HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
28 May 2014

INSPRA 25 mg, film-coated tablet
B/30 (CIP: 34009 366 570 5 2)
B/90 (CIP: 34009 390 981 1 1)
B/50 (CIP: 34009 566 157 4 2)

INSPRA 50 mg, film-coated tablet
B/30 (CIP: 34009 366 574 0 3)
B/90 (CIP: 34009 390 994 6 0)
B/50 (CIP: 34009 566 160 5 3)

Applicant: PFIZER

INN	eplerenone
ATC Code (2013)	C03DA01 (Aldosterone antagonists)
Reason for the review	**Re-assessment of the actual benefit at the Committee's request**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123 2)**
Indication concerned	**"Eplerenone is indicated in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction"**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**In view of:** - **the efficacy results in terms of mortality and morbidity shown only versus placebo in the EPHESUS study,** - **the absence of comparative data versus spironolactone,** - **the absence of differentiation in the role of two mineralocorticoid receptor antagonists (spironolactone and eplerenone) in the therapeutic strategy according to current guidelines (ESC 2011 and 2012),** - **the adverse effects most commonly observed in real life with eplerenone (in particular hyperkalaemia),** **the Committee considers that in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction, INSPRA does not provide an improvement in actual benefit (IAB V, non-existent) in the therapeutic strategy of care, particularly including spironolactone (ALDACTONE and generic drugs).**
Therapeutic Use	**Given the results of the EPHESUS study, eplerenone may be proposed in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (mutual recognition): 5 January 2005 An RMP was combined with the extension of indication (patients with NYHA class II heart failure) obtained in 2012: safety elements followed in this plan are: myocardial infarction, hyperkalaemia, renal failure, pruritus and rash.
Prescribing and dispensing conditions/special status	List I
ATC Classification	2013 C Cardiovascular system C03 Diuretics C03D Potassium-sparing agents C03DA Aldosterone antagonists C03DA01 eplerenone

02 BACKGROUND

The proprietary medicinal product INSPRA (eplerenone) obtained a Marketing Authorisation in January 2005 in the indication "in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction". A Transparency Committee opinion was delivered on 8 June 2005 (substantial AB, IAB III). An opinion for renewal of inclusion was then delivered in July 2010 (continuation of substantial AB).

On 18 September 2013, the Transparency Committee reviewed the request for extension of indication "to adult patients with NYHA class II (chronic) heart failure with left ventricular systolic dysfunction (LVEF ≤ 30%)". This indication was obtained on the basis of the results of the EMPHASIS-HF study and it concluded the following:

- substantial AB,
- IAB V in the therapeutic strategy of care including spironolactone (ALDACTONE and generic drugs).

At the end of this review, the Transparency Committee, given the results of the post-marketing study PERGAME and the new guidelines for management of patients with heart failure, wanted to re-assess INSPRA in its initial indication; this re-assessment is covered in this opinion.

03 THERAPEUTIC INDICATIONS

"Eplerenone is indicated:

- **in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction.**

- in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤ 30%)."

04 DOSAGE

For post-myocardial infarction heart failure patients:
"The recommended maintenance dose of eplerenone is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks, taking into account the blood potassium level (see Table 1 of the SPC). Eplerenone therapy should usually be started within 3-14 days after an acute myocardial infarction. "

05 THERAPEUTIC NEED[1,2]

Myocardial dysfunction frequently occurs after myocardial infarction during the acute and subacute phases. Rapid improvement in ventricular function is usually observed after early revascularisation of the artery responsible for myocardial infarction via PCI or thrombolysis.
However, in the event of transmural lesions and/or microvascular obstruction, myocardial infarction may be complicated by heart failure exacerbating the patient's prognosis for survival and function, heart failure being a significant risk factor for mortality.

Management of patients with stable heart failure after recent myocardial infarction combines, in most cases, the prescription of:

- a loop diuretic, a converting enzyme inhibitor (with angiotensin II receptor antagonists as an alternative), a nitrate derivative in the event of an increase in blood pressure, and a mineralocorticoid receptor antagonist if the LVEF is ≤ 40% for patients with myocardial infarction with ST-segment elevation and class II heart failure.
- a loop diuretic, a nitrate derivative in the absence of hypotension, and a mineralocorticoid receptor antagonist if the LVEF is ≤ 40% for patients with myocardial infarction with ST-segment elevation and class III heart failure.
- a beta-blocker, a converting enzyme inhibitor (with angiotensin II receptor antagonists as an alternative), and a mineralocorticoid receptor antagonist in the event of ventricular dysfunction and heart failure, for patients with myocardial infarction with ST-segment depression.

Two mineralocorticoid receptor antagonists (aldosterone antagonists) are currently available: low dose spironolactone (ALDACTONE and generic drugs) and eplerenone (INSPRA).

[1] Hamm, C.W., et al., ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011; 32: 2999-3054.
[2] Steg, P.G., et al., ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation (Task Force on the management of ST segment elevation acute myocardial infarction of the European Society of Cardiology). Eur Heart J 2012; 33: 2569-619.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The clinically relevant comparators are medicinal products with a Marketing Authorisation or recommended, in addition to standard therapy (CEI or angiotensin II receptor antagonists +/- beta-blockers, nitrate derivatives etc.) in the management of stable patients with left ventricular dysfunction and clinical evidence of heart failure after recent myocardial infarction:

NAME (INN) *Company*	Same TC* Yes/No	Indication	Date of opinion	AB/IAB (Wording)
ALDACTONE (spironolactone) Pfizer	YES	Treatment of stage III or IV heart failure according to the NYHA classification (systolic ejection fraction ≤ 35%), in combination with a treatment comprising a loop diuretic, a converting enzyme inhibitor, and also a digitalis glycoside in the majority of cases**	**3/04/2002**	**Substantial AB** **IAB I** for patients with stage III or IV heart failure according to the NYHA classification system.

*therapeutic category
**although the Marketing Authorisation indication of ALDACTONE is not strictly transferable to that of INSPRA, current guidelines place these two proprietary medicinal products at the same stage in the therapeutic strategy.

06.2 Other health technologies

In patients with myocardial infarction with ST-segment elevation, the following are also recommended:

- oxygen therapy to maintain saturation,
- myocardial revascularisation.

In patients with myocardial infarction with ST-segment depression, the following are also recommended:

- coronary revascularisation,
- cardiac resynchronisation therapy and/or implantable cardioverter defibrillators, in some patients.

◗ Conclusion

Given the role of INSPRA in the therapeutic strategy considered in this indication, the clinically relevant comparator is spironolactone (ALDACTONE).

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
Germany	YES	Initial indication
Australia		
Austria		
Canada		
Cyprus		
Denmark		
Spain		
Greece		
Ireland		
Italy		
Japan		
Norway		
Netherlands		
Sweden		
Switzerland		
UK		
US		

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for the request)	8/06/2005 Inclusion
Indication	Eplerenone is indicated in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction.
AB (wording)	Substantial
IAB (wording)	The Transparency Committee considers that INSPRA provides a moderate improvement in actual benefit (IAB III) in the subpopulation of patients with heart failure after recent myocardial infarction.
Studies requested	The Transparency Committee would like to have the results of a follow-up study of patients treated with INSPRA so as to become aware of the conditions of use of this proprietary medicinal product and to describe the follow-up methods of patients.

Date of opinion (reason for the review)	21/07/2010 Renewal of inclusion
Indication	Eplerenone is indicated in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction.
AB (wording)	Substantial
Date of opinion (reason for the review)	18/09/2013 Extension of indication

Indication	Eplerenone is indicated in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤ 30%)
AB (wording)	Substantial
IAB (wording)	In view of: - the efficacy results in terms of mortality and morbidity shown only versus placebo in the EMPHASIS-HF study, - the questionable choice of placebo as a comparator in this study, while patients included presented with a dysfunctional LVEF at the same level as those of the patients included in the RALES study, performed with spironolactone, - the absence of available comparative data versus spironolactone, - the absence of differentiation in the role of two aldosterone antagonists (spironolactone and eplerenone) in the therapeutic strategy according to current guidelines, - the serious adverse effects commonly observed with eplerenone (hyperkalaemia and renal conditions), the Committee considers that in patients with NYHA class II (chronic) heart failure with left ventricular systolic dysfunction (LVEF ≤ 30%), INSPRA does not provide an improvement in actual benefit (IAB V, non-existent) in the therapeutic strategy of care, including spironolactone (ALDACTONE and generic drugs).

