HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 June 2007

PLAVIX 75 mg, film-coated tablets
B/28 (CIP: 347 945-7)
B/50 (CIP: 347 946-3)

PLAVIX 75 mg, film-coated tablets in blister packs
B/28 (CIP: 350 644-4)
B/50 (CIP: 562 020-4)

Applicant: SANOFI-AVENTIS FRANCE

clopidogrel

List I

ATC code: B01AC04

Date of the MA with the new indication: 1 September 2006

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication
"ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy".

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance
clopidogrel

1.2. Indications
Clopidogrel is indicated in adults for the prevention of atherothrombotic events in :

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

- Patients suffering from acute coronary syndrome :
  - Non-ST segment elevation acute coronary syndrome (unstable angina or non Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
  - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

1.3. Dosage
ST segment elevation acute myocardial infarction : clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg loading dose in combination with ASA and with or without thrombolytics. For patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification 2006:
B: Blood and haematopoietic organs
01: Antithrombotic agents
A: Antithrombotic agents
C: Inhibitors of platelet aggregation, excluding heparin
04: Clopidogrel

2.2. Medicines in the same therapeutic category
Combined with aspirin: no medicinal products

2.3. Medicines with a similar therapeutic aim
- Medicines aiming to decrease or limit the enlargement of a arterial thrombus: thrombolytic treatment, anticoagulants such as the heparins and all platelet antiaggregants.
- Other medicines which are used in the management of myocardial infarction, such as the beta-blockers, nitrates, analgesics, or ACE inhibitors and statins.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and tolerability of clopidogrel in patients with acute MI with ST segment elevation was assessed in 2 placebo-controlled, randomised, double-blind studies: CLARITY and COMMIT.

CLARITY Study[1]

Aim: to compare the efficacy and tolerability of clopidogrel (n=1,752) with that of placebo (n=1,739), as combined treatments with aspirin, in patients with acute MI with ST segment elevation and receiving fibrinolytic treatment.

Methodology:

- Placebo-controlled, randomised, double-blind study.
- Inclusion criteria: men and women between 18 and 75 years of age, admitted to hospital in the first 12 hours of MI with ST segment elevation, for whom thrombolytic treatment has been planned.
- The patients received clopidogrel (loading dose of 300 mg followed by 75 mg/day) or placebo, combined with aspirin (150 to 325 mg as a loading dose followed by 75 to 162 mg/day), with fibrinolytic agent and, if indicated, with heparin.
- The patients were followed up for 30 days.
- The primary endpoint was a combined endpoint defined by the occurrence of: death due to any cause, occlusion of the artery responsible for the infarction seen on coronary angiography performed before discharge from hospital and recurrence of the MI before the coronary angiography. For patients who did not undergo coronary angiography, the primary endpoint was death or recurrence of the MI before the 8th day or before discharge.

Results:

- Of the study population, 29.2% were over 65 years of age and 19.7% were women. Among these, 99.7% received fibrinolytics, 89.5% a heparin, 78.7% beta-blockers, 54.7% ACE inhibitors and 63% statins. Coronary angioplasty was subsequently performed in 57.2% of patients in the clopidogrel group and in 56.6% of patients in the placebo group.
- 15% of patients in the clopidogrel group and 21.7% of patients in the placebo group presented with one of the primary endpoint events, this being a reduction of 6.7% in absolute risk and 36% in relative risk in favour of clopidogrel (CI 95%: [24-47]; p<0.001). This effect was basically due to a decrease in the risk of a new occlusion in the artery responsible for the infarct (cf. table 1).
- No difference was observed between the two groups with respect to overall mortality, one of the secondary endpoints of this study.

[1] Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction sith ST-segment elevation. *N Engl J Med* 2005; 352:1179-89

Table 1: Clarity study

	clopidogrel (n=1,752)	placebo (n=1,739)	RRR (CI 95%)	p
Primary endpoint (overall mortality, recurrence of infarction, new occlusion of the artery on coronary angiography)	262 (15.0%)	377 (21.7%)	0.64 [0.53 – 0.76]	p<0.001
Overall mortality	45 (2.6%)	38 (2.2%)	1.17 [0.75 – 1.82]	NS
Recurrence of infarction	44 (2.5%)	62 (3.6%)	0.70 [0.47 – 1.04]	NS
New occlusion (coronary angiography)	192 (11.7%)	301 (18.4%)	0.59 [0.48 – 0.72]	p<0.001

Overall, this study has shown that in patients under 75 years of age, combined platelet antiaggregation treatment (clopidogrel and aspirin) enables the risk of occurrence of a new occlusion of the coronary artery following MI with ST segment elevation to be reduced more significantly than treatment with aspirin in patients who have received fibrinolytic treatment (RRR [relative risk reduction] of 36% and RR[relative risk] of 6.7% for the combined endpoint described above). No difference was observed in overall mortality or in recurrence of infarction.

