

Application for inclusion of carvedilol (Paediatrics)

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

There are currently no beta-blockers 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 carvedilol is added to the EMLc.

In summary, beta-blockers such as carvedilol 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

Carvedilol (CAS No: 72956-09-3)

5. Dosage form or strength proposed for inclusion

Tablets: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg.

6. International availability - sources, if possible manufacturers

Tablets: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg are widely available, for example:

Australia: Dilasig – Sigma; Dilatrend – Roche; Kredex - Macarthur

Brazil: Cardilol – Libbs; Divelol - Baldacci

France: Kredex - Roche

India: Carloc – Cipla; Carvil - Zydus

Indonesia: Carbloxal – Sandoz, Dilbloc - Roche

United Kingdom: generic – Tillomed; Eucardic - Roche

United States: generic – Apotek; Coreg – GSK,

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

Individual medicine

Although a number of beta-blockers have been shown to be effective in treatment of heart failure in adults (bisoprolol, carvedilol, metoprolol and nebivolol), a more limited range have been evaluated in paediatric heart failure and of these carvedilol is the most widely studied.

Although it is possible that all beta-blockers may possess useful effects in treating heart failure, it is generally considered preferable to use a specific beta-blocker which has been studied in the condition and where the dosing schedule has been described.

It should also be noted that there are pharmacodynamic differences between the various beta-blockers which have been evaluated in heart failure. Some, such as propranolol are non-selective (beta-1 and beta-2 antagonists), others such as metoprolol and bisoprolol are selective for beta-1 receptors; whilst carvedilol possesses alpha-antagonist properties as well as non-selective beta-antagonist effects.

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

This application for the inclusion of carvedilol on the EMLc is for use in paediatric cardiac failure. 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)

Carvedilol is administered orally and is well absorbed from the gastrointestinal tract. It is subject to considerable first-pass metabolism in the liver; the absolute bioavailability is about 25%. Peak plasma concentrations occur 1 to 2 hours after an oral dose. It has high lipid solubility and is more than 98% bound to plasma proteins. It is extensively metabolised in the liver, primarily by the cytochrome P450 system, and metabolites are excreted mainly in the bile. The elimination half-life is around 6 to 10 hours.

Beta-blockers should be initiated in children by specialists experienced in their use. The following doses are those recommended by the British National Formulary for Children (2008):

Child 2–18 years: initially 50micrograms/kg (max. 3.125mg) twice daily, double dose at intervals of at least 2 weeks up to 350micrograms/kg (max. 25mg) twice daily

It should be noted that the upper limits of the doses recommended above are the same as those used in adults. Some research suggests that children need a higher dose per kg than is used in adults in order to provide equivalent exposure, due to differences in the pharmacokinetics between adults and children. Refer to the attached report, Cardiac Failure in Children, for further information.

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 beta-blockers and specifically carvedilol in the management of cardiac failure in children, search strategy etc.

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**

Carvedilol has been in clinical use for over 10 years and is the most widely evaluated beta-blocker in heart failure amongst both adults and children.

Use of beta-blockers in heart failure requires careful consideration and should be only be undertaken with the supervision of those experienced in their paediatric use.

Adverse effects from carvedilol are typical of beta-blockers and may include: hypotension, bradycardia, heart block, bronchospasm, fatigue and sleep disturbance. Most beta-blockers are also associated with troublesome peripheral vasoconstriction as a result of unopposed beta-blockade, however this may be less of a problem with carvedilol, due to its alpha-antagonist properties.

Although beta-blockers are used to treat heart failure, they can also precipitate or worsen heart failure. It is therefore important that they are only commenced in stable heart failure patients, at low dose and titrated slowly in accordance with a recognised schedule. In some patients with heart failure the introduction of beta-blockers and subsequent dose increases, may precipitate an initial deterioration of symptoms. This may require a temporary increase in the dose of diuretic therapy and if severe or sustained, a reduction in dose or discontinuation of the beta-blocker.

Very few beta-blockers are available in a licensed liquid formulation and those which are e.g. Atenolol (some nations only), have not been formally evaluated in heart failure, either in adults or children.

Carvedilol requires twice daily dosing. Although bisoprolol is given in a single daily dose and has been proven to be effective in adult heart failure, it has not been studied in children with this condition.

There is very limited data comparing the effectiveness of different beta-blockers in heart failure, but the one study that has been carried out compared carvedilol with metoprolol and concluded that carvedilol was more effective in adults

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)

Carvedilol is patent expired and available from various manufacturers as generic medicines, typical costs quoted in September 2008 are:

3.125 mg tablets		
Aus \$18.53 / 30 tabs	UK £5.73/28 tabs	U.S. \$14.99/30 tabs
6.25 mg tablets		
Aus \$62.71 / 60 tabs	UK £6.09 / 28 tabs	U.S. \$14.99 / 30 tabs
12.5 mg tablets		
Aus \$76.87 / 60 tabs	UK £1.51 / 28 tabs	U.S. \$14.99 / 30 tabs
25 mg tablets		
Aus \$94.60 / 60 tabs	UK £2.46 / 28 tabs	U.S. \$15.99 / 30 tabs

Carvedilol is not included in the International Drug Price Indicator Guide.

