HAUTE AUTORITÉ DE SANTÉ

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

BUSILVEX (busulfan)

Conditioning treatment prior to conventional haematopoietic stem cell transplantation:
- No clinical benefit demonstrated in adults compared to other available conditioning regimens.
- Minor clinical benefit in infants, children and adolescents compared to total body irradiation.

Main points

- BUSILVEX has Marketing Authorisation in 3 indications for conditioning treatment prior to conventional haematopoietic stem cell (HSC) transplantation:
  - BUSILVEX followed by cyclophosphamide in adults,
  - BUSILVEX followed by cyclophosphamide or melphalan in infants, children and adolescents,
  - BUSILVEX administered after fludarabine in adults eligible for a reduced intensity conditioning (RIC).
- New data confirm that busulfan IV-based regimens are an effective therapeutic strategy in the myeloablative conditioning treatment of infants, children and adolescents and adults, as well as in reduced intensity conditioning in adults.
- Busulfan IV-based conditioning regimens prior to HSC transplantation are first-line treatments.

Therapeutic use

- The purpose of conditioning is to ensure sufficient immunosuppression of a recipient to allow the transplant and prevent rejection of the transplant. It must also, to a varying degree, destroy the tumour cells. It is therefore both immunosuppressant and myelotoxic.
- The choice of conditioning regimen depends on a number of criteria, in particular the patient's general condition, age, comorbidities and the type of haematological disease. It is thus commonly accepted that the age limit for undergoing a myeloablative conditioning transplant is 50-55 years, whereas this limit extends to 65 years for reduced conditioning transplants.
- Myeloablative conditioning involves various chemotherapy regimens that may include alkylating agents or antimetabolites (cyclophosphamide, busulfan IV, melphalan, thiotepa, cytarabine) and may be combined with total body irradiation (in malignant haematological diseases in particular). In children, the cyclophosphamide-busulfan combination is favoured because it allows a reduction in endocrine sequelae associated with total body irradiation (TBI).
- Reduced intensity conditioning is based on the use of powerful immunosuppressants and in particular fludarabine with a variable combination with other immunosuppressants (anti-lymphocyte serum, mycophenolate mofetil), and low doses of chemotherapy (cyclophosphamide, busulfan IV, aracytin) or low doses of TBI. The busulfan + fludarabine regimen is considered standard in clinical practice for patients not eligible for myeloablative conditioning, such as elderly subjects, or subjects with co-morbidities or with an altered general state.
- **Role of the medicinal product in the therapeutic strategy**
  Busulfan IV-based conditioning regimens prior to HSC transplantation are first-line treatments in infants, children, adolescents, adults and in reduced intensity conditioning in adults.

Clinical data

BUSILVEX + cyclophosphamide in myeloablative conditioning in adults

- The new data are based on the results of 2 retrospective observational studies comparing cyclophosphamide + busulfan conditioning (IV and oral depending on the study) to cyclophosphamide + TBI conditioning in 2 889 adults with AML requiring an HSC allograft.
- The results should be interpreted with caution given the methodological limitations of the studies. In one study (n=1 230 patients who received allografts between 2000 and 2006), the percentage of overall survival at 5 years (primary endpoint) was higher in the busulfan IV + cyclophosphamide (Bu+Cy) group compared to the cyclophosphamide + total body irradiation (Cy+TBI) group (58% versus 43%; RR=0.68; 95% CI [0.52-0.88]; p=0.0084). In another study (n=1 659 patients who received allografts between 2004 and 2010), the percentage of disease-free survival at 2 years (primary endpoint) was not statistically different between the Bu IV+Cy group and the Cy+TBI group (61% versus 64%).

BUSILVEX + cyclophosphamide or melphalan in myeloablative conditioning in infants, children and adolescents.

- The new data are based on the results of 2 studies:
    - A retrospective study, conducted in 226 children with acute myeloblastic leukaemia showed that the percentage of overall survival at 5 and 10 years was higher in the Bu IV+ Cy group compared to the Cy+TBI group (67.8% versus 52.9%, p=0.015 and 66.6% versus 52.9%, p=0.02). These results should be interpreted with caution because use of the Cy+TBI regimen in children is seldom to never used and considering the methodological limitations.
    - A non-comparative study demonstrated the benefit of cyclophosphamide + busulfan IV conditioning with a 95% transplantation rate in 19 children with infantile malignant osteopetrosis requiring an HSC allograft. At two years, the percentage of overall survival was 84.2% and disease-free survival was 73.7%. A total of 12 patients had an acute GVHD.

BUSILVEX + fludarabine in reduced intensity conditioning in adults

The efficacy data are based on well-established use.

Special prescribing conditions

- Medicinal product reserved for hospital use
- Medicine for restricted medical prescription.

Benefit of the medicinal product

- The actual clinical benefit* of BUSILVEX is substantial in its 3 indications.
- In the two regimens for use of BUSILVEX as conditioning treatment prior to HSC transplantation in adults, BUSILVEX does not provide any clinical added value ** (CAV V) by comparison with other available conditioning regimens prior to HSC transplantation, considering:
    - clinical data available, essentially retrospective, and its low level of evidence,
    - the absence of methodologically admissible comparative data versus other conditioning regimens currently used,
    - developments in the therapeutic strategy with the exclusion of the oral form of busulfan a decade ago.
- In the regimen for use of BUSILVEX as conditioning treatment prior to HSC transplantation in infants, children and adolescents, BUSILVEX provides a minor improvement in actual clinical benefit** (IACB IV) compared to TBI, considering:
    - clinical data available, essentially based on a retrospective comparative study versus total body irradiation,
    - developments in the therapeutic strategy with the exclusion of the oral form of busulfan a decade ago,
    - and the therapeutic need in this population
- Recommends continued inclusion on the list of reimbursable products for hospital use.

HAS
HAUTE AUTORITÉ DE SANTÉ
This document was created on the basis of the Transparency Committee Opinion of 29 June 2016 (CT15040 and CT-14429) and is available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a 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 ACB, 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".