HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

4 October 2006

TEMERIT 5 mg, quarter-scored tablet
B/28 / B/30 / B/90

Laboratoires MENARINI

nebivolol

List I

Date of the marketing authorisation: 15 May 2006

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the new indication

"Treatment of mild and moderate stable chronic heart failure, in combination with conventional treatments in patients aged 70 and over"

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

nebivolol

1.2. Indication

- Treatment of essential hypertension
- Treatment of mild and moderate stable chronic heart failure in combination with conventional treatments in patients aged 70 and over.

1.3. Dosage

Treatment of stable chronic heart failure must start with a dose adjustment phase until the optimal individual maintenance dosage is achieved.

Patients must present stable chronic heart failure, with no acute episodes over the past 6 weeks. It is recommended that treatment be provided by a doctor experienced in handling patients with chronic heart failure.

In patients receiving conventional treatment including diuretics and/or digoxin and/or converting enzyme inhibitors and/or angiotensin II antagonists, the dosage of these medicinal products must be stabilised during the 2 weeks prior to treatment with NEBILOX.

The initial titration phase must be carried out in accordance with the following regime at intervals of 1 – 2 weeks, depending on tolerance:

- 1.25 mg once daily for 1 - 2 weeks. If the treatment is well tolerated, increase to:
- 2.5 mg once daily for 1 - 2 weeks. If the treatment is well tolerated, increase to:
- 5 mg once daily for 1 - 2 weeks. If the treatment is well tolerated, increase to:
- 10 mg once daily.

The maximum recommended dose is 10 mg once a day daily.

The treatment and successive dose increases must be undertaken by a doctor experienced in handling patients with chronic heart failure. It requires monitoring for a period of at least 2 hours to ensure that the patient's clinical condition remains stable (in particular, blood pressure, heart rate, conduction disorders, signs of aggravation of heart failure).

The maximum recommended dosage cannot be achieved in all patients due to the occurrence of adverse effects. Where necessary, the dosage achieved may be reduced gradually and then restarted in accordance with the dosage regime.

In the event of aggravation of the heart failure or signs of intolerance to the treatment during the dose adjustment phase, it is recommended first to reduce the dose of nebivolol, and even to discontinue the treatment immediately, if necessary (in the case of severe hypotension, aggravation of the heart failure accompanied by acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or atrioventricular block).

Treatment of stable chronic heart failure with nebivolol is usually a long-term treatment. Treatment with nebivolol must not be discontinued suddenly as this could induce transient aggravation of the heart failure. If the treatment needs to be discontinued, the dosage must be gradually reduced halfing each week.

The tablets may be taken at mealtimes.

(Cf. SPC)

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2004):

C : Cardiovascular system
07 : Beta-blockers
AB : Selective beta-blockers
12 : Nebivolol

2.2. Medicines in the same therapeutic category

Selective beta-blockers indicated for the treatment of heart failure

bisoprolol:	CARDENSIEL/CARDIOCOR
carvedilol:	KREDEX
metoprolol:	SELOZOK

The efficacy and tolerance of these three beta-blockers for the treatment of heart failure have been assessed within randomised placebo-controlled studies (carvedilol – US Carvedilol and COPERNICUS programme, bisoprolol - CIBIS II and metoprolol - MERIT-HF).. The average age of the included patients was about 62, most of them presented systolic type heart failure

A meta-analysis[1] taking into account these studies demonstrated the efficacy of the beta-blockers in the oldest patients included. It analysed data from 4 617 “elderly” patients and evaluated carvedilol, bisoprolol, metoprolol and bucindolol (no marketing authorisation for this indication). According to the studies, the definition of the subjects ranged from $\geq$ 60 years to $\geq$ 70 years. In this meta-analysis, the relative risk of death for all causes was 0.76 (95% CI 0.64 – 0.90) in patients treated with beta-blockers compared with those who had received a placebo.

