HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 July 2010

DUOPLAVIN 75 mg/75 mg, film-coated tablet
B/30 (CIP code: 359 022-6)
B/30 (CIP code: 382 063-7)

DUOPLAVIN 75 mg/100 mg, film-coated tablet
B/30 (CIP code: 359 848-1)

Applicant: SANOFI-AVENTIS FRANCE

clopidogrel / acetylsalicylic acid
ATC code: B01AC30

List I

Date of Marketing Authorisation (centralised procedure): 15/03/2010

Reason for the request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance
clopidogrel / acetylsalicylic acid

1.2. Indication
"DuoPlavin is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). DuoPlavin is a fixed-dose combination medicinal product for continuation of therapy in:
– 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
– ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy

For further information please see section 5.1 of the SPC."

1.3. Dosage
"Adults and elderly: DuoPlavin should be given as a single daily 75 mg/75 mg or 75 mg/100 mg dose. DuoPlavin is used following the initiation of therapy with clopidogrel and ASA given separately.

In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months (see section 5.1 of the SPC). If the use of DuoPlavin is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

In patients with ST segment elevation acute myocardial infarction: 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 (see section 5.1 of the SPC). For patients older than 75 years of age, therapy should be initiated without a loading dose. If the use of DuoPlavin is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

If a dose is missed:
– Less than 12 hours after the regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
– More than 12 hours after the regular scheduled time: patients should take the next dose at the regular scheduled time and should not double the dose.

Pharmacogenetics: CYP2C19 poor metaboliser status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolisers has yet to be determined (see section 5.2 of the SPC).

Paediatric population: The safety and efficacy of DuoPlavin in children and adolescents under 18 years old have not been established. DuoPlavin is not recommended in this population.

Renal impairment: DuoPlavin must not be used in patients with severe renal impairment (see section 4.3 of the SPC). Therapeutic experience is limited in patients with mild to moderate renal impairment (see section 4.4 of the SPC). Therefore DuoPlavin should be used with caution in these patients.

Hepatic impairment: DuoPlavin must not be used in patients with severe hepatic impairment (see section 4.3 of the SPC). Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4 of the SPC). Therefore DuoPlavin should be used with caution in these patients.

Method of administration: Oral use. It may be given with or without food."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

B : Blood and blood-forming organs
B01 : Antithrombotic agents
B01A : Antithrombotic agents
B01AC : Inhibitors of platelet aggregation, excluding heparin
B01AC30 : Combinations

2.2. Medicines in the same therapeutic category

The following medicinal products, consisting of separate doses of:

- 75 mg of clopidogrel (PLAVIX and generics) and acetylsalicylic acid (ASA) 75 or 100 mg;
- 10 mg of prasugrel (EFIENT) and acetylsalicylic acid, indicated for "the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI)."

All other platelet aggregation inhibitors used as monotherapy:

	Class	Indication(s)
Clopidogrel PLAVIX 75 mg and 300 mg, film-coated tablets	Platelet aggregation inhibitor, thienopyridine	In adults, clopidogrel is indicated for the prevention of events associated with atherothrombosis: – 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. – In 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.
Ticlopidine TICLID 250 mg, tablets	Platelet aggregation inhibitor, thienopyridine	Prevention of subacute thrombosis of coronary endoprosthesis (stent). Prevention of atherothrombotic complications (cerebral vascular accident, myocardial infarction, vascular death) after an initial atherosclerosis-linked cerebral ischaemic event. One clinical trial has shown that ticlopidine has a slightly greater efficacy than aspirin in secondary prevention of atherothrombotic complications, although this efficacy should be weighed against the adverse effects of ticlopidine.
Acetylsalicylic acid: Aspirin 75 to 325 mg/day KARGEGIC 75 mg; ASPIRINE UPSA 325 mg; ASPIRINE PROTECT 300 mg; PRAVADUAL CARDIOSOLUPSAN 100 mg;	Platelet aggregation inhibitors, cyclooxygenase inhibitor	Secondary prevention (including in emergency situations) following an initial cerebral or myocardial ischemic event linked to atherosclerosis – reduction in cardiovascular mortality and morbidity: . following myocardial infarction; . in stable and unstable angina; . during transluminal coronary angioplasty; . following transient or established cerebral ischaemic event; – reduction of graft occlusion following aortocoronary bypass. PRAVADUAL, a combination of 81 mg aspirin and 40 mg pravastatin: It is indicated for "Secondary prevention: reduction in cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina and normal or raised cholesterol levels, in cases in which the combination of pravastatin and a low dose of acetylsalicylic acid is considered to be appropriate, taking into account other risk factors".
Abciximab:	Platelet aggregation inhibitor, anti-GPIIb/IIIa	As an adjunct to heparin and acetylsalicylic acid for: – Percutaneous coronary intervention: The prevention of ischaemic cardiac

