EFIENT 10 mg, film-coated tablets
B/30 (CIP code: 392 120-3)
B/90 (CIP code: 574 530-2)

Applicant: LILLY

Prasugrel hydrochloride

ATC code: B01AC22

List I

Date of Marketing Authorisation (centralised European procedure): 25 February 2009
(Rapporteur states: Denmark/Spain)

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

N.B.: in the context of the temporary authorisation for use by a named patient [ATU nominative in French] granted by AFSSAPS from 29 September 2008 to 12 June 2009, 35 patients were given prasugrel “in the treatment of ACS managed by percutaneous coronary intervention (PCI) with stent implantation complicated by a stent thrombosis despite administration of PLAVIX at a dose of at least 150 mg/d”.

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

Prasugrel hydrochloride

1.2. Background

Prasugrel is a member of the thienopyridine family. It is a prodrug which is metabolised into an active metabolite and then into inactive metabolites.

1.3. Indication

“EFIENT, co-administered with acetylsalicylic acid (ASA), 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)”.

1.4. Dosage

“Efient should be initiated with a single 60 mg loading dose and then continued at 10 mg once a day for 12 months, unless suspension is clinically indicated. Patients should also take acetylsalicylic acid daily (75 mg to 325 mg).

Specific situations:

- Patients > 75 years old: The use of EFIENT is generally not recommended. In the phase III study, these patients were at greater risk of bleeding, including fatal bleeding, compared with patients < 75. The 10 mg maintenance dose is not recommended. If, after careful assessment of the individual risk/benefit ratio by the prescribing physician, treatment is regarded as necessary, a lower maintenance dose of 5 mg must be prescribed after a loading dose of 60 mg. However, data on the 5 mg dose is based only on pharmacodynamic and pharmacokinetic analyses; no safety data for this dose from these patients is currently available.
- There is limited experience with the therapeutic use of prasugrel among patients of Asian origin.

- Patients weighing < 60 kg: EFIENT should be given as a single 60 mg loading dose and then continued as a 5 mg once daily dose. The 10 mg maintenance dose is not recommended. This is due to an increase in exposure to the active metabolite of prasugrel, and an increased risk of bleeding in patients with body weight < 60 kg when given a 10 mg once daily dose compared with patients ≥ 60 kg. Efficacy and safety of the 5 mg dose have not been prospectively assessed.

- Children and adolescents (aged < 18): EFIENT is not recommended due to a lack of data on safety and efficacy.

- Mild to moderate renal and/or hepatic impairment: no dose adjustment is recommended, but there is limited therapeutic experience in these patients”.

2
## 2. SIMILAR MEDICINAL PRODUCTS

### 2.1 ATC Classification (2009):

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Blood and blood forming organs</td>
</tr>
<tr>
<td>B01A</td>
<td>Antithrombotic agents</td>
</tr>
<tr>
<td>B01AC</td>
<td>Platelet aggregation inhibitors excluding heparin</td>
</tr>
<tr>
<td>B01AC22</td>
<td>Prasugrel</td>
</tr>
</tbody>
</table>

### 2.2 Medicines in the same therapeutic category

Other platelet aggregation inhibitors, thienopyridine:

<table>
<thead>
<tr>
<th>Class</th>
<th>Indication(s)</th>
</tr>
</thead>
</table>
| **Clopidogrel** | Clopidogrel is indicated for adults to prevent atherothrombosis-related events:  
- In patients who have had a myocardial infarction (between a few days ago and less than 35 days ago), an ischaemic cerebrovascular accident (between more than seven days ago and less than six months ago) or who have been diagnosed with obliterative arteriopathy of the lower limbs.  
- In patients suffering from acute coronary syndrome:  
  - Acute coronary syndrome without ST segment elevation (unstable angina or non-Q wave myocardial infarction), including patients undergoing coronary angioplasty with stent insertion, in combination with acetylsalicylic acid (ASA).  
  - Acute myocardial infarction with ST segment elevation in combination with ASA in patients undergoing drug treatment and suitable for thrombolytic treatment. |
| **Ticlopidine** | Ticlopidine is indicated for adults to prevent sub-acute thrombosis in patients with a coronary endoprosthesis (stent).  
Prevention of arterial thrombotic complications (cerebrovascular accident, myocardial infarction, death from vascular cause) following an initial ischaemic cerebral accident related to atherosclerosis. A clinical study has found ticlopidine to be slightly superior to aspirin in the secondary prevention of these thrombotic complications. This efficacy must be set against the adverse effects of ticlopidine. |
### 2.3 Medicines with a similar therapeutic aim (antithrombotics)

#### 2.3.1 Antithrombotics, platelet aggregation inhibitor

<table>
<thead>
<tr>
<th>Class</th>
<th>Indication(s)</th>
</tr>
</thead>
</table>
| **Acetylsalicylic acid:** Aspirin 75 to 325 mg/d KARGEGIC 75 mg; ASPIRIN UPSA 325 mg; ASPIRIN PROTECT 300 mg; PRAVADUAL CARDIOSOLUPSAN 100 mg; | Secondary prevention (including in emergency situations) following an initial ischaemic myocardial or cerebral accident related to atherosclerosis:  
- reduction of cardiovascular mortality and morbidity:  
  - following a myocardial infarction;  
  - in the context of stable and unstable angina;  
  - during transluminal coronary angioplasty;  
- after a transient ischaemic attack, or a cerebral accident with lasting effects;  
  - reduction in graft occlusion following aortocoronary bypass.  

