HAUTE AUTORITÉ DE SANTÉ

HAEMATOLOGY
New indication
January 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

FRAXIPARIN (nadroparin calcium), antithrombotic

Low clinical benefit in the prophylactic treatment of thromboembolic disorders in patients immobilised for acute medical condition, but no demonstrated clinical advantage in the therapeutic strategy.

Main points

- FRAXIPARIN has now been granted a marketing authorisation for the prophylactic treatment of thromboembolic disorders in patients suffering from an acute medical condition (e.g. acute heart failure, respiratory failure, severe infection or rheumatic disease) and with reduced mobility, at high venous thromboembolic risk.
- Its impact on the prevention of deep vein thrombosis (DVT) has been demonstrated versus placebo in a sub-population of the marketing authorisation: intensive care patients, immobilised and on mechanical ventilation for acute decompensation of chronic obstructive pulmonary disease (COPD).
- No impact on mortality was demonstrated compared to the placebo.
- No efficacy data compared to other low molecular weight heparins (LMWH), non-fractionated heparins (NFH) or to fondaparinux was available, even though these comparisons could have been made.
- Its safety profile is similar to that of other LMWHs.

Pre-existing indications*

FRAXIPARIN has already been granted a marketing authorisation for the prophylactic treatment of thromboembolic disorders, particularly in cases of venous thromboembolic disease in surgery, in moderate to high-risk situations, prevention of extracorporeal circulation circuit coagulation, during haemodialysis, curative treatment of established deep vein thrombosis, treatment of unstable angina and of acute phase non-Q wave myocardial infarction, in combination with aspirin.

Therapeutic strategy

- In immobilised patients suffering from an acute medical condition and considered to be at high thromboembolic risk, thromboprophylactic measures are systematically prescribed. These may involve medicinal products (LMWH, NFH or fondaparinux) and/or mechanical means (elastic compression, intermittent pneumatic compression). The occurrence of a potentially fatal haemorrhage is the primary risk associated with taking these medicinal products. Factors increasing the haemorrhagic risk are advanced age, low body weight and overdose by accumulation following impaired anticoagulant elimination. Kidney failure is particularly associated both with increased risk of a venous thromboembolic event and with haemorrhagic risk.
- Should the haemorrhagic risk outweigh the expected benefit of medicinal thromboprophylaxis, or in the event of contraindication to antithrombotic agents, mechanical measures alone are recommended. If the thromboembolic risk is greater than the haemorrhagic risk, first-line medicinal thromboprophylaxis should be considered, in combination with mechanical measures, until the patient is capable of active ambulation: LMWH (LOVENOX, FRAGMIN and INNOHEP), NFH (CALCIPARIN) or fondaparinux (ARIXTRA 2.5 mg) in absence of any major haemorrhagic risk (low body weight, moderate to severe kidney failure or very elderly patients).

* This summary does not concern these indications.

- The patient's renal function should be taken into consideration when selecting an antithrombotic agent. NFHs are the conventional treatment in patients presenting with severe to terminal kidney failure (ClCr < 30 ml/min.).
  LMWHs and fondaparinux are preferable to NFHs considering their greater ease of use, reduced haemorrhagic risk (LMWHs), reduced risk of thrombocytopenia induced by heparin and the lack of haemorrhagic risk with fondaparinux compared to placebo in this medical context. In patients hospitalised for an acute medical condition whose thrombotic risk is increased, thromboprophylaxis should not be continued beyond the immobilisation or hospitalisation period. Should these patients present with high haemorrhagic risk, thromboprophylaxis by elastic compression or intermittent pneumatic compression is recommended and medicinal thromboprophylaxis is initiated once the haemorrhagic risk decreases.
- **Role of the medicinal product in the therapeutic strategy**
  FRAXIPARIN is a first-line prophylactic treatment for venous thromboembolic disorders in patients immobilised for acute medical condition and with increased venous thromboembolic risk, like other LMWHs, NFHs and fondaparinux.

Clinical data

- The assessment of nadroparin in the prophylactic treatment of venous thromboembolic disease in patients immobilised for acute medical condition relies primarily on two comparative studies versus placebo and one comparative safety study versus NFH.
- The two randomised, double-blind studies versus placebo were designed to assess the thromboprophylactic efficacy of subcutaneous nadroparin in hospitalised patients on mechanical ventilation for acute decompensated COPD, or in hospitalised patients immobilised for an acute medical condition. The first study (n=223 patients) demonstrated, after a mean duration of 11 days of treatment, a significantly lower incidence of DVT in the nadroparin group than in the placebo group: 15.5% versus 28.2% (p=0.045). No data relevant to the prevention of pulmonary embolism were available (secondary exploratory endpoint). In the second study (n=2,474 patients), there was no significant difference in overall mortality between nadroparin and the placebo on the 21st day after treatment initiation: 10.1% versus 10.3% (RR=0.02; CI95% [-0.27; 0.25]; NS).
- The efficacy of nadroparin was demonstrated in the prevention of DVT by comparison to placebo in a sub-population of the marketing authorisation, corresponding to patients in intensive care, immobilised and on mechanical ventilation for acute COPD decompensation. The efficacy of enoxaparin, dalteparin and fondaparinux 2.5 mg, which are clinically relevant comparators, was demonstrated on a combined morbidity and mortality endpoint in the broader marketing authorisation population (patients immobilised for acute medical condition, such as acute heart failure, respiratory failure, severe infection or rheumatic disease). As for enoxaparin, dalteparin and fondaparinux 2.5 mg, the data available for nadroparin failed to show any impact on mortality, whatever the cause, by comparison to the placebo.
- The randomised, open, single-centre descriptive safety study was intended to compare the safety of nadroparin prophylaxis to that of heparin calcium for 10 days in 99 patients over the age of 70 years, hospitalised and presenting with additional thromboembolic risk factors. Two major haemorrhages were reported under heparin calcium (4%) and none under nadroparin. No bruising was observed at the injection site.
- The observed safety profile in the studies was similar to that known for nadroparin, underpinned in particular by cases of haemorrhage and thrombocytopenia.

Benefit of the medicinal product

- The actual clinical benefit* of FRAXIPARIN is low.
- FRAXIPARIN does not provide any clinical added value ** (CAV V) in the prophylactic strategy.
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 23 January 2019 (CT-16700) available at **www.has-sante.fr**

* 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 may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".