09 ANALYSIS OF AVAILABLE DATA

The dossier is based on:

- A summary of the clinical data available at the initial inclusion of INSPRA (TC opinion of 8/06/2005): EPHESUS study.
- The new data provided by the company:
    - o two post-hoc studies of subgroups from the EPHESUS study (Deedwania[3] et al. 2011 and Ukena[4] et al. 2012),
    - o an efficacy study (Zhang[5] et al. 2010) which will not be covered in this opinion to the extent that economic considerations are not taken into account in the Transparency Committee opinions.

09.1 Efficacy

9.1.1 Summary of available data during the initial registration: EPHESUS study

The objective of this study was to evaluate the effect of eplerenone compared with placebo on mortality and morbidity in post myocardial infarction heart failure patients. (see opinion of 8/06/2005)

"Study design: double-blind, controlled study versus placebo lasting 3 years, conducted in 6632 patients who had had myocardial infarction, with left ventricular dysfunction (with an ejection fraction [LVEF] ≤ 40%) and clinical evidence of heart failure. The mean age was 64 years (20% were over 74 years of age) and most were men (71%).

Results:

- *14.4% of patients who received eplerenone and 16.7% of patients who received the placebo died. Thus, the combination of eplerenone with standard therapy has reduced the risk of all-cause mortality by 15% (RR 0.85; 95% CI, 0.75-0.96; p = 0.008) as compared with the placebo, primarily reducing cardiovascular mortality (12.3% against 14.6%). The reduction in the absolute risk in terms of all-cause mortality was 2.3%.*
- *26.7% of patients who received eplerenone and 30.0% who received the placebo presented the combined endpoint of cardiovascular mortality or hospitalisation due to cardiovascular disease. Thus, this risk was reduced by 13% with eplerenone (RR 0.87; 95% CI, 0.79-0.95; p=0.002). The reduction in the absolute risk in terms of cardiovascular mortality or hospitalisation was 3.3%*

- *The incidence of hyperkalaemia was 3.4% in the eplerenone group against 2.0% in the placebo group (p<0.001). The incidence of hypokalaemia was 0.5% in the eplerenone group against 1.5% in the placebo group (p<0.001).*
- *No effect due to eplerenone in terms of heart rate, QRS duration or PR or QT interval was observed in 147 normal subjects whose electrocardiographic changes were evaluated during the pharmacokinetic studies. "*

9.1.2 New available data

[3]Deedwania, P.C., et al., Impact of diabetes mellitus on outcomes in patients with acute myocardial infarction and systolic heart failure. Eur J Heart Fail 2011; 13: 551-9.
[4] Ukena, C., et al., Hypo- and hyperglycemia predict outcome in patients with left ventricular dysfunction after acute myocardial infarction: data from EPHESUS. J Card Fail 2012; 18: 439-45.
[5]Zhang, Z., et al., Cost effectiveness of eplerenone in patients with heart failure after acute myocardial infarction who were taking both ACE inhibitors and beta-blockers: subanalysis of the EPHESUS. Am J Cardiovasc Drugs 2010; 10: 55-63.

Deedwania[3] et al. study. :
The objective of this post-hoc analysis of the EPHESUS study was to investigate the association of diabetes with recurrence of fatal or non-fatal acute myocardial infarction (MI) in patients with systolic heart failure after acute myocardial infarction.
The authors concluded that in patients with systolic heart failure after acute myocardial infarction, diabetes is a significant independent risk factor for the recurrence of short-term non-fatal acute myocardial infarction (HR 1.68, 95% CI [1.23; 2.31] p=0.001), but it is not associated with fatal acute myocardial infarction (HR 1.42, 95% CI [0.88; 2.28], NS).
The study design of this study (study of subgroups defined *a posteriori*) gives the results an exploratory character; as a result, this study will not be discussed in this opinion.

