BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KENGREXAL, (cangrelor), platelet aggregation inhibitor for injection

In angioplasty, no clinical benefit demonstrated by comparison with clopidogrel

Main points

- KENGREXAL has Marketing Authorisation in combination with acetylsalicylic acid (ASA) for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention who have not received oral P2Y₁₂ receptor inhibitors before this procedure and in whom the oral route for such treatment is not feasible or desirable.

- It is administered intravenously, unlike the three comparators: clopidogrel, prasugrel and ticagrelor.

- The cangrelor/clopidogrel/aspirin strategy has demonstrated its superiority relative to the aspirin/clopidogrel strategy on reducing ischemic event risk at 48 hours. The modest benefit observed mainly relies on the reduction of stent thrombosis risk, with no reduction in mortality. This benefit is nevertheless accompanied by an increased bleeding risk.

- KENGREXAL is restricted to use in patients who need to undergo emergency angioplasty and who cannot swallow (intubated or sedated patients, in a context like cardiac arrest or cardiogenic shock) or in whom digestive absorption is greatly impaired.

Therapeutic use

- **Acute coronary syndromes (ACS)**
  In the acute phase of an ACS treated with an acute coronary procedure, the platelet inhibition treatment prescribed includes aspirin (unless contraindicated). It is recommended to combine it with clopidogrel, prasugrel or ticagrelor (P2Y₁₂ receptor inhibitors).
  In patients who cannot receive oral administration and require an emergency angioplasty, in particular in a context of cardiac arrest, P2Y₁₂ inhibitor tablets are usually crushed to be administered by nasogastric tube if it is possible to set up one, often after the procedure. Otherwise, this treatment is not administered to them. In these most serious patients, digestive absorption may be impaired, which does not provide optimal efficacy of a treatment administered orally.

- **Stable angina**
  In addition to secondary preventive measures (dietary and lifestyle rules, aspirin, statin) that are indicated in patients with coronary artery disease, the symptomatic treatment of stable angina uses beta blockers as a first-line treatment. Revascularisation by angioplasty and/or coronary artery bypass may be considered in patients who resist medical treatment.
  In patients who need to have a percutaneous coronary intervention (PCI), platelet aggregation inhibitor treatment with 600 mg of clopidogrel is recommended preferably at least two hours before the PCI, when the coronary anatomy is known. It is no longer recommended to pre-treat patients with clopidogrel if the coronary anatomy is not known. The administration of ASA is indicated before elective stent implant. Glycoprotein GP IIb/IIIa antagonists should only be considered as rescue treatment.

- **Role of the medicinal product in the therapeutic strategy**
  Given the reservations on the results observed in clinical studies that evaluated cangrelor and their transposability, the role of KENGREXAL should be strictly limited to patients who need to receive an emergency angioplasty:

  - for whom oral administration of a P2Y₁₂ receptor inhibitor is not feasible, i.e. patients who cannot swallow (intubated or sedated patients, in a context like cardiac arrest or cardiogenic shock) and those whose digestive absorption is greatly impaired;
  - and who have not received oral P2Y₁₂ inhibitors before this procedure.

KENGREXAL should only be used for an administration duration of 2 to 4 hours. At the end of infusion, the platelet aggregation inhibition of cangrelor decreases quickly due to its short half-life. In practice, the sequential intravenous/
oral therapy with an oral P2Y12 receptor inhibitor at the end of infusion, as recommended by the Marketing Authorisation and evaluated in the studies is to be addressed. Administration by nasogastric tube is only validated for ticagrelor, but has not been evaluated in these studies.

Clinical data

- No study evaluated cangrelor in the population targeted by the Marketing Authorisation, i.e., patients in whom the administration of an oral P2Y12 inhibitor is not feasible or desirable.
- Three studies compared the efficacy of the intravenous cangrelor + oral clopidogrel strategy versus oral clopidogrel, in combination with aspirin and standard treatments in patients with stable angina, NSTEMI or STEMI.
- Two studies were terminated prematurely on the advice of a monitoring committee judging that the primary objective of demonstrating the superiority of cangrelor could not be attained.
- One study included more than 11,000 who needed to undergo an angioplasty, mainly for stable angina. Fewer than 20% were treated for a STEMI. Cangrelor was administered before the PCI, followed by a dose of 600 mg of clopidogrel immediately after infusion was discontinued. In the comparator group, the loading dose of clopidogrel could be 300 mg or 600 mg orally, administered before, during or immediately after the PCI. At 48 hours, the cardiovascular event rate (primary endpoint combining stent thromboses, death, MI and revascularisation induced by ischemia) was lower in the cangrelor group than in the clopidogrel group: 4.7% versus 5.9. The modest benefit observed (absolute difference of 1.2%) mainly relies on the reduction of stent thrombosis risk, particularly during the procedure, with no reduction in mortality.
- More intracranial bleeding was observed in the cangrelor group than the clopidogrel group in all three studies (11 versus 3 at day 30).
- Dyspnea was more common in the cangrelor group than in the clopidogrel group.
- Cangrelor is contraindicated in patients with a history of stroke or TIA.
- Treatment with KENGREXAL could also increase the risk of cardiac tamponade compared to clopidogrel.

Benefit of the medicinal product

- The actual benefit* of KENGREXAL is low.
- KENGREXAL, in combination with aspirin and clopidogrel, does not provide any clinical added value (CAV V) compared to the combination of oral clopidogrel and aspirin in the management of patients who need to undergo an angioplasty and cannot receive a P2Y12 receptor antagonist orally, given:
  - the modest benefit provided, only observed in the PHOENIX study, in terms of reduced morbidity (efficacy on stent thromboses), which is accompanied by an increased bleeding risk, especially intracranial bleeding,
  - and the reservations concerning the demonstration and relevance of this benefit.
- Recommends inclusion on the list of reimbursable products for hospital use.

* 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. HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

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

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