PRAVADUAL contains 81 mg of aspirin + 40 mg of pravastatin. It is indicated in "secondary prevention: reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina and a normal or elevated cholesterol level when the combination of pravastatin and a low dose of acetylsalicylic acid is regarded as appropriate, in addition to correction of other risk factors". |
| **Abciximab:** REOPRO 2mg/ml sol inj by inf | Platelet aggregation inhibitor, anti GPIIb/IIIa | As a complement to administration of heparin and acetylsalicylic acid in:  
- Percutaneous coronary intervention: prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention (balloon angioplasty, atherectomy and insertion of a stent); see Pharmacodynamics.  
- Unstable angina: short-term (one month) reduction in the risk of myocardial infarction in patients suffering from unstable angina that does not respond to conventional drug treatment and who are scheduled to undergo a percutaneous coronary intervention. |
| **Eptifibatide:** INTEGRILIN 0.75 and 2 mg/ml | Platelet aggregation inhibitor, anti GPIIb/IIIa | In combination with acetylsalicylic acid and unfractionated heparin to prevent early myocardial infarction in patients suffering from unstable angina or non-Q wave myocardial infarction with the last episode of chest pain occurring within the past 24 hours, accompanied by electrocardiographic changes and/or elevated cardiac enzymes. |
| **Tirofiban:** AGRASTAT 50 and 250 µg/ml | Platelet aggregation inhibitor, anti GPIIb/IIIa | In combination with aspirin and unfractionated heparin:  
- to prevent early myocardial infarction in patients suffering from unstable angina or non-Q wave myocardial infarction with the last episode of chest pain occurring within the past 12 hours, accompanied by electrocardiographic changes and/or elevated cardiac enzymes. |
### 2.3.2 Antithrombotics, anticoagulant

<table>
<thead>
<tr>
<th>Class</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enoxaparin:</strong> (1) and (2) <strong>LOVENOX</strong>&lt;br&gt;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</td>
<td>Low molecular weight heparins (LMWH)&lt;br&gt;(1)- Treatment of unstable angina and non-Q wave myocardial infarction in the acute phase, in combination with aspirin.&lt;br&gt;(2)- Treatment of acute myocardial infarction with ST segment elevation, in combination with thrombolytic treatment, in patients who are either suitable or not suitable for secondary coronary angioplasty.</td>
</tr>
<tr>
<td><strong>Dalteparin sodium:</strong> (1) <strong>FRAGMIN</strong>&lt;br&gt;7,500 IU anti-Xa/0.75 ml&lt;br&gt;10,000 IU anti-Xa/1 ml</td>
<td></td>
</tr>
<tr>
<td><strong>Nadroparin calcium:</strong> (1) <strong>FRAXIPARINE</strong> 9,500 IU/ml</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium heparin</strong> <strong>CALCIPARINE</strong></td>
<td>Unfractionated heparins (UFH)&lt;br&gt;Treatment of Q wave and non-Q wave myocardial infarction and unstable angina, in the acute phase.</td>
</tr>
<tr>
<td><strong>Sodium heparin</strong> <strong>HEPARIN CHOAY</strong> <strong>HEPARIN PANPHARMA</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Fondaparinux sodium:</strong> <strong>ARIXTRA</strong> 2.5 mg</td>
<td>Treatment of unstable angina or non-ST segment elevation myocardial infarction (Non-STEMI) in patients not suitable for management by means of an emergency (within 120 minutes) invasive strategy (percutaneous coronary intervention: PCI).&lt;br&gt;Treatment of ST segment elevation myocardial infarction (STEMI) in patients who are undergoing thrombolytic treatment or who are not initially being treated by any other reperfusion technique.</td>
</tr>
<tr>
<td><strong>Bivalirudin</strong> <strong>ANGIOX</strong> 250 mg</td>
<td>Treatment of patients suffering from acute coronary syndrome (ACS; unstable angina/non-ST segment elevation myocardial infarction (Non-STEMI)) due to undergo intervention as an emergency case or whose planned intervention has been brought forward. <strong>ANGIOX</strong> must be administered with aspirin and clopidogrel.&lt;br&gt;Anticoagulant for patients undergoing a percutaneous coronary intervention (PCI).</td>
</tr>
</tbody>
</table>

N.B. Other medication, such as beta-blockers, nitrates, analgesics, ACE inhibitors and statins, are used in the management of myocardial infarction.