Ukena[4] et al. study. :
The objective of this post-hoc analysis of the EPHESUS study was to investigate the prognostic value of blood sugar on the clinical results in patients after admission due to myocardial infarction complicated by heart failure.
The authors concluded that:
- Hypoglycaemia was associated with higher levels of death from all causes combined (HR 1.38, 95% CI [1.06; 1.81], p = 0.002).
- Hyperglycaemia was associated with higher levels of death from all causes combined and mortality due to cardiovascular disease or hospitalisations (NS).

The study design of this study (study of subgroup defined *a posteriori*) gives the results an exploratory character; as a result, this study will not be discussed in this opinion.

09.2 Adverse effects

9.2.1 PSUR data

The analysis of previous periodic safety update reports (PSUR) covering the period from 16 March 2009 to 15 March 2012 allowed the exposure of patients to INSPRA to be estimated at 949,637 patient-years. During this period, 608 medically confirmed cases were reported (914 adverse effects), including 284 considered serious.
The most common adverse effects were:
- hyperkalaemia (12.3%),
- gynaecomastia (6.4%),
- increases in blood potassium (4.3%).

Overall, 17 cases of fatal outcome were also reported.

The analysis of all these data has not identified any new safety information allowing any changes to be made to the risk/benefit ratio for eplerenone.

9.2.2 Risk Management Plan

A risk management plan was implemented as part of the extension of indication in the reduction of the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure with left ventricular systolic dysfunction (LVEF ≤ 30%) [see TC opinion of 18/09/2013]. It includes in particular monitoring of the following safety elements:
- myocardial infarction,
- hyperkalaemia,
- renal impairment,
- pruritus,
- rash.

09.3 Usage data

9.3.1 Data from the post-marketing study

In its opinion of 8/06/2005, the Transparency Committee had wanted to "have the results of a follow-up study of patients treated with INSPRA so as to become aware of the conditions of use of this proprietary medicinal product and to describe the follow-up methods of patients". For this study, the following had to be described: "the population treated with INSPRA, the methods of using INSPRA, the follow-up methods for these patients (particularly follow-up of blood potassium), as well as clinical events and outcomes of haemodynamic parameters." This request for a study was included as part of the agreement signed between PFIZER and CEPS [Healthcare Products Pricing Committee] on 29/07/2005.

To respond to this request, the company presented the final results of the PERGAME study, which took place from September 2008 to December 2010.

The PERGAME study was a prospective observational study performed on a sample of 160 patients included by 75 independent cardiologists.

This cohort was made up of patients currently being treated with eplerenone, whose start date was known and who were likely to be monitored by the same doctor over a minimum period of 12 months. They were included consecutively during a consultation with the participating cardiologist. The patient follow-up period was 12 months.

Data were collected by the doctors at baseline and at each follow-up consultation carried out within a minimum follow-up period of 12 months after inclusion.

Results:

Description of the PERGAME cohort:

Out of 1703 independent cardiologists contacted to participate in the study, 143 agreed to participate in the study and 75 included at least one patient.
Overall, 160 patients meeting inclusion criteria were included out of the 500 initially planned and only 148 patients were included in the analysis.

The main characteristics of patients at baseline were the following:

- 75.7% of patients were men;
- the mean age was 67.9 years (± 11.8);
- the mean LVEF in the study was 41.2 (± 13.0) % (n=127) but was lower during the hospitalisation 36.8 (± 10.3) % (n=102);
- the degree of heart failure was class I according to the NYHA classification in 25 patients (16.9%), **class II in 80 patients (54.1%), class III in 42 patients (28.4%),** and class IV in 1 patient (0.7%);
- the main associated co-morbidities were: hypercholesterolaemia in 92 patients (62%), arterial hypertension in 78 patients (53%) and obesity in 50 patients (34%);
- the main co-prescriptions were CEIs (62%), beta-blockers (79%), statins (70%) and antithrombotics (87%);
- of the 148 patients analysed, the eplerenone treatment was started in 96 patients for evidence of heart failure associated with myocardial infarction (MI) (65%); in 44 patients for evidence of heart failure (30%); in 7 patients for another reason (5%), mostly for arterial hypertension.
- the median delay between starting eplerenone and inclusion in the study was 2 months [-0.3 - +40 months].
- Among the 96 patients with a history of myocardial infarction, 51 patients had been treated by primary angioplasty when the myocardial infarction occurred, 25 by secondary angioplasty, 10 by bypass and 10 by thrombolysis.
- the median delay between myocardial infarction and inclusion in the study was 7.1 months [0.0 - 159.4 months].

