HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

27 May 2009

CARDENSIEL 1.25 mg, film-coated tablet
B/30 (CIP code: 352 968-1)

CARDENSIEL 2.5 mg, film-coated tablet
B/30 (CIP code: 352 970-6)

CARDENSIEL 3.75 mg, film-coated tablet
B/30 (CIP code: 352 972-9)

CARDENSIEL 5 mg, film-coated tablet
B/30 (CIP code: 352 974-1)

CARDENSIEL 7.5 mg, film-coated tablet
B/30 (CIP code: 353 129-3)

CARDENSIEL 10 mg, film-coated tablet
B/30 (CIP code: 353 131-8)

Applicant: MERCK LIPHA SANTE

Bisoprolol (hemifumarate)
List I
Medicine requiring special monitoring during treatment. Medicine subject to initial prescription restricted to specialists in cardiology and general medicine.
ATC code: C07AB07

Date of the Marketing Authorisation: 4/01/2000
Date of the extension of indication: 28/07/2008

Reason for request:
Modification of the wording of the indication: “Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to angiotensin-converting enzyme (ACE) inhibitors, and diuretics, and optionally cardiac glycosides”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Bisoprolol hemifumarate

1.2. Indication

New indication wording:

"Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to angiotensin-converting enzyme (ACE) inhibitors, and diuretics, and optionally cardiac glycosides."

Previous indication wording

"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, and diuretics, and optionally cardiac glycosides."

1.3. Dosage

"Standard treatment of chronic heart failure consists of an angiotensin-converting enzyme inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocking agent, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.

Titration phase: The treatment of stable chronic heart failure with bisoprolol requires a titration phase. The treatment with bisoprolol is to be started with a gradual up titration according to the following steps:

- 1.25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for a further week, if well tolerated increase to
- 3.75 mg once daily for a further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to
- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to
- 10 mg once daily for the maintenance therapy.

The maximum recommended dose is 10 mg once daily. Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating the therapy.

Treatment modification: If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered. In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation. The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

Administration: Bisoprolol tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

Special populations:
Renal or liver insufficiency: There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired liver or renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

Elderly: No dosage adjustment is required.

Children: Bisoprolol is not recommended for use in children due to a lack of data on safety and efficacy."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

C : Cardiovascular system
C07 : Beta blocking agents
C07A : Beta blocking agents
C07AB : Beta blocking agents, selective
C07AB07 : Bisoprolol

2.2. Medicines in the same therapeutic category

Bisoprolol: CARDIOCOR, medicinal product identical to CARDENSIEL

Other beta blocking agents indicated in heart failure:

- Carvedilol: KREDEX, indicated in the "Treatment of chronic, stable, mild, moderate and severe heart failure (ejection fraction < 35%) in combination with conventional treatment consisting of angiotensin-converting enzyme inhibitor, diuretic and, most often, cardiac glycoside"
- Metoprolol: SELOZOK, indicated in the "Treatment of chronic, stable, moderate-to-severe heart failure with reduced systolic ventricular function (ejection fraction ≤ 40%), as an adjunct to angiotensin-converting enzyme (ACE) inhibitors and diuretics and, most often, cardiac glycosides"
- Nebivolol: NEBILOX, TEMERIT, indicated in the "Treatment of chronic, stable, mild and moderate heart failure, in combination with standard treatments in patients aged 70 or above"

2.3. Medicines with a similar therapeutic aim

These are all the other medicinal products indicated in heart failure.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The evaluation of the efficacy and safety of bisoprolol in this new indication is based on one clinical study, the CIBIS III study[1].

Objective: to compare the efficacy and safety (non-inferiority) of starting treatment (6 months) with bisoprolol with that of starting treatment with enalapril in patients with mild-to-moderate chronic stable heart failure.

Method: open-label, randomised, parallel-group non-inferiority study conducted in 1,010 patients with mild-to-moderate stable heart failure followed up for 24 months.

Inclusion criteria: adults over 65 years of age with mild-to-moderate stable heart failure (NYHA class II and III) and an ejection fraction of ≤ 35%, based on echocardiography.