REOPRO 2 mg/mL solution for injection or infusion		complications in patients undergoing percutaneous coronary intervention (balloon angioplasty, atherectomy and stent): see Pharmacodynamics section of the SPC. – Unstable angina: The short-term (1-month) reduction of the risk of myocardial infarction, in patients with unstable angina, not responding to full conventional therapy, who have been scheduled for percutaneous coronary intervention.
Eptifibatide: INTEGRILIN 0.75 and 2 mg/mL	Platelet aggregation inhibitor, anti-GPIIb/IIIa	For use with acetylsalicylic acid and unfractionated heparin for the prevention of early myocardial infarction in adults presenting with unstable angina or non-Q-wave myocardial infarction with the last episode of chest pain occurring within 24 hours and with electrocardiogram (ECG) changes and/or elevated cardiac enzymes.
Tirofiban: AGGRASTAT 50 and 250 µg/ml	Platelet aggregation inhibitor, anti-GPIIb/IIIa	For use with acetylsalicylic acid and unfractionated heparin: Prevention of early myocardial infarction in patients presenting with unstable angina or non-Q-wave myocardial infarction with the last episode of chest pain occurring within 12 hours and with ECG changes and/or elevated cardiac enzymes.

Anticoagulant antithrombotics:

	Class	Indication(s)
Enoxaparin: (1) and (2) *LOVENOX* 6,000 IU anti-Xa/0.6 mL, 8,000 IU anti-Xa/0.8 mL, 10,000 IU anti-Xa/1 mL, 30,000 IU anti-Xa/3 mL Dalteparin sodium: (1) FRAGMIN 7,500 IU anti-Xa/0.75 mL 10,000 IU anti-Xa/0.75 mL Nadroparin calcium (1) FRAXIPARINE 9,500 IU/ml	Low-molecular-weight heparin (LMWH)	(1)- Treatment of unstable angina and non-Q-wave myocardial infarction in the acute phase, in combination with aspirin. (2)- Treatment of acute ST-elevation myocardial infarction, combined with thrombolytic treatment in patients who are eligible or ineligible for secondary coronary angioplasty.
Heparin calcium CALCIPARINE Heparin sodium HEPARINE CHOAY HEPARINE PANPHARMA	Unfractionated heparins (UFH)	Treatment of Q-wave and non-Q-wave myocardial infarction and unstable angina, in the acute phase.
Fondaparinux sodium: ARIXTRA 2.5 mg		Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 mins) invasive management (PCI) is not indicated. Treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who are to receive no other form of reperfusion therapy initially.
Bivalirudin ANGIOX 250 mg		Treatment of patients with acute coronary syndrome (unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)) planned for urgent or early intervention. Angiox should be administered with aspirin and clopidogrel. Anticoagulant in patients undergoing percutaneous coronary intervention (PCI).

2.3. Medicinal products with the same therapeutic objective:

All other medicinal products used in the management of myocardial infarction, such as beta blockers, nitrates, analgesics, ACE inhibitors and statins.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy dossier is based on three bioequivalence studies (BDR4659, BDR5000 and BEQ10600) in which two different dosage combinations were assessed: clopidogrel 75 mg/ASA 75 mg and clopidogrel 75 mg/ASA 100 mg.

Study BDR4659 demonstrated that DUOPLAVIN 75/75 and a free combination of clopidogrel 75 mg and ASA 75 mg were bioequivalent for the kinetic parameters that were studied (Cmax, Tmax, T1/2 and AUC). This study also showed a reduction in ASA Tmax and absorption rate with DUOPLAVIN in comparison with separate dosing with the active substances.

Study BDR5000 demonstrated that DUOPLAVIN 75/100 and a free combination of clopidogrel 75 mg and ASA 100 mg were bioequivalent for the kinetic parameters that were studied (Cmax, Tmax, T1/2 and AUC). This study also showed a reduction in ASA Tmax and absorption rate with DUOPLAVIN in comparison with separate dosing with the active substances.

Study BEQ106000 demonstrated that DUOPLAVIN 75/100 and a free combination of clopidogrel 75 mg and ASA 100 mg were bioequivalent for the kinetic parameters that were studied (Cmax, Tmax, T1/2 and AUC). This study also showed an increase in ASA Cmax with DUOPLAVIN in comparison with separate dosing with the active substances.

