HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
Update
February 2018

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KYPROLIS (carfilzomib), antineoplastic

High clinical benefit in combination with lenalidomide and with dexamethasone for multiple myeloma in patients having previously received at least one treatment line and moderate clinical added value compared to the lenalidomide and dexamethasone combination

Main points

- KYPROLIS has been granted a marketing authorisation in combination with lenalidomide and with dexamethasone alone for the treatment of multiple myeloma in adults who have received at least one prior treatment. Its tritherapy dosage is different to that for bitherapy.
- The superiority of the tritherapy combining KYPROLIS with lenalidomide and with dexamethasone over the lenalidomide plus dexamethasone combination has been demonstrated in terms of progression-free survival (absolute gain of 8.7 months) and overall survival (absolute gain of 7.9 months).
- Cardiac disorders (onset and/or worsening of heart failure, myocardial ischaemia, and myocardial infarction), haematological disorders (particularly thrombocytopoenia), hydroelectrolytic disorders (hypokalaemia) and thromboembolic events have been reported more frequently during treatment with carfilzomib/lenalidomide/dexamethasone than in the case of lenalidomide/dexamethasone. The incidence of heart failure is also more frequent with the carfilzomib/lenalidomide/dexamethasone combination than with lenalidomide/dexamethasone: 6.4% versus 4.1%.
- Cardiac monitoring is advised for patients treated with KYPROLIS, regardless of the dosage schedule.

Pre-existing indication*

KYPROLIS has also been granted a marketing authorisation in combination with dexamethasone alone for the same indication.

Therapeutic strategy

- The first-line treatment is dependent on whether the subject is eligible for intensive chemotherapy combined with autologous peripheral stem cell (PSC) transplantation. After autologous transplantation, the use of consolidation chemotherapy, followed by a potential maintenance treatment, remains the subject of debate.
- There is no standard treatment for the first recurrence of multiple myeloma. The therapeutic decision is dependent on age, prior treatments, general health and comorbidities. For young patients, after remedial therapy, autologous, or less commonly allogeneic, haematopoietic stem cell transplantation is proposed. In other cases, a number of combinations are used: VELCADE (off-label) as part of combinations, particularly with immunomodulators (lenalidomide or thalidomide) and with cyclophosphamide. Lenalidomide (REVLIMID) is used in combination with dexamethasone only. It is routine practice to administer an immunomodulator to a patient having received bortezomib as first-line treatment.
- Recently, further medicinal products were added to the therapeutic arsenal for second-line treatment such as ixazomib (NINLARO), daratumumab (DARZALEX) or carfilzomib (KYPROLIS), with all three to be combined with lenalidomide and/or with dexamethasone.
  Failing a comparison between these new substances available for adult patients suffering from multiple myeloma having relapsed following at least one prior treatment, the therapeutic choice should be guided in particular by the

* This summary does not concern this indication.

patients' clinical profile, the safety profile, the nature of the prior treatments received and the time to onset of recurrence.

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

  KYPROLIS, in combination with lenalidomide and with dexamethasone, is a treatment for relapsed multiple myeloma.

Clinical data

- A randomised open-label study assessed the efficacy and safety of carfilzomib in combination with lenalidomide and with dexamethasone (KRd group) versus the lenalidomide/dexamethasone combination (Rd group) in 781 patients suffering from relapsed multiple myeloma having received between 1 and 3 prior treatment lines.
- The final analysis of progression-free survival (primary endpoint) after a median follow-up period of 31.4 months in the KRd group and 30.1 months in the Rd group showed a median progression-free survival of 26.3 months in the KRd group and 17.6 months in the Rd group, i.e. an absolute gain of 8.7 months (HR=0.69; 95% CI [0.57; 0.83]; p<0.0001).
- The final analysis of overall survival showed, after a median follow-up period of 67.1 months in each group, a median overall survival of 48.3 months in the KRd group and 40.4 months in the Rd group, i.e. an absolute gain of 7.9 months (HR=0.794; 95% CI [0.667; 0.945]; p= 0.0045).
- The percentages of patients with treatment-related adverse events (AEs) were similar between the groups (85%). However, a higher toxicity was reported in the KRd group in terms of cardiac disorders (onset and/or worsening of heart failure, myocardial ischaemia, and myocardial infarction), haematological disorders (particularly thrombocytopoenia), hydroelectrolytic disorders (hypokalaemia) and thromboembolic events. Cases of heart failure were more frequent in the KRd group than in the Rd group: 6.4% (3.1% ≥ grade 3) versus 4.1% (0.8% ≥ grade 3).

Special prescription requirements

- Medicinal product for hospital use only.
- Prescription reserved for haematology specialists and departments or physicians with expertise in blood disorders.

Benefit of the medicinal product

- The actual clinical benefit* of KYPROLIS, in tritherapy, is high.
- KYPROLIS provides a clinical added value** (CAV III, moderate) compared to the lenalidomide and dexamethasone combination in the therapeutic strategy.
- Approval for hospital treatment.

HAS
HAUTE AUTORITÉ DE SANTÉ
This document was drafted on the basis of the Transparency Committee opinion dated 21 February 2018 (CT-16445) 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".