Reminder of the recommended dosages for clopidogrel (PLAVIX SPC):

- **NSTEMI**: loading dose of 300 mg followed by 75 mg once a day (in combination with ASA at a daily dose of 75 mg to 325 mg). As the highest doses of ASA have been associated with a greater risk of bleeding, practitioners are advised not to exceed a daily dose of 100 mg ASA. The optimum duration for this treatment has not been formally established. Clinical trial data supports its use for up to 12 months, and the maximum benefit has been observed at three months.

- **STEMI**: loading dose of 300 mg, either alone or in combination with a thrombolytic treatment, followed by 75 mg once a day in combination with ASA. There is no loading dose for patients aged over 75. The combination drug treatment must be initiated as soon as possible after the symptoms appear, and continued for at least four weeks. The advantages of combination treatment involving clopidogrel and ASA after four weeks have not been investigated in this context.
EFIENT (prasugrel) has been investigated in a phase III comparative clinical study: the TRITON-TIMI 38 study.

**TRITON-TIMI 38 study** (Trial to assess improvement in therapeutic outcomes by optimizing platelet Inhibition with prasugrel thrombolysis in myocardial Infarction)-38 \(^1,^2\)

Primary objective of the study: to demonstrate the superiority of prasugrel (EFIENT) + aspirin versus clopidogrel (PLAVIX) + aspirin in the treatment of patients with acute coronary syndrome (ACS) requiring percutaneous coronary intervention (PCI) after a median monitoring period of at least 12 months treatment (secondary cardiovascular prevention).

**Study design**: double-blind, randomised, comparative superiority study. Patients were randomised to one of the two following groups: prasugrel + aspirin or aspirin + clopidogrel (control group). Randomisation was stratified according to ACS type (unstable angina and NSTEMI or STEMI).

Four clinical situations were possible:
- unstable angina (UA) with a moderate to high risk of myocardial infarction (TIMI severity score > 3);
- moderate to high risk NSTEMI (TIMI score ≥ 3);
- STEMI, with the onset of symptoms occurring within the past twelve hours;
- STEMI, with the onset of symptoms occurring more than 12 hours previously: patients who had had drug treatment and who were suitable for PCI within 14 days (for example, allowing them to be transferred to a centre with the necessary facilities);

**Inclusion criteria**: patients aged 18 or more suffering from acute chest pain and with electrocardiographic and biological signs pointing to a diagnosis of ACS. These patients would undergo PCI after having an angiography.

**Non-inclusion criteria**: patients at risk of haemorrhage (with a history of haemorrhagic stroke or recent ischaemic stroke, for example).

**Doses of the treatments being compared**:
- Prasugrel: a loading dose of 60 mg followed by 10 mg daily, oral administration.
- Clopidogrel: a loading dose of 300 mg followed by 75 mg daily, oral administration.
- Aspirin: a loading dose of 75 to 325 mg (oral administration) or 250 to 500 mg (IV administration) within the 24 hours preceding the angioplasty, followed by 75 to 162 mg daily.

**N.B.**
- The loading dose was to be administered after randomisation and before the end of the angioplasty procedure (i.e. within an hour of the patient leaving the catheterisation room). The following loading dose administration options were available:
  - for patients with NSTEMI or STEMI that had developed more than 12 hours ago: as soon as an angiography had clarified their coronary anatomy;
  - for patients with STEMI that had developed less than 12 hours ago, or for patients whose coronary anatomy was already known: as soon as the angioplasty was first considered.
- The percutaneous coronary intervention was to be performed immediately after randomisation or at any point within the 28 hours following the loading dose and before the first maintenance dose. The maintenance dose was to be administered 20 to 28 hours after the loading dose.

\(^2\) In the European Public Assessment Report (EPAR), the TRITON TIMI-38 study is the H7T-MC-TAAL pivotal study.
Primary efficacy endpoint: time from randomisation to the first of the following events: death from a cardiovascular cause (CV death), non-fatal myocardial infarction or non-fatal stroke (composite endpoint).

The secondary endpoints and other endpoints included:
- death from any cause
- any of the elements in the primary efficacy endpoint at 30 and 90 days
- stent thrombosis incidence (median monitoring period of at least 12 months)
- composite endpoint: death from any cause, non-fatal MI, non-fatal stroke (net clinical benefit)
- haemorrhagic risk not related to coronary revascularisation by means of a bypass: see Adverse effects section below.

