BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

DINUTUXIMAB BETA EUSA (dinutuximab beta), monoclonal antibody

Substantial clinical benefit and minor clinical added value in the management of the maintenance phase of high-risk neuroblastoma but no clinical added value demonstrated in the management of relapsed or refractory neuroblastoma

Main points

- DINUTUXIMAB BETA EUSA has Marketing Authorisation in the treatment of patients > 12 months of age with high-risk neuroblastoma, who have previously received an induction chemotherapy and had at least a partial response, followed by a myeloablative therapy and a haematopoietic stem cell transplant, as well as in patients with relapsed or refractory neuroblastoma, with or without residual disease.
- The only comparative study available in the maintenance phase of high-risk neuroblastoma did not demonstrate a benefit from adding an interleukin-2 (IL-2) to the combination of dinutuximab beta and isotretinoin.
- The efficacy data in the treatment of relapsed or refractory neuroblastoma, with or without residual disease, are of a low level of evidence.
- The main characteristics of the safety profile are pain, reduced by the use of a continuous perfusion, and capillary leak syndrome.
- There is insufficient evidence on possible long-term consequences, especially neurological consequences, of treatment with dinutuximab beta for the target population of young children.

Therapeutic use

- The treatment of high-risk neuroblastoma includes three phases:
  - multi-agent induction chemotherapy,
  - consolidation with intensive chemotherapy (busulfan + melphalan) followed by injection of autologous stem cells in patients who have at least a very good partial response in metastases, local treatment combining tumour surgery and primary site radiation,
  - maintenance.
- Treatment of relapsed/refractory neuroblastoma includes, depending on the clinical presentation and progress under treatment, strategies that combine salvage chemotherapies, radiotherapy, sometimes a treatment with metaiodobenzylguanidine “MIBG” (ADREVIEW) for children with an MIBG-avid (or MIBG-positive) disease and autologous haematopoietic stem cell transplantation.
- **Role of the medicinal product in the therapeutic strategy**
  After induction chemotherapy with at least a partial response, followed by a consolidation treatment with high-dose chemotherapy and an autologous graft of stem cells, dinutuximab beta in combination with isotretinoin has a role in the maintenance phase of high-risk neuroblastoma.
  In relapsed or refractory neuroblastoma, after at least two prior treatments including a haematopoietic stem cell transplant, with or without residual disease, dinutuximab beta is a therapeutic option worth considering.
Clinical data

- In high-risk neuroblastoma, the benefit of using dinutuximab in maintenance phase was demonstrated in a study published in 2010. Since then, it is recommended to combine isotretinoin with an anti-GD2 antibody. In addition, the clinical study, whose initial objective was to compare dinutuximab beta combined with isotretinoin to isotretinoin alone (which had been the recommended maintenance therapy since 1999), only included 34 patients and could not be completed.
- In maintenance therapy for high-risk neuroblastoma, the efficacy and safety of dinutuximab beta were evaluated in a study whose objective was to evaluate the benefit of adding IL-2 to dinutuximab beta (in daily infusions) in combination with isotretinoin. A total of 370 children received dinutuximab beta and isotretinoin or without IL-2. The results show that the addition of IL-2 to dinutuximab beta (in daily infusions) and isotretinoin does not provide a gain in event-free survival.
- In relapsed or refractory neuroblastoma, a retrospective analysis of 54 patients treated with dinutuximab beta in continuous infusion, in combination with IL-2 and isotretinoin, showed that the tumour response rate was 31% (8.1% complete response, 24.3% partial response) for the 37 patients who had an evaluable disease (secondary endpoint). One dose-finding study, which is still ongoing, has shown, about 6 to 8 months after start of treatment (in combination with IL-2) or earlier in case of progressive disease, a tumour response in 14/33 patients (42%) with detectable disease at the beginning of the study.
- In all studies including 514 patients treated, the most common severe (grades 3 and 4) adverse events (AEs) were pain, blood and liver disorders, fever, infections, allergic reactions and capillary leak syndrome. The most common grade 4 AEs were a decreased platelet count, decreased neutrophil count, neutropenia, thrombocytopenia, pain in the extremities and septicemia. Seven patients died due to a reason other than progression of the disease. Four deaths were considered possibly related to the treatment. The most common serious adverse events were infections, pyrexia, hypotension and thrombocytopenia.
- Continuous administration of dinutuximab beta seems to be less painful than discontinuous infusions. There are no results on the impact of dinutuximab beta on quality of life or on the organisation of care.

Special prescribing conditions

- Medicinal product reserved for hospital use
- Prescription medicinal product reserved for cancer treatment and clinical oncology specialists
- Medicinal product requiring special monitoring during treatment.

Benefit of the medicinal product

- The actual benefit* of DINUTUXIMAB BETA EUSA is substantial.
- DINUTUXIMAB BETA EUSA provides minor clinical added value (CAV IV) in the management of the maintenance phase of high-risk neuroblastoma and no clinical added value (CAV V) in the management of relapsed or refractory neuroblastoma.
- Recommends inclusion on the list of reimbursable products for hospital use.

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* 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”.