HAUTE AUTORITÉ DE SANTÉ

RHEUMATOLOGY
New medicinal product
April 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

ZURAMPIC (lesinurad), uricosuric

Low clinical benefit, in combination with an xanthine oxidase inhibitor (IXO), in gout-related hyperuricaemia under conditions of IXO failure, though no clinical advantage in the therapeutic strategy.

Main points

- ZURAMPIC has been granted marketing authorisation, in combination with an IXO, in adults, for the adjuvant treatment of hyperuricaemia in patients suffering from gout (with or without tophus) who failed to reach the target uric acid levels with an appropriate dose of IXO administered alone.
- When used in combination with an IXO (allopurinol or febuxostat), it has demonstrated its efficacy *versus* placebo in terms of the proportion of patients reaching target uricaemia levels after 6 months of treatment.
- It has not demonstrated its efficacy in terms of reduction of goutflares.

Therapeutic strategy

- The aim of gout management is to lower and maintain uric acid levels below the sodium urate saturation threshold (≤ 360 µmol/l or 60 mg/l). Dietary hygiene measures should be preferred, along with discontinuation of any hyperuricaemia-inducing medicinal products, in particular any diuretics. The treatment is associated with the correction of co-morbidities and with the management of cardiovascular risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity and smoking.
- Flare treatment involves colchicine and NSAIDs. Colchicine has a small therapeutic window and is associated with numerous precautions for use. In particular, it is contraindicated in cases of kidney or liver failure.
  In the presence of persistent and symptomatic hyperuricaemia, an hypouricaemia-inducing treatment may be prescribed. Flares may occur during the initial months of treatment, thus requiring NSAID or colchicine prophylaxis (3 to 6 months, or even longer in cases of tophus).
  Allopurinol (IXO) is the conventional treatment for chronic hyperuricaemia. Its dosage should be adjusted for age, kidney status and tolerance.
  Uricosuric agents (probenecide, benzbromarone) are alternatives in the event of allopurinol failure or intolerance, once normal uricosuria has been ascertained and in the absence of a history of urinary lithiasis.
  Access to these medicinal products, however, is very limited (available via import, or named temporary use authorisation).
  Febuxostat (ADENURIC), IXO, can represent an alternative to allopurinol in the event of mild to moderate kidney failure. No dose adjustment is required, though its use requires precautions, particularly in cases of ischaemic disease or congestive heart failure. It is associated with a risk of severe hypersensitivity reactions. Consequently, ADENURIC is indicated in the treatment of chronic hyperuricaemia only when tophus is observed.
- **Role of the medicinal product in the therapeutic strategy**

  ZURAMPIC is second-line treatment that should only be used in combination with an IXO, in adults suffering from gout (with or without tophus), who have failed to reach the target uricaemia levels with an appropriate dose of IXO administered alone.

Clinical data

- Lesinurad 200 mg/day was evaluated, in combination with an IXO, in 3 six-month randomised, double-blind, phase III, placebo-controlled studies in adults with hyperuricaemia. The primary endpoint of these studies was the fraction of patients reaching uricaemia target values (< 6 mg/dl in the CLEAR 1 and 2 studies and < 5 mg/dl in the CRYSTAL study) after 6 months of treatment.
  In the CLEAR 1 and CLEAR 2 studies, patients were failing allopurinol, with uricaemia ≥ 6.0 mg/dl at D-7 and at least 2 gout flares during the 12 months preceding the study.
  In the CRYSTAL study, patients were failing allopurinol or febuxostat, with uricaemia ≥ 6.0 mg/dl at the time of the selection visit, or uricaemia ≥ 8 mg/dl in the absence of hypouricaemia-inducing treatment and at least one measurable tophus in the hands/wrists and/or ankles, measuring ≥ 5 mm and ≤ 20 mm along their longest diameter. Lesinurad and the placebo were administered in combination with allopurinol (300 to 800 or 900 mg/day) in the CLEAR 1 and 2 studies, and with febuxostat (80 mg/day) in the CRYSTAL study.
  The proportion of patients who reached the target uricaemia level of < 6 mg/dl after 6 months was higher in the lesinurad 200 mg + allopurinol group than in the placebo + allopurinol group (54.2% *versus* 27.9% in CLEAR 1 and 55.4% *versus* 23.3% in CLEAR 2; p < 0.0001).
  In the CRYSTAL study, one third of patients had not been treated with IXO; no significant difference in the proportion of patients who reached the target uricaemia level of < 5 mg/dl after 6 months of treatment was detected between the lesinurad 200 mg + febuxostat group (56.6%) and the placebo + febuxostat group (46.8%)
  Lesinurad failed to demonstrate is superiority for the secondary endpoints, particularly the occurrence of goutflares, thus not supporting the uricaemia reduction results. In the CRYSTAL study, febuxostat was not used at an optimal dose. No 12-month data are available, beyond the IXO treatment-start gout episode risk period.
- The most frequently observed adverse events in the phase III studies were: upper respiratory tract infections, flu, arthralgia, dorsalgia, hypertension, headaches, diarrhoea and hypercreatininaemia (generally transient). Most adverse event were mild to moderate.

Benefit of the medicinal product

- The actual clinical benefit* of ZURAMPIC is low.
- ZURAMPIC does not provide any clinical added value** (CAV V) over the therapeutic strategy for the treatment of severe gout after IXO failure.
- Approved for non-hospital pharmacy reimbursement or for hospital treatment.

HAUTE AUTORITÉ DE SANTÉ
This document was drafted on the basis of the Transparency Committee opinion dated 04 April 2018 (CT-16642) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) is its benefit particularly on the basis of its clinical performances and the severity of the disease 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) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement"