Application for inclusion of captopril (Paediatrics)

1. Summary statement of the proposal for inclusion, change or deletion

There are currently no Angiotensin Converting Enzyme (ACE) inhibitors included in the Essential Medicines List for children (EMLc). The subcommittee on the Selection and Use of Essential Medicines recently identified the need for a review of the drugs used in paediatric heart failure, as a result of which it is now considered appropriate to propose that captopril, as a representative of the ACE inhibitor group, is added to the EMLc.

In summary, ACE inhibitors are now established as a cornerstone of heart failure management in adults and there is growing evidence from clinical trials and specialist experience that these drugs also provide significant benefits for children with cardiac failure.

Further information supporting this application will be found in the attached report.

2. Name of the focal point in WHO submitting or supporting the application

TBA

3. Name of the organization(s) consulted and/or supporting the application

TBA

4. International Nonproprietary Name (INN, generic name) of the medicine

Captopril (CAS No: 62571-86-2)

5. Dosage form or strength proposed for inclusion

Tablets: 12.5mg, 25mg and 50mg
Oral liquid: 5mg/ml

6. International availability - sources, if possible manufacturers

Tablets: 12.5mg, 25mg and 50mg
Suspension: 5mg/ml

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Example of therapeutic group. Other examples of the ACE inhibitor group have also been proven to be effective in children (e.g. Enalapril) and in adults (e.g. Enalapril, Ramipril, Lisinopril). Please refer to attached report for justification of choosing
Captopril as the example in children, rather than Enalapril which is already on the EML for adults.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

This application for the inclusion of captopril (as a representative of the ACE inhibitor group) on the EMLc is for use in paediatric cardiac failure. Please refer to the attached report, Cardiac Failure in Children, for further information on the burden of the disease etc.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

Captopril is administered orally, the average minimal absorption is approximately 75%, peak plasma concentrations are reached within 60-90 minutes. In some nations, captopril product literature recommends dosing one hour before food, as food has been reported to reduce absorption by about 30-40%. Unlike many other ACE inhibitors, captopril does not require biotransformation for therapeutic activity.

ACE inhibitors should be initiated in children by specialists experienced in their use, test doses given under supervision and whilst the child is supine. The following doses are those recommended by the British National Formulary for Children (2008):

**Neonates:** (caution) test dose, 10–50 micrograms/kg (10 micrograms/kg in neonate less than 37 weeks postmenstrual age), monitor blood pressure carefully for 1–2 hours; if tolerated give 10–50 micrograms/kg 2–3 times daily increased as necessary to max. 2 mg/kg daily in divided doses (max. 300 micrograms/kg daily in divided doses in neonate less than 37 weeks post menstrual age)

**Child 1 month–12 years:** test dose, 100 micrograms/kg (max. 6.25 mg), monitor blood pressure carefully for 1–2 hours; if tolerated give 100–300 micrograms/kg 2–3 times a day, increased as necessary to max. 6 mg/kg daily in divided doses (max. 4 mg/kg daily in divided doses for child 1 month–1 year)

**Child 12–18 years:** test dose, 100 micrograms/kg or 6.25 mg, monitor blood pressure carefully for 1–2 hours; if tolerated give 12.5–25 mg 2–3 times a day, increased as necessary to max. 150 mg daily in divided doses

There are no existing guidelines for the management of cardiac failure in children, although ACE inhibitors are recommended in guidelines for the management of the condition in adults produced in Europe, the U.S. and Australia.
10. Summary of comparative effectiveness in a variety of clinical settings:
• Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)
• Summary of available data (appraisal of quality, outcome measures, summary of results)
• Summary of available estimates of comparative effectiveness

Please refer to the attached report, Cardiac Failure in Children, for further information on the evidence for captopril and other ACE inhibitors in the management of cardiac failure in children. A recent review stated that there was no compelling clinical case to choose one ACE inhibitor over another for heart failure in children (see report).

11. Summary of comparative evidence on safety:
• Estimate of total patient exposure to date
• Description of adverse effects/reactions
• Identification of variation in safety due to health systems and patient factors
• Summary of comparative safety against comparators

Captopril was the first ACE inhibitor to be marketed and remains in widespread use. As a group the ACE inhibitors have become commonly used in the management of cardiac failure (and other conditions, such as hypertension) based on clinical experience over a period which now approaches 20 years. During this time the benefits of treatment with ACE inhibitors has been shown to exceed the risks.

Adverse effects from captopril (and other ACE inhibitors) are predictable from the pharmacology and include, hypotension (in particular after the first dose and postural), electrolyte disturbance (especially rises in serum potassium and creatinine), and cough. More rarely angioedema, hepatic damage and renal damage have been reported. Captopril may be associated with a higher incidence of loss of taste, skin reactions and blood dyscrasias than other ACE inhibitors, possibly as a result of the sulphhydryl group within the drug molecule.

Captopril is however one of the few ACE inhibitors for which published trial data in paediatric heart failure is available.

Captopril (unlike some other ACE inhibitors e.g. enalapril) is also known to be potentially stable as a liquid formulation, in some nations a licensed liquid is available, in others it is available as an extemporaneous preparation (see attached report).

