HAUTE AUTORITÉ DE SANTÉ

CARDIOLOGY
New medicinal product
April 2016

**BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION**

# **ZIMINO** (levosimendan), cardiac stimulant

**Low clinical benefit in the short-term treatment of acute decompensated severe chronic heart failure reserved as a last resort in adults in an emergency situation, especially in cases of refractory cardiac decompensation who failed weaning from inotropes or circulatory support.**

## Main points

- ZIMINO, Euro generic of SIMDAX, has marketing authorisation in the short-term treatment of acutely decompensated severe chronic heart failure (ADHF) in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate in adults.
- The available clinical data do not justify its efficacy in the marketing authorisation indication.
- However its use under its temporary authorisation for use by a named person since 2004 confirms a substantial therapeutic need. Only a few results with a very low level of evidence appear to show its benefit.

## Therapeutic use

- Generally, first-line treatments for ADHF rely on the use of:
  - oxygen to correct hypoxemia,
  - intravenous diuretics to relieve oedema and dyspnea,
  - vasodilators (nitrates) to increase stroke volume especially in cases of high blood pressure and to increase cardiac output.

  More selectively established treatments are also available depending on the patient's symptomatology (opioids, non-invasive ventilation, inotropic medicines such as dobutamine, phosphodiesterase inhibitors such as milrinone or vasopressors such as norepinephrine or dopamine).
  In cases of severe heart failure, under certain conditions, heart transplant or implant of a left ventricular assist device can be considered.
- **Therapeutic Use**
  Given the absence of clinical data with a good level of evidence to justify its efficacy and safety in the marketing authorisation indication, ZIMINO cannot be proposed in this entire population. However, it has a limited role in adult patients in an emergency situation, especially in cases of refractory decompensation, in failure of withdrawal from inotropes or circulatory support as a last resort where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate.

## Clinical data

- In one study, after 24 hours, a significantly greater proportion of patients with improvement in haemodynamic parameters (primary endpoint) was observed in the levosimendan group compared to the dobutamine group: 28% (29/103) versus 15% (15/100), RR=1.9, 95% CI = [1.10 – 3.30], p = 0.022. This result is based solely on the reduction of at least 25% of the pulmonary capillary wedge pressure (RR 1.67, 95% CI [1.19; 2.33]; no significant difference having been observed in terms of increased cardiac index of at least 30% and use of IV vasodilators or positive inotrope treatments. In the absence of data demonstrating the benefit of ZIMINO in the marketing authorisation population and given a significant therapeutic need, a post hoc analysis of this study was requested on 34/203 patients with advanced HF and awaiting cardiac transplant (19/103 patients in the levosimendan group and 15/100 patients in the dobutamine group). This analysis appears to confirm this benefit.

- In a program composed of the studies REVIVE I and REVIVE II:
  - In REVIVE I (n=100), there was no difference on the primary endpoint (number of patients whose general condition is qualified as “improved” after 24 hours and 5 days in comparison to the number of patients whose general condition is qualified as “worsened” at any time during the 5 days) versus placebo,
  - In REVIVE II, the percentage of "improved" patients (primary endpoint same as REVIVE I with an additional self-assessment time at 6 h) was 19.4% (58/299) patients in the levosimendan group and 14.6% (44/301) patients in the placebo group and that for “worsened” patients was 19.4% (58/299) in the levosimendan group and 27.2% (82/301) patients in the placebo group (p = 0.015). The difference between the groups is small and is not linked to a difference in mortality, which is 5 deaths in the levosimendan group and 1 death in the placebo group.
- In one study, levosimendan has not demonstrated superiority versus dobutamine on the primary endpoint: at 180 days, the death rate between the two groups was not significantly different: HR = 0.91; 95% CI = [0.74 - 1.13].
- The meta-analyses fail to demonstrate a real benefit of levosimendan in this indication, given the low level of evidence and the disparity of the clinical trials included in the meta-analyses.
- The most commonly reported adverse reactions (> 10%) are headache, ventricular tachycardia and hypotension. An RMP was set up to monitor the major risks identified for levosimendan: hypotension, supraventricular tachyarrhythmia, ventricular tachyarrhythmia, as well as patients with torsades de pointes, ischemia or hypokalemia.

## Special prescribing conditions

- Medicinal product reserved for hospital use.

## Benefit of the medicinal product

- The actual benefit* of ZIMINO is low in a limited population:  adults in an emergency situation, especially in cases of refractory decompensation, who failed withdrawal from inotropes or circulatory support.
- ZIMINO does not provide clinical added value** (CAV V) in the management of these patients.
- Recommends inclusion on the list of reimbursable products for hospital use.

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[i] * 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 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".