HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

22 July 2009

COVERAM 5 mg / 5 mg, tablet
B/30 (CIP: 385 802-5)
B/90 (CIP: 385 806-0)
B/100 (CIP: 572 845-6)

COVERAM 5 mg / 10 mg, tablet
B/30 (CIP: 385 814-3)
B/90 (CIP: 385 819-5)
B/100 (CIP: 572 848-5)

COVERAM 10 mg / 5 mg, tablet
B/30 (CIP: 385 827-8)
B/90 (CIP: 385 831-5)
B/100 (CIP: 572 852-2)

COVERAM 10 mg / 10 mg, tablet
B/30 (CIP: 385 839-6)
B/90 (CIP: 385 843-3)
B/100 (CIP: 572 855-1)

Applicant: SERVIER

Perindopril arginine / amlodipine

ATC code: C09BB04

List I

Date of marketing authorisation: 20 October 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance (boxes of 30 and 90 tablets) and approved for hospital use (boxes of 30, 90 and 100 tablets).

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients
Perindopril arginine / amlodipine

1.2. Indication
“COVERAM is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.”

1.3. Dosage
One tablet per day as a single dose, preferably to be taken in the morning and before a meal.
The fixed dose combination is not suitable for initial therapy.
If a change of posology is required, the dose of COVERAM could be modified or individual titration with free combination may be considered.

Patients with renal impairment and elderly (see sections 4.4 and 5.2)
Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.
COVERAM can be administered in patients with Clcr ≥ 60ml/min, and is not suitable for patients with Clcr < 60ml/min. In these patients, an individual dose titration with the monocomponents is recommended.
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Patients with hepatic impairment (see sections 4.4 and 5.2)
A dosage regimen for patients with hepatic impairment has not been established. Therefore, COVERAM should be administered with caution.

Children and adolescents
COVERAM should not be used in children and adolescents as the efficacy and tolerability of perindopril and amlodipine, alone or in combination, have not been established in children and adolescents."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)
C : Cardiovascular system
C09 : Agents acting on the renin-angiotensin system
C09B : ACE inhibitors, combinations
C09BB : ACE inhibitors and calcium channel blockers
C09BB04 : perindopril and amlodipine

2.2. Medicines in the same therapeutic category
COVERSYL (perindopril arginine) 5 or 10 mg and AMLOR and its generics (amlodipine) 5 or 10 mg taken separately.

2.3. Medicines with a similar therapeutic aim
All medicines indicated for the treatment of essential hypertension and/or stable coronary disease prescribed as monotherapy or in combination.

The following ACE inhibitor/calcium-channel blockers indicated for the treatment of hypertension are currently available:

trandolapril 2 mg	+	verapamil 180 mg:	TARKA LP ; OKADRIK LP.
enalapril 10 mg	+	lercanidipine 10 mg:	LERCAPRESS, ZANEXTRA

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The dossier is based on three bioequivalence studies (PKH-05985-001, PKH-05985-002 and PKH-05985-003) in which three dose levels were assessed: perindopril arginine 10 mg/amlodipine 10 mg, perindopril arginine 5 mg/amlodipine 10 mg, perindopril arginine 10 mg/amlodipine 5 mg.

Study PKH-05985-001 showed the combination perindopril arginine 10 mg/amlodipine 10 mg to be bioequivalent to perindopril tert-butylamine 8 mg + amlodipine 10 mg in respect of the kinetic parameters investigated (Cmax, Tmax, area under the curve).

Study PKH-05985-002 showed the combination perindopril arginine 10 mg/amlodipine 5 mg to be bioequivalent to perindopril tert-butylamine 8 mg + amlodipine 5 mg in respect of the kinetic parameters investigated (Cmax, Tmax, area under the curve).

Study PKH-05985-003 showed the combination perindopril arginine 5 mg/amlodipine 10 mg to be bioequivalent to perindopril tert-butylamine 4 mg + amlodipine 10 mg in respect of the kinetic parameters investigated (Cmax, Tmax, area under the curve).

The dossier also includes one study (PKH-05985-004) showing no interaction between perindopril arginine 10 mg and amlodipine 10 mg in 35 healthy volunteers.

3.2. Adverse effects

The adverse effects linked to COVERAM are similar to those reported with perindopril or amlodipine taken separately.

The SPC states that the most common adverse effects (≥ 1/100) are:

- nervous system disorders: somnolence, dizziness, headache, paraesthesia, vertigo,
- ENT disorders: visual disturbances, tinnitus,
- cardiovascular disorders: palpitations, flushing, hypotension,
- respiratory disorders: cough, dyspnoea,
- gastro-intestinal disorders: abdominal pain, nausea, vomiting, dyspepsia, dysgeusia, diarrhoea, constipation.

3.3. Conclusion

The studies (PKH-05985-001, PKH-05985-002 and PKH-05985-003) have demonstrated bioequivalence between:

- The combination perindopril arginine 10 mg/amlodipine 10 mg and perindopril tert-butylamine 8 mg + amlodipine 10 mg,
- The combination perindopril arginine 10 mg/amlodipine 5 mg and perindopril tert-butylamine 8 mg + amlodipine 5 mg,
- The combination perindopril arginine 5 mg/amlodipine 10 mg and perindopril tert-butylamine 4 mg + amlodipine 10 mg.

No data is available for COVERAM 5 mg / 5 mg.

The marketing authorisation lists the indications for COVERAM as: “substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level". The studies supplied in the dossier do not document the clinical efficacy of COVERAM in these indications. Furthermore, the benefit of COVERAM (fixed combination) in terms of reducing morbidity-mortality has not been established.

The advantage of COVERAM (fixed combination) over taking the active ingredients separately has not been established.

The clinical benefit of COVERAM (fixed combination) compared to other antihypertensive combinations (medicines in the same classes or other classes) has not been documented.

Studies have found no difference in the safety profile of COVERAM compared to the known safety profiles of the two active ingredients (perindopril arginine and amlodipine). The adverse effects most frequently observed were: somnolence, dizziness, headache, paraesthesia, vertigo, visual disturbances, tinnitus, palpitations, flushing, hypotension, cough, dyspnoea, and gastro-intestinal disorders.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hypertension and stable coronary disease are potentially life-threatening, either directly or as a result of complications.

This medicine is intended for use as part of preventive therapy.

The efficacy/adverse effects ratio is considerable. The various forms of COVERAM (fixed combinations) have not shown any impact in terms of reducing morbidity-mortality.

These fixed combinations of perindopril arginine and amlodipine (COVERAM) are third-line medicines, for use as a substitute treatment for patients whose blood pressure has been brought under control and stabilised by perindopril arginine and amlodipine taken separately at the same doses as in the combination.

Public health benefit:

Essential hypertension and the cardiovascular pathologies for which it is a risk factor form a significant public health burden.

The reduction in morbidity-mortality that can be attributed to hypertension is a public health need (priority identified by the GTNDO* and in the Public Health Act).

However, existing treatments (including the free combination of perindopril arginine and amlodipine) already help to cover this need.

There is no argument showing that this fixed combination offers any treatment advantage compared to the free combination of these two active ingredients (including in terms of compliance). Consequently, COVERAM is not expected to benefit public health in this indication.

** GTNDO: National Technical Group for Definition of Objectives (DGS-2003)*

There are several alternative medicinal products which have been shown to have an impact in terms of reducing morbidity-mortality: diuretics, beta-blockers, calcium-channel blockers, ACE inhibitors and renin-angiotensin system antagonists.

The actual benefit of the various forms of COVERAM is substantial.

4.2. Improvement in actual benefit

The various presentations of COVERAM (5 mg / 5 mg, 5 mg / 10 mg, 10 mg / 5 mg, 10 mg / 10 mg, fixed combinations of perindopril arginine 5 or 10 mg and amlodipine 5 or 10 mg) provide no improvement in actual benefit (IAB V) compared to the simultaneous administration of each ingredient taken separately.

4.3. Therapeutic use

Hypertension[1]:

The aim of antihypertensive treatment is to prevent the cardiovascular and renal complications associated with AHT. The goal is to normalise blood pressure. Diuretics, beta-blockers, calcium-channel blockers and renin-angiotensin system antagonists have been shown to be capable of reducing the occurrence of cardiovascular complications. Therefore, national and international guidelines suggest that patients be started on one of these drugs to control their hypertension.

Stable coronary disease[2,3,4]:

The management of patients with coronary disease is based on an overall approach including: management of associated risk factors: smoking (giving up), excess weight (BMI target value <25kg/m^2), diabetes (HbA1C target value < 7%), dyslipidaemia (LDL-c target value <100 mg/dl) and hypertension (target value <140/90 mm Hg or <130/80 mm Hg in the case of patients with diabetes or renal failure), exercise: 30 minutes a day, prevention of cardiovascular complications.

Various classes of drugs can be used to reduce cardiac events in patients with stable coronary disease (antihypertensives – beta-blockers and ACE inhibitors, lipid-lowering drugs, anti-aggregant drugs, etc.). The aim is to reduce cardiovascular risk factors and help prevent cardiovascular complications.

COVERAM is suitable for the management of patients whose condition is already being controlled by the two active ingredients taken separately at the same doses.

The Committee notes that the benefit of a fixed-dose combination in the management of patients with hypertension and/or stable coronary disease, compared to separate management by means of the (two) drugs, has not been established.

These drugs are not suitable for management of all patients.

4.4. Target population

Hypertension:

The prevalence of AHT which has been diagnosed and/or is being treated is thought to be around 6.5 to 7.4 million patients (HCSP 2002 and CREDES 1999 data, extrapolated to the French population in 2003, THALES/CEMKA 2001).

However, the real prevalence of hypertension could be greater than the figure given for cases of AHT which have been diagnosed and/or are being treated. The MONICA survey found that only 52.2% of hypertensive people aged between 35 and 64 were aware that they had hypertension.

If we extrapolate the MONICA data, and assume that only 52.2% of patients with AHT have been diagnosed and/or are undergoing treatment, the real prevalence of AHT could be of the order of 12.5 to 14.2 million people.

1 “Management of adults with essential hypertension” HAS guidelines, July 2005.

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.

It is interesting to note that a study on the AHT management options in general practice (THALES/CEMKA 2001) found that 49% of patients were being treated with one drug, 34% with two, 13% with three and 4% with four or more.

Stable coronary disease:
The target population for COVERAM consists of patients with stable coronary disease as a substitute treatment for patients whose condition is already being controlled by perindopril and amlodipine taken simultaneously at the same dosage.
It can be estimated based on the following data:
- A prevalence of stable angina of approximately 2% to 2.5% in the general population (Datamonitor Base, 2002; Montaye, 2006; ESC, 2006), i.e. approximately 1.3 to 1.6 million people in France.
- Approximately 20% of these patients (expert opinion) have asymptomatic left ventricular dysfunction contra-indicating the use of calcium antagonists that slow the heart rate, i.e. 260,000 to 320,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance (B/30 and B/90) and on the list of medicines approved for hospital use and various public services (B/30, B/90 and B/100) in the indications and at the posology in the marketing authorisation.

Packaging: suitable for the conditions of prescription.

Reimbursement rate: 65%