- the starting dosage at the start of treatment was 25 mg/kg in 125 patients (84.5%);
- a change of dosage between the start of treatment and inclusion occurred in 25 patients (27 changes of dose); 80% concerned an increase in dose. The reasons reported were mostly a lack of efficacy (9 cases), worsening of heart failure (5 cases), and intolerance to treatment (7 cases).
- at the start of the eplerenone treatment, the mean blood potassium level was 4.2 mmol/l (± 0.4) (n= 140) and mean creatinine clearance was 72 (± 23) ml/min (n=93).
- At baseline in the study, 14 patients had blood potassium > 5 mmol/l and/or creatinine clearance < 50 ml/min.

Of the 148 patients included in the analysis, the mean duration of follow-up was 11 (±5) months ranging from 7 days to 23 months. However, only 92 (62.2%), 71 (48.0%), 58 (39.2%) and 70 (47.3%) patients underwent a follow-up at 3, 6, 9 and 12 months respectively.

Compliance with the Marketing Authorisation indication at baseline:
Among the 96 patients with evidence of post-myocardial infarction failure, 94 had an LVEF measurement and only 75/148 had LVEF ≤ 40%[6] i.e. **only 50.7% of patients treated met the strict indication of the eplerenone Marketing Authorisation.**

Patient follow-up:
During the follow-up period of 1 year, 128 of the 148 patients included in the analysis had at least 1 laboratory result for blood potassium. The mean number of blood potassium assays carried out varies from 0 to 12 times with a median of 2 measurements.
During this follow-up, 20 patients had at least one blood potassium measurement > 5 mmol/l (most with a value close to 5). One patient had severe hyperkalaemia at 6 mmol/l.

The mean duration under treatment was 17.8 (±12.1) months.
The dosage at the start was maintained during the follow-up for most patients (76%), was increased in 30 patients and reduced in 5 patients.

Overall, 19 temporary or definitive treatment discontinuations were reported, including 15 considered definitive. The reasons for discontinuation were death in 9 cases, an adverse event in 7 cases, an LVEF > 40% in one case and 2 treatment discontinuations occurring during a hospitalisation without any reason reported.

As for safety, 65 adverse events were reported, including 20 regarded as treatment-related and 27 considered serious.

Nine patients died, including at least 5 from cardiovascular disease.
During this follow-up period, 40 hospitalisations were reported in 33 patients. The reasons for hospitalisation were mostly due to cardiovascular disease (65% of cases): 8 cases of cardiac decompensation, 3 cases of acute coronary syndrome, 1 bypass, 3 angioplasties, 3 placements of cardiac defibrillators.
Among the cardiovascular and renal events, 3 patients had moderate renal impairment, 1 patients renal colic, 6 patients acute decompensated heart failure, 3 coronary disease and 2 ventricular tachycardia. No cases of serious hyperkalaemia > 6 mmol/l were reported.

At 12 months of follow-up (n=70), the NYHA classification did not progress compared with what it was at baseline for 41 patients (59%), improved for 25 patients (26%) and deteriorated for 4 patients (6%).

[6] Data with imputation based on LVEF data collected during previous hospitalisation

Conclusion:
The results of the PERGAME study indicate that the Marketing Authorisation indications for INSPRA are inadequately respected. Thus, only 50.7% of patients treated met the strict indication of the eplerenone Marketing Authorisation.
The results of this study should, however, be interpreted with caution on account of the following:

- the low number of inclusions, very much lower than the numbers initially set in the protocol (< 30%) and the absence of elements allowing the representativeness of patients included to be guaranteed.
- the low participation (4.4%) of doctors selected at random and the selection bias of doctors likely to result.
- the number of patients lost to follow-up at the end of the study corresponding to less then 50% of the initial number.

However, these results confirm the results of the OLYMPIE study performed in the intensive care and cardiology units where the percentage of patients who received INSPRA in line with the precautions for use of the product (that is start within 3 to 14 days after myocardial infarction and left ventricular ejection fraction < 40%, blood potassium < 5 mmol/l and creatinine clearance > 50 ml/min on the day of starting treatment or the day before) was only 34.6% (see report of the OLYMPIE study page 44/50).

