Scottish Medicines Consortium

Re-Submission

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

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The Scottish Medicines Consortium (SMC) 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 re-submission

nebivolol (Nebilet®) is accepted 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.

Compared to placebo, 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 are no direct comparisons with other beta-blockers that are available at a lower acquisition cost.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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

Dosing information

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

Product availability date

February 2006

Summary of evidence on comparative efficacy

Beta-adrenergic blockade is an established treatment choice for patients with heart failure. The use of beta-blocker drugs as additional therapy for patients already treated with standard therapy that includes diuretics and ACE inhibitors (unless contra-indicated) is supported by national and international guidelines. Most evidence for the benefit of this approach comes from patients with impaired left ventricular function.

Two phase III placebo-controlled double-blind trials have investigated the efficacy of nebivolol in elderly patients with chronic heart failure (CHF). In both trials patients were required to receive standard therapy such as ACE inhibitors, angiotensin II receptor antagonists, diuretics or, optionally, cardiac glycosides.

The first trial recruited patients aged ≥70 years who had experienced either reduced left ventricular ejection fraction (LVEF ≤35%) within 6 months or had been hospitalised within the previous 12 months with a discharge diagnosis of congestive heart failure. 2,135 patients were randomized in a 1:1 ratio to placebo or nebivolol titrated to a target maximum of 10mg daily and all patients randomized were included in an intention to treat (ITT) analysis (except for six patients from one centre excluded from the study and one who was randomized but not treated). The primary end-point was a composite of all cause mortality or cardiovascular hospital admissions, and this occurred in 31% (332/1,067) of patients randomised to nebivolol and 35% (375/1,061) allocated to placebo, representing an absolute reduction in risk of 4.2% and a hazard ratio (HR) of 0.86 (95% confidence interval (CI): 0.74 to 0.99).

Planned sub-group analysis for the primary outcome stratified by clinical factors, including age, ejection fraction, gender, diabetes and prior myocardial infarction, suggests that those factors did not modify the effect of nebivolol: the difference between nebivolol and placebo was significant in both the adjusted and unadjusted analyses (p=0.039 and p=0.034 respectively).

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 cardiovascular hospitalisation.

In an unplanned sub-group analysis involving patients aged less than 75 years (the median age in the trial population) and with an ejection fraction ≤35% (n=342 for both nebivolol and placebo) the HR for the primary outcome was 0.73 (95% CI: 0.56 to 0.96).

The second trial screened 354 patients aged >65 years with reduced left ventricular ejection fraction (LVEF ≤35%) and 260 patients were included in the ITT analysis. The primary end-point was the change in LVEF from baseline to end-point after 8 weeks' 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). 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).

Summary of evidence on comparative safety

Adverse events were as expected with beta-blocking agents (e.g. bradycardia, hypotension, fatigue and an initial worsening of heart failure). However, there are no comparative data to indicate whether the incidence and/or severity differs from other licensed agents.

Summary of clinical effectiveness issues

There are no trials providing a direct comparison between nebivolol and the other beta-blockers licensed for chronic heart failure.

The first trial described above recruited elderly patients (≥70 years) who either had LVEF ≤35% or had been hospitalised with a discharge diagnosis of CHF. Thus patients with LVEF >35% could be recruited, and represented about 35% of the study population in the ITT analysis. Other pivotal trials involving beta-blockers in the treatment of CHF have recruited across a wider age range (with mean or median age in the low 60s) and patients were required to have a specified degree of left ventricular dysfunction (LVEF <25 to 40% across trials).

Based on unplanned sub-group analysis, the authors of the first study suggest that, in younger patients with impaired LV function, the effects of nebivolol are similar to those seen with other beta-blockers. However there are major differences in target population and methodology between the relevant trials that are sufficient to make indirect comparison inappropriate.

Thus it is not clear how nebivolol compares with other beta-blockers either in the target (elderly) population for its licensed indication or in younger patients with ventricular dysfunction.

In the first trial seven patients were randomized but not included in the ITT analysis, including six from one centre excluded from the trial. Although the numbers excluded are small, an ITT analysis should include all patients randomized, and no reason is given for the exclusion of a study centre.

The second trial recruited patients with a lower age threshold (>65 years) who were required to have LVEF ≤35%. However the primary outcome in this trial was change in LVEF after 8 months of treatment, which is a proxy measure for more clinically meaningful end-points such as survival and cardiovascular events.