The applicant also refers to three other studies:

- the COMMIT and CLARITY studies, which evaluated the efficacy of clopidogrel 75 mg in patients with acute ST-elevation myocardial infarction, in combination with ASA (162 mg in the COMMIT study and 75–162 mg in the CLARITY study) in medically treated patients eligible for thrombolytic treatment (see the Transparency Committee opinion dated 06/06/2007);
- the CURE study, which evaluated the efficacy of clopidogrel 75 mg in patients with acute non-ST-elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), in combination with ASA 75–325 mg (see the Transparency Committee opinion dated 18/12/2002);

These studies, which did not specifically study the combination of clopidogrel 75 mg and ASA 75 or 100 mg, were examined in the previous opinions concerning PLAVIX. These studies will not be further examined in this opinion.

3.2. Adverse effects

The adverse effects of clopidogrel and ASA are known. According to the SPC, the most common adverse effects (≥ 1/100) are: haematoma, epistaxis, gastrointestinal bleeding, diarrhoea, abdominal pain, dyspepsia and contusion.
The adverse effects that are linked to DUOPLAVIN have been studied in bioequivalence studies in healthy subjects.

3.3. Conclusion

In studies (BDR4659, BDR5000 and BEQ10600) bioequivalence has been shown between: DUOPLAVIN 75/75 and 75/100 and free combinations of clopidogrel 75 and ASA 75 or 100 mg.

According to the marketing authorisation, the indications for DUOPLAVIN are as follows: "DUOPLAVIN is indicated for the prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). DUOPLAVIN is a fixed-dose combination medicinal product for continuation of therapy in 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, or ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy." The studies provided in this dossier do not constitute evidence that DUOPLAVIN is effective in these indications. In addition, the specific usefulness of combinations of clopidogrel 75 mg / ASA 75 or 100 mg, in terms of reduction in morbidity and mortality, has not been established.

According to the SPC, the most common adverse effects observed for clopidogrel and ASA are: haematoma, epistaxis, gastrointestinal bleeding, diarrhoea, abdominal pain, dyspepsia and contusion.

Special attention should be paid if DUOPLAVIN is discontinued, particularly if an invasive medical or surgical procedure is to be performed; dual therapy should in all cases be replaced by a platelet aggregation inhibitor (ASA or clopidogrel) given as monotherapy, in line with current guidelines[1].

1 "Management of oral platelet aggregation inhibitor treatment in patients with coronary stents", SFAR 2006.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit:

Acute coronary syndromes (ST-elevation and non-ST-elevation) require management by a specialised team. The immediate seriousness of non-ST-elevation coronary syndromes (unstable angina, non-ST-elevation myocardial infarction) depends on the clinical situation: whether the situation is stable or unstable, whether the condition is life-threatening or not in the short term, and on risk factors. The level of seriousness will influence patient management. Two treatment methods are available: drug treatment and, for some patients, an invasive strategy involving coronary angiography and revascularisation using angioplasty (PCI) or aortocoronary bypass. The choice[1] between the two techniques depends on the clinical situation, and in particular the length of time that has elapsed since symptoms began. These clinical situations are life-threatening.

DUOPLAVIN products are second-line therapies that are indicated for adult patients who are already being treated with clopidogrel and acetylsalicylic acid (ASA) at the same dosage levels.

The efficacy/adverse effects ratio for these products is high.

There are alternative medicinal products available.

> Public Health Benefit:
> Ischaemic heart disease is a major public health burden. The burden represented by non-ST-elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) and ST-elevation acute myocardial infarction in medically treated patients eligible for thrombolytic treatment is moderate, because of the restricted numbers of patients affected.
> Reduction in the mortality that is associated with ischaemic heart disease is a public health priority (GTNDO 2003 report). However, existing treatments (including free combinations of clopidogrel and acetylsalicylic acid) already help to meet this need.
> Given the available data, the expected impact in terms of morbidity and mortality for this proprietary product cannot be quantified. There is no indication that these fixed-dose combinations have any added benefit (even in terms of increased compliance) over free combinations of the two active substances.
>
> Consequently, DUOPLAVIN is not expected to benefit public health in this indication.

The actual benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit

DUOPLAVIN 75 mg/75 mg and 75 mg/100 mg, which are fixed-dose combinations of clopidogrel 75 mg and acetylsalicylic acid 75 or 100 mg, provide no improvement in actual benefit (IAB V) in comparison with concurrent use of their separate components.

4.3. Therapeutic use

In the acute phase of non-ST-elevation ACS:

The objective of management is to avoid death and the onset of transmural myocardial infarction. Three clinical situations can be identified:

- Immediately life-threatening: emergency use of an immediate invasive strategy (within 120 minutes) is justified.
- Not life-threatening but an acute risk of complications: in such cases, an invasive strategy (coronary angiography and possible reperfusion procedure) can be postponed until up to 72 hours after diagnosis.

