Scottish Medicines Consortium

clopidogrel 75mg tablets (Plavix®) No. (390/07)

sanofi-aventis UK and Bristol-Myers Squibb Pharmaceuticals Ltd.

6 July 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

clopidogrel (Plavix®) is accepted for restricted use within NHS Scotland for patients with ST segment elevation acute myocardial infarction (MI), in combination with aspirin, in medically treated patients eligible for thrombolytic therapy.

The addition of short-term treatment with clopidogrel to long-term low dose aspirin has improved the patency rate of the infarct related artery as well as clinical endpoints. Treatment with clopidogrel in these patients is restricted to continuation for 4 weeks.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Patients suffering from acute coronary syndrome – ST segment elevation acute MI, in combination with aspirin in medically treated patients eligible for thrombolytic therapy.

Dosing information

Following an initial loading dose (300mg) in combination with aspirin, and with or without thrombolytic, clopidogrel 75mg daily. Patients over 75 years should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least 4 weeks.

Date of licensing

September 2006

Summary of evidence on comparative efficacy

Clopidogrel acts to inhibit platelet aggregation by irreversibly and selectively blocking adenosine diphosphate (ADP) at its platelet receptor.

The pivotal study of clopidogrel in this new indication enrolled 3,491 patients, aged 18 to 75 years, who presented within 12 hours of onset of ST-segment elevation MI (defined as ischaemic discomfort at rest for > 20 minutes and ST-segment elevation of at least 0.1 mV in at least two contiguous limb leads, ST-segment elevation of at least 0.2 mV in at least two contiguous precordial leads, or left bundle-branch block (BBB) that was not previously diagnosed). All patients were scheduled to receive a fibrinolytic agent, heparin when appropriate and aspirin (150-325mg on the first day followed by 75-162mg daily). Patients were randomised to receive either clopidogrel (300 mg loading dose followed by 75 mg daily, n=1752) or placebo (n=1739) until and including the day of angiograph. This was performed 48-192 hours after the start of study drug treatment to assess late patency of the infarct-related artery (IRA). For patients who did not have angiography, study drug treatment was continued until day 8 or hospital discharge, whichever came first. The primary endpoint was the composite of an occluded IRA [defined as Thrombolysis in Myocardial Infarction (TIMI) flow grade (TFG) 0 or 1], death from any cause before angiography or recurrent MI before angiography; or death or recurrent MI by day 8 or hospital discharge in those who did not undergo angiography.

The mean duration of study drug treatment was 4.5 days in the clopidogrel and 4.4 days in the placebo group. Angiography was performed in 94% of patients after a median of 84 hours. The composite primary endpoint was reported in 15% (262/1752) in the clopidogrel group compared with 22% (377/1739) of patients in the placebo group; representing an absolute reduction of 6.7% and a 36% reduction in the odds of the endpoint in favour of clopidogrel (95% CI, 24 to 47%; $p<0.001$). In terms of the individual components of the composite endpoint, an occluded IRA was reported in 12% of clopidogrel- and 18% of placebo-treated patients (41% reduction in odds, $p<0.001$), death in 2.6% and 2.2% of patients respectively ($p=0.49$) and recurrent MI in 2.5% and 3.6% of patients respectively (30% reduction in odds, $p=0.08$). By day 30, the addition of clopidogrel to aspirin therapy had reduced the composite endpoint of cardiovascular death, recurrent MI or recurrent ischaemia leading to the need for urgent revascularisation from 14% to 12% (20% reduction in odds, $p=0.03$). A separate analysis in the 1863 patients who underwent PCI after angiography found that the composite endpoint of cardiovascular death, MI, or stroke, measured from PCI to 30 days post randomisation, occurred in 3.6% of clopidogrel-treated patients versus 6.2% of placebo patients, $p=0.008$.

A second larger study was conducted in 1250 hospitals in China and co-ordinated by the Clinical Trials Service Unit at the University of Oxford. This study enrolled 45,852 patients who presented within 24 hours of the onset of symptoms of suspected acute MI with ST-segment elevation or depression or left BBB. Patients were randomised in a 2 X 2 factorial design to receive clopidogrel (75mg daily) or placebo and metoprolol or placebo for up to 4 weeks in hospital or death or hospital discharge whichever came first. All patients received aspirin (162mg daily). This design allowed separate assessment of the effects of clopidogrel and metoprolol. Results are presented for the clopidogrel analysis only. There were two co-primary endpoints: 1) the composite of death, reinfarction or stroke and 2) death from any cause until hospital discharge or 28 days whichever came first.

