**SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION**

**BESPONSA** (inotuzumab ozogamicin), antineoplastic monoclonal antibody

- For the treatment of relapsed or refractory CD22 positive B-cell precursor acute lymphoblastic leukaemia, Philadelphia chromosome-negative (Phi-): low clinical benefit and no proven clinical added value compared to standard chemotherapies.
- Philadelphia chromosome-positive (Phi+): clinical benefit considered insufficient to justify public funding.

**Main points**

- **BESPONSA** has been granted a marketing authorisation for the treatment of adults with relapsed or refractory CD22 positive B-cell precursor acute lymphoblastic leukaemia (ALL). Adult patient with Philadelphia chromosome-positive (Phi+) should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).
- In relapsed or refractory B cell ALL, no gain in overall survival has been demonstrated compared to standard chemotherapies. The haematological remission rate (80.7% versus 29.4%) and use of haematopoietic stem cell transplant (43% versus 11%) were higher in the inotuzumab ozogamicin group than in the standard chemotherapy group, with however a higher 100-day mortality post-transplant with BESPONSA than with standard chemotherapies (26% versus 6%).
- There is a higher risk of hepatic veno-occlusive disease/sinusoidal obstruction syndrome with BESPONSA than with standard chemotherapies; this adverse event may be serious or even fatal.
- In relapsed or refractory Phi+ ALL, BESPONSA has no place in the therapeutic strategy.

**Therapeutic strategy**

- The objective of the treatment of relapsed or refractory B cell ALL is to obtain complete remission in order to graft patients, the only curative treatment to date. The strategy is to get them to transplant in the best possible conditions in respect of remission and general health. The treatment is curative and is based on an intensive polychemotherapy regimen for a period of about 6 months, including successively an induction phase followed by a consolidation phase and depending on the treatment risk, includes a 2-year maintenance chemotherapy regimen or stem cell transplant (HSCT). Prevention of neuromeningeal injury by intrathecal chemotherapy or encephalic irradiation is required.
- The presence of a Philadelphia chromosome (Phi+ ALL) or of a BCR-ABL fusion transcript must be known as it provides early guidance for treatment which is then administered specifically with a tyrosine kinase inhibitor (such as imatinib as a first-line treatment), combined with chemotherapy.
- For relapsed or refractory Phi- B cell ALL, the treatments are polychemotherapy regimens based on (without particular order): fludarabine and anthracycline, cytarabine, alkylating agents, liposomal vincristine (off-label) and clofarabine (marketing authorisation only for the treatment of childhood ALL), blinatumomab, inotuzumab ozogamicin. The US NCCN guidelines state that blinatumomab must be used preferentially over chemotherapies.
- For relapsed or refractory Phi+ B cell ALL, several tyrosine kinase inhibitors are indicated, optionally in combination with chemotherapy. Dasatinib (SPRYCEL) represents a second-line therapeutic alternative to imatinib, and ponatinib (ICLUSIG) is the alternative treatment for resistance or intolerance to dasatinib. Other TKIs such as nilotinib or bosutinib, indicated in chronic myeloid leukaemia, are cited (off-label) in US and European guidelines.

**Role of the medicinal product in the therapeutic strategy**

For relapsed or refractory Phi- B cell ALL.
Given:
- the presence in the therapeutic arsenal of blinatumomab that has demonstrated a statistically significant gain in overall survival compared to standard chemotherapies,
- the lack of direct comparison of inotuzumab ozogamicin versus blinatumomab in this population and the lack of robust data on the third-line use of inotuzumab ozogamicin after blinatumomab treatment failure,
- the safety profile of BESPONSA, especially the increased risk of veno-occlusive disease compared to chemotherapies, without the predictive factors being clearly defined,
- the high medical need,
the place of BESPONSA in the therapeutic strategy is marginal.
the Committee therefore, recommends that the decision to initiate BESPONSA treatment be made in the context of multidisciplinary review meetings with regard to the points listed above.

For relapsed or refractory Phi+ ALL
BESPONSA has no place in the therapeutic strategy given:
- the lack of comparative data versus a TKI for second-line treatment, particularly versus dasatinib, a clinical relevant comparator, even though this comparison was possible;
- the lack of available data with a sufficient level of evidence, for the third-line or more treatment of Phi+ B cell ALL, after the failure of two TKIs.

Clinical data

The efficacy data for inotuzumab ozogamicin (IO) are based on an open-label phase III study, comparing IO to a chemotherapy regimen chosen by the investigator amongst 3 regimens on 326 patients with relapsed or refractory Phi- or Phi+ CD22+ B cell ALL.
The patients received either IO (n=164), or one of the 3 following regimens: FLAG (n=102/162), MXN/Ara-C (n=38/162) and HIDAC (n=22/162).
The superiority of IO was demonstrated over the control group on the complete remission rate with or without partial haematological recovery, (initial primary endpoint): 80.7% (95% CI [72.1; 87.7]) versus 29.4% (95% CI [21.0; 38.8]), i.e. an absolute difference of +51.4% in favour of IO (97.5% CI [38.4; 64.3]) (p < 0.0001).
There was no statistically significant difference between the groups on the overall survival (added retrospectively as co-primary endpoint).
The overall incidence of serious adverse effects was similar in both groups. less grade ≥ 3 haematological adverse effects (thrombocytopenia, leukopenia, febrile neutropenia, anaemia) were reported in the IO group versus the control group. Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) was reported more frequently in the IO group (13.4% versus 0.7%).

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for haematology specialists or physicians with expertise in blood disorders
- Medicinal product requiring special monitoring during treatment.

Benefit of the medicinal product

- For relapsed or refractory CD22 positive B-cell precursor ALL,
  - Philadelphia chromosome-negative (Phi-): the actual clinical benefit* is low,
  - Philadelphia chromosome-positive (Phi+): the actual clinical benefit* is insufficient to justify public funding.
- For relapsed or refractory Phi- B cell ALL, BESPONSA provides no clinical added value** (CAV V) compared to standard chemotherapies.
- Approval for hospital treatment for relapsed or refractory Phi- B cell ALL.

This document was drafted on the basis of the Transparency Committee opinion dated 07 February 2018 (CT-16460) 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”.

© French National Authority for Health 2018