COMMIT Study[2]

Aim: to compare the efficacy and tolerability of clopidogrel (n=22,961) with that of placebo (n=22,891), as combined treatments with aspirin, in patients with acute MI.

Methodology:

- Study conducted in China according to a 2 x 2 factorial design, placebo-controlled, randomised, double-blind.
- Inclusion criteria: men and women admitted to hospital in the 24 hours after the appearance of symptoms associated with ECG abnormalities (ST segment elevation, ST segment depression or left bundle branch block).
- The patients received clopidogrel (75 mg/day) or placebo, combined with aspirin (162 mg/day) for 28 days or until being discharged from hospital.
- The patients were followed up for 28 days.
- The two primary endpoints were death from any cause and the 1st occurrence of an event from a combined endpoint including recurrence of infarction, cerebrovascular accident or death.

Results:

- In the study population, 58.4% were over 60 years of age (26% were 70 years or older), 27.8% were women; 54.5% received fibrinolytic treatment.
- The rate of death from all causes was 7.5% in the clopidogrel group and 8.1% in the placebo group, this being a reduction in relative risk of 7% (p=0.029) and a reduction in absolute risk of 0.6%.
- The relative risk for the combined endpoint including recurrence of infarction, cerebrovascular accident or death was reduced by 9% (p=0.002), this being a reduction in absolute risk of 0.9%. This benefit was independent of age, sex and the presence or absence of fibrinolytic treatment and was observed in the first 24 hours.

Table 2: Commit study

[2] COMMIT collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controled trial. *Lancet* 2005; 366:1607-21

	Clopidogrel (n=22,961)	Placebo (n=22,891)	RRR (CI 95%) ARR	p
Combined endpoint (death from all causes, recurrence of infarction, cerebrovascular accident)	2,121 (9.2%)	2,310 (10.1%)	0.91 [0.86 – 0.97] ARR = 0.9%	p=0.002
Death from all causes	1,726 (7.5%)	1,845 (8.1%)	0.93 [0.87 – 0.99] ARR = 0.6%	p=0.03

Overall, this study has shown that platelet antiaggregation treatment combined with clopidogrel and aspirin enabled a reduction in overall mortality (RRR of 7% and ARR of 0.5%) and in the occurrence of recurrent infarction, cerebrovascular accident or death (RRR of 9% and ARR of 0.9%) in patients hospitalised on account of MI. Half of the patients received fibrinolytic treatment while hospitalization.

3.2. Adverse effects

In patients with acute MI with ST segment elevation, the tolerability of clopidogrel was assessed in two studies, each lasting 1 month, CLARITY and COMMIT.

Bleeding problems: in the two studies, the frequency of severe haemorrhage was similar between the two groups (CLARITY: 1.3% in the clopidogrel group *versus* 1.1% in the placebo group; COMMIT: 0.6% *versus* 0.5%).

In the CLARITY study, the frequency of intracranial haemorrhages (0.5% *versus* 0.7% in the clopidogrel+ASA and placebo+ASA groups) did not differ between the two groups.

3.3. Conclusion

The efficacy and tolerability of clopidogrel in patients with acute MI with ST segment elevation was assessed over a limited period of 1 month in 2 placebo-controlled, randomised, double-blind studies: CLARITY and COMMIT.

The CLARITY study has shown that in patients under 75 years of age, combined platelet antiaggregation treatment (clopidogrel and aspirin) enables the risk of occurrence of a new occlusion of the coronary artery following MI with ST segment elevation to be reduced more significantly than treatment with aspirin alone in patients who have received fibrinolytic treatment (RRR of 36% and ARR of 6.7% for the combined endpoint taking into account this element). No difference was observed for overall mortality and recurrence of infarction.

The COMMIT study showed that 28 days of combined platelet antiaggregation treatment (clopidogrel and aspirin) enabled a reduction in overall mortality (RRR of 7% and ARR of 0.5%) and in the occurrence of recurrent infarction, cerebrovascular accident or death (RRR of 9% and ARR of 0.9%) in patients admitted to hospital on account of MI, half of whom received fibrinolytic treatment while in hospital. The effect was thus minimal in size.