The mean study treatment duration in survivors in both treatment groups was 15 days. The composite primary endpoint of death, reinfarction or stroke occurred in 9.2% (2,121/22,961) clopidogrel patients and 10% (2,310/22,8911) in placebo patients, representing a 9% relative risk reduction (95% CI: 3%, 14%, p=0.002). Death from any cause was reported in 7.5% (1,726/22,961) clopidogrel and 8.1% (1,845/22,891) placebo patients; representing a 7% relative risk reduction (95% CI: 1%, 13%, p=0.03). Patients treated with clopidogrel had a lower rate of fatal and non-fatal re-infarction (2.1% versus 2.4% in the placebo group); representing a 14% relative risk reduction (95% CI: 3%, 24%, p=0.02). However, there was no significant difference in the incidence of any type of stroke between the groups (0.9% versus 1.1% respectively, p=0.11).

Summary of evidence on comparative safety

The two studies conducted in patients with ST segment elevation MI raised no new safety issues with clopidogrel. The incidence of major bleeding was low and similar in each treatment group of the pivotal study (1.3% in the clopidogrel plus aspirin group versus 1.1% in the aspirin group, p=0.64) as was the incidence of minor bleeding (1.0% versus 0.5% respectively, p=0.17). The rates of fatal bleeding and intracranial haemorrhage were also low and similar (0.8% versus 0.6% respectively and 0.5% versus 0.7% respectively). However, the proportion of patients reporting any bleeding was significantly higher in the clopidogrel group (17% versus 13%, p<0.001). In the second, larger study, the combined incidence of transfused, fatal or cerebral bleeds was 0.58% in the clopidogrel group and 0.55% in the placebo group, p=0.59. There was no excess of fatal bleeds or major non-fatal bleeds in the clopidogrel group. However, there was a small but significant excess in non-major bleeding in the clopidogrel group (3.6% versus 3.1% respectively, p=0.005).

Summary of clinical effectiveness issues

The reduction in the composite primary endpoint in the pivotal trial was mainly driven by the effect on the IRA which was considered as a surrogate endpoint. There was no significant difference between treatments in the hard outcomes of the primary endpoint (i.e. death or recurrent MI). However, the study was not sufficiently powered to detect benefits in individual components of the composite or in the hard clinical outcomes. Indeed, the number of deaths was numerically higher in the clopidogrel group. The second study used well-established clinical endpoints and the results demonstrate significant reduction in the composite of death, recurrent MI or stroke and of death alone. However there has been some concern over the appropriateness of extrapolating these results to the European ST segment elevation MI population.

This is mainly due to differences in background clinical care, particularly the low use of beta-blockers which are considered standard practice in Europe. There was also a much higher mortality rate (8.1% in the placebo group) compared to < 5% in the pivotal study. Indeed the population of the pivotal study was considered to be of relatively low risk.

In both studies the follow-up period was one month, therefore the long term effects of clopidogrel in these patients remains to be determined.

The optimal duration of clopidogrel treatment is difficult to determine due to the lack of data on a longer period of treatment (mean clopidogrel treatment duration was only 4.5 days in the pivotal study and 15 days in the second study). The SPC notes that combined treatment should be started as early as possible after symptoms start and continued for at least 4 weeks. However the benefit of the combination beyond 4 weeks has not been studied in this setting. Furthermore, the Scottish Intercollegiate Guidelines Network (SIGN) recommends that clopidogrel should be added to long-tem aspirin in patients with ST segment elevation acute coronary syndrome (ACS) for up to 4 weeks.