– The patient's clinical condition does not require an invasive strategy.

Drug treatment involves in particular the combination of unfractionated or low-molecular-weight heparin, aspirin (ASA) and a beta blocker. It is useful to combine clopidogrel (PLAVIX) with aspirin. It is possible to give this combination from the start of treatment, regardless of the therapeutic strategy later used for these patients (invasive or conservative) and the estimated risk level.

In the acute phase of ST-elevation ACS:

According to the 2007 French consensus conference[2], early removal of coronary artery obstruction improves patient prognosis. The choice between the two available techniques (angioplasty or fibrinolysis) is made with consideration of the clinical situation, primarily the time elapsed since the onset of symptoms. Fibrinolysis is recommended if the time between first medical attention and arrival in the interventional cardiology unit is estimated to be greater than 45 minutes. After fibrinolysis, the patient must be referred to a centre that has a diagnostic and interventional coronary angiography suite. The chosen reperfusion strategy will depend on the time at which symptoms began; fibrinolysis can be considered if the episode began less than 3 hours prior to arrival in the emergency department.

Drug treatment consists of a combination of an anticoagulant (unfractionated heparin or low-molecular-weight heparin), aspirin and anti-GPIIb/IIIa, which should be considered if angioplasty is involved. Clopidogrel (PLAVIX) is prescribed either in combination with aspirin or alone if aspirin is contraindicated. The recommended loading dose is 300 mg for patients under 75 years of age and 75 mg for patients over 75 years of age.

Strategy for the management of acute coronary syndrome outside the acute phase (post-hospitalisation):

Drug treatment consists primarily of aspirin, in combination for 9–12 months (at least 12 months if a drug-eluting stent is present) with clopidogrel (PLAVIX) 75 mg/day.

Role of DUOPLAVIN products:

DUOPLAVIN 75/75 and 75/100 are second-line therapies and may only be prescribed for adult patients who have already been treated with clopidogrel and ASA at the same doses.

The Committee wishes to emphasise that the usefulness of a fixed-dose combination in the management of acute coronary syndrome patients, in comparison with separate doses of the two drugs, has not been established. In addition, these products are not suitable for all patients to take.

4.4. Target population

The target population for DUOPLAVIN consists of acute coronary syndrome patients having ST elevation (STEMI) and eligible for thrombolytic treatment or without ST elevation (NSTEMI and unstable angina).

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

Patients with diagnosis of myocardial infarction with or without ST elevation

The FAST-MI registry makes it possible to estimate the incidence of myocardial infarction with or without ST elevation in France[3]. All patients admitted to hospital with a diagnosis of myocardial infarction during October 2005 in the 233 cardiac intensive care units (CICUs) that participated in the registry (around 60% of French CICUs) were included.

2 Consensus Conference. Management of acute-phase myocardial infarction outside cardiology units French SAMU (emergency medical services) with methodological and financial assistance from the French National Authority for Health (HAS); 06 February 2007

3 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 Vaiss. 2007;100:524–534.

A total of 3,059 patients were included in this registry: 53% (1,617 patients) had ST-elevation MI and 47% (1,442 patients) had non-ST-elevation MI.
On the basis of these data, it seems that there are around 32,000 (1,617 x 12 x 100/60) patients admitted annually to cardiac intensive care units in France with a diagnosis of ST-elevation MI, and around 30,000 (1,442 x 12 x 100/60) with a diagnosis of non-ST-elevation MI.

Considering that 29% of patients with ST-elevation MI receive thrombolytic treatment, the target population for DUOPLAVIN among patients with ST-elevation MI is estimated at between 9,000 and 16,000 patients per year.

The estimated target population for DUOPLAN among patients with non-ST-elevation MI is approximately 30,000 patients per year.

Patients with a diagnosis of unstable angina
According to PMSI-MCO data, in 2008 there were 47,492 hospital stays in France involving a primary diagnosis of unstable angina[4].
Hence the estimated target population for DUOPLAVIN (patients with unstable angina) is approximately 47,000 patients per year.

Total
The target population of DUOPLAVIN in the indications given in the marketing authorisation is estimated to be between 86,000 and 93,000 patients per year.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the posology in the marketing authorisation.

Packaging: appropriate for the prescription conditions.

Reimbursement rate: 65%

4 Number of short-duration healthcare facility stays (medicine, surgery, obstetrics & gynaecology) involving ICD-10 code for unstable angina as the primary diagnosis (ICD-10 code I200) (source: www.atih.sante.fr)