HAUTE AUTORITÉ DE SANTÉ

**ONCOLOGY**
**New indication**
**January 2018**

**SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION**

# **KYPROLIS** (carfilzomib), antineoplastic

**High clinical benefit in combination with dexamethasone alone for multiple myeloma in patients having previously received at least one treatment line and minor clinical added value compared to the bortezomib and dexamethasone combination in the therapeutic strategy.**

## Main points

- KYPROLIS has been granted a marketing authorisation in combination with dexamethasone alone for the treatment of multiple myeloma in adults who have received at least one prior treatment. Its bitherapy dosage is different to that for tritherapy.
- The superiority of the bitherapy combining KYPROLIS with dexamethasone over the bortezomib + dexamethasone combination has been demonstrated in terms of progression-free survival (absolute gain of 9.3 months). A 21% reduction in the risk of death compared to the bortezomib plus dexamethasone combination has been observed.
- The KYPROLIS + dexamethasone combination increases the risk of heart failure compared to the bortezomib + dexamethasone combination: 8.6% versus 3.3% and in particular a decrease in the ventricular ejection fraction of 2.4% versus 0.9%.
- Screening for potential heart disorders is required in order to set up treatment, particularly by means of echocardiography, and all patients should be monitored during treatment to detect signs of fluid overload, particularly patients presenting with a risk of heart failure.

## Pre-existing indication*

- KYPROLIS was initially granted a marketing authorisation in combination with lenalidomide and dexamethasone 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 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 a 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.

* This summary does not concern this indication.

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 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 dexamethasone alone, is a treatment for relapsed multiple myeloma.

## Clinical data

- A randomised open-label study assessed the efficacy and safety of carfilzomib in combination with dexamethasone alone (Kd group) versus the bortezomib/dexamethasone combination (Vd group) in 929 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 11.9 months in the Kd group and 11.1 months in the Vd group showed a median progression-free survival of 18.7 months in the Kd group and 9.4 months in the Vd group, i.e. an absolute gain of 9.3 months (HR=0.533; 95% CI [0.437; 0.651]; p<0.0001).
  The final analysis of overall survival showed, following a median follow-up period of 37.5 months in the Kd group and 36.9 months in the Vd group, a 21% reduction in the risk of death (HR=0.791; 95% CI [0.648; 0.964]; p=0.0100).
- The percentage of treatment-related adverse events (AEs) was similar in both groups (90%) with the most frequent AEs in the Kd group being: anaemia (43%), diarrhoea (36%), fatigue (32%), dyspnoea (32%), pyrexia (32%) and hypertension (32%). Serious AEs were more frequent in the Kd group (59%) than in the Vd group (40%) such as: pneumonia (8%), pyrexia (4%), dyspnoea (4%), and acute kidney failure (2%).
  Cases of heart failure were more frequent in the Kd group: 8.6% (5.2% ≥ grade 3) versus 3.3% (2.0% ≥ grade 3) with decreases in the ventricular ejection fraction of 2.4% versus 0.9%.

## 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 bitherapy, is high.
- KYPROLIS provides a clinical added value** (CAV IV, minor) compared to the bortezomib and dexamethasone combination in the therapeutic strategy.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 24 January 2018 (CT-16176) 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".