HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

23 January 2008

COVERSYL 2 mg tablets
Box of 30 (CIP: 331032-7) Box of 90 (CIP: 331035-6) Box of 100 (CIP: 558521-2)

COVERSYL 4 mg scored tablets
Box of 30 (CIP 331024-4); Box of 90 (CIP 331026-7); Box of 100 (CIP 558334-8)

COVERSYL 8 mg tablets
Box of 30 (CIP 362503-1); Box of 90 (CIP 362505-4); Box of 100 (CIP 362506-0)

Applicant SERVIER

perindopril

List I

Date of initial marketing authorisations:
COVERSYL 2 and 4 mg tablets: 22 June 1988
COVERSYL 8 mg: 16 December 2003

Extension of indication to “stable coronary artery disease”:
COVERSYL 2 and 4 mg: 3 February 2006 (mutual recognition)
COVERSYL 8 mg: 6 September 2006 (national procedure):

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance (B/30 and B/90) and approved for hospital use (B/30, B/90 and B/100) for the new indication: “Stable coronary artery disease: Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation”.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance
perindopril

1.2. Indications
Hypertension: Treatment of hypertension.
Heart failure: Treatment of symptomatic heart failure (COVERSYL 2 and 4 mg)
Stable coronary artery disease: Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

1.3. Dosage
It is recommended that COVERSYL is taken once daily in the morning before a meal. The dose should be individualised according to the patient profile and blood pressure response.

Stable coronary artery disease:
COVERSYL should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated. Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function. The dose should be increased only if the previous lower dose is well tolerated. (Refer to SPC)

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification 2006

C : Cardiovascular system
09 : Agents acting on the renin-angiotensin system
A : Angiotensin-converting enzyme inhibitors (ACE-inhibitors), plain:
A : Angiotensin-converting enzyme inhibitors (ACE-inhibitors), plain
04 : Perindopril

2.2. Medicines in the same therapeutic category:

Other ACE inhibitors indicated for secondary prevention (indications not necessarily identical):

TRIATEC (ramipril): “prevention of cardiovascular complications in patients at high risk of vascular damage (particularly patients with coronary artery disease or diabetes) with confirmed ischaemic artery disease. Long-term ramipril treatment significantly improved survival in this population, according to the HOPE study”.

CAPTOLANE, LOPRIL (captopril): “Post myocardial infarction in patients with left ventricular dysfunction (ejection fraction ≤ 40%) and in the absence of clinical signs of heart failure. Long-term captopril treatment improves long-term survival and reduces the risk of repeat infarction as well as the risk of developing heart failure”.(SAVE study).

ODRIK (trandolapril): “After myocardial infarction: secondary prevention after myocardial infarction in patients with left ventricular dysfunction (ejection fraction ≤ 35%) with or without clinical signs of heart failure, resulting in: – reduction in overall mortality, and reduction in occurrence of severe or resistant heart failure. Treatment of a group of 876 patients for between 24 and 50 months prevented 65 deaths (7.4%)”. (TRACE Study).

ZOFENIL (zofenopril): “treatment initiated within the first 24 hours after acute myocardial infarction with or without signs and symptoms of heart failure in patients who are haemodynamically stable and have not received thrombolytic therapy” (SMILE study).

2.3. Medicines with a similar therapeutic aim

Other medicinal products indicated for secondary prevention in patients with coronary artery disease: antiplatelet agents, beta-blockers and statins.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Evaluation of the efficacy and safety of COVERSYL in this new indication is based on a clinical study (the EUROPA study)[1].

Objective: to compare the efficacy and safety of perindopril 8 mg/day with placebo in patients with stable coronary artery disease with no clinical signs of heart failure.

Method: Placebo controlled, randomised double-blind study conducted in 12,218 patients (perindopril arm: n = 6,110; placebo arm: n = 6,108) with stable coronary artery disease with no clinical signs of heart failure, followed up for 4 years.

Inclusion criteria: adult patients with stable coronary artery disease with:

- a history of myocardial infarction > 3 months before screening;
- and/or coronary revascularisation > 6 months before screening;
- and/or angiographic evidence of at least 70% narrowing of one of the main coronary arteries;
- and/or men with a history of chest pain and a positive stress test.

Exclusion criteria: clinical signs of heart failure, uncontrolled hypertension, myocardial hypertrophy, clinical signs of obstructive valve disease.

Treatment:
Enrolled patients received COVERSYL 4 mg/day for 2 weeks, followed by 8 mg/day for the following 2 weeks if the lower dose was well tolerated. At the end of the run-in period, patients were randomly assigned to one of two groups:

- COVERSYL 8 mg/day (n=6,110)
- Placebo (n=6,108)

Primary endpoint: composite endpoint including cardiovascular death, non-fatal myocardial infarction, and/or cardiac arrest with successful resuscitation.