Results:

Study population characteristics
Out of the 13,608 patients who were randomised (including 146 French nationals):
- mean age 61 years-old; 13% aged over 75; 73% men
- almost 10% had a creatinine clearance of < 60 ml/min
- almost 23% were diabetic.

As regards to the ACS type, most of the patients (74%) were included because they had UA/NSTEMI. Almost a third (1,094 of 3,534 patients) had STEMI (ST+ ACS) which had developed more than 12 hours ago. The STEMI patients had less cardiovascular history than those with Non-STEMI; there was a difference of almost two to one in terms of patients with a history of myocardial infarction (around 10% and 20%) or stenosis of over 50% revealed by coronaryography (around 9% and 23%). Only 6% of these patients had already undergone angioplasty, compared to 15% in the case of UA/NSTEMI patients. Only 2% had already had a bypass, compared to over 9% in the case of UA/NSTEMI patients.

Treatment timetables
- the median time from the onset of the first symptoms to randomisation was 28 hours. The median time from the onset of the first symptoms to administration of the loading dose was 4.5 hours (prasugrel) and 4.6 hours (clopidogrel) for STEMI patients whose symptoms had developed within the previous 12 hours; 29.5 hours for UA/NSTEMI patients in both treatment groups and 48.2 hours (prasugrel) and 47.9 hours (clopidogrel) for STEMI patients whose symptoms had developed more than 12 hours ago.

Patients were treated for a median duration of 14.5 months (range: 6-15 months).

In addition to aspirin (100 to 200 mg/day for almost half the patients), other treatments such as heparin and GPIIb/IIIa receptor inhibitors were administered at the doctor’s discretion. Approximately 40% of patients (in each treatment group) were given GPIIb/IIIa receptor inhibitors (no information is available as to the types of GPIIb/IIIa receptor inhibitors used). Approximately 98% of patients (in each treatment group) were given antithrombinic anticoagulants (heparin, low molecular weight heparin, bivalirudin or another agent) directly as a complement to the PCI.

The two cohorts (UA/NSTEMI and STEMI) had different underlying risks and their initial management varied considerably:
- UA/NSTEMI patients were more likely to have undergone multiple PCI (16% versus 8%),
- the UA/NSTEMI cohort had a higher proportion of drug eluting stents (52% of patients), while bare metal stents were more common in the STEMI cohort (65% of patients),
- anti-GPIIb/IIa drugs were administered more often to STEMI patients (54%) than to UA/NSTEMI patients (35%).

**Efficacy results (intention-to-treat analysis)**

The basis for the analysis of the endpoint in the overall population was prior demonstration of the superiority of prasugrel compared to clopidogrel in the UA/NSTEMI cohort. The results in the overall population and in the patients in both cohorts are presented below:

Results in the overall population and for individual ACS types on the basis of the primary efficacy endpoint and its components

<table>
<thead>
<tr>
<th>Endpoint events</th>
<th>Prasugrel + aspirin</th>
<th>Clopidogrel + aspirin</th>
<th>Relative risk (95% CI)</th>
<th>Value of p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population (ACS)</td>
<td>6,813</td>
<td>6,795</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>643 (9.4)</td>
<td>781 (11.5)</td>
<td>0.812 (0.732; 0.902)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>133 (2.0)</td>
<td>150 (2.2)</td>
<td>0.886 (0.701; 1.118)</td>
<td>0.307</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>475 (7.0)</td>
<td>620 (9.1)</td>
<td>0.757 (0.672; 0.853)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>61 (0.9)</td>
<td>60 (0.9)</td>
<td>1.016 (0.712; 1.451)</td>
<td>0.930</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>188 (2.8)</td>
<td>197 (2.9)</td>
<td>0.953 (0.781; 1.164)</td>
<td>0.639</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint events</th>
<th>Prasugrel + aspirin</th>
<th>Clopidogrel + aspirin</th>
<th>Relative risk (95% CI)</th>
<th>Value of p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA/NSTEMI</td>
<td>5,044</td>
<td>5,030</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>469 (9.3)</td>
<td>565 (11.2)</td>
<td>0.820 (0.726; 0.927)</td>
<td>0.002</td>
</tr>
<tr>
<td>CV death</td>
<td>90 (1.8)</td>
<td>92 (1.8)</td>
<td>0.979 (0.732; 1.309)</td>
<td>0.885</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>357 (7.1)</td>
<td>464 (9.2)</td>
<td>0.761 (0.663; 0.873)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>40 (0.8)</td>
<td>41 (0.8)</td>
<td>0.979 (0.633; 1.513)</td>
<td>0.922</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>130 (2.6)</td>
<td>121 (2.4)</td>
<td>1.076 (0.840; 1.378)</td>
<td>0.563</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint events</th>
<th>Prasugrel + aspirin</th>
<th>Clopidogrel + aspirin</th>
<th>Relative risk (95% CI)</th>
<th>Value of p</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>1,769</td>
<td>1,765</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>174 (9.8)</td>
<td>216 (12.2)</td>
<td>0.793 (0.649; 0.968)</td>
<td>0.019</td>
</tr>
<tr>
<td>CV death</td>
<td>43 (2.4)</td>
<td>58 (3.3)</td>
<td>0.738 (0.497; 1.094)</td>
<td>0.129</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>118 (6.7)</td>
<td>156 (8.8)</td>
<td>0.746 (0.588; 0.948)</td>
<td>0.016</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>21 (1.2)</td>
<td>19 (1.1)</td>
<td>1.097 (0.590; 2.040)</td>
<td>0.770</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>58 (3.3)</td>
<td>76 (4.3)</td>
<td>0.759 (0.539; 1.068)</td>
<td>0.113</td>
</tr>
</tbody>
</table>
Other results
- Fewer patients in the prasugrel group than in the clopidogrel group were thought to "probably or definitely have a stent thrombosis" at the end of the study (0.9% versus 1.8%; p < 0.001), which is a 50% reduction in the relative risk during the 15-month follow-up period. This advantage was observed from the start of treatment and beyond 30 days for bare metal stents and drug eluting stents.
- Fewer patients in the prasugrel group than in the clopidogrel group underwent urgent target-vessel revascularisation (2.5% versus 3.7%; p < 0.001).
- Patients in the prasugrel group had a 2.1% reduction in their absolute risk (p<0.001) and a 20% reduction in their relative risk in respect of the composite ischaemic endpoint compared to patients in the clopidogrel group in this study population. This advantage was mainly related to a reduction in the occurrence of myocardial infarction.

