HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
April 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

TASIGNA (nilotinib), tyrosine kinase inhibitor (ITK)

High clinical benefit in the treatment of children with Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML) in the chronic phase, in the event of resistance or intolerance to imatinib, and minor clinical improvement in the therapeutic strategy.

Insufficient clinical benefit to justify its reimbursement in the treatment of children recently diagnosed with Ph+ CML in the chronic phase.

Main points

- TASIGNA has MA in the treatment of paediatric patients recently diagnosed with Ph+ CML in the chronic phase and in the event of resistance or intolerance to imatinib.
- In children, its short-term efficacy is demonstrated on the cytogenic and molecular responses, without efficacy being demonstrated on mortality.
- It provides a response to an unmet medical need in children resistant or intolerant to imatinib, first-line gold standard treatment.
- In light of the limited data and the absence of direct comparison to imatinib, its role in recently diagnosed children is not established.

Pre-existing indication*

TASIGNA already has MA in the treatment of adults with Ph+CML (see SPC for further details).

Therapeutic strategy

- Management of patients with CML is based on the prescription of tyrosine kinase inhibitors (TKI) BCR-ABL, the introduction of which in the therapeutic strategy has significantly improved the prognosis.
  Pending confirmation of the diagnosis, hydroxyurea, possibly associated with leukapheresis can be used to reduce the leukocytosis which is often severe in child patients.
- When Ph+ CML is diagnosed in children, it is fitting to start GLIVEC (imatinib), first-generation TKI treatment. The treatment response is assessed at various stages of management according to cytogenetic and molecular efficacy criteria.
- In the event of non-response or sub-optimal response to imatinib, a second-generation TKI is used: TASIGNA (nilotinib) used off-label until then, or SPRYCEL (dasatinib), used off-label in paediatrics.
  Use of haematopoietic stem cell transplantation in the chronic phase, the only curative treatment for CML, is now only used in certain patients with identical HLA donor identified, in second-line, in the presence of a T315I mutation, or in third-line after failure of at least 2 TKIs or in the event of sub-optimal response to a TKI.
- **Role of the medicinal product in the therapeutic strategy**

  TASIGNA is the gold standard treatment in children with Ph+ CML in the chronic phase, in the event of resistance or intolerance to imatinib.

* This summary does not concern these indications.

In the absence of direct comparison with imatinib and considering the limited data, especially for safety, TASIGNA does not have a role in the strategy for the treatment of paediatric patients recently diagnosed with Ph+ CML in the chronic phase.

Clinical data

- The data available are taken from an intermediate analysis of a phase 2, non-comparative study which assessed the efficacy of nilotinib in terms of molecular and cytogenic response in children with Ph+ CML in the chronic phase. The intermediate analysis covered 33 patients resistant or intolerant to a previous treatment, including imatinib and on 25 recently diagnosed patients.
- Concerning the patients in second-line treatment (resistant or intolerant to imatinib or dasatinib, the percentage of patients in major molecular response (MMR, BCR-ABL/control gene ratio < 0.1 %) at the 6th treatment cycle visit (primary endpoint) was 39.4%, CI95% [22.9; 57.9] corresponding to 13 patients (out of 33) 6 of whom were already in MMR at inclusion and in whom the response was sustained.
- In the cohort of 25 recently diagnosed children, the results for the two co-primary endpoints showed that 16 patients out of 25 (64.0%, CI95% [42.5; 82.0]) had a MMR between the 1st and 12th treatment cycle and that 16 children (64.0%, CI95% [42.5; 82.0]) were in Complete Cytogenetic Response (CCyR, corresponding to 0% Ph+ chromosome in the metaphases) in the 12th cycle.
- The efficacy of TASIGNA after 12 treatment cycles and its impact on mortality are not demonstrated.
- The safety profile in the paediatric population, with hindsight limited to 12 treatment cycles, seems comparable to that observed in adults, except for abnormal blood test results including hyperbilirubinaemia and elevated transaminases reported at a higher frequency in children.
  The long-term effects of chronic nilotinib treatment in children and adolescents, on growth especially, are not known.

Special prescription requirements

- Medicinal product subject to initial half-yearly hospital prescription.
- Initial prescription and repeat prescription by oncology specialists haematologists, or physicians with oncology expertise.

Benefit of the medicinal product

- The actual clinical benefit* of TASIGNA in paediatric patients with Ph+ CML is:
  - high in the chronic phase in the event of resistance or intolerance to imatinib;
  - insufficient in the chronic phase in recently diagnosed patients.
- TASIGNA provides a minor improvement in actual clinical benefit** (IACB IV) in the treatment of paediatric patients with Ph+ CML in the chronic phase, resistant or intolerant to imatinib.
- Approved for non-hospital pharmacy reimbursement and for hospital management for the treatment of paediatric patients resistant or intolerant to imatinib only.

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This document was drafted on the basis of the Transparency Committee opinion dated 18 April 2018 (CT-16675) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product 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 improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"