Secondary endpoints: Only results relating to the components of the composite primary endpoint initially specified in the protocol are given in this opinion: cardiovascular death, non-fatal myocardial infarction, cardiac arrest with successful resuscitation, unstable angina and overall mortality.

Results: analysis was based on intention to treat.
At baseline, the characteristics of patients in both groups in terms of cardiovascular risk were similar. 90% of patients had a history of MI and/or coronary revascularisation.
Most patients received the study drug in addition to their usual therapy, which included antiplatelet agents, lipid-lowering therapy and beta-blockers.
The mean age of included patients was 60 years (±9).

1 Fox K. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease : randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). The Lancet 2003 ; 362 : 782-788.

Primary endpoint:
Results relating to the composite primary endpoint are presented in table 1.

Table 1: Number and percentage of events observed after 4 years of follow-up

	COVERSYL 8 mg/day n=6,110	Placebo n=6,108	Relative risk reduction [95% CI]	p
Composite primary endpoint:	**488 (8%)**	**603 (9.9%)**	**20% [9 – 29]**	**0.0003**
- cardiovascular death	215 (3.5%)	249 (4.1%)	14% [-3 – 28]	NS
- non-fatal myocardial infarction	295 (4.8%)	378 (6.2%)	22% [10 – 33]	0.001
- cardiac arrest with successful resuscitation	6 (0.1%)	11 (0.2%)	46% [-47 – 80]	NS

A significant 20% reduction in the composite primary endpoint including cardiovascular death, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation was observed in the COVERSYL arm 8mg/day compared to placebo: absolute risk reduction 1.9%.

Secondary endpoints:
A 22% reduction in the number of cases of non-fatal myocardial infarction was observed with COVERSYL compared to placebo: absolute risk reduction 1.4%.
No significant difference between the two groups was reported in terms of:
- unstable angina (342 events (5.6%) with COVERSYL versus 367 (6%) events with placebo)
- cardiovascular death (215 events (3.5%) with COVERSYL versus 249 (4.1%) events with placebo)
- total mortality (375 deaths (6.1%) with COVERSYL versus 420 (6.9%) deaths with placebo).

3.2. Adverse effects
During the EUROPA study, only serious adverse events were recorded. Few patients experienced serious adverse events: 16 (0.3%) of the 6,122 patients on perindopril and 12 (0.2%) of the 6,107 patients on placebo. In patients treated with perindopril, hypotension was observed in 6 patients, angio-oedema in 3 patients and cardiac arrest in 1 patient. Treatment was stopped because of cough, hypotension or other intolerance in 6% (n=366) of patients on perindopril versus 2.1% (n=129) on placebo.

These adverse events are similar to those observed during perindopril treatment for other indications; no specific adverse effect related to the new indication was identified.

3.3. Conclusion
In the EUROPA study, efficacy and safety of COVERSYL were evaluated in patients with stable coronary artery disease with history of myocardial infarction and/or revascularisation with no ventricular dysfunction.

After a mean follow-up period of 4 years, COVERSYL 8 mg/day was shown to be effective for the composite primary endpoint, combining cardiovascular death, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation, when compared to placebo: 488 (8%) events were reported in the COVERSYL 8 mg/day group versus 603 (9.9%) in the placebo group: a 20% reduction in relative risk. The reduction in the absolute risk was 1.9%, which corresponds to a NNT of 54.
A reduction in the number of cases of non-fatal myocardial infarction with COVERSYL 8 mg/day compared to placebo was also observed (a 1.4% reduction in absolute risk).

No significant difference between the two groups was reported in terms of mortality:

- cardiovascular death: 215 events (3.5%) were reported in the COVERSYL 8 mg/day group versus 249 (4.1%) in the placebo group
- overall mortality: 375 events (6.1%) were reported in the COVERSYL 8 mg/day group versus 420 (6.9%) in the placebo group.

There are no available data concerning direct comparison with other ACE inhibitors indicated for secondary prevention.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The conditions in the extension to the indication for this medicinal product are immediately life-threatening or may cause fatal complications.

These proprietary products are used as a preventive treatment.

The efficacy/safety ratio of COVERSYL is high in this extension to the indication.

These proprietary products are used in first-line treatment.

There are other alternative medications.

Public health benefit:
Ischaemic heart disease is a major public health burden.
Improvement of the secondary prevention of ischaemic heart disease is still a public health need that falls within the scope of identified priorities (GTNDO priority*).
In view of the available data, and in the absence of any comparative studies involving other ACE inhibitors, the additional impact of COVERSYL over other ACE inhibitors in terms of morbidity, mortaility and quality of life cannot be quantified.
There is no guarantee that the results of trials can be transposed into clinical practice, for the following reasons:

- the small number of patients (212) included in the EUROPA study in France (patient profile and in particular management may be different in France)
- the nature of treatment combinations may differ in practice, considering that only 56% of patients in the EUROPA study received statin treatment (*probably because the patients were included a long time ago)*, although this treatment is currently recommended and should be given routinely in clinical practice.