2.3. Medicines with a similar therapeutic aim

All medicinal products indicated for the treatment of heart failure.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy of nebivolol for the new indication has been demonstrated within the SENIORS study (Eur Heart J 2005 Feb;26(3):215-25)

Aim: To assess the efficacy and tolerance of nebivolol (n=1 067) versus placebo (n=1 061) in patients aged over 70 years with stable heart failure .

Methodology:

- Randomised, placebo-controlled study conducted among patients with stable chronic insufficiency with or without impairment of left ventricular ejection fraction and aged over 70 years.

1 Dulin et al. Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. Am J Cardiol. 2005 Apr 1;95(7):896-8

- The primary efficacy endpoint was a combined endpoint including total mortality and hospitalisations of cardiovascular origin. The secondary efficacy endpoints include total mortality, which was the primary efficacy endpoint adopted in the studies conducted with the other beta-blockers such as carvedilol (US Carvedilol and COPERNICUS), bisoprolol (CIBIS II) and metoprolol (MERIT-HF).
- Nebivolol was administered in addition to the chronic heart failure treatments, with a gradual dose adjustment phase upwards of 1.25 mg/d to achieve the target maintenance dose (maximum recommended) of 10 mg/d.

Results:
- The average age was 76 years; most patients were in class II (56.4%) and III (38.7%) of the NYHA classification (only 2% presented class IV heart failure according to the NYHA classification). The mean LVEF was 36%, with 81% of patients having an LVEF < 45%
- The patients were monitored for an average period of 20 months.
- Among the patients in the two groups, 85% were taking a diuretic and 82% a CEI. Other medicinal products were used. Proportions of medicine use was comparable between the two groups.
- Compared with placebo, nebivolol reduced the primary efficacy endpoint "total mortality and hospitalisations on cardiovascular origin" by 4.2% in absolute terms (35.3% for nebivolol versus 31.1% for placebo), equivalent to a relative risk reduction of 14% (RR = 0.86, 95% CI [0.74; 0.99], p=0.039). This finding was reported after 6 months of treatment and was maintained throughout the treatment. No impact from age, sex or LVEF on the effect of the treatment was identified. Nevertheless, the number of patients with a LVEF > 45% was small. It was then impossible to conclude any efficacy of nebivolol in patients with heart failure and left ventricular function intact. The differences between the two treatments on each elements of the combined primary endpoint are of the same proportion as that reported for the primary endpoint, but without achieving the significance threshold.
- About secondary endpoints, only the combined endpoint of "cardiovascular mortality or hospitalisation on cardiovascular grounds" was reduced in a statistically significant manner (HR = 0.81, 95% CI [0.72; 0.98], p=0.027).

	Nebivolol (n=1067)	Placebo (n=1061)	RRR with 95% CI
Primary endpoint: Total mortality and hospitalisations on cardiovascular origin	332 (31.1%)	375 (35.3%)	0.86 [0.74-0.99]
- Total mortality taken into account in the primary endpoint	76 (7.1%)	99 (9.3%)	NS
- Hospitalisations on cardiovascular origin taken into account in the primary endpoint	256 (24.0%)	276 (26.0%)	NS
Secondary endpoints: Cardiovascular mortality or hospitalisations on cardiovascular origin	305 (28.6%)	350 (33.0%)	0.84 [0.72-0.98]
Total mortality (primary endpoint in studies conducted with the other beta-blockers)	169 (15.8%)	192 (18.1%)	NS

3.2. Adverse effects

The tolerance profile of nebivolol in the SENIORS study does not differ from that reported with beta-blockers in this indication. Bradycardia (nebivolol 11%, placebo 2%) and dizziness (nebivolol 11% and placebo 7%) are the adverse events most frequently reported with nebivolol compared with placebo.

Adverse reactions that have “at least a possible” relationship with the treatment include the following: aggravation of heart failure (nebivolol 5.8%, placebo 5.2%); orthostatic hypotension (nebivolol 2.1%, placebo 1.0%); intolerance to the treatment (nebivolol 1.6%, placebo 0.8%); first-degree atrioventricular block (nebivolol 1.4%, placebo 0.9%); lower limbs oedema (nebivolol 1.0%, placebo 0.2%). These adverse effects are also expected for beta-blockers in this indication.

