Scottish Medicines Consortium

nebivolol tablets 5mg (Nebilet®) No. (214/05)

Menarini Pharmaceuticals UK SRL

4 August 2006

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Nebivolol (Nebilet®) is not recommended for use within NHS Scotland for the treatment of stable mild and moderate chronic heart failure (CHF) in addition to standard therapies in elderly patients ≥70 years. Nebivolol, added to standard therapy, was associated with improved left ventricular function and a reduction in a composite endpoint combining all cause mortality and cardiovascular hospitalisation rates in elderly patients with chronic heart failure. There is no comparison with other beta-adrenoceptor blockers.

Cost effectiveness relative to other beta-adrenoceptor blockers in common use in chronic heart failure has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

nebivolol tablets 5mg (Nebilet®)

Indication

Treatment of stable mild and moderate chronic heart failure (CHF) in addition to standard therapies in elderly patients ≥70 years.

Dosing information

Titration according to patient tolerability from 1.25 mg once daily in defined increments to the maximum recommended dose of 10 mg once daily

UK launch date

February 2006

Comparator medications

Bisoprolol and carvedilol are both licensed for moderate to severe heart failure and carvedilol is licensed for mild heart failure.

Cost of relevant comparators

Costs below are based on the maximum dose of beta-adrenergic blockers licensed for use as an adjunct in stable moderate to severe heart failure.

Regimen	Cost of one year's treatment
Nebivolol (Nebilet) 10 mg daily	£240
Bisoprolol fumarate 10 mg once daily	£33
Carvedilol (non-proprietary) 25 mg twice daily*	£219
Carvedilol (non-proprietary) 50 mg twice daily**	£438

* Patients with severe heart failure or body weight <85 kg
** Patients with body weight >85 kg

Summary of evidence on comparative efficacy

Beta-adrenergic blockade is an established treatment choice in patients with heart failure. Most evidence for the benefit of this approach comes from patients with impaired left ventricular function.

Two phase III placebo-controlled trials have investigated the efficacy of nebivolol in elderly patients with chronic heart failure (CHF). One trial recruited patients aged >65 years with reduced left ventricular ejection fraction (LVEF ≤35%), while the second recruited slightly older patients (≥70 years) with or without left ventricular dysfunction. In both trials patients were required to be receiving standard therapy such as ACE inhibitors, angiotensin II antagonists, diuretics or cardiac glycosides.

The primary end-point in the first trial was the change in LVEF from baseline to end-point at 12 months, (4 months dose titration and 8 months at the maintenance dose). For nebivolol the absolute increase in LVEF was 6.5% from a baseline of 25% and for placebo it was 4.0% from a baseline of 26% (p=0.027). The finding of a difference between nebivolol and placebo was consistent across sub-groups e.g. by gender and disease characteristics at baseline.

In the second trial the primary end-point was a composite of all cause mortality or cardiovascular hospitalisation, and this occurred in 332/1067 (31%) of patients randomised to nebivolol and 375/1061 (35%) allocated to placebo, representing an absolute reduction in risk of 4.2%. This represented a hazard ratio of 0.86 (95% confidence intervals 0.74, 0.99). The difference was almost identical whether the effect of the randomised treatment was adjusted for baseline age, gender and LVEF, or was analysed as a single covariate. It was significant in both cases (p=0.039 and p=0.034 respectively).

In the first trial there were no significant differences in any of the secondary measures i.e. clinical status, quality of life, hospitalisation rate, survival rate and safety parameters. In the second trial there was no significant difference for secondary end-points including the individual components of the composite end-point, cardiovascular mortality, and all cause hospitalisation. There was a significant difference in favour of nebivolol for a second composite end-point: cardiovascular mortality or hospitalisation.

Summary of evidence on comparative safety

Adverse events were as expected with beta-adrenoceptor blocking agents. However, there are no comparative data to indicate whether the incidence and/or severity differs from other licensed agents.

Summary of clinical effectiveness issues

Nebivolol has not been compared in trials with other beta-adrenoceptor blockers licensed for this indication: evidence is restricted to placebo-controlled trials. Post-hoc subgroup analysis of the second study shows that, in younger patients with impaired LV function, the effects of nebivolol are similar to those seen with other beta-adrenoceptor blockers. The magnitude and impact of the effects in older patients and those with normal LV function are uncertain.

In the first trial, LVEF is a proxy measure for more clinically meaningful end-points such as survival and cardiovascular events.

Nebivolol is not licensed for severe heart failure.

Summary of comparative health economic evidence

The manufacturer presented a cost utility analysis of nebivolol compared to placebo in elderly patients with heart failure. The model gave an incremental cost effectiveness ratio of £2,345 (£2,157 to £2,567) per quality adjusted life year. The main weakness of the submission is that the comparator is placebo and not an existing licensed treatment such as carvedilol.

The model adopts a cohort of 2,000 patients with heart failure and a starting age of 70 on model entry. Patients could remain in a stable condition, or be hospitalised for cardiovascular reasons, or die from sudden death or other causes. Clinical data and resource use came

from the second trial and a trial of cardiac re-synchronisation therapy. Unit costs are from DOH Reference Costs.

The model assumes no difference in utility values for the two arms, consistent with the absence of any quality of life gain seen in the SENIORS trial. The absolute level of the utility value applied has not been disclosed but it is unlikely to change any decision.

Sensitivity analyses were conducted on the clinical outcomes and cost of drugs but not on age of entry to the model. This is a weakness since the mean age in the trial was 76 years. Such patients are likely to have higher mortality rates and shorter life expectancies than those adopted in the model. Applying the higher mortality rates to 70 year olds is likely to overestimate the gain in life years but it is not possible to quantify the effect of this potential bias.

In the absence of a relevant comparator, the manufacturer has failed to demonstrate that using nebivolol is cost effective.

Patient and public involvement

A Patient Interest Submission was not made.

Budget impact

The manufacturer estimates the budget impact as £212K to treat 955 patients in year 1, rising to £292K to treat 1,320 patients in year 5 Assuming nebivolol displaces bisoprolol then savings of £84K in year 1, rising to £116K in year 5 would be made, giving a net cost of £128K and £176K in years 1 and 5 respectively.

Guidelines and protocols

SIGN guidelines recommend that patients already treated with diuretics and/or digoxin and an ACE inhibitor, who are clinically stable and in NYHA classes I-III, should be considered for treatment with a beta-blocker licensed for use in heart failure, under careful specialist supervision. It adds that clinical trial evidence relates to patients with clinically stable, mild to moderately symptomatic (NYHA class I-III) heart failure caused by left ventricular systolic dysfunction The guideline dates from 1999, but this approach continues to be supported in more recent guidelines from NICE and from the European Society of Cardiology.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 14 July 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission.

NICE Clinical Guideline No. 5. Chronic Heart Failure: National clinical guideline for diagnosis and management in primary and secondary care. July 2003.

The European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). Eur Heart J 2005:26: 1115-1140.

SIGN Publication No. 35. Diagnosis and Treatment of Heart Failure due to Left Ventricular Systolic Function. A National Clinical Guideline. February 1999.

Flather MD, Shibata MC, Coats AJS et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26: 215-225.

Edes I, Gasior Z and Wita K. Effects of nebivolol on left ventricular function in elderly patients with chronic heart failure: results of the ENECA study. Eur J Heart Failure 2005;7: 631-639.