Treatment: The study was conducted in two successive phases:
Phase I: 6 months in duration
- bisoprolol 10 mg per day, n=505
- enalapril 10 mg, twice daily, n=505

Phase 2: 6-24 months: all the patients received combined bisoprolol/enalapril

Primary efficacy endpoint: a combined endpoint of all-cause mortality and hospitalisations after 24 months of treatment.
Non-inferiority was demonstrated if the upper limit of the confidence interval of the absolute difference was below a limit fixed at 5% (1.17 for the hazard ratio).

Results: cf. Table 1
On inclusion, the patients' characteristics were comparable.

Table 1: Number and percentage of events observed after 24 months

	Bisoprolol 10 mg per day	Enalapril 10 mg twice daily	Reduction in the relative risk [95% CI]	Absolute difference [95% CI]
Per protocol analysis	n=503	n=498		
Number of events (%)	163 (32.4%)	165 (33.1%)	HR 0.97 95% CI [0.78; 1.21]	- 0.7% 95% CI [-6.6; 5.1]
Intention to treat analysis	n=505	n=505		
Number of events (%)	178 (35.2%)	186 (36.8%)	HR 0.94 95% CI [0.77; 1.16]	-1.6% 95% CI [-7.6; 4.4]

After 24 months of treatment, 163/503 (32.4%) of the patients who started treatment with bisoprolol 10 mg per day compared with 165/498 (33.1%) of the patients who started treatment with enalapril 10 mg twice daily experienced a cardiovascular event (combined endpoint of all-cause mortality and hospitalisations), HR 0.97, 95% CI [0.78 – 1.21], absolute difference -0.7% 95% CI [-6.6; 5.1%].
The upper limit of the confidence interval is higher than the limit fixed at 5%; the non-inferiority of the treatments was not demonstrated (per protocol analysis).

1 Willenheimer et al. "Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence. Results of a randomized cardiac insufficiency bisoprolol study (CIBIS III)". Circulation. 2005; 112:2426-35

3.2. Adverse effects

In the CIBIS III study, 160/504 (31.7%) of the patients in the bisoprolol group compared with 126/502 (25.1%) of the patients in the enalapril group experienced adverse effects.

The adverse effects encountered most frequently were as follows:

- hypotension: 109/504 (21.6%) compared with 118/502 (23.5%)
- heart failure: 93/504 (18.5%) compared with 95/502 (18.9%)
- bradycardia: 85/504 (16.9%) compared with 57/502 (11.4%)
- vertigo: 41/504 (8.1%) compared with 39/502 (7.8%)
- fatigue: 41/504 (8.1%) compared with 31/502 (6.2%)
- peripheral oedema: 40/504 (7.9%) compared with 41/502 (8.2%)

These adverse events were similar to those observed during treatment with bisoprolol in the original indication; no specific adverse effect related to the extension of the indication has been identified.

3.3. Usage data

The data relating to the conditions under which these medicinal products are used are presented and analysed in the annex.

3.4. Conclusions

In the CIBIS III study, the efficacy and safety of bisoprolol were evaluated in patients with mild-to-moderate stable heart failure.

After 24 months of treatment, 163/503 (32.4%) of the patients who started treatment with bisoprolol 10 mg per day compared with 165/498 (33.1%) of the patients who started treatment with enalapril 10 mg twice daily experienced a cardiovascular event (combined outcome of all-cause mortality and hospitalisations), HR 0.97, 95%CI [0.78-1.21], absolute difference -0.7% 95%CI [-6.6; 5.1%]. The non-inferiority of the treatments was not demonstrated (per protocol analysis).

The most frequent adverse effects (> 5%) were: hypotension, heart failure, bradycardia, vertigo, fatigue, peripheral oedema.

There is no direct comparison data with other beta blocking agents indicated in mild-to-moderate heart failure.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Mild-to-moderate stable heart failure is a condition which can progress to more advanced and serious stages. As a result of its complications, it can be life-threatening.

