HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French Version

TRANSPARENCY COMMITTEE

OPINION

7 December 2011

BRILIQUE 90 mg, film-coated tablets
B/60 (CIP code: 498 874-1)
B/180 (CIP code: 578 938-6)
B/100 (CIP code: 578 940-0)

Applicant: ASTRAZENECA

Ticagrelor

ATC Code: B01AC24

List I

Date of Marketing Authorisation: 3 December 2010 (centralised European registration procedure)

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance (B/60) and approved for hospital use (B/180 and B/100).

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Ticagrelor

1.2. Background

Ticagrelor is an active oral platelet aggregation inhibitor from a new therapeutic class of agents, the cyclopentyltriazolopyrimidines. Its chemical structure is similar to that of adenosine. It is a selective reversible ADP (adenosine diphosphate) receptor antagonist acting on the P2Y12 platelet receptor of ADP (adenosine diphosphate) which inhibits the activation and aggregation of platelets mediating from ADP.

1.3. Indication

"BRILIQUE, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG)."

1.4. Dosage

"Treatment with BRILIQUE should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily.
Patients taking Brilique should also take ASA daily, unless specifically contraindicated. Following an initial dose of ASA, Brilique should be used with a maintenance dose of ASA of 75-150 mg.
Treatment is recommended for up to 12 months unless discontinuation of BRILIQUE is clinically indicated. Experience beyond 12 months is limited.
In patients with Acute Coronary Syndromes (ACS), premature discontinuation with any antiplatelet therapy, including BRILIQUE, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.
Lapses in therapy should also be avoided. A patient who misses a dose of Brilique should take only one 90 mg tablet (their next dose) at its scheduled time.
Patients treated with clopidogrel can be directly switched to BRILIQUE if needed. Switching from prasugrel to BRILIQUE has not been investigated.

Special populations

Elderly population: No dose adjustment is required in the elderly.

Renal impairment: No dose adjustment is necessary for patients with renal impairment. No information is available concerning treatment of patients on renal dialysis and therefore BRILIQUE is not recommended in these patients.

Hepatic impairment: No dose adjustment is necessary for patients with mild hepatic impairment. Brilique has not been studied in patients with moderate or severe hepatic impairment. Its use in patients with moderate to severe hepatic impairment is therefore contraindicated.

Paediatric population: The safety and efficacy of BRILIQUE in children below the age of 18 in the approved adult indication has not been established. No data is available.

Method of administration

For oral use. Brilique can be administered with or without food."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

B	Blood and blood-forming organs
B01A	Antithrombitic agents
B01AC	Platelet aggregation inhibitors, excluding heparin
B01AC24	Ticagrelor

2.2. Medicines in the same therapeutic category

2.2.1 Other reversible antagonists of the P2Y12 ADP receptor: none.

2.2.2 Irreversible antagonists of the P2Y12 ADP receptor (substantial AB):

INN	Products	Indication
clopidogrel	PLAVIX 75 mg and 300 mg film-coated tablets and its generics co-administered with aspirin: DUOPLAVIN1	Clopidogrel is indicated in: - Adult 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. - Adult patients suffering from acute coronary syndrome: o 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). o ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy
prasugrel	EFIENT 10 mg film-coated tablets	co-administered with acetylsalicylic acid (ASA), it is 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).
ticlopidine	TICLID 250 mg film-coated tablets	Prevention of arterial thrombotic complications (stroke, myocardial infarction and vascular cause of death) after an initial ischaemic stroke related to atherosclerosis. A clinical study highlighted an efficacy that was slightly greater than ticlopidine compared to aspirin in the secondary prevention of these thrombotic complications; an efficacy that needs to be balanced with the adverse reactions of ticlopidine. Prevention of major ischaemic accidents, especially coronary, in patients with chronic peripheral artery disease of the lower limbs with authenticated intermittent claudication. Prevention of repeated thromboses of arteriovenous sites in chronic haemodyalisis. Prevention of sub-acute thrombosis in patients with a coronary endoprothesis (stent).

1DuoPlavin is indicated in the prevention of events related to atherothrombosis in adults previously treated with clopidogrel and acetylsalicylic acid (ASA). DuoPlavin is a set concomitant for the continued treatment for a non-ST elevation acute coronary syndrome (unstable angina or non-Q wave Myocardial Infarction), including patients having coronary angioplasty with insertion of a stent and for acute myocardial infarction with ST elevation in medically treated patients who are eligible for thrombolytic treatment.

2.3. Medicines with a similar therapeutic aim (antithrombotics)

2.3.1 Platelet aggregation inhibitors (substantial AB)

	Class	Marketing Authorisation indication(s)
Acetylsalicylic acid: Aspirin 75 to 325 mg/day KARDEGIC 75 mg ASPIRIN UPSA 325 mg ASPIRIN PROTECT 300 mg CARDIOSOLUPSAN 100 mg	Cyclooxygenase inhibitor	as secondary prevention (including in emergency situations) after an initial ischaemic myocardial or cerebral accident related to atherosclerosis: - reduction in mortality and morbidity due to cardiovascular causes: . after a myocardial infarction; . within the context of stable or unstable angina; . during transluminal coronary angioplasty; . after a transient ischaemic attack or cerebral vascular accident; - reduction in graft occlusion after coronary artery bypass.
PRAVADUAL	Cyclooxygenase inhibitor, statin	PRAVADUAL co-administered with 81 mg of aspirin + 40 mg pravastatin: indicated for "Secondary prevention: reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina, with either normal or increased cholesterol levels, when co-administered with pravastatin and a low dose of acetylsalicylic acid is considered as appropriate, and as an adjunct to the correction of other risk factors".
Abciximab: REOPRO 2 mg/ml solution for injection or infusion	Glycoprotein IIb/IIIa antagonists (anti GPIIb/IIIa)	an adjunct to heparin and acetylsalicylic acid for: - percutaneous Coronary Intervention: the prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention (balloon angioplasty, atherectomy, and stent). - unstable Angina: The short-term (one-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		intended 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		intended for use with aspirin 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.

2.3.2 Anticoagulants (substantial AB)

	Class	Indication (s)
Enoxaparin: 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: FRAGMIN 7,500 IU anti-Xa/0.75 ml 10,000 IU anti-Xa/1 ml Nadroparin calcium: FRAXIPARIN 9,500 IU/ml	Low Molecular Weight Heparins (LMWH)	(1)- Treatment of unstable angina and acute non-Q wave myocardial infarction co-administered with aspirin. (2)- Treatment of acute ST-segment elevation myocardial infarction, co-administered with thrombolytic treatment, in patients who are eligible, or not, for secondary coronary angioplasty. For LOVENOX: (1) and (2) For FRAGMIN: (1) For FRAXIPARIN: (1)
Heparin calcium: CALCIPARIN Heparin sodium: HEPARIN CHOAY HEPARIN PANPHARMA	Unfractionated Heparin (UH)	Treatment of acute Q-wave or non-Q wave myocardial infarction and unstable angina.
Fondaparinux sodium: ARIXTRA 2.5 mg	Activated factor X inhibitor (Xa)	Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in adults for whom urgent (< 120 mins) invasive management (PCI) is not. Treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.
Bivalirudine: ANGIOX 250 mg	Direct thrombin inhibitor	Angiox is indicated as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. Angiox is also indicated for the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention. Angiox should be administered with aspirin and clopidogrel.

3. ANALYSIS OF AVAILABLE DATA

The assessment of ticagrelor (BRILIQUE), co-administered with aspirin (ASA), is based on the results of a comparative phase III Platelet Inhibition and Patient Outcomes (PLATO)[2] clinical study versus clopidogrel.
An indirect comparison of the efficacy and adverse effects of ticagrelor, prasugrel and clopidogrel in acute coronary syndromes is also presented.

3.1 Efficacy data from the PLATO study

Study Objective: demonstrate, after 12 months of treatment, that ticagrelor co-administered with aspirin is more effective than clopidogrel in the prevention of cardiovascular events and death in adult patients treated in the first 24 hours for an acute coronary syndrome (ACS) regardless of the revascularisation methods.

Study design: comparative, double-blind, randomised, multicentre study of superiority versus clopidogrel, (862 centres in 43 countrieswhich enrolled 18,758 patients between 2006 and 2008).

Inclusion criteria: adult patients (at least 18 years) admitted to hospital for a suspected ACS which started in the previous 24 hours.
The ACS treated are defined as:
For ACS of ST- type (NSTEMI), patients should have at least two of the following criteria:

- Myocardial ischaemia demonstrated by an ST segment change on the ECG
- elevation of reference biomarkers for myocardial necrosis (80% had a positive test for troponine I)
- at least one risk factor for chronic renal impairment defined by a creatinine clearance of < 60 ml/min
- previous history of myocardial infarction (MI) or coronary artery bypass grafting,
- coronary disease with stenosis ≥ 50% in at least two arteries
- previous history of ischaemic stroke, transient ischaemic attacks (TIA), carotid artery stenosis (≥ 50%) or cerebral revascularisation
- type 2 diabetes mellitus and peripheral artery disease of the lower limbs

For ACS of ST+ type (STEMI), patients should have:

- a persistent ST segment elevation ≥ 1 mm in at least two leads or a left bundle branch blocka scheduled percutaneous coronary intervention (PCI or primary angioplasty).

Among non-inclusion criteria:

- existence of a high risk of bradycardia,
- fibrinolysis planned or carried out in the 24 hours prior to randomisation
- concomitant intake of a medicinal product which might interact with CYP3A.

Dosage of platelet inhibitors:

- Ticagrelor: single loading dose of 180 mg then 90 mg x 2/day;
- Clopidogrel: loading dose of between 300 mg and 600 mg, then 75 mg/day (except if the patient had already received this treatment, then continue without loading dose).

An additional loading dose was given in cases of angioplasty when this procedure was performed more than 24 hours after randomisation: 90 mg of ticagrelor or 300 mg of clopidogrel.

Aspirin: after a loading dose of 325 mg if not received previous treatment, 75 to 100 mg/day.

[2] Wallentin L et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-57.

Primary efficacy endpoint: occurrence, up to 12th month of treatment, of the first of the following events: death from a cardiovascular cause, non-fatal myocardial infarction (MI) or a non-fatal stroke (Kaplan-Meier survival curves).

The secondary endpoints were:

- each of the events of the primary efficacy endpoint (death from a cardiovascular cause, MI and stroke);
- death fromall causes combined;
- occurrence of a stent thrombosis;
- major and minor bleedings, related, or not, to a procedure. A major bleeding is defined as a fatal bleeding, an intra-cranial haemorrhage, a tamponade, hypovolaemic shock, with a fall in haemoglobin of more than 5 g/dl or when a transfusion of at least four units of packed red blood cells is necessary.
- other adverse events.

Method and results analysis strategy at 12 months: the randomisation was stratified based on the treatment with angioplasty or by coronary artery bypass grafting. The intention to treat analysis was based on the delay in the occurrence of one of the events in the composite endpoint. The calculation of the number of subjects required was determined under the following hypotheses: (1) an event frequency at 12 months of 11% in the clopidogrel arm, (2) a reduction in risk of 13.5% in the ticagrelor group and (3) an increase of 90% and an alpha risk of 5%. According to these hypotheses 1,780 events were necessary to demonstrate a difference between the treatment groups.