Nebivolol is not licensed for severe heart failure, whereas bisoprolol and carvedilol are licensed for this indication.

Summary of comparative health economic evidence

The manufacturer presented a cost utility analysis comparing nebivolol to carvedilol in a cohort of heart failure patients aged 70 years old. Within the model, patients could either improve or remain in a stable condition, be hospitalised for cardiovascular reasons or die (from cardiovascular or other causes). The information to derive the results was from an indirect comparison of information from two trials. The results indicated that the incremental cost per QALY of nebivolol compared to carvedilol was £398 per QALY. If the age of patients in the model was 75, the incremental cost effectiveness ratio (ICER) rose to £612 per QALY.

Several points should be noted. The analysis compared nebivolol to carvedilol, which is the more expensive of the two available beta-blockers that could have been used in the comparison. As such, the cost-effectiveness of nebivolol compared to bisoprolol is not known. The age of patients is a key determinant of the ICER and the model's baseline ICER operates with a mean age of 70, which was 6 years less than the mean age in the clinical trial (and likely age of the population of interest in Scotland). This is a weakness as it is likely to overestimate the gain in life. Using an age of 75 as the baseline in the model increased the ICER by 50%, albeit to a not very high value.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published an updated guideline on the management of chronic heart failure in 2007. It states that all patients with heart failure due to left ventricular systolic dysfunction of all NHYA functional classes should be started on beta-blocker therapy as soon as their condition is stable (unless contraindicated by history of asthma, heart block or symptomatic hypotension).

Bisoprolol, carvedilol or nebivolol should be the beta-blocker of first choice for the treatment of patients with chronic heart failure due to left ventricular systolic dysfunction.

Recently updated (2005) European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of chronic heart failure also include nebivolol, bisoprolol, carvedilol and metoprolol succinate in their recommendations for treating CHF. They advocate that beta-blockers should be considered for the treatment of all patients with stable, mild, moderate or severe heart failure from ischaemic or non-ischaemic cardiomyopathies and reduced LVEF on standard treatment, including diuretics and ACE inhibitors, unless there is a contraindication.

Additional information: previous SMC advice

Following a full submission, the Scottish Medicines Consortium advised in August 2006 that: 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-blockers.

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

Following a full submission, the Scottish Medicines Consortium advised in March 2005 that: Candesartan (Amias®) is accepted for use within NHS Scotland for the treatment of patients with heart failure and left ventricular systolic dysfunction (left ventricular ejection fraction = 40%) as add-on therapy to ACE inhibitors or in patients who are unable to tolerate ACE inhibitors. Treatment with candesartan reduces mortality and hospitalisation due to heart failure.

Candesartan may be used as a second-line agent in patients with chronic heart failure and LVEF = 40% following treatment with an ACE inhibitor and diuretic and with or without a beta-blocker.

Additional information: comparators

Bisoprolol fumarate is licensed for the treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction ≤35%, based on echocardiography) in addition to ACE inhibitors, diuretics, and optionally cardiac glycosides.

Carvedilol is licensed for the treatment of stable mild, moderate and severe chronic heart failure as adjunct to standard therapies (e.g. diuretics, digoxin and ACE inhibitors in patients with euvolaemia).

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Nebivolol (Nebilet)	**10 mg daily**	**£240**
Carvedilol (non-proprietary)	50 mg twice daily*	£204
Carvedilol (non-proprietary)	25 mg twice daily**	£102
Bisoprolol fumarate	10 mg once daily	£30

* Patients with severe heart failure or with mild to moderate heart failure and body weight <85 kg
** Patients with mild to moderate heart failure and body weight >85 kg
Doses are maximum doses in the treatment of chronic heart failure (following titration). They are for general comparison and do not imply therapeutic equivalence.
Costs from eVADIS database, obtained 2nd May 2007.

Additional information: budget impact

The manufacturer estimated that the gross drug budget impact of nebivolol would be £211,522 in year one rising to £292,406 by year five. 955 patients were assumed to receive nebivolol in year one rising to 1,320 patients by year five. The calculations assumed a market share of 5% in year one rising to 6.9% by year five. These would mainly be patients that are switched from other beta-blockers. The net costs would be dependant on the beta blocker that nebivolol replaced

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 15 June 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

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.

Flather M, Shibata M, Coats J et al on behalf of the SENIORS Investigators. 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.