3.3. Conclusion

The efficacy of nebivolol in the treatment of mild and moderate stable chronic heart failure, in combination with conventional treatments in elderly patients aged 70 and over has been demonstrated in a phase III study comparing nebivolol with placebo. Nebivolol reduced total mortality and hospitalisations on cardiovascular grounds by 4.2% in absolute terms (35.3% for nebivolol versus 31.1% for placebo), which is equivalent to a 14% relative risk reduction (HR = 0.86, 95% CI [0.74; 0.99], p=0.039). This risk reduction in was reported after 6 months of treatment and was maintained throughout the treatment (median duration: 18 months).

The tolerance profile in the SENIORS study does not differ from what has been reported for beta-blockers in this indication.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Mild to moderate stable heart failure is a condition which can develop into more advanced and serious forms. In the event of complications, it may become life-threatening.

This medicine is for curative therapy.

The efficacy/adverse effects profile, which has been demonstrated within the SENIORS study for a combined morbidity and mortality endpoint, is attractive.

This medicine can be used as a first-line treatment.

There are alternatives among the beta-blockers. Nevertheless, nebivolol has been the first to be studied specifically in an elderly population with characteristics approximating the population treated in actual practice.

Benefit in terms of public health:

- The burden on public health from mild and moderate stable chronic heart failure in patients aged 70 and over is significant.
- The improvement in the handling of this disorder is a public health need that forms part of an identified priority (Public Health Act). Existing beta-blockers met this need. Nevertheless, the latter have been studied within a younger population that does not constitute the majority of patients treated in practice.
- Regarding the SENIORS study data about the combined endpoint of morbidity and mortality, a slight impact is expected from nebivolol.

- The data from this study seem to be transposable because nebivolol has been studied in a population presenting characteristics that approximate reality (elderly subjects aged 70 and over with systolic or diastolic heart failure).
- Therefore, considering these data, a public health benefit is expected for nebivolol in this indication. This benefit may be quantified as low.

The actual benefit is substantial.

4.2. Improvement in actual benefit

The SENIORS study provides proof of efficacy, in terms of morbidity and mortality, for nebivolol in combination with the conventional treatment in patients aged 70 and over who have mild to moderate stable chronic heart failure. This population accounts for a large proportion of patients in needing such treatment in actual practice. There was no specific studies performed with other beta-blockers indicated for heart failure in this population.

As a result, the Transparency Committee considers that NEBILOX brings about a moderate improvement in actual benefit (IAB III) in the handling of patients aged 70 and over who have mild to moderate stable chronic heart failure, with or without systolic dysfunction.

4.3. Therapeutic use

The occurrence of heart failure in an individual aged over 70 requires an overall approach with the aim of improving symptoms and reducing the risk of cardiovascular morbidity and mortality.

Certain beta-blockers, diuretics, CEIs and sartans have demonstrated their efficacy in these situations.

Among the beta-blockers, the prescriber can use bisoprolol, metoprolol, carvedilol and nebivolol. Nebivolol may be used in the case of mild and moderate heart failure, in combination with conventional treatments. Patients must present stable chronic heart failure, with no acute episodes over the past 6 weeks. It is recommended that the treatment be initiated by a doctor experienced in handling these patients. The treatment should start with dosages of 1.25 mg/d, tablets with such dosages could be taken easily by elderly.

4.4. Target population

The target population for nebivolol in this new indication comprises patients aged over 70 with mild to moderate stable chronic insufficiency. It may be estimated from the following data:

- Approximately 500 000 to 600 000 patients with heart failure in France;
- of these, around two thirds are thought to be over the age of 70 and three quarters of these are thought to have mild to moderate stable heart failure.

Based on this data, the target population for nebivolol for this new indication is estimated at 260 000 to 300 000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the new indication.

The Transparency Committee considers that the tablets of 1.25 mg dosage could facilitate the start of treatment by patients over the age of 70.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%