HAUTE AUTORITÉ DE SANTÉ

HAEMATOLOGY
New indication
July 2017

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

TRISENOX (arsenic trioxide), antineoplastic

High clinical benefit for the treatment of acute promyelocytic leukaemia in combination with all-trans retinoic acid and minor clinical added value compared to the all-trans retinoic acid - chemotherapy combination

Main points

- TRISENOX has been granted a marketing authorisation for remission induction and consolidation for adults suffering from newly diagnosed acute promyelocytic leukaemia (APL) at a low or intermediate risk (leukocyte count: ≤ 10 x 10^3/µL), in combination with all-trans retinoic acid (ATRA or tretinoin), characterised by the presence of t(15;17) translocation and/or the presence of the PML/RAR-alpha gene.
- The superiority of the ATRA-arsenic trioxide combination has been demonstrated compared to the ATRA-chemotherapy combination in terms of 2-year event-free survival.
- No gain in overall survival or in quality of life has been demonstrated.
- The ATRA-arsenic trioxide combination is a first-line treatment for this indication.

Pre-existing indications*

TRISENOX has already been granted a marketing authorisation for remission induction and consolidation for relapsed or refractory adult APL patients

Therapeutic strategy

- In the case of newly diagnosed APL, patients receive an induction treatment including the ATRA-chemotherapy (anthracycline) combination optionally combined with aracytine C until remission. The ATRA-chemotherapy combination induction treatment results in complete remission for at least 75% of patients. The consolidation treatment is based on the use of 2 to 3 anthracycline chemotherapy cycles combined with ATRA. Patients presenting with detectable t(15;17) persistent disease receive a maintenance treatment including long-term ablative chemotherapy (methotrexate) and ATRA.
- For patients with relapsed or refractory disease, TRISENOX induction treatment is implemented until complete remission.
- Patients at a very high risk of relapse may be candidates for allogeneic haematopoietic stem cell transplantation or for high-dose consolidation chemotherapy with autologous stem cell retransfusion.
- **Role of the medicinal product in the therapeutic strategy**
  TRISENOX in combination with ATRA is a first-line remission induction and consolidation treatment for adult patients suffering from newly diagnosed low- or intermediate-risk APL, characterised by the presence of t(15;17) translocation and/or the presence of the PML/RAR-alpha gene.

* This summary does not concern this indication.

Clinical data

- An open-label, randomised non-inferiority study assessed the efficacy and safety of the ATRA-arsenic trioxide (ATO) combination versus ATRA-chemotherapy as a first-line treatment for newly diagnosed APL patients.
  After a median follow-up period of 34.4 months, non-inferiority in terms of the 2-year event-free survival rate in the ATRA-ATO group and in the ATRA-chemotherapy group with respective rates of 97% and 85% i.e. a difference of 12% (95% CI: [2-23], p< 0.001 in the per protocol population).
- A benefit in the ATRA-ATO group compared to the ATRA-chemotherapy group was observed in terms of infections/infectious complications as well as febrile neutropoenia and fever observed in 11 versus 3 patients in the ATRA/chemotherapy and ATRA-ATO groups, respectively. On the other hand, in the group treated with ATRA-ATO, a higher percentage of liver toxicity was observed. This event has been included in the SPC with a grade 3-4 increase in transaminases which was 44% in the ATRA-ATO group versus 3% in the ATRA-chemotherapy group. One death occurred in the ATRA-ATO and 7 in the ATRA-chemotherapy group.
- No evidence of a gain in overall survival or in quality of life was demonstrated.

Special prescription requirements

- Medicinal product for hospital use only

Benefit of the medicinal product

- The actual clinical benefit* of TRISENOX in combination with ATRA is high
- Given:
  - the evidence of non-inferiority in terms of the primary endpoint of 2-year event-free survival,
  - and the superiority test subsequently conducted inferring the superiority of the ATRA-arsenic trioxide combination over the ATRA-chemotherapy combination,
  - the lack of evidence of a gain in overall survival and in quality of life,

  TRISENOX, in combination with ATRA, provides a minor clinical added value (CAV IV) compared to the ATRA-chemotherapy combination for the marketing authorisation indication.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 19 July 2017 (CT-16115) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) consists of 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".