total amount of intracellular calcium. Similarly relaxation of peripheral vascular smooth muscle due to elevations of intracellular cyclic AMP promoted by enoximone in these tissues may be responsible for vasodilatory properties of the drug and resultant decreases in systemic vascular resistance.

### Place in therapy

Oral Enoximone can be used for 2 different situations

1. **Part of a cardiomyopathy medication regime**
   - Child should be already established on diuretics, captopril or hydralazine (top dose, as tolerated) and maybe carvediolol.

2. **Wean a cardiomyopathy child off long-term intravenous inotropes**

### Dosing regime

This is an unlicensed use and route of a licensed medicine.

**Oral dosing (not on milrione):**
All ages; 1mg/kg/dose three times a day

**Dose in renal impairment**
The dose of enoximone should be reduced when creatinine clearance falls below 20ml/minute/1.73m²

**Please contact your ward pharmacist for further information**

**Switching from intravenous milrinone to oral enoximone**
Continue the milrinone infusion at the current rate and start oral enoximone at 0.5mg/kg/dose three times a day for 1 day. If the oral enoximone is tolerated then the dose should be increased to 1mg/kg/dose three times a day.

Then gradually reduce the dose of milrinone and once enoximone has taken full effect (usually 2-3 hours after third dose of enoximone 1mg/kg/dose) the milrinone infusion...
can be stopped
Continue monitoring to ensure oral enoximone is efficacious (see monitoring below)

<table>
<thead>
<tr>
<th>Administration², ³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoximone is available in injection form: 100mg in 20ml</td>
</tr>
<tr>
<td>This can be used orally.</td>
</tr>
</tbody>
</table>

**Oral administration**
- The injection can be given orally, however the solution has a very alkaline pH and should therefore be mixed with milk feeds or orange juice.
- Once an ampoule is open, draw up the next three doses required in syringes and these may be kept at room temperature for up to 24 hours.
- Hyperosmolality and lactic acidosis may occur with large doses of enoximone infusion as injection contains 43.4% of propylene glycol.
- Plastic apparatus should be used during the administration of enoximone as crystallisation may occur if glass is used.

<table>
<thead>
<tr>
<th>Monitoring Requirements¹, ³</th>
</tr>
</thead>
<tbody>
<tr>
<td>When oral enoximone is initiated monitoring is necessary to ensure it is having the intended effects. The following parameters should be monitored every hour for the first four hours for the initial dose and any increase in dose and then 4 hourly thereafter until the patient has been established on enoximone (po) for 3 days. The monitoring can then be reduced to 12 hourly if patient’s condition allows and an ECG performed weekly for the first few weeks.</td>
</tr>
<tr>
<td>- Heart rate</td>
</tr>
<tr>
<td>- Oxygen saturations</td>
</tr>
<tr>
<td>- Blood pressure</td>
</tr>
<tr>
<td>- Respiratory rate</td>
</tr>
<tr>
<td>- Electrocardiogram</td>
</tr>
</tbody>
</table>

Also as enoximone injection contains a large content of propylene glycol then for the first few weeks, weekly blood lactate levels must be done.

<table>
<thead>
<tr>
<th>Pharmacokinetics¹, ³</th>
</tr>
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<tbody>
<tr>
<td>The majority of pharmacokinetic data is in relation to intravenous administration of enoximone.</td>
</tr>
<tr>
<td>- The half-life of enoximone is approximately 8 hours and it takes approximately 1-2 hours to have an effect.</td>
</tr>
<tr>
<td>- Half-life may increase in severe liver impairment causing accumulation</td>
</tr>
</tbody>
</table>

**References and Provenance**
3. Personal communication on 30/06/2010 with Sara Arenas PICU pharmacist at Evelina children’s hospital.

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Quality Assurance Check by: Paediatric Cardiology Team

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