**BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION**

**PROCORALAN** (ivabradine), selective If channel inhibitor

**Does not recommend the continuation of reimbursement in the symptomatic treatment of chronic stable angina**

**Main points**

- **PROCORALAN** has Marketing Authorisation in the symptomatic treatment of chronic stable angina in adults with coronary artery disease with normal sinus rhythm and heart rate greater than or equal to 70 bpm. Ivabradine is indicated:
  - in adults unable to tolerate or with a contraindication to the use of beta-blockers,
  - or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose (non-reimbursable indication).

- In this indication, the efficacy of ivabradine has only been demonstrated on the basis of pharmacodynamic or symptomatic criteria, particularly the maintenance of the reduction in heart rate and the ergometric parameters; it has not been shown to have benefits in relation to the clinical criteria of morbidity and mortality.

- An increase in the risk of the occurrence of cardiovascular events (composite endpoint combining cardiovascular mortality and non-fatal myocardial infarction) relative to placebo has been demonstrated in a subgroup of patients with class II to IV angina.

- According to the available data, there is also an important risk of bradycardia and atrial fibrillation with ivabradine.

**Other indications**

**PROCORALAN** has Marketing Authorisation in the treatment of NYHA class II to IV chronic heart failure with systolic dysfunction in patients with normal sinus rhythm and heart rate greater than or equal to 75 bpm, in combination with the standard treatment comprising beta-blockers or when beta-blockers are not tolerated or are contraindicated. This summary does not cover this indication.

**Therapeutic use**

In addition to secondary preventive measures (dietary and lifestyle rules, aspirin, statin) that are indicated in patients with coronary heart disease, the objective of the symptomatic treatment of stable angina is to relieve the symptoms and prevent the recurrence of angina attacks.

The first-line treatment are beta-blockers that reduce the myocardial oxygen demand by a combination of a negative chronotropic (bradycardic) effect, a negative inotropic effect, and a slight decrease in the systolic blood pressure, and revascularisation by angioplasty and/or aortocoronary bypass in patients who are resistant to medicinal treatment. Bradycardic (verapamil, diltiazem) and non-bradycardic (amlodipine, etc.) calcium channel blockers, long-acting nitrate derivatives and nicorandil may be used on their own or in combination with beta-blockers (non-bradycardic antagonists and nitrate derivatives) and especially as second-line treatment and when beta-blockers are not tolerated or are contraindicated.

**RANEXA** (ranolazine) may also be used in patients with poorly controlled stable angina or who do not tolerate beta-blockers or calcium-channel blockers (not currently reimbursable).

**Role of the medicinal product in the therapeutic strategy**

In view of the new efficacy and safety data that are available as well as the coverage of therapeutic need in patients with stable angina, **PROCORALAN** no longer has a role in the therapeutic strategy for this indication.
Clinical data

- The efficacy of ivabradine has only been demonstrated on the basis of pharmacodynamic or symptomatic criteria, particularly the maintenance of the reduction in heart rate and the ergometric parameters. The BEAUTIFUL study failed to demonstrate the efficacy of ivabradine with respect to placebo in terms of morbidity and mortality (composite endpoint combining cardiovascular mortality, hospitalisations for acute myocardial infarction and hospitalisations for the occurrence or worsening of heart failure). Similarly, the SIGNIFY study failed to demonstrate the efficacy of ivabradine with respect to placebo in terms of morbidity and mortality (composite endpoint combining cardiovascular mortality and non-fatal myocardial infarction). In addition, it showed an increase in the risk of the occurrence of these events (cardiovascular mortality and non-fatal myocardial infarction) in a subgroup of patients with class II to IV angina, defined a priori.

- In terms of safety, the available data point to an important risk of bradycardia and atrial fibrillation with ivabradine.

- Taking all the available data into account, the benefit of ivabradine in patients with stable angina with respect to the numerous available alternatives (calcium-channel blockers, nitrate derivatives, ranolazine, nicorandil) has been called into question.

Benefit of the medicinal product

- The actual benefit* of PROCORALAN is insufficient in the treatment of chronic stable angina to justify reimbursement by National Health Insurance.

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

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* The actual benefit (AB) of a proprietary 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 AB, which can be substantial, moderate, low or insufficient for reimbursement by the National Health Insurance.