These medicinal products are intended as curative therapy.

The efficacy / adverse effects ratio, demonstrated within the scope of the CIBIS III study using a combined outcome of morbidity and mortality, is high.

These medicinal products are first-line therapies.

Public health benefit:
The public health burden represented by mild and moderate chronic stable heart failure is substantial.
Improving the management of this condition constitutes a public health need within the scope of an identified priority (GTNDO, public health law). This need is met partly by existing beta blocking agents.
In view of the results of the CIBIS study, the medicinal product CARDENSIEL is not expected to have any additional impact in the treatment of chronic heart failure.
As a consequence, it is not expected that the medicinal product CARDENSIEL will provide an additional public health benefit in this extension of indication.

The actual benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit (IAB) for the new indication wording

CARDENSIEL does not provide any improvement in actual benefit (IAB V) in the management of chronic stable heart failure with reduced systolic left ventricular function in addition to angiotensin-converting enzyme (ACE) inhibitors, and diuretics, and optionally cardiac glycosides.

4.3. Therapeutic use[2]

The management of patients with mild, moderate and severe heart failure with reduced systolic ventricular function (ejection fraction less than or equal to 40%) combines treatment with a loop diuretic, an angiotensin-converting enzyme inhibitor and a cardiac glycoside in the majority of cases; prescription of a beta blocking agent (bisoprolol, carvedilol, metoprolol or nebivolol) may be considered in patients with “stable” heart failure. It enables an additional reduction in mortality to be achieved.

For patients with NYHA class III and IV heart failure: the addition of spironolactone in low doses (25-50 mg/day) leads to a reduction in all-cause and cardiovascular mortality and in the risk of hospitalisation because of worsening heart failure; patients must have serum potassium levels below 5.5 mmol/l and serum creatinine levels below 220 µmo/l.

2 Task force for the diagnosis and treatment of chronic heart failure, European Society of Cardiology. “Recommandations pour le diagnostic et le traitement de l’insuffisance cardiaque congestive”. Arch Mal Cœur Vaisseaux, 2006, 99 (Suppl 2)

4.4. Target population

The target population for bisoprolol according to its new indication wording is represented by patients with stable systolic heart failure. It can be estimated on the basis of the following data:

- a number of patients with symptomatic heart failure of between 600,000 and 800,000 in France
- 60% with heart failure of systolic origin[3]

On this basis, the target population for bisoprolol according to this new indication wording would be between 360,000 and 480,000 patients.

Thus, the extension of indication (patients with mild heart failure) increases the target population by 100,000 patients compared with the previous indication.

4.5. Transparency Committee recommendations

The Transparency Committee recommends maintenance on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indication with its new wording and at the dosage in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%

3 Guide ALD. "Insuffisance cardiaque systolique symptomatique chronique". HAS March 2007

ANNEX

OPINION OF THE PUBLIC HEALTH INTEREST GROUP
ON THE DEFINITIVE RESULTS (December 2007)
OF THE CARDENSIEL®[4] POST-REGISTRATION STUDY

PROTOCOL:	Study on the conditions of use of the medicinal product CARDENSIEL®
VERSION :	Definitive report dated December 2007
MEDICINAL PRODUCT:	CARDENSIEL®
PHARMACEUTICAL COMPANY:	Merck
OPINION DATE:	26/02/2008

1. Reminder of the context and of the study application

CARDENSIEL® is a beta blocker which requires special monitoring during treatment and the initial prescription of which is restricted to specialists in cardiology and general medicine. It is indicated in the treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction less than or equal to 35%, based on echocardiography) in addition to angiotensin-converting enzyme (ACE) inhibitors, and diuretics, and optionally cardiac glycosides.
The Transparency Committee has not requested a post-registration study. The study request originates from the DGS (General Directorate of Health) and was included in the addendum to the CEPS agreement signed on 26/12/02 (cf. doc. attached).
The new referral dates from 20/07/04 (regularisation). The wording is:
"The pharmaceutical company will conduct an observational study of prescribing (medical condition leading to the prescription, concomitant prescriptions relating to the medical condition) by patient in order to ascertain that this medical product is being prescribed correctly within the indication in which it obtained its IAB.
This study may incorporate, for comparison purposes, an analysis of prescriptions of bisoprolol-based medicinal products, along with an analysis of prescriptions of other beta blockers indicated in heart failure."
The study protocol was validated by the public health interest group on 31/01/06. The Transparency Commission received the definitive results of this study in December 2007.