The proprietary drug COVERSYL does not therefore seem to provide an additional response to the identified public health need.
Consequently, given the current knowledge of the subject, COVERSYL is not expected to benefit public health benefit in this indication.
** GTNDO: National Technical Group for Defining Objectives (DGS-2003)*

The actual medical benefit of these medicinal products is substantial

4.2. Improvement in actual benefit

The Transparency Committee considers that COVERSYL provides a minor improvement in actual benefit (IAB IV) in terms of efficacy in the management of patients with stable coronary artery disease and a history of myocardial infarction and/or revascularisation with no ventricular dysfunction, as evaluated in the EUROPA study.

4.3. Therapeutic use[2,3,4]

Management of patients with coronary artery disease is based on overall management combining the following:
- management of associated cardiovascular risk factors: smoking (to be stopped), excess weight (target BMI<25 kg/m^2), diabetes (target HbA1C < 7%), dyslipidaemia (target LDL-c level < 100 mg/dL) and hypertension (target <140/90 mmHg or <130/80 mmHg in patients with diabetes or renal failure).
- physical exercise: 30 minutes per day
- prevention of cardiovascular complications.

Several therapeutic categories of medicinal product (hypertension treatments such as beta-blockers and ACE inhibitors, lipid-lowering treatments, anti-platelet agents etc) can be used to reduce cardiac events in patients with stable coronary artery disease, with the aim of reducing cardiovascular risk factors and preventing cardiovascular complications.

Low-dose of acetylsalicylic acid (75-160 mg/day) is used as a first-line anti-platelet agent in secondary prevention after myocardial infarction. If the patient has significant intolerance to aspirin, clopidogrel and ticlopidine are alternatives.

Some statins have been shown to be effective in secondary prevention in patients with coronary artery disease[5]:
- Pravastatin: history of myocardial infarction (MI) (CARE study), stable angina or recent MI (LIPID study)
- Simvastatin: stable angina or recent history of MI (4S study)
- Fluvastatin: patients who have undergone coronary angioplasty (LIPS study).

Long-term beta-blocker treatment[3] has been shown to be effective in terms of morbidity and mortality, and is recommended for patients with a history of MI, acute coronary syndrome or left ventricular failure, if such treatment is not contraindicated. Long-term beta-blocker treatment can also be offered to other patients with coronary artery disease or patients with vascular conditions or diabetes.

Long-term ACE inhibitor treatment has been shown to be effective in terms of morbidity and mortality, and is recommended for patients with coronary artery disease and left ventricular dysfunction (ejection fraction ≤ 40%), hypertension, diabetes or chronic kidney disease. ACE inhibitors may also be offered to other patients with coronary artery disease.

In the EUROPA study, the efficacy of perindopril (COVERSYL) was demonstrated for a composite endpoint combining cardiovascular death, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation when this product is used for secondary prevention in patients with stable coronary artery disease and a history of myocardial infarction and/or revascularisation with no ventricular dysfunction.

2 The Task Force ACE inhibitors of the European Society of Cardiology. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease, European Heart Journal 2004;25:1454-1470.
3 AHA/ACC Guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: update 2006, Circulation 2006;113:2363-72.
4 The Task Force on the management of stable angina pectoris of the European Society of Cardiology. Guidelines on the management of stable angina pectoris, European Heart Journal 2006;25:1454-1470.
5 Prise en charge thérapeutique du patient dyslipidémique, (Therapeutic management of patients with dyslipidaemia), AFSSAPS recommendation March 2005

4.4. Target Population

The target population that could most benefit from COVERSYL is the population with stable coronary artery disease with history of myocardial infarction and/or revascularisation with no ventricular dysfunction.

The size of this population can be estimated on the basis of the following data:

- In France, the annual incidence of MI leading to hospital admission is 80,000 (Fast MI register 2006). Of these patients, around 5% die during the first ten days following MI (Fast MI 2006 register). There are around 76,000 survivors per year.
- Of patients who have had myocardial infarction, 20% (Fast MI register 2006) have left ventricular dysfunction (left ventricular ejection fraction ≤ 40%) and clinical signs of heart failure. There are therefore around 64,000 patients with no clinical signs of heart failure per year.
- According to national registers, 120,000 patients underwent revascularisation procedures without infarction in 2006.

Based on this data, the target population for COVERSYL in this new indication is likely to be between 64,000 and 184,000 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for hospital use and various public services in the marketing authorisation's extension of indication and dosage.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%