HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
July 2017

TRANSPARENCY COMMITTEE OPINION SUMMARY

NINLARO (ixazomib), antineoplastic agent

Substantial clinical benefit in combination with lenalidomide and dexamethasone in the treatment of multiple myeloma for patients who have received at least one prior therapy and no clinical benefit demonstrated compared to the lenalidomide and dexamethasone combination

Main points

- NINLARO has been granted marketing authorization (MA) in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- The results of a study with low robustness on primary endpoint (progression-free survival) do not show any clinical benefit from NINLARO combined with lenalidomide and dexamethasone compared to the lenalidomide and dexamethasone combination.

Therapeutic strategy

- First-line treatment is dependent on whether the subject is eligible for intensive chemotherapy combined with stem cell transplant(SCT). After autologous transplant, 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, previous treatments, general