Treatment with twice daily carvedilol 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 products available in: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Mexico, Netherlands, Norway, New Zealand, Philippines, Poland, Portugal, Russia, South Africa, Singapore, Spain, Sweden, Switzerland, Thailand, Turkey, United Kingdom, United States and Venezuela

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

14. Availability of pharmacopoeial standards

Carvedilol is listed in the European pharmacopoeia

15. Proposed (new/adapted) text for the WHO Model Formulary

12. CARDIOVASCULAR MEDICINES

12.4 Medicines used in heart failure

Drug	Formulation
Carvedilol	Tablets: 3.125 mg, 6.25 mg, 12.5 mg and 25 mg

Consideration should be given to any entry in the EMLc for a beta-blocker e.g. carvedilol, 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 carvedilol entry in EMLc for Heart Failure

Beta-adrenoceptor blocking drugs

Beta-adrenoceptor blocking drugs (beta-blockers) block the beta-adrenoreceptors in the heart, peripheral vasculature, bronchi, pancreas, and liver.

Many beta-blockers are available but experience in children is limited to the use of only a few.

Differences between beta-blockers may affect choice. The water-soluble beta-blockers, atenolol and sotalol, are less likely to enter the brain and may therefore cause less sleep disturbance and nightmares. Water-soluble beta-blockers are excreted by the kidneys and dosage reduction is often necessary in renal impairment.

Some beta-blockers, such as atenolol, have an intrinsically longer duration of action and need to be given only once daily. Carvedilol and labetalol are beta-blockers which have, in addition, an arteriolar vasodilating action and thus lower peripheral resistance. Although carvedilol and labetalol possess both alpha- and beta-blocking properties, these drugs have no important advantages over other beta-blockers in the treatment of hypertension.

Beta-blockers slow the heart and can depress the myocardium; they are contra-indicated in children with second- or third-degree heart block. Sotalol may prolong the QT interval, and it occasionally causes life-threatening ventricular arrhythmias (important: particular care is required to avoid hypokalaemia in children taking sotalol).

Beta-blockers can precipitate asthma and they should be avoided in children with a history of asthma or bronchospasm; if there is no alternative, a cardioselective beta-blocker can be used with extreme caution under specialist supervision. Atenolol and metoprolol have less effect on the beta₂ (bronchial) receptors and are, therefore, relatively *cardioselective*, but they are not *cardiospecific*. They have a lesser effect on airways resistance but are not free of this side-effect.

Beta-blockers are also associated with fatigue, coldness of the extremities, and sleep disturbances with nightmares (may be less common with the water-soluble beta-blockers, see above).

Beta-blockers are not contra-indicated in diabetes; however, they can lead to a small deterioration of glucose tolerance and interfere with metabolic and autonomic responses to hypoglycaemia. The cardioselective beta-blockers (e.g. atenolol and metoprolol) may be preferable in diabetes but beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia.

Heart failure

Beta-blockers may produce benefit in heart failure by blocking sympathetic activity and the addition of a beta-blocker such as carvedilol to other treatment for heart failure may be beneficial. Treatment should be initiated by those experienced in the management of heart failure.

CARVEDILOL

Cautions

see under Propranolol Hydrochloride; monitor renal function during dose titration in children with heart failure who also have low blood pressure, renal impairment, ischaemic heart disease, or diffuse vascular disease; severe heart failure, avoid in acute or decompensated heart failure requiring intravenous inotropes

Pregnancy

see under Propranolol Hydrochloride; also lack of experience in human pregnancy limits any assessment of fetal risk

Breast-feeding

present in milk in *animal* studies but amount probably too small to be harmful; monitor infant for symptoms of alpha- and beta-blockade

Contra-indications

see under Propranolol Hydrochloride; severe chronic heart failure

Hepatic impairment

avoid

Side-effects

postural hypotension, dizziness, headache, fatigue, gastro-intestinal disturbances, bradycardia; occasionally diminished peripheral circulation, peripheral oedema and painful extremities, dry mouth, dry eyes, eye irritation or disturbed vision, impotence, disturbances of micturition, influenza-like symptoms; rarely angina, AV block, exacerbation of intermittent claudication or Raynaud's phenomenon; allergic skin reactions, exacerbation of psoriasis, nasal stuffiness, wheezing, depressed mood, sleep disturbances, paraesthesia,

heart failure, changes in liver enzymes, thrombocytopenia, leucopenia also reported

Licensed use

not licensed for use in children under 18 years