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:
• Range of costs of the proposed medicine
• Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

Captopril (and most other ACE inhibitors e.g. enalapril, ramipril, lisinopril and perindopril erbumine) are patent expired and available from various manufacturers as generic* medicines, typical costs quoted in September 2008 are:
12.5mg tablets
Aus $16.25 / 90 tabs UK £0.72 / 56 tabs U.S. $12.99 / 100 tabs

25mg tablets
Aus $20.84 / 90 tabs UK £0.90 / 56 tabs U.S. $14.99 / 100 tabs

50mg tablets
Aus $35.27 / 90 tabs UK £1.53 / 56 tabs U.S. $12.99 / 60 tabs

5mg/ml oral liquid*
Aus $111.39 / 95ml Not available Not available

* Capoten brand, generic oral liquid not commercially available in Australia

In addition, captopril is included in the International Drug Price Indicator Guide, from which the following information was taken:

<table>
<thead>
<tr>
<th></th>
<th>12.5mg tab/cap</th>
<th>25mg tab/cap</th>
<th>50mg tab/cap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplier median unit price</td>
<td>$0.0070</td>
<td>$0.0189</td>
<td>$0.0191</td>
</tr>
<tr>
<td>Buyer median unit price</td>
<td>$0.0114</td>
<td>$0.0109</td>
<td>$0.0252</td>
</tr>
</tbody>
</table>

Twice or three times daily treatment with captopril will be required long term (life-long or in some cases until surgical treatment), estimates of cost per QALY are not available for use in paediatric cardiac failure.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Licensed captopril products available in: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Israel, Italy, Malaysia, Mexico, Netherlands, Norway, New Zealand, Philippines, Portugal, Russia, South Africa, Singapore, Spain, Sweden, Switzerland, Thailand, Turkey, United Arab Emirates, United Kingdom, United States, Venezuela:

It should however be noted that captopril is unlicensed for use in children in those countries where the relevant literature has been identified.


Chinese, European, International, Japanese and United States pharmacopoeias
15. Proposed (new/adapted) text for the WHO Model Formulary

12. CARDIOVASCULAR MEDICINES

12.4 Medicines used in heart failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>Oral liquid: 5mg / ml</td>
</tr>
<tr>
<td></td>
<td>Tablets: 12.5mg, 25mg and 50mg</td>
</tr>
</tbody>
</table>

Consideration should be given to any entry in the EMLc for an ACE inhibitor e.g. captopril, being accompanied by appropriate guidance and cautionary warnings, such as those currently included in the British National Formulary for Children, which are reproduced in Appendix 1.
Appendix 1.

Example text to accompany an ACE inhibitor entry in EMLc for Heart Failure

Heart Failure
ACE inhibitors have a valuable role in all grades of heart failure, usually combined with a loop diuretic. Potassium supplements and potassium-sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia. In adults, a low dose of spironolactone may be beneficial in severe heart failure and can be used with an ACE inhibitor provided serum potassium is monitored carefully. Profound first-dose hypotension can occur when ACE inhibitors are introduced to children with heart failure who are already taking a high dose of a loop diuretic (see Cautions below). Temporary withdrawal of the loop diuretic reduces the risk, but can cause severe rebound pulmonary oedema.

Renal effects
Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if features mentioned below are present). Hyperkalaemia and other side-effects of ACE inhibitors are more common in children with impaired renal function and the dose may need to be reduced (see under individual drugs). Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics (or potassium-containing salt substitutes) increase the risk of hyperkalaemia.

In children with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney), ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure. They are therefore contra-indicated in children known to have these forms of critical renovascular disease.

ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in children with severe unilateral renal artery stenosis and a normal contralateral kidney, but glomerular filtration is likely to be reduced (or even abolished) in the affected kidney and the long-term consequences are unknown.

ACE inhibitors are therefore best avoided in those with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If they are used in these circumstances renal function needs to be monitored. ACE inhibitors should also be used with particular caution in children who may have undiagnosed and clinically silent renovascular disease. ACE inhibitors are useful for the management of hypertension and proteinuria in children with nephritis. They are thought to have a beneficial effect by reducing intra-glomerular hypertension and protecting the glomerular capillaries and membrane.

Cautions
ACE inhibitors need to be initiated with care in children receiving diuretics (important: see Concomitant diuretics, below); first doses can cause hypotension especially in children taking high doses of diuretics, on a low-sodium diet, on dialysis, dehydrated or with heart failure (see above). Renal function should be monitored before and during treatment, and the dose reduced in renal impairment (see also above and under individual drugs). For use in known renovascular disease, see Renal Effects above. The risk of agranulocytosis is possibly increased in collagen vascular disease.
ACE inhibitors should be used with care in children with severe or symptomatic aortic stenosis (risk of hypotension) and in hypertrophic cardiomyopathy. They should be used with care (or avoided) in those with a history of idiopathic or hereditary angioedema. Children with primary aldosteronism and Afro-Caribbean children may respond less well to ACE inhibitors. Interactions: Appendix 1 (ACE inhibitors).

**Anaphylactoid reactions**

To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulphate; they should also be withheld before desensitisation with wasp or bee venom.

**Concomitant diuretics**

ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted children; treatment should therefore be initiated with very low doses. In some children the diuretic dose may need to be reduced or the diuretic discontinued at least 24 hours beforehand (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic therapy cannot be stopped, close observation is recommended after administration of the first dose of ACE inhibitor, for at least 2 hours or until the blood pressure has stabilised.

**Contra-indications**

ACE inhibitors are contra-indicated in children with hypersensitivity to ACE inhibitors (including angioedema) and in bilateral renovascular disease (see also above). ACE inhibitors should not be used in pregnancy; they may adversely affect fetal and neonatal blood pressure control and renal function, and possibly cause skull defects and oligohydramnios; toxicity in animal studies has been reported.

**CAPTOPRIL**

**Cautions**

see notes above; acute porphyria

**Renal impairment**

see notes above; start with low dose and adjust according to response

**Breast-feeding**

present in milk—manufacturer advises avoid

**Contra-indications**

see notes above

**Pregnancy**

avoid

**Side-effects**

see notes above; tachycardia, serum sickness, weight loss, stomatitis, maculopapular rash, photosensitivity, flushing and acidosis

**Licensed use**

not licensed for use in children under 18 years