2. Comments relating to methodology

2.1. Cardiologist study

The inclusion objectives were almost achieved for the cardiologists: the cardiologists in practice had a similar profile (sex, age, type of practice) to those who agreed to participate in the study. The doctors in practice did not differ (in terms of sex and age) from the cardiologists in practice at a national level, but they were less likely to practise in the private sector.

The data collected on site were subjected to quality control.

The profile (age and sex) of the patients who refused to participate, compared with that of the participating patients, showed men to be over-represented among the participants (70% compared with 63%): this selection bias may be classified as moderate, however.

The definition of a good usage criterion less than or equal to 40% was introduced retrospectively, at the analysis stage, in view of the results, at the request of the scientific committee. It did not appear in the original protocol. The percentage of non-compliant usage remains high even with this new criterion (44%). More generally, the "percentage of prescriptions in conformity with the Marketing Authorisation" objective was differentiated considerably, a posteriori, in view of the results.

4 This study was conducted on the basis of the previous wording of the Marketing Authorisation: "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, and diuretics, and optionally cardiac glycosides"

2.2. General Practitioner study

The same comment as previously (cf. Cardiologist study) can be made regarding the definition of a good usage criterion.

The heart failure stage is known only for a small proportion of the patients (21%): a significant selection bias therefore exists.
The prospective study (conducted with a view to identifying the characteristics of the original indication), in which 112 General Practitioners participated, included 295 patients, 218 of whom were eligible for analysis. Because these numbers were low (it was planned to include 600 general practitioners and 1,200 patients), the results of this study must be viewed with caution.

2.3. Weighted overall data

It is regrettable that the analysis does not include any overview of the percentage of prescriptions which complied with the Marketing Authorisation (cardiologists and General Practitioners together), taking into account the probable majority weighting of those made out by General Practitioners, the results of which, in terms of the characteristics of the heart failure, are mediocre and moreover biased.

3. Main results

3.1. Cardiologists

490 cardiologists included 1,932 patients, 1,927 of whom were analysed.

When the cardiologist was seen within the scope of the study, the patients had been under treatment with CARDENSIEL for almost 18 months on average and, at the time of starting, the treatment was prescribed for 2 months on average (median = 1 month), at a dosage of 1 daily dose for 93.6% of the patients.

Whether as a first or repeat prescription, CARDENSIEL was prescribed for heart failure in more than 80% of the cases. The other reasons for prescription were as follows: coronary insufficiency (around 11%), dysrhythmias (around 4%), hypertension (2%).

At the time of starting treatment with CARDENSIEL, the (NHYA) class of chronic heart failure was documented for almost all the patients: 86.5% had moderate-to-severe (class II-IV) heart failure, and only 12% of the patients were asymptomatic (class I).
The ventricular ejection fraction (VEF) was determined for 96.9% of the patients, most often by ultrasonography (87.5%). It was less than or equal to 35% in 39.7% of cases, which corresponds to the indication in the Marketing Authorisation.

The dosages prescribed appear to comply with the SPC overall:
- at the start, the average dosage was 1.9 mg/day (median of 1.2 mg/day)
- the current dosage is between 1.25 mg and 10 mg/day for 99.8% of the patients

For 86% of the patients, CARDENSIEL is prescribed in a single daily dose.

With regard to the concomitant prescriptions:
- When first prescribed, CARDENSIEL was prescribed concomitantly in 86.5% of cases with at least one ACE inhibitor and/or a diuretic (it should be noted, 6.3% “other”, which could be cardiac glycosides, but the information is not provided for this drug class in particular). For the current prescription, this percentage is 88.1%. Furthermore, in 3.2% of cases (first prescription) and 4.9% of cases (current prescription), CARDENSIEL was also prescribed concomitantly with an AIIRA (without ACE inhibitor or diuretics).
- The most frequently encountered combination was CARDENSIEL + diuretics + ACE inhibitor + other: 38.5% at the first prescription and 39.3% for the current prescription
- In 4% (first prescription) and 1.5% (current prescription) of cases, CARDENSIEL was prescribed alone

In summary, combining the 3 criteria (heart failure, acceptable current concomitant prescriptions and VEF <= 35), 34.0% of the patients followed up by cardiologists are being treated with CARDENSIEL in conformity with the complete indication in the Marketing Authorisation.

3.2. General Practitioners

Over the year 2006, 1,071 General Practitioners prescribed CARDENSIEL to 4,347 patients.

The main results extracted from the Thalès database are as follows:

- CARDENSIEL was prescribed for heart failure in 72.3% of the patients (23.6% with NYHA class I, 49.5% with class II, 21.7% with class III and 5.2% with class IV) and for angina or hypertension in 27.7% of the patients

- The dosages prescribed were less than or equal to 2.5 mg for 62.5% of the patients. The average dosage was 3.6 mg/day, and 8.4% of the patients received a dosage of 10 mg or more per day

- With regard to the concomitant prescriptions, 18.4% of patients are treated with CARDENSIEL alone, the other patients usually being under triple agent therapy (CARDENSIEL + ACE inhibitor + diuretics in 22.9% of cases) or two agent therapy (CARDENSIEL + ACE inhibitor in 15.5% of cases). Furthermore, 11.5% of the patients were under treatment with four or more agents. Around 70% of patients are likely to receive CARDENSIEL in combination with the other drug classes mentioned in the indication in the Marketing Authorisation (the medicinal products used in four-agent therapy are not known precisely)

- In summary, combining the 3 criteria (heart failure, acceptable current concomitant prescriptions and VEF <= 35), 10.6% of the patients treated by General Practitioners are treated with CARDENSIEL in conformity with the complete indication in the Marketing Authorisation

The main results concerning the prospective study are as follows:

- The duration of treatment was 20.8 months (median) if the treatment had been initiated by cardiologists and 12.1 months if it had been initiated by General Practitioners

- CARDENSIEL was prescribed as a single daily dose in 93% of cases

- Whichever doctor initiated the treatment, the LVEF was known in 72.5% of cases and, when it was documented, it was less than or equal to 35% for 20.3% of the patients. For the patients as a group, the NHYA classification was as follows: class I: 24.3%, class II: 46.7%, class III: 15.4%, class IV: 3.3% and class unknown: 10.3%
When a cardiologist initiates the treatment, 95.8% of the patients have a documented LVEF (20.7% of whom have an LVEF of <= 35%), compared with 54.1% of the patients when the treatment is initiated by a General Practitioner (19.7% of whom have an LVEF of <= 35%). In both cases, ultrasonography was the method most used.
With regard to the class of heart failure, 71% of the patients (when the treatment was initiated by a cardiologist) and 65.4% of the patients (initiator = General Practitioner) had class II-IV heart failure. The class was not known by the General Practitioner in 10.3% of cases.

- In summary, combining the 3 criteria (heart failure, acceptable current concomitant prescriptions and VEF <= 35), 10.6% of patients followed up by General Practitioners (14.6% when a cardiologist had initiated the treatment with CARDENSIEL and 7.4% when it was a General Practitioner) are treated with CARDENSIEL in conformity with the complete indication in the Marketing Authorisation

4. Conclusion

Despite its methodological limitations, this study made it possible to determine the conditions of use of the medicinal product CARDENSIEL in an outpatient setting among cardiologists and General Practitioners.
Attention should be drawn to the significant percentage (all criteria combined) of non-conformity with the complete indication in the Marketing Authorisation, particularly on account of failure to take into account the LVEF, even among cardiologists (the percentage of non-conformity affecting the patients followed up by General Practitioners more particularly, however).