- No significant difference was observed between the two groups in respect of mortality from a cardiovascular cause or any cause in the three populations (overall, STEMI and UA/NSTEMI).

Comments
- Except for STEMI patients whose clinical signs had started within the 12 hours prior to management and who could have received treatment prior to angiography as soon as angioplasty was being considered, clopidogrel was administered at a loading dose of 300 mg and after the angiography results were known. This strategy was discussed by the EMEA. A loading dose of 600 or 900 mg might be more effective, and this is the current ESC recommendation (2007 guidelines). However, the level of evidence of the clinical data available to support these doses is low (no randomised comparative data), and the results of the TRITON study do not appear to have been influenced by administration time (similar results for analyses carried out for events occurring within the first three days and for those occurring from day four onwards). The EMEA was of the opinion that the 300 mg loading dose is acceptable provided that it is administered as soon as possible.
- In the TRITON study, no significant interaction was seen between the time of administration of the loading dose and the result for the primary efficacy endpoint in relation to the 25% of patients who received the loading dose prior to undergoing PCI.

These results indicate that after a median follow-up time of 15 months of treatment the prasugrel + aspirin combination was more effective than the clopidogrel + aspirin combination in preventing myocardial infarction (morbidity), but that there was no difference in respect of death from a cardiovascular cause (and in general).

3.2 Adverse effects

Assessment of the adverse effects of prasugrel is based mainly on data from the phase III study versus clopidogrel (TRITON TIMI-38) in which 6,741 patients were treated with prasugrel for a median period of 14.5 months (5,802 patients were treated for over 6 months and 4,136 for over a year). 7.2% of patients in the prasugrel group stopped taking the medication as a result of adverse effects, compared to 6.3% of patients in the clopidogrel group. Bleeding was the adverse effect which was most often the reason for withdrawal for both study drugs (2.5% for prasugrel and 1.4% for clopidogrel).
Bleeding unrelated to coronary artery bypass grafting (CABG)

Incidence of haemorrhage unrelated to CABG\(^a\) (% of patients)

<table>
<thead>
<tr>
<th>Event</th>
<th>All ACS</th>
<th>UA/NSTEMI</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prasugrel (^b) +ASA (N=6,741)</td>
<td>Clopidogrel (^b) +ASA (N=6,716)</td>
<td>Prasugrel (^b) +ASA (N=5,001)</td>
</tr>
<tr>
<td>Major bleeding (^c)</td>
<td>2.2</td>
<td>1.7</td>
<td>2.2</td>
</tr>
<tr>
<td>life-threatening (^d)</td>
<td>1.3</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.3</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Symptomatic ICH (^e)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Requiring inotropics</td>
<td>0.3</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Requiring surgery</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Requiring a transfusion (≥ 4 units)</td>
<td>0.7</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Minor bleeding (^f)</td>
<td>2.4</td>
<td>1.9</td>
<td>2.3</td>
</tr>
</tbody>
</table>

\(a\) Events assessed centrally and defined by the criteria laid down by the TIMI (thrombolysis in myocardial infarction) study group.

\(b\) Other usual treatments were applied if necessary.