9.3.2 Data from the EPPM [Permanent Survey of Medical Prescription]

According to IMS-EPPM data (moving annual total November 2013), 146,000 prescriptions of INSPRA (108,000 prescriptions of INSPRA 25 mg and 38,000 prescriptions of INSPRA 50 mg) were observed.
INSPRA is mostly prescribed for:

- heart failure (14 to 28.6% of prescriptions depending on doses and presentation),
- arterial hypertension, **off-label indication** (7.4 to 34.8% of prescriptions depending on doses and presentation),
- ischaemic heart disease (7.1 to 21.4% of prescriptions depending on doses and presentation).

09.4 Summary & discussion

Eplerenone (INSPRA) in its indication "in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction" was evaluated in a placebo-controlled trial (EPHESUS) conducted in 6632 patients.
This study showed the efficacy of eplerenone in combination with standard therapy compared with the placebo in terms of two defined co-primary endpoints:

- All-cause mortality: 14.4% of patients in the eplerenone group versus 16.7% in the placebo group died: RR = 0.85; 95% CI, [0.75-0.96], p = 0.008,
- The combined endpoint for cardiovascular mortality or hospitalisation for cardiovascular disease was 26.7% in the eplerenone group versus 30.0% in the placebo group: RR = 0.87; 95% CI, [0.79-0.95], p = 0.002.

No study versus spironolactone (ALDACTONE) is available. However, the results of the PERGAME study and the consumption data from EPPM indicate that eplerenone and spironolactone are prescribed in the same patients even if they do not strictly speaking have the same indications approved by their Marketing Authorisations. Moreover, although spironolactone does not have any specific indication in patients with LVEF ≤ 40% and clinical evidence of heart failure after recent myocardial infarction, the latest guidelines[1,2] in force do not differentiate between the two mineralocorticoids available for the management of these patients. Thus, the only comparison with placebo does not allow any differentiation to be made between eplerenone and spironolactone in the management of these patients.

The adverse effects most commonly observed with eplerenone (INSPRA) are hyperkalaemia and renal conditions.

09.5 Planned studies

The company has not reported any studies, either in progress or to come.

010 THERAPEUTIC USE[1,2]

Management of patients with stable heart failure after recent myocardial infarction combines various treatments, depending on the type of myocardial infarction observed.

After myocardial infarction with ST-segment elevation (ST+), the management:

- for class II heart failure patients is based on:
  - the prescription of a loop diuretic, a converting enzyme inhibitor (with angiotensin II receptor antagonists as an alternative), a nitrate derivative in the event of an increase in blood pressure, and a mineralocorticoid receptor antagonist if the LVEF is ≤ 40%,
  - oxygen therapy to maintain saturation > 95%.
- for class III heart failure patients is based on:
  - the prescription of a loop diuretic, a nitrate derivative in the absence of hypotension, and a mineralocorticoid receptor antagonist if the LVEF is ≤ 40%,
  - oxygen therapy and assisted breathing, if applicable,
  - revascularisation may be required.

After acute coronary syndrome (myocardial infarction with non-ST-segment elevation [(ST-]), the management is based on:

- the prescription of a beta-blocker, a converting enzyme inhibitor (with angiotensin II receptor antagonists as an alternative), and a mineralocorticoid receptor antagonist,
- Cardiac resynchronisation and/or implantable cardioverter defibrillators may also be proposed with severe ventricular dysfunction 1 month after the event.

Two mineralocorticoid receptor antagonists (aldosterone antagonists) are currently available: low dose spironolactone (ALDACTONE and generic drugs) and eplerenone (INSPRA).

Given the results of the EPHESUS study, eplerenone may be proposed in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

◗ Left ventricular dysfunction after recent myocardial infarction is a serious condition which can be life-threatening.

◗ These medicinal products are intended as curative therapy.

◗ In the EPHESUS study, the efficacy of eplerenone was demonstrated versus placebo in terms of the two co-primary endpoints (*all-cause mortality and combined endpoint associating cardiovascular mortality or hospitalisations due to cardiovascular disease)* in combination with standard therapy in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction. In these patients, the efficacy/adverse effects ratio is high.