Analysis of the secondary endpoints was performed according to a hierarchical sequential approach.

Results

Baseline population characteristics (see Appendices 1 and 2)

The trial concerned 18,624 randomised patients, of which 421 patients included were in France. The majority of patients were male (71.6%), with a median age of 62 years (15% were over 75 years), and a median body weight of 80 kg with a BMI of 27, Caucasian (91%), smokers (36%), hypertensive (65%), with a previous history of MI (20%) or PCI (13.6%).
The median delay between the occurence of the initial pain and inclusion was 11.3 hours; angioplasty was performed within a median time of 20 minutes for patients with a STEMI and 3.9 hours for patients with a NSTEMI after the first dose of studied treatment.

A total of 97% of patients were admitted with an ACS: ST+ type for 38% of them and ST- type for 43% of them; 17% had an unstable angina diagnosis.
A coronary angiography was performed on 81.5% of patients; 61% then had a percutaneous coronary intervention (PCI or angioplasty) with the insertion of a stent for 60% of them or a coronary artery bypass grafting for 10%.

In the clopidogrel arm, the loading dose was at least 300 mg for 79.1% of patients and at least 600 mg for 19.6% of patients.
Regarding other treatments, 97% of patients received aspirin in the acute phase, 56% unfractionated heparin, 51% low molecular weight heparin and 26% a GPIIb/IIIa inhibitor. On discharge from the hospital, 89% of patients had a prescription for beta-blockers, 88% for a renin-angiotensin antagonist, 90% for a statin and 45% for a proton pump inhibitor.

Nearly one out of two patients(46%) had already received clopidogrel before randomisation into the two groups.

It was noted that 50% of patients from North America received 325 mg/day of aspirin throughout the duration of the trial. Patients that had a stent received 325 mg/day for six months.

Nearly a quarter of patients also received a GPIIB/IIIA inhibitor.

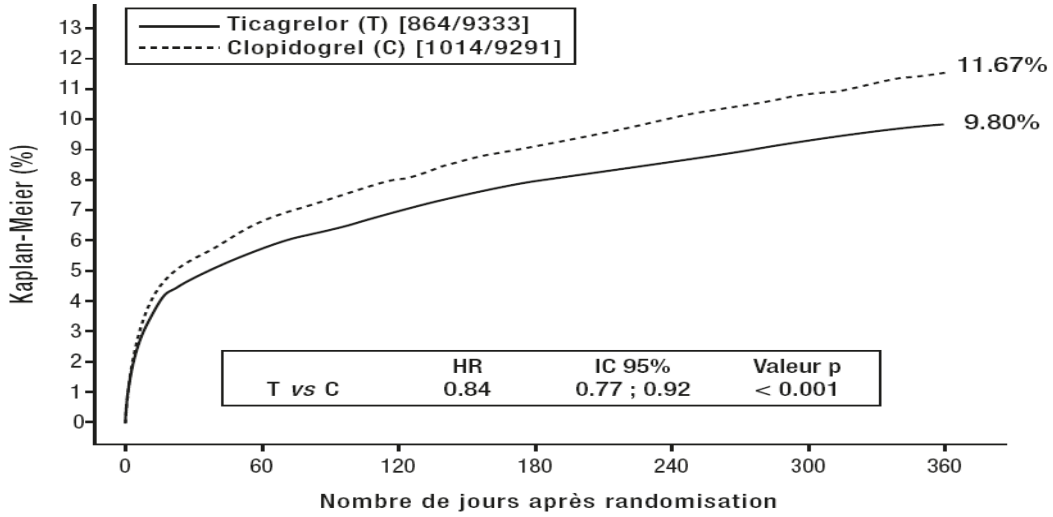
Efficacy results

There were 23.4% of patients who stopped the trial in the ticagrelor arm versus 21.5% in the clopidogrel arm. The compliance rate was 82.8%, with a median length of exposure to treatment of 277 days (or close to nine months).

Primary efficacy endpoint:

In the ticagrelor group, the incidence of the primary efficacy endpoint was reduced compared to the clopidogrel group: 9.8% versus 11.7% or an absolute reduction in favour of ticagrelor of 1.9% and a relative reduction in the risk of an event of 16% (RR = 0.84; 95% CI [0.77 to 0.92], (p = 0.0003) after 12 months of treatment.

Figure 1: results for the primary efficacy endpoint in the PLATO trial



N à risque							
T	9333	8628	8460	8219	6743	5161	4147
C	9291	8521	8362	8124	6650	5096	4074

Corresponding terms:

Source	**Target**
Nombre de jours après randomisation	Number of days after randomisation
N à risque	N at risk
Valeur P	P value
IC	CI
HR	HR

Secondary efficacy endpoints:

Table 1: Secondary efficacy endpoints – full PLATO analysis

	BRILIQUE 90 mg 2x/day N=9,333		**Clopidogrel 75 mg/day N=9,291**			
Secondary endpoint	**Patients with an event**	**%/ year**	**Patients with an event**	**%/ year**	**HR [95% CI]**	**p**
composite endpoint all causes of death/MI (excluding silent MI)/stroke	901 (9.7%)	10.2%	1,065 (11.5%)	12.3%	0.84 [0.77, 0.92]	0.0001
Cardiovascular deaths, /MI stroke including TIA A, severe simultaneous cardiac ischaemia, recurrent cardiac ischaemia, or other atherothrombotic events	1,290 (13.8%)	14.6%	1,456 (15.7%)	16.7%	0.88 [0.81, 0.95]	0.0006
Cardiovascular death	353 (3.8%)	4.0%	442 (4.8%)	5.1%	0.79 [0.69, 0.91]	0.0013
MI (excluding silent MI)	504 (5.4%)	5.8%	593 (6.4%)	6.9%	0.84 [0.75, 0.95]	0.0045
stroke	125 (1.3%)	1.5%	106 (1.1%)	1.3%	1.17 [0.91, 1.52]	0.2249
Death from any cause	*399 (4.3%)*	*4.5%*	*506 (5.4%)*	*5.9%*	*0.78 [0.69, 0.89]*	*0.0003*

From the different elements of the primary efficacy endpoint, ticagrelor had a superior efficacy to clopidogrel for the incidence of deaths from cardiovascular causes (4.0 versus 5.1%; RR = 0.79; 95% CI: [0.69; 0.91], p = 0.0013) and myocardial infarctions (5.8 versus 6.9%, RR = 0.84; 95% CI: [0.75; 0.95], p = 0.0045), although it was not different for stroke (1.3% versus 1.1%).

For deaths from any cause, the hierarchical sequential approach planned to be investigated after the comparison on cases of stroke which proved not significant , did not make it possible to draw a formal conclusion for the comparison between ticagrelor and clopidogrel , even though it appears to be statistically significant (p = 0.0003). Death from any cause is primarily related to deaths from cardiovascular causes.

The consistency of results was studied based on 31 factors: the results from these planned sub-group analyses show a consistency of results for the composite endpoint, especially for patients with or without a previous history of ischaemic stroke or transient ischaemic attacks (TIA), those older or younger than 75 years and whose weight was greater or less than 60 kg. The results were consistent whatever the type of ACS (ACS-ST+, ACS-ST-, see table 2) or the method of management (invasive or medical therapy, see table 3).

Table 2: efficacy results based on the type of ACS

	STEMI N = 7026 HR, 95% CI, p	NSTEMI N= 7955 HR, 95% CI, p	Unstable angina and NSTEMI N = 11067 HR, 95% CI, p
Primary composite endpoint	0.84 [0.72; 0.98] p=0.0292	0.83 [0.73; 0.94] p=0.0038	0.86 [0.76; 0.96] p=0.0073
Total mortality	0.81 [0.65; 1.00] p=0.0538	0.80 [0.65; 0.97] p=0.0235	0.78 [0.66; 0.93] p=0.0056

Table 3: Efficacy results based on the type of management

	Invasive management N = 13,408 HR, 95% CI, p	Coronary angioplasty N = 11,520 HR, 95% CI, p	Coronary artery bypass grafting N = 1,884 HR, 95% CI, p	Medical treatment N = 5,216 HR, 95% CI, p
Primary composite endpoint	0.84 [0.75; 0.94] p=0.0025	0.88 [0.78; 0.99] p=0.04	1.01 [0.70; 1.46] p=0.961	0.78 [0.67; 0.90] p=0.0006
Total mortality	0.82 [0.68; 0.98] p=0.025	0.92 [0.75; 1.11] p=0.379	0.49 [0.28; 0.85] p=0.011	0.72 [0.59; 0.87] p=0.0006

In contrast, for patients included in North America, which was close to 2,000 patients in the study (10%), the comparison of the two anti-platelet agents for the primary efficacy endpoint was in favour of clopidogrel (HR = 1.25, 95% CI [0.93; 1.67], p = 0.045 for the interaction between the effect of treatment and the region).
This *post-hoc* analysis was carried out at the request of the Food and Drug Administration. One possible explanation for this, apart from chance, is a negative interaction between ticagrelor and high doses of aspirin. Indeed, a reduction in the efficacy of ticagrelor was observed with high doses of ASA. Additional analyses supplied to the FDA suggested that the interaction (treatment effect × region) was reduced when the analysis was adjusted to take into account the dose of aspirin. On the basis of this analysis, the FDA granted a Marketing Authorisation for BRILIQUE. It should be noted that the quality of data and a different validation strategy (CRO or sponsor) were also discussed.[3]

Reduction in the risk of stent thrombosis compared to clopidogrel:

More than 60% of patients were treated via angioplasty with stent placement. Ticagrelor reduced the incidence of stent thrombosis compared to clopidogrel (1.3% vs. 1.9%) i.e. an absolute reduction of 0.6% (RR: 0.67 [0.50-0.91] p=0.009).

Table 4: incidence of stent thrombosis in the PLATO study

Stent thrombosis – Number of patients receiving a stent /Total (%)	Ticagrelor	Clopidogrel	Relative Risk (CI at 95%)	p
Definite	71/5, 640 (1.3)	106/5, 649 (1.9)	0.67 (0.50 - 0.91)	0.009
likely or definite	118/5, 640 (2.2)	158/5, 649 (2.9)	0.75 (0.59 - 0.95)	0.02
Possible, likely or definite	155/5, 640 (2.9)	202/5, 649 (3.8)	0.77 (0.62 – 0.95)	0.01

3 Serebruany VL. Paradoxical excess mortality in the PLATO trial should be independently verified. Thromb Haemost 2011; 105: 1-8.

3.2. Indirect comparisons

There is no study available that directly compared ticagrelor to prasugrel because of their concomitant development.

Based on the results of the TRITON (prasugrel) and PLATO (ticagrelor) studies, the level of effect for the composite primary efficacy endpoint was similar, with almost comparable events frequencies in the clopidogrel arm. In contrast, there were fewer deaths (total or cardiovascular) but more non-fatal myocardial infarctions (enzyme definition etc.) in the TRITON study, potentially attributable to a less at-risk patient profile or there being more selected patients: the patients had similar characteristics but they had a scheduled PCI with 25% of ACS ST+.
To compare the risk of bleeding, it was necessary to use a common definition. For bleedings not related to a coronary artery bypass grafting (CABG), the frequencies and estimations of the level of effect appeared to be in the same order of magnitude. For coronary artery bypass grafting related bleedings, the frequency on clopidogrel was lower in the TRITON study (with a loading dose of 300 mg of clopidogrel), clopidogrel being associated with an excess of risk. This, however, was not the case with ticagrelor.
The TIMI major or minor bleeding element was comparable between each of the two study groups, but varied greatly between the TRITON and PLATO studies.

Finally, it is not possible to draw any conclusions regarding the (historical) comparison of the results of these two studies.

3.3. Adverse effects

The assessment of the adverse events with ticagrelor is primarily based on the data from the comparative, phase III trial versus clopidogrel (PLATO), during which patients were treated over a median duration of 277 days (close to nine months). Duration of exposure to treatment and duration of follow up were comparable between the two arms. A safety analysis was performed based on data from 9,235 patients who received at least one dose of ticagrelor and 9,186 patients who received at least one dose of clopidogrel during the study.

The percentage of treatment discontinuation due to adverse events at 12 months was higher with ticagrelor than with clopidogrel (7.4% versus 5.4%, p<0.0001).

3.3.1 Bleeding risk (SPC, data from PLATO study)

In the PLATO study, the frequency of “fatal major / life-threatening " bleedings, or "total major" bleedings, according to the PLATO study criteria, and major TIMIs and minor TIMIs did not differ between ticagrelor and clopidogrel. However, more major and minor bleedings occurred according to the PLATO trial definition on ticagrelor than on clopidogrel.

No sub-group of patients at risk of bleedings was identified: no factors investigated (age, gender, weight, ethnic origin, geographic origin, concomitant disorders, associated treatment, previous medical history including stroke and transient ischaemic attacks) appeared to be predicative of the risk of haemorrhagic risk (overall or major bleedings not related to an interventional procedure).

Bleedings not related to a coronary artery bypass grafting or a procedure

No difference was observed between the two groups in terms of "fatal major/ life-threatening" bleedings in patients who did not undergo CABG, but "total major" bleedings according to the PLATO study criteria, major TIMIs and major and minor TIMIs were more frequent with ticagrelor. If all bleedings from a procedure are excluded, more bleedings occurred with ticagrelor than with clopidogrel.

Treatment discontinuation due to a bleeding not related to a procedure was more frequent with ticagrelor (2.9%) than with clopidogrel (1.2%; p<0.001).

Intracranial bleeding

There were more non-procedure related intracranial bleedings in the ticagrelor group (27 bleedings in 26 patients, 0.3%) than in the clopidogrel group (14 bleedings, 0.2%), of which 11 were fatal for ticagrelor compared to 1 with clopidogrel.

Fatal bleedings related to a coronary artery bypass grafting

There were very few, and there was a similar incidence of fatal bleedings between the two groups: 20 (0.2%) with ticagrelor and 23 (0.3%) with clopidogrel.
Twelve percent of patients (1,584 patients) had a coronary artery bypass grafting (CABG): there was no difference between the two groups for fatal a life-threatening major bleedings, according to the PLATO study criteria (effect observed in 42% of these patients); fatal bleedings were observed in six patients from each group.

3.3.2 Other adverse events (Data from the PLATO trial)

Dyspnoea

Dyspnoea (at rest, exertional, night time paroxystic and night time) and the feeling of breathlessness were more commonly reported in the group receiving ticagrelor (13.8%) than in the one receiving clopidogrel (7.8%, $p<0.001$). The risk of dyspnoea has previously been demonstrated in a phase 2 trial (DISPERSE 2). These events were considered to be related to treatment by the clinical trial investigators in 2.2% of patients on ticagrelor and in 0.6% of those taking clopidogrel. They might be explained by an "adenosine like" effect.

Cases of dyspnoea mainly occurred at the start of treatment, their intensity being judged mostly as mild to moderate, and for approximately 30% of such cases of dyspnoea it had disappeared in less than seven days. These cases were not associated with a change in respiratory function or cardiac decompensation.

An increase in the occurrence of non-serious dyspnoea (3.29% on ticagrelor versus 0.53% on clopidogrel) and serious dyspnoea (0.38% on ticagrelor versus 0.00% on clopidogrel) was observed in the sub-group of patients with asthma / COPD and this risk was even greater in the total PLATO population.

The number of patients who discontinued the anti-platelet treatment due to dyspnoea was higher in the BRILIQUE group (0.9% vs. 0.1%).

It is therefore recommended to use ticagrelor with caution in patients with a history of asthma and/or COPD or in cases of chronic heart failure, as a precautionary measure.

Bradycardia

Ventricular pauses, essentially asymptomatic, were observed in a phase 2 clinical study.
During the Holter sub-study, more patients from the ticagrelor group than the clopidogrel group had ventricular pauses ≥ 3 seconds during the acute phase of an acute coronary syndrome. The increase in the number of ventricular pauses detected with ticagrelor was more substantial in patients with chronic heart failure (CHF) than in the general study population during the acute phase of ACS; there were no clinical adverse effects associated with this disorder. No clinically significant adverse events (including syncope, placement of a pacemaker) were observed.

Patients at risk of bradycardia, such as those with sick sinus syndrome without a pacemaker, a second or third degree atrioventricular block or syncope related to bradycardia, were excluded from the pivotal PLATO study. The SPC states that for these patients, ticagrelor (BRILIQUE) should be used with caution. Precautions should also be taken when giving ticagrelor in association with bradycardia-inducing medicinal products.

Anomalies in biological analysis results:

Reported increases in serum creatinine

In the PLATO trial, increases in serum creatinine levels by over 30% were reported in 25.5% of patients on ticagrelor compared to 21.3% of patients on clopidogrel. Serum creatinine levels increased by over 50% in 8.3% of patients on ticagrelor and in 6.7% of those on clopidogrel.

These increases were more common in patients over 75 years (13.6% on ticagrelor and 8.8% on clopidogrel), in cases of severe renal failure at inclusion (17.8% on ticagrelor and 12.5% on clopidogrel) and in case of co-prescription with an angiotensin receptor antagonist (ARA II: 11.2% on ticagrelor and 7.1% on clopidogrel).

No difference was seen for the treatment groups when it came to serious adverse events related to renal function, or for adverse events resulting in discontinuation of the studied treatment in these sub-groups. The total number of adverse renal events reported was 4.9% on ticagrelor and 3.8% on clopidogrel; however, a similar percentage of adverse events considered by the clinical trial investigators as being related to treatment (54 (0.6%) with ticagrelor and 43 (0.5%) with clopidogrel) was observed.

It is recommended that specific care is taken in elderly patients (> 75 years), in those with moderate/severe renal failure and in those receiving an ARA II agent.

Hyperuricaemia

In the PLATO study, serum uric acid exceededthe upper limit of normal in 22% of patients receiving ticagrelor and in 13% of those receiving clopidogrel. Mean serum uric acid levels increased by approximately 15% on ticagrelor and by approximately 7.5% on clopidogrel and after stopping treatment, a decrease by approximately 7% was observed on ticagrelor but not on clopidogrel. Among adverse events, such as elevated serum uric acid, reported (0.5% in the ticagrelor group and 0.2% in the clopidogrel group), 0.05% on ticagrelor and 0.02% with clopidogrel were considered as being related to treatment by the clinical trial investigators. For gouty arthritis, there were 0.2% adverse events on ticagrelor and 0.1% on clopidogrel; none of these events were considered as being related to treatment by the clinical investigators.

As a precautionary measure, ticagrelor is not recommended in case of uric acid nephropathy and should be used with caution in case of a medical history of hyperuricaemia or gout.

3.4. Discussion

Interpretation of the results of the PLATO study raised several comments:

- Fifteen percent of patients did not have a final visit at 12 months and 10% of patients left the study.
- A high proportion (46%) of patients assigned to the TICAGRELOR group also received CLOPIDOGREL with the same loading dose.
- Only 20% of patients assigned to the CLOPIDOGREL group received a loading dose of 600 mg.
- The mortality rates and the vascular mortality /infarction ratio generated discussions.
- To determine the impact of ticagrelor compared to clopidogrel, it is justifiable to look into evaluating the clinical benefit while taking into account the risk of haemorrhage. In this instance, the clinical benefit of ticagrelor compared to clopidogrel would be less.

Table 5: Net clinical benefit of ticagrelor in the PLATO study

	Treatment					
	ticagrelor 90 mg 2 times/day N = 9,333		**clopidogrel 75 mg/day N = 9,291**			
	Patients with bleedings	*KM%	Patients with bleedings	*KM%	Hazard ratio (95% CI)	p
Excluding the CABG related bleedings** without life-threatening prognosis						
MI/ stroke / CV death /Major Bleedings	1,462	15.7%	1,575	(17.0%)	0.92 (0.86, **0.99**)	0.0257
MI/ stroke / Death from any cause /Major bleedings	1,486	16.6%	1,605	(18.2%)	0.92 (0.86, **0.99**)	0.0201
Including all CABG related bleedings (including those not resulting in a life-threatening prognosis)						
MI/ stroke / CV death /Major Bleedings	1,782	19.9%	1,891	(21.3%)	0.94 (0.88, **1.00**)	0.0449
MI/ stroke / Death from any cause /Major bleedings	1,758	19.6%	1,864	(21.0%)	0.94 (0.88, **1.00**)	0.0493

Ref.: Transparency file *: KM: Kaplan-Meier **CABG: coronary artery bypass grafting

3.5. Conclusion

In the treatment of acute coronary syndromes (ACS), ticagrelor (BRILIQUE) was evaluated in a randomised, double-blind superiority study (PLATO study), versus clopidogrel. A total of 18,624 patients were admitted to hospital for unstable angina (17% of cases), a moderate to severe risk ST- ACS (43% of cases) or a ST+ ACS (38% of cases). Patients were managed by concomitant usual medical therapy (unstable angina) in cases of ACS ST- or for ST+ with revascularisation by coronary angioplasty (64% of cases) or with a coronary artery bypass grafting (10% of cases). An endoprothesis was inserted in 61% of cases (stents made from bare metal were two times more frequent than drug-eluting stents).

In the ticagrelor group after 12 months of treatment, the incidence of the primary composite efficacy endpoint (cardiovascular death, MI, non-fatal stroke) is reduced compared to the clopidogrel group (9.8% versus 11.7%) with an absolute reduction in favour of ticagrelor of 1.9% ($p < 0.001$, RR = 0.84; 95% CI [0.77; 0.92]).

The reduction in the incidence of each event in the primary efficacy endpoint was in favour of ticagrelor, except for stroke. The reduction in death from any cause in the overall trial population was not formally demonstrated, given the approach used to take into account the multiplicity of comparisons made. For patients that had an endoprothesis inserted, stent thrombosis were less common on ticagrelor than on clopidogrel.

These results were observed, in addition to usual treatments and in combination with aspirin, for treatment duration of between 6 and 12 months, with half of patients receiving at least 9 months of treatment. Monitoring was carried out for a limited period.

Despite the trial including heterogeneous patients, with a risk of different adverse events and thus requiring different treatments (especially in terms of procedure and the co-administration of medicinal products), the majority of multiple sub-group analyses were consistent and reinforced the result in favour of ticagrelor.

In contrast, for patients included in North America (10% of the sample population), the primary endpoint was in favour of clopidogrel, which may be related to the higher doses of aspirin used in North America. However, it is not possible to exclude the fact that this could have happened due to chance or another unidentified factor.

The European SPC recommends that ticagrelor not be used with high doses of aspirin (> 300 mg/day) and in France, in the long-term therapy, the daily dose of aspirin recommended for ACS is from 75 to 150 mg/day.

The benefit observed is modest, but clinically significant. Its transferability to French clinical practice has not been established.

Fatal (rare) or serious bleedings were similar between the two groups according to the TIMI and PLATO definitions of bleeding risk.

The following events were more common with ticagrelor than with clopidogrel:

- discontinuations of treatment due to adverse effects (7.4% vs. 5.4%; p<0.0001)
- discontinuations of treatment due to bleedings not related to a procedure (2.9% vs. 1.2%).
- major and minor bleedings
- intracranial bleedings not related to a procedure (0.3% vs. 0.2%), of which 11 were fatal with ticagrelor compared to 1 for clopidogrel.
- serious bleedings not related to a coronary artery bypass grafting (4.5% vs. 3.8%).
- dyspnoea (13.8% vs. 7.8%, p<0.001).

A bradycardia-inducing effect of ticagrelor is possible.

Serum uric acid levels should be monitored, as hyperuricaemia was observed on ticagrelor.

In the oldest patients, the risk of bleeding and dyspnoea should be taken in to consideration.

A trial, PEGASUS-TIMI 54 (*Prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin*), is currently being run. Its objective is to compare the long-term efficacy of TICAGRELOR versus placebo, co-administered with aspirin, in the prevention of the following events: cardiovascular death, major coronary events, non-fatal stroke in patients with a previous history of myocardial infarction associated with a high risk of developing atherothrombotic events.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Acute coronary syndromes (both ST+ and ST- types) are serious clinical events that have a life-threatening prognosis.

Compared to clopidogrel, ticagrelor does have an additional clinical benefit but the benefit is modest in terms of cardiovascular deaths and recurrent myocardial infarctions. A reduction in morbidity and mortality is thus expected, but at the cost of a possible increase in adverse effects: risk of bleeding, dyspnoea and problems with cardiac rhythm disorders requiring monitoring. Its efficacy/adverse effects ratio is considered as high.

The benefit of ticagrelor compared to prasugrel has not been investigated.

Public health benefit

The burden of ischaemic heart disease is considerable. The burden of acute coronary syndromes is also considered as substantial. The reduction in mortality from ischaemic heart disease is one of the objectives of the public health law of 2004, whose renewal was proposed by the Haut conseil de la santé publique (HCSP) in 2010. Improvement of secondary prevention of acute coronary syndromes is thus a public health need.

The available data, from a controlled, randomised trial versus clopidogrel (PLATO trial) showed superiority for ticagrelor in terms of efficacy, no difference in terms of fatal bleedings or life-threatening bleedings, but a more common risk of non-major bleedings, as well as the occurrence of dyspnoea and cardiac rhythm disorders.

Finally, based on this data, and the significant number of patients admitted to hospital for an acute coronary syndrome in France, ticagrelor (BRILIQUE) is expected to have a moderate impact on morbidity and mortality.

The transferability of the results of studies to French clinical practice is not assured, given:

- the low proportion of French patients included in the PLATO trial (421/18,624) and the differences in the profiles between patients in the trial and French patients, based on data in the FAST-MI register, especially in terms of age and the level of risk;

- the uncertainties concerning the clinical consequences, in real life adverse effects of moderate severity, such as bleedings;

- the specific aspects of the management of the French patients (loading dose of clopidogrel, frequency of angioplasties, etc.).

Given the absence of data recording the impact of adverse events on the management of patients, it is not expected that ticagrelor (BRILIQUE) will have an impact on the healthcare system.

Consequently, in the current state of knowledge, BRILIQUE is expected to have a small public health benefit.

BRILIQUE (ticagrelor), in combination with aspirin, is a first-line treatment in the management of acute coronary syndromes.

Alternative medicinal products exist, primarily, clopidogrel (PLAVIX and generics) and prasugrel (EFIENT), in combination with aspirin.

In conclusion, the actual benefit of BRILIQUE (ticagrelor) is substantial.

4.2. Improvement in actual benefit (IAB)

Co-administered with aspirin, BRILIQUE provides a minor improvement in actual benefit (IAB level IV) compared to clopidogrel in the management of acute coronary syndromes in terms of efficacy.

4.3. Therapeutic use

In the acute phase of an ST- ACS, the aim of treatment is to avoid death and the occurrence of a transmural myocardial infarction. There are three identifiable clinical scenarios:

- A life-threatening prognosis is given immediately: action with an immediate (within 120 minutes) emergency invasive strategy is therefore justified.
- A life-threatening prognosis is not given straight away despite there is an acute risk of complications: in this situation, an invasive strategy (coronary angiography and potentially a reperfusion procedure) may be deferred until 72 hours after this diagnosis.
- The clinical condition of the patient does not require an invasive strategy.

Treatment with a medicinal product is in particular combined with an anticoagulant (unfractionated or low molecular weight heparin), aspirin (ASA) or a beta-blocker. It is beneficial to combine clopidogrel (PLAVIX) with aspirin from the start of treatment, regardless of the previous therapeutic strategy (invasive or conservative) and the level of estimated risk. Prasugrel (EFIENT), an alternative to clopidogrel (PLAVIX and generics), may be more active than clopidogrel, but has a higher risk of haemorrhage.

In the acute phase of an ST+ ACS, according to a French consensus in 2007, the early unblocking of the coronary artery contributes in improving the prognosis of patients. The choice between the two techniques available (angioplasty or fibrinolysis) is based on the clinical situation; primarily regarding the time elapsed from when the symptoms started. Fibrinolysis is recommended if the required interval between the initial medical contact and arrival in the cardiology department is estimated as being over 45 minutes. After fibrinolysis, the patient should be taken to a centre which has a diagnostic and interventional coronary angiography laboratory. A reperfusion strategy is dependent on the time the symptoms started; fibrinolysis is possible when the attack started less than three hours before arriving in the emergency department.
Treatment with a medicinal product, especially in combination with an anticoagulant (unfractionated or low molecular weight heparin), aspirin, or a GPIIb/IIIa inhibitor is discussed in cases of angioplasty. Clopidogrel (PLAVIX loading dose 300 mg before 75 years of age and 75 mg after 75 years) is co-prescribed with aspirin, or alone if aspirin is contraindicated. Prasugrel (EFIENT), an alternative to clopidogrel (PLAVIX and generics), may be more active than clopidogrel, but has a higher risk of haemorrhage.

Variability in the platelet inhibition function of clopidogrel is described. But "poor responding" patients are not recorded in daily practice.

<u>The place of ticagrelor in the management of ACS</u>

The Committee considers that the place of ticagrelor in the management of ACS remains to be established:

- Compared to clopidogrel: based on the results from the PLATO trial, ticagrelor represents an alternative[4] to clopidogrel, regardless of the type of ACS and their methods of management.
- Compared to prasugrel (EFIENT): in the absence of a direct comparison, it is difficult to compare the role of ticagrelor to that of prasugrel. The indirect comparison of data from studies that compared prasugrel to clopidogrel and ticagrelor to clopidogrel is not possible (populations different in terms of treatment, leading to a different Marketing Authorisation indication for the two products). Prasugrel is not indicated for patients with ACS treated with PCI.

4 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. European Heart Journal Advance Access published 26 August 2011.

Variability in the platelet inhibition function of clopidogrel is described. But "poor responding" patients are not recorded in daily practice.
Prasugrel (EFIENT), as with clopidogrel (PLAVIX and generics), is an irreversible P2Y12 receptor inhibitor; it may be more active than clopidogrel, but has a higher risk of haemorrhage.

The assessment of ticagrelor in general practice will be beneficial to better estimate compliance with a treatment that requires two doses a day, the incidence and the impact of bleedings during a 12 month treatment, dyspnoea and bradycardic effects.

4.4. Target population

The target population is defined as patients with an acute coronary syndrome.
The incidence of acute coronary syndromes in France is difficult to evaluate.
According to data from PMSI-MCO, there were 161,063 patients admitted to hospital at least once with a primary diagnosis of angina pectoris (CIM-10 code I20.x) or myocardial infarction (I21.x) in 2010.[5]
According to data from the French register of ischaemic heart disease in 2006, and projected for the French population in 2011, the incidence of acute coronary syndromes in France would be about 117,509 to 136,064 cases per year.[6]

On this basis, the target population for BRILIQUE is estimated at between 117,000 and 161,000 patients per year.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use and various public services.

Study request

The Transparency Committee would like to have additional data on BRILIQUE, gathered during real-life situations of use, in order to compare, after a minimum monitoring period, the frequency of serious events (death, cardiovascular death, myocardial infarction, stroke and bleedings) in patients treated with BRILIQUE versus other platelet aggregation inhibitors.
The Committee would also like information concerning:

- baseline patient characteristics (demographic information, disease history, previous medical history, cardiovascular risk factors, etc.);
- conditions of use (indication, treatment duration, dosage, contaminant treatment, etc.);
- the frequency of discontinuation of treatment and the reasons;
- the frequency of moderate bleedings and unexpected adverse events highlighted in the PLATO study;
- variables that may be used as indicators in the occurrence of cardiovascular and haemorrhagic events;
- the use of care and healthcare departments in the year following admission to hospital.
- The monitoring period, determined by a scientific review board, should be justified and adequate to meet the requests of the Transparency Committee. Data should be available at the time of the inscription renewal of BRILIQUE.

In situations where the scheduled or ongoing studies, especially within the scope of the European Risk Management Plan, may not answer all the questions raised by the Transparency Committee, a specific study should be carried out.

5 Number of patients that had at least one stay in short-term care in a healthcare establishment including a main diagnosis with a CIM-10 code of I20.X (angina pectoris) or I21.X (myocardial infarction)
6 Calculation carried out by J. Dallongeville based on MONICA register of ischaemic heart disease 2006 (Ducimetière et al. BEH 2011 in press)

Reasons for the request for POST-INSCRIPTION information

For BRILIQUE, a new platelet aggregation inhibitor, indicated in the prevention of atherothrombotic events in adult patients with acute coronary syndrome, a request for additional data was made by the Transparency Committee during its meeting on 5 October 2011.

Given the questions concerning the transferability of results from the PLATO trial to the patient population treated in France, the Committee would like to verify the expected impact in terms of morbidity and mortality in real life usage situations. Additional information is therefore expected concerning:

- the preventative effect of BRILIQUE in real life usage situations in the occurrence of serious atherothrombotic events;
- the frequency of the occurrence of serious bleedings;
- the frequency of the occurrence of moderate adverse events for which the PLATO trial had demonstrated a higher frequency than with clopidogrel (minor bleedings, dyspnoea, cardiac rhythm disorders, etc.) and their impact on morbidity and on the healthcare system.

Such data will allow the impact on public health for BRILIQUE to be evaluated.

4.5.1. Reimbursement rate: 65%

4.5.2. Packaging: Appropriate for the prescription conditions.