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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

VELCADE (bortezomib), proteasome inhibitor

Moderate improvement of actual clinical benefit in patients with previously untreated multiple myeloma, eligible or not for a haematopoietic stem cell transplant

Main points

- In the treatment of previously untreated multiple myeloma, VELCADE is a standard treatment, in patients:
  - eligible for intensive chemotherapy, accompanied by a haematopoietic stem cell transplant in induction treatment, in combination with dexamethasone and thalidomide (VTD regimen).
  - not eligible for intensive chemotherapy, accompanied by a haematopoietic stem cell transplant, in combination with melphalan and prednisone (MPV regimen).
- Given the lack of comparative data between VELCADE in combination with the products mentioned above and other current standard treatments, in particular MPT (Melphalan/Prednisone/Thalidomide) and more recently the combination of REVLIMID (lenalidomide) with dexamethasone until progression in patients not eligible for transplant and not previously treated, the place of thalidomide and lenalidomide compared to VELCADE is not established.

Therapeutic use

- The first-line treatment depends on the patient's eligibility or non-eligibility for intensive chemotherapy combined with an autologous haematopoietic stem cell transplant. This therapeutic approach has significantly increased the survival of patients aged under 65 years. After an autologous transplant, recourse to consolidation chemotherapy and then any maintenance treatment remains controversial and is under investigation.

- **Role of the medicinal product in the therapeutic strategy**
- In patients not previously treated, eligible for intensive chemotherapy accompanied by a haematopoietic stem cell transplant, several induction protocols including VELCADE are recommended. VELCADE, in combination with dexamethasone and thalidomide, is a standard treatment.
- In patients aged 65 years or older or who are ineligible for an autologous haematopoietic stem cell transplant and who have not been previously treated, treatment is based on Melphalan and Prednisone (MP) based treatment regimens, in combination with one of the following medicines:
  - thalidomide: Melphalan/Prednisone/Thalidomide (MPT) combination
  - bortezomib: Melphalan/Prednisone/VELCADE (MPV) combination.

  REVLIMID (lenalidomide), administered in combination with dexamethasone until disease progression, is a new treatment option in the management of patients with multiple myeloma not previously treated and not eligible for transplant.
  Given the lack of comparative data, the place of thalidomide and lenalidomide with regard to VELCADE is unknown.
  Bendamustine (LEVACT) in combination with prednisone is another regimen that has Marketing Authorisation in patients with clinical neuropathy at the time of diagnosis, ruling out the use of thalidomide according to the MPT regimen or bortezomib according to the VMP regimen.

Clinical data

- In patients not eligible for transplant and not previously treated, a 5.7-month extension of time-to-progression was demonstrated with the addition of VELCADE to the Melphalan/Prednisone (VMP) combination compared to Melphalan/Prednisone (MP) during an interim analysis of a study (20.7 months versus 15.0 months; HR = 0.540, p=0,000002).
  An update of overall survival data, which was a secondary endpoint, showed an extension of the median overall survival of around one year with the VMP combination compared to MP alone: 56.4 months versus 43.1 months, HR = 0.69, 95% CI [0.57–0.85]; p < 0.001, after a median follow-up of 5 years.
- In patients eligible for transplant and not previously treated, an increase in the percentage of complete response post-induction and post-transplant was demonstrated with the addition of VELCADE versus the induction treatment protocols: VAD (vincristine, doxorubicin and dexamethasone) or TD (thalidomide and dexamethasone) in three studies. There is no data demonstrating an impact of VELCADE on overall survival.
- These pivotal studies have been compared to the chemotherapy protocols that are no longer the standard of treatment, since the evolution of first-line management of myeloma.
  There is no data comparing VELCADE in combination with other products and other standard treatments, in particular MPT (Melphalan/Prednisone/Thalidomide) and more recently the combination of Lenalidomide/Dexamethasone, to progression in patients not eligible for transplant and not previously treated.
- The safety of VELCADE is primarily marked by its haematological toxicity, peripheral neuropathies (especially sensory), low blood pressure and gastrointestinal toxicity.

Benefit of the medicinal product

- The actual clinical benefit* of VELCADE remains substantial.
- In the context of treatment of multiple myeloma not previously treated, VELCADE offers a moderate improvement in actual clinical benefit (IACB III) in patients:
  - eligible for intensive chemotherapy, accompanied by a haematopoietic stem cell transplant in induction treatment, in combination with dexamethasone, or dexamethasone and thalidomide (VTD regimen).
  - not eligible for intensive chemotherapy, accompanied by a haematopoietic stem cell transplant, in combination with melphalan and prednisone (MPV regimen);
- Recommends continued inclusion on the list of reimbursable products for hospital use.

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* 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. HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The improvement of actual clinical benefit (IACB) describes the improvement in treatment provided by a medicinal product compared with existing treatments. HAS Transparency Committee assesses the degree of IACB on a scale from I (major) to IV (minor). A level V IACB (equivalent of “no IACB”) means "no clinical added value".