Although the incidence of major bleeding was low and similar in both treatment groups of each study, in one study the number of patients reporting any bleeding was significantly higher in the clopidogrel group while in the other the addition of clopidogrel was associated with a small but significant excess in non-major bleeding.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis of adding clopidogrel to aspirin in a 60-year old patient with ST segment elevation MI. Costs and benefits were estimated over the patient's lifetime using a Markov model. Data to extend the analysis beyond the end of the randomised control trial were taken from a trial of clopidogrel in non-ST segment elevation MI and registry data from England and Germany. Using the protocol from the trial conducted in China, the cost per QALY was £2,284 for 1 month of treatment and £3,891 for 1 year of treatment. Using the protocol from the pivotal trial the cost per QALY was £1,857 for 1 month of treatment and £2,925 for 1 year of treatment.

The analysis included several conservative assumptions that could have lowered this figure still further. However, there are several factors that could increase the cost per QALY:

- The application of relative risk reductions that were not statistically significant, however sensitivity analysis did not indicate this seriously impacted on results
- the extent of the extrapolation in the economic model from one month of randomised control trial follow-up to over 20 years in the future was a cause of concern, however, sensitivity analysis suggested this did not seriously impact on the results
- The mix of different clinical studies used in the analysis raised some concerns about whether they were truly comparable

The manufacturer sought to make a case for one year of treatment with clopidogrel based on experience in treating non-ST segment elevation MI but further clinical evidence is required to support this claim before it can be accepted.

Summary of patient and public involvement

A Patient Interest group Submission was not made.

Additional information: guidelines and protocols

SIGN guideline number 93, Acute Coronary Syndromes (ACS) published in February 2007 recommends that for patients with ST-segment elevation ACS, in the presence of ischaemic electrocardiographic (ECG) changes or elevation of cardiac markers, immediate treatment with both aspirin (300mg) and clopidogrel (300mg). Clopidogrel should be continued for up to 4 weeks in patients with ST-segment elevation ACS, in addition to long-term aspirin.

The National Institute for Health and Clinical Excellence (NICE) clinical guideline on MI secondary prevention (May 2007) recommends that after an ST-segment elevation MI, patients treated with a combination of aspirin and clopidogrel during the first 24 hours after the MI should continue this treatment for at least 4 weeks. Thereafter standard treatment including low-dose aspirin should be given, unless there are other indications to continue dual antiplatelet therapy.

Additional information: previous SMC advice

Enoxaparin (Clexane®) is accepted for use within NHS Scotland for the treatment of acute ST-segment elevation MI including patients to be managed medically or with subsequent PCI. Enoxaparin has demonstrated a reduction in death or non-fatal MI compared to unfractionated heparin which has to be balanced against an increased number of major and minor bleeding events in the enoxaparin group. This advice will not be on the SMC website until June 2007.

Additional information: comparators

There are no direct comparators for this indication. Clopidogrel is licensed for use in addition to aspirin and other standard therapy.

Cost of relevant comparators

Drug	Dose regimen	Cost per one month course (£)
Clopidogrel	**300mg loading dose then 75mg daily**	**40.35**
Aspirin	300mg loading dose then 75mg daily	0.88

Doses are for general comparison and do not imply therapeutic equivalence.
Costs from eVadis on 10 May 2007

Additional information: budget impact

The manufacturer estimated that the additional cost of clopidogrel alone (gross budget impact) would be between £30k and £70k in year one, rising to £80k by year 5, based on one month of treatment per patient

The recent SIGN guideline estimated there were 3,295 STEMIs in Scotland each year. Compared to this, the manufacturer's submission assumed a low estimate of 857 treated in year one to 2,142 by year 5. Market share estimates ranged from 20% to 40% based on experience with statin prescribing; it was not clear why statin prescribing practice was thought to be relevant to prescribing immediately post MI.

Taking a cost £40.35 for a 300mg loading dose followed by 75mg daily for 29 days, the maximum budget impact if every possible patient were treated would be £158k.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 14 June 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Sabatine MS, Cannon CP, Gibson CM et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179-1189.

Chen ZM, Jiang LX, Chen YP et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-1621.

Sabatine MS, Cannon CP, Gibson CM et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA 2005; 294: 1224-1232.

European Medicines Agency (EMEA). European Public Assessment Report (EPAR) for clopidogrel for patients suffering from acute coronary syndrome with ST segment elevation acute MI, in combination with aspirin in medically treated patients eligible for thrombolytic therapy. www.emea.eu.int