BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

PLAVIX (clopidogrel), platelet aggregation inhibiting drug

Insufficient clinical benefit in combination with aspirin in the prevention of atherothrombotic and thromboembolic events in atrial fibrillation

Main points

- PLAVIX 75 mg, film-coated tablet, has a new Marketing Authorisation in combination with aspirin in the prevention of atherothrombotic and thromboembolic events secondary to atrial fibrillation (AF) associated with at least one risk factor for vascular events, in patients who cannot be treated by a vitamin K antagonists (VKAs) and who have a low risk of bleeding.
- The clopidogrel/aspirin combination was less effective than VKA treatment in the prevention of major cardiovascular events.
- The benefit of a double platelet anti-aggregation by clopidogrel and aspirin compared to aspirin alone has not been demonstrated.
- The addition of clopidogrel reduced the risk of ischaemic stroke, without demonstrating benefit in the reduction of myocardial infarcts or systemic embolisms, or total or cardiovascular mortality. Major bleeding was more common in the clopidogrel + aspirin group (especially intracranial haemorrhage), as well as minor bleeding.

Pre-existing indications

PLAVIX already has Marketing Authorisation in adults as secondary prevention of atherothrombotic events.

Therapeutic use

Antithrombotic treatment is essential for preventing thromboembolic complications, unless the AF is isolated in a patient aged under 65 years with no associated thromboembolic risk factors.

VKAs are the standard oral anticoagulant treatment in case of atrial fibrillation in patients at high thromboembolic risk. Three non-vitamin K antagonist direct oral anticoagulants (DOACs) are available in case of non-valvular atrial fibrillation when it is associated with at least one risk factor (i.e. a CHA2DS2-VASc score ≥ 1): apixaban (ELIQUIST), rivaroxaban (XARELTO) and dabigatran (PRADAXA).

There is currently no argument for replacing an effective vitamin K antagonist that has a well-balanced INR and is well tolerated with another oral anticoagulant. DOACs are second-line alternatives.

Role of PLAVIX in the treatment strategy

The wording of the Marketing Authorisation targets a narrow population, namely adult patients with atrial fibrillation who have at least one risk factor for vascular events, who cannot be treated by VKAs and who have a low risk of bleeding.

In patients undergoing oral anticoagulant therapy who cannot receive VKAs, DOACs are currently recommended.

The role of aspirin is currently very limited. Its prescription should be considered only in patients who cannot receive oral anticoagulation with VKAs or DOACs and in the absence of contraindications. The clopidogrel + aspirin combination has no role in the current treatment strategy for atrial fibrillation.

* This summary does not cover these indications.

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Clinical data

- Two clinical studies have evaluated the efficacy of the clopidogrel + aspirin combination in prevention of thromboembolic events in adults with atrial fibrillation and at least one of the following risk factors: age ≥ 75 years; age between 55 and 74 years associated with either type 2 diabetes requiring drug treatment, a documented history of MI, or documented heart diseases; treated arterial hypertension; history of stroke, transient ischaemic attack (TIA) or systemic embolism outside of the CNS; left ventricular dysfunction with an LVEF < 45%; documented peripheral vascular disease.

- The primary endpoint was the time to onset of the first of the following major cardiovascular events: stroke, systemic embolism outside of CNS, myocardial infarction or death from vascular causes.

- One study conducted versus VKAs was discontinued early on the recommendations of the independent monitoring committee, due to the superiority of treatment with VKA compared to treatment with PLAVIX + aspirin in terms of reduction of risk of major cardiovascular events (7.0% versus 4.9%; HR = 1.43; 95% CI [1.17-1.75]). Given these results, the Marketing Authorisation is restricted to patients who cannot be treated with a vitamin K antagonist.

- A second study compared the combination of clopidogrel/aspirin to aspirin alone in patients judged not eligible for treatment with VKAs. The addition of clopidogrel to aspirin reduced the risk of major vascular events (stroke, MI, systemic embolism outside of CNS, death from vascular causes) compared to aspirin in monotherapy: 22.1% versus 24.4%, RRR = 11.1% 95% CI [2.4-19.1], i.e. a reduction in absolute risk of 2.3%. This difference favouring the combination is based primarily on the reduction of the occurrence of stroke (7.9% versus 10.8%), in particular in ischaemic strokes, without demonstration of a benefit in reduction of MIs or SEs, or total mortality or mortality from cardiovascular causes. However, major bleeding was more common in the clopidogrel group + ASA than in the ASA alone group (6.7% versus 4.3%), in particular intracranial bleeding (1.4% versus 0.8%). Minor bleeding was also clearly more common in patients receiving the combination (10.8% versus 4.6%).

Benefit of the medicinal product

- The actual benefit* of PLAVIX is insufficient for reimbursement by National Health Insurance in the indication of the “Prevention of atherothrombotic and thromboembolic events in atrial fibrillation”.

- Does not recommend inclusion on the list of reimbursable products for supply by pharmacists and for hospital use in this indication.

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* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The improvement of actual clinical benefit (IACB) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of IACB on a scale from I (major) to IV (minor). A level V IACB (equivalent of “no IACB”) means “no clinical added value”.

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