\(c\) According to the TIMI criteria: Any intracranial haemorrhage or any clinically obvious bleeding associated with a fall of ≥ 5 g/dL in haemoglobin.

\(d\) Life-threatening bleeding is a sub-set of major bleeding according to the TIMI criteria, and includes the types mentioned in the lines below. Patients could be recorded on more than one line.

\(e\) ICH = intracranial haemorrhage.

\(f\) According to the TIMI criteria: clinically obvious bleeding associated with a fall in haemoglobin levels of ≥ 3 g/dL but < 5 g/dL.

The incidence of major bleeding (TIMI criteria) unrelated to coronary bypass, including life-threatening or fatal haemorrhage, and the incidence of minor bleeding (TIMI criteria) were significantly higher in the patients being treated with prasugrel compared to those being treated with clopidogrel in the overall ACS population and in the UA/NSTEMI population. No significant difference was observed in the STEMI population.

The most common site of spontaneous bleeding was the gastrointestinal tract (1.7% in the prasugrel group and 1.3% in the clopidogrel group); the most common site of non-spontaneous bleeding was the arterial puncture site (1.3% in the prasugrel group and 1.2% in the clopidogrel group).
Patients aged over 75

The TRITON-TIMI 38 study found the following rates of major or minor bleeding, unrelated to CABG, for patients in the two age groups:

<table>
<thead>
<tr>
<th>Age (N)</th>
<th>Prasugrel % (% fatal)</th>
<th>Clopidogrel % (% fatal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 75 (1,785)</td>
<td>9.0 (1.0)</td>
<td>6.9 (0.1)</td>
</tr>
<tr>
<td>&lt; 75 years (11,672)</td>
<td>3.8 (0.2)</td>
<td>2.9 (0.1)</td>
</tr>
</tbody>
</table>

These patients therefore had an increased risk of bleeding, including fatal bleeding, compared to patients under 75.

Patients weighing under 60 kg

The TRITON-TIMI 38 study found the following rates of major or minor bleeding according to the TIMI criteria, unrelated to CABG, for patients in the two weight groups:

<table>
<thead>
<tr>
<th>Body weight (N)</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 kg (664)</td>
<td>10.1% (0% fatal)</td>
<td>6.5% (0.3% fatal)</td>
</tr>
<tr>
<td>≥ 60 kg (12,672)</td>
<td>4.2% (0.3% fatal)</td>
<td>3.3% (0.1% fatal)</td>
</tr>
</tbody>
</table>

The rates of major or minor bleeding according to the TIMI criteria and unrelated to CABG among patients weighing over 60 kg and aged under 75 were 3.6% in the prasugrel group and 2.8% in the clopidogrel group; rates of fatal bleeding were 0.2% in the prasugrel group and 0.1% in the clopidogrel group.

Bleeding related to coronary artery bypass grafting (CABG)

In the TRITON study 437 patients had had a CABG (i.e. 3.2% of the total number of patients). The rates of CB-related major or minor bleeding according to the TIMI criteria among these patients were 14.1% in the prasugrel group and 4.5% in the clopidogrel group.

The increased risk of bleeding events among patients being treated with prasugrel lasted until seven days after the final dose of the study drug. For patients who had been given thienopyridine in the three days prior to the CABG, rates of major or minor bleeding according to the TIMI criteria were 26.7% (12 out of 45 patients) in the prasugrel group compared to 5.0% (3 out of 60 patients) in the clopidogrel group. The rates were lower among patients who had received their final dose of thienopyridine four to seven days prior to the CABG: 11.3% (9 out of 80 patients) in the prasugrel group and 3.3% (3 out of 90 patients) in the clopidogrel group. The rates of CABG-related bleeding observed beyond seven days after withdrawal of the medication were similar in both treatment groups.

In the light of this increase in bleeding in the prasugrel group, the therapeutic advantage was maintained with a reduction of 6.6% in the absolute risk for the primary composite endpoint (21.4% versus 28%) and of 4.3% in the risk of mortality from any cause (3.3% versus 7.6%).

Overdose: No data is available on neutralisation of the pharmacological effect of prasugrel; however, transfusion of platelets and/or other blood products can be considered if a rapid correction of prolonged bleeding time is required.
Patients with and without a history of TIA or stroke

<table>
<thead>
<tr>
<th>History of TIA or stroke</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (518 patients)</td>
<td>6.5% (2.3 % ICH*)</td>
<td>1.2 % (0 % ICH*)</td>
</tr>
<tr>
<td>No (13,090 patients)</td>
<td>0.9 % (0.2 % ICH*)</td>
<td>1.0 % (0.3 % ICH*)</td>
</tr>
</tbody>
</table>

*ICH = intracranial haemorrhage

Prasugrel is contraindicated for patients with a history of stroke or transient ischaemic attack (TIA).