In addition, the question arises of how transferable are the results of this study to the population and management of care in France.

In the two studies, the frequency of severe haemorrhage was similar between the two groups (CLARITY: 1.3% in the clopidogrel group *versus* 1.1% in the placebo group; COMMIT: 0.6% *versus* 0.5%).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The risks of recurrence or exacerbation following myocardial infarction with or without fibrinolytic treatment represent serious, frequently life-threatening situations.

In these cases, the efficacy/adverse effects ratio of a platelet antiaggregation treatment combining clopidogrel and aspirin is significant.

The treatment is intended for preventive use. The aim of this treatment is to prevent reocclusion of the coronary artery following fibrinolysis or to prevent exacerbation of the infarction.

The only alternative treatment is aspirin alone. The combination of clopidogrel / aspirin has shown better efficacy than aspirin alone and thus is able to answer a therapeutic need.

Public health benefit:

In terms of public health, ischaemic heart diseases represent a major burden. That of myocardial infarction with ST elevation eligible for thrombolytic treatment is small due to the limited number of patients affected.

Improvement of the secondary prevention of MI with ST elevation is still a public health need coming within the scope of identified public health priorities (GTNDO priority).

Taking into account early management with angioplasty, which is the standard treatment, the target population for PLAVIX in this indication is decreased. In addition, taking into account the available data and existing therapies, the expected impact in terms of morbidity and mortality for this product can only be small.

Finally, there is no certainty that the results of the Chinese COMMIT study are transferable to French clinical practice (the profile of the patients and the system for management of care may differ, absence of information in the study on the use of angioplasty).

Consequently, given the current state of knowledge and in view of the existence of other currently available treatments, PLAVIX is expected to benefit public health in this indication. This benefit is slight.

The actual benefit of PLAVIX in this new indication is substantial.

4.2. Improvement in actual benefit:

The Transparency Committee considers that in this new indication, PLAVIX provides a moderate improvement in actual benefit (IAB III) for patient management.

4.3. Therapeutic use

According to the recent French consensus conference[3], early restoration of coronary patency in the acute phase of MI contributes to improving the prognosis for patients. The choice between the two available techniques (angioplasty or fibrinolysis) is made with regard to the clinical situation, above according to the time elapsed since the appearance of symptoms.

When antithrombotic treatment is required, its aim is to prevent an excessive thrombotic reaction being triggered by the thrombolysis or angioplasty and also to prevent reocclusion of

[3] Conférence de Consensus. Prise en charge de l'infarctus du myocarde à la phase aigue en dehors des services de cardiologie. SAMU de France avec le partenariat méthodologique et le concours financier de la Haute Autorité de santé; 06 février 2007

the artery. The use of clopidogrel is recommended, either in combination with aspirin or alone if aspirin is contraindicated.

Choice of the technique for restoration of coronary patency
According to the 2003 recommendations of the European Society for Cardiology, primary angioplasty is to be favoured if it can be performed within 90 minutes following contact with the emergency team. Thrombolytics are indicated when it is difficult or impossible to reach a centre capable of performing emergency angioplasties within a reasonable time (90 min); also in this case thrombolysis is more likely to succeed if it is started early, even prior to reaching the hospital. It is frequently followed by a subsequent coronary angiography with angioplasty if necessary.

4.4. Target Population

The target population is represented by patients experiencing myocardial infarction with ST segment elevation, who are eligible for thrombolytic treatment.
It can be estimated on the basis of the following data:

- According to PMSI 2004 data supplied, this situation affects approximately 56,000 patients per year in France.
- One in three of these are currently being receiving thrombolytic treatment with or without subsequent angiography.

Based on this data, the target population for PLAVIX in this new indication is likely to be more than 18,000 patients.

4.5. Recommendations of the Transparency Committee

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance (B/28) and on the list of medicines approved for use by hospitals and various public services (B/28; B/50) in its new indication

The Committee points out that a study was requested by DGS following the previous opinion on PLAVIX. This study, which is about to start, includes notably patients treated with clopidogrel + aspirin following acute MI with or without ST segment elevation. The Committee wishes to be sent the results of this study.

4.5.1 Packaging: appropriate for the prescription conditions

The Committee points out that in accordance with its decision of 20 July 2005 it recommends that pack sizes for one-month treatments be harmonised as 30-day packs.

4.5.2 Reimbursement rate: 65%