◗ Alternatives are available and in particular another aldosterone antagonist (spironolactone, ALDACTONE and generic drugs).

◗ These medicinal products are second-line therapies in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction.

◗ <u>Public health benefit:</u>

The impact of heart failure on public health can be considered substantial because of its high prevalence, estimated in Europe as being between 2 and 3% by the European Society of Cardiology. This impact is increasing given the increase in life expectancy, better management of ischaemic heart disease and the reduction in the post-myocardial infarction lethality and frequent re-hospitalisations it entails, particularly in elderly patients.

Reduction in the cardiovascular mortality to which the medicinal product could contribute is a public health need that is an established priority (Object 73 of the Law of 9 August 2004 concerning public health policy aiming to reduce mortality and the frequency of acute cardiac decompensation in people with heart failure).

In view of:

- the results of the EPHESUS trial versus placebo;
- the absence of comparative data for mortality and morbidity compared with spironolactone;
- and the results of the post-marketing studies (OLYMPIE and PERGAME) showing evidence on the one hand of non-compliance with the strict indications of INSPRA, whose indications are in current medical practice transferable to that of spironolactone, and on the other hand, insufficient compliance in following the precautions for use associated with the treatment (particularly in terms of monitoring blood potassium and blood creatinine levels);

the additional impact on mortality and morbidity of the proprietary medicinal product INSPRA compared with the current management of patients with heart failure in France has not been confirmed.

The proprietary medicinal product INSPRA is therefore unable to provide any additional response to the identified public health need.
Consequently, given the new data presented, the proprietary medicinal product INSPRA can no longer be considered to be of public benefit compared with the current management of patients (including in particular spironolactone).

Taking account of these points, the Committee considers that the actual benefit of eplerenone (INSPRA) is substantial in the indication "in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction".

The Committee recommends inclusion/continued inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the indication "in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction" and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

011.2 Improvement in actual benefit (IAB)

In view of:
- **the efficacy results in terms of mortality and morbidity shown only versus placebo in the EPHESUS study,**
- **the absence of comparative data versus spironolactone,**
- **the absence of differentiation in the role of two mineralocorticoid receptor antagonists (spironolactone and eplerenone) in the therapeutic strategy according to current guidelines (ESC 2011 and 2012),**
- **the adverse effects most commonly observed in real life with eplerenone (in particular hyperkalaemia),**

the Committee considers that in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction, INSPRA does not provide an improvement in actual benefit (IAB V, non-existent) in the therapeutic strategy of care, particularly including spironolactone (ALDACTONE and generic drugs).

011.3 Target population

The target population of INSPRA in the indication: "in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction" can be estimated from the following data:
- Based on the FAST-MI registry data[7] (French registry of acute coronary syndromes with or without ST-segment elevation/2007) extrapolated to the whole of France, the number of patients admitted each year to cardiological intensive care units with a diagnosis of myocardial

[7] Cambou JP, Simon T, Mulak G, Bataille V, Danchin N. The French registry of Acute ST elevation or non-ST-elevation Myocardial Infarction (FAST-MI): study design and baseline characteristics. Arch Mal Coeur Vaisseaux 2007; 100: 524 - 34.

infarction (MI) is estimated at around 62,000 (32,000 patients with a diagnosis of MI ST+ and 30,000 with a diagnosis of MI ST-). In-hospital mortality was 5.8% for MI ST+ and 4.9% for MI ST-, which would correspond to approximately 3300 patients per year.

- Between 13 and 40%[8,9,10,11,12,13] of patients had left heart failure and/or left ventricular dysfunction at the acute stage of myocardial infarction, i.e. between 7600 and 23,500 patients a year.

The target population of INSPRA in clinically stable patients with left ventricular systolic dysfunction and clinical evidence of heart failure after recent myocardial infarction can be estimated at between 7600 and 23,500 patients newly treated each year.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

[8] Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont MC, Lopez-Sendon J et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation 2004; 109: 494-9.

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[13] Vaur L, Danchin N, Genes N, Dubroca I, Etienne S, Ferrieres J et al. Epidemiology of myocardial infarction in France: therapeutic and prognostic implications of heart failure during the acute phase. Am Heart J 1999; 137: 49-58