Thrombotic thrombocytopenic purpura (TTP)

No cases of TTP have been associated with prasugrel in the clinical studies described in the marketing authorisation dossier.

3.3. Conclusion

The results of the TRITON TIMI-38 study, a randomised double-blind study carried out on 13,608 patients treated for acute coronary syndrome, found that the combination of prasugrel (EFIENT) + aspirin was associated with a significant reduction in ischaemic events, including stent thrombosis, compared to the combination of clopidogrel (PLAVIX) + aspirin after a median follow-up of 15 months treatment. The difference in risk (absolute benefit) was 2.1% (9.4% versus 11.5% in the overall population, p < 0.001) in favour of the prasugrel group. This effect was essentially due to a reduction in the risk of experiencing a non-fatal myocardial infarction (9.1% in the clopidogrel group and 7.0% in the prasugrel group, p<0.001). No difference between the two groups was observed in mortality (from any cause or from a cardiovascular cause).

Premature cessation because of a bleeding event was more frequent in the prasugrel group (2.5%) than in the clopidogrel group (1.4%). A higher rate of bleeding was observed in the prasugrel group: major bleeding not related to CABG (2.17% in the prasugrel group and 1.65% in the clopidogrel group, p=0.029); potentially life-threatening bleedings (1.26% in the prasugrel group versus 0.83% in the clopidogrel group, 0=0.015) including fatal bleedings (0.31% versus 0.07%, p=0.002). This increased risk of bleeding was observed in patients aged over 75 (taking the 10 mg dose which the SPC advises against) and those weighing less than 60 kg (taking the 10 mg dose which the SPC advises against).

In patients with a history of stroke or TIA the risk-benefit ratio of prasugrel (EFIENT) was unfavourable: treatment with EFIENT is contraindicated.

In the TRITON-TIMI 38 study, the additional clinical benefit attributable to the combination of prasugrel + aspirin appears modest compared with the combination of aspirin + clopidogrel; it relates mainly to a reduction in the occurrence of new infarctions, which has not been shown to be translated into mortality, and is associated with an increased risk of severe bleeding. It is not certain that this result can be extrapolated to the target population (as defined by the SPC), particularly because of the increased risk of bleeding that has been ascertained for patients of low body weight and those aged over 75. It is also questionable for patients with other haemorrhagic risk factors.

The TRITON study protocol compared EFIENT to clopidogrel in patients due to undergo revascularisation by PCI. But 437 patients in the study (approximately 3% of patients) underwent a bypass instead. The incidence of major and minor bleeding was 14.1% in the EFIENT group compared to 4.5% in the clopidogrel group.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Acute coronary syndrome (both STEMI and NSTEMI) needs to be treated by a specialist team. The immediate severity of non-ST segment elevation coronary syndrome (unstable angina, NSTEMI) depends on the clinical situation: whether the patient's condition is stable or unstable, whether his or her life is immediately threatened, and what risk factors are present. The clinical situation governs how patients are managed. Two treatment options are available: drug treatment and, for some patients, an invasive strategy comprising coronaryography and revascularisation surgery by angioplasty (PCI) or aortocoronary bypass (ACB). Surgery is performed within 120 minutes (rather unusual) or within 24 to 72 hours where, although there is an acute risk of complications, the patient's life is not immediately threatened. These clinical situations are serious and potentially life-threatening.

EFIENT is a first-line medicinal product prescribed in combination with aspirin. It is a secondary prevention medicinal product aimed at reducing morbidity and mortality associated with ACS.

Public health benefit
Ischaemic cardiopathies represent a major burden. The burden caused by acute coronary syndrome requiring a percutaneous coronary intervention is regarded as significant. Improving the secondary prevention of these clinical situations is a public health need. The results of the phase III clinical trial TRITON (reduction in cardiovascular events) indicate that an impact on morbidity is likely. Administration of the comparator treatment (dosage and introduction), the relative risk of the patients taking part in the trial and the mode of inclusion in the study (whether an angiography was performed) need to be taken into account when considering the transposability of these results. Efient is a new therapeutic alternative.

Consequently, in the current state of knowledge and in view of the uncertainties as to the population likely to benefit from this medicinal product (according to age, weight and haemorrhagic risk, especially for patients undergoing surgery), EFIENT is not expected to have any public health benefit.

Prasugrel has a high efficacy/adverse effects ratio in patients aged under 75 and weighing more than 60 kg. The efficacy/adverse effects ratio for patients aged over 75 and/or weighing under 60 kg is still being assessed (see post-marketing authorisation studies).

There is a treatment alternative: the combination of clopidogrel + aspirin.

Conclusion: the actual benefit of EFIENT 10 mg is substantial.

4.2 Improvement in actual benefit (IAB)

The combination of EFIENT (prasugrel) 10 mg + aspirin does not offer any improvement in actual benefit (IAB level V) compared to the combination of clopidogrel + aspirin for the treatment of patients with acute coronary syndrome who are to undergo percutaneous coronary intervention.
4.3 Therapeutic use of EFIENT in the treatment of acute coronary syndrome

- **In the acute phase of NSTEMI**, the aim of treatment is to prevent death or the onset of transmural myocardial infarction. It is important to draw a distinction between three clinical situations:
  - The patient’s life is immediately threatened: emergency invasive treatment (within 120 minutes) is then justified.
  - The patient’s life is not immediately threatened, though there is an acute risk of complications: in this case, invasive treatment (coronarography and if appropriate reperfusion surgery) can be postponed for up to 72 hours after this diagnosis.
  - The patient’s clinical condition does not require invasive treatment.

Drug treatment involves in particular the prescription of a combination of an unfractionated heparin or low molecular weight heparin, aspirin (ASA) and a beta-blocker. Combining clopidogrel (PLAVIX) with aspirin is beneficial. This combination can be given from the start of treatment, irrespective of the subsequent patient treatment strategy (invasive or conservative) and the estimated level of risk.

- **In the acute phase of STEMI**, according to a French consensus conference held in 2007, early coronary revascularisation helps improve patient prognosis. The choice between the two techniques available (angioplasty or fibrinolysis) is made in the light of the clinical situation, and especially the length of time that has passed since the onset of symptoms. Fibrinolysis is recommended if it is thought that more than 45 minutes is bound to elapse between the first contact between the patient and a medical practitioner and arrival in the unit where cardiology interventions can be performed. After undergoing fibrinolysis the patient must be referred to a centre which has a diagnostic and interventional coronarography room. The reperfusion strategy depends on when the symptoms first occurred; fibrinolysis is an option if they started less than three hours before the patient first received medical help. Drug treatment involves in particular an anticoagulant (unfractionated heparin or low molecular weight heparin), aspirin, and possibly an anti-GPIIb/IIIa for patients due to undergo angioplasty. Clopidogrel (PLAVIX) is prescribed either in combination with aspirin or alone if aspirin is contraindicated. The recommended loading dose is 300 mg for patients aged under 75 and 75 mg for patients aged over 75.

**ACS management strategy in the non-acute phase (after discharge from hospital)**
Drug strategy involves in particular aspirin plus clopidogrel (PLAVIX) at a dose of 75 mg/day; clopidogrel is continued for 9 to 12 months (at least 12 months in the case of patients who have received an active stent).

**Role of EFIENT 10 mg in the management of ACS**

For patients undergoing angioplasty (PCI) for acute coronary syndrome who are under 75 and weigh over 60 kg, prasugrel (EFIENT) is an alternative to the prescription of clopidogrel (PLAVIX). It must be prescribed in combination with aspirin.

The 10 mg/tablet strength of prasugrel (EFIENT) is not recommended for patients aged over 75 or who weigh less than 60 kg.

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3 Consensus Conference. Prise en charge de l'infarctus du myocarde à la phase aiguë en dehors des services de cardiologie. SAMU de France avec le partenariat méthodologique et le concours financier de la haute Autorité de santé [Management of myocardial infarction in the acute phase outside cardiology units. French Emergency Medical Services with the methodological and financial support of the Haute Autorité de Santé]; 6 February 2007
4.4 Target population

The target population for EFIENT is comprised of patients with acute coronary syndrome being treated with primary or delayed percutaneous coronary intervention (PCI). Patients aged over 75, weighing less than 60 kg or with a history of TIA or stroke are excluded from this population. Data from the official French health statistics database (PMSI) for 2007 shows that 125,000 patients underwent percutaneous coronary intervention in France in 2007.

French data from the APTOR observational study, and from a study conducted by IMS using the IMS disease analyzer database, has allowed the following estimates to be produced:

- among patients with ACS undergoing PCI, the proportion of patients with the UA/NSTEMI clinical form (IMS: 65%; APTOR: 53%) and the STEMI clinical from (IMS: 35%; APTOR: 47%).
- the proportion of patients with no history of CVA, weighing over 60 kg and aged under 75 (APTOR: 78.07% of STEMI patients and 74.90% of UA/NSTEMI patients).

It is thought that, among the population of ACS patients undergoing PCI with no history of CVA, weighing > 60 kg and aged under 75, the incidence of UA/NSTEMI forms of ACS would be around 50,000 to 61,000 new cases a year and that of the STEMI forms would be between 34,000 and 46,000 new cases a year.

PCI procedures are carried out either during/immediately after an ACS or some time later (60% of cases according to the expert opinion): EFIENT is not indicated in the latter case.

It is thought that the target population for EFIENT 10 mg is between 84,000 and 107,000 new patients a year.

4.5 Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the posology in the marketing authorisation.

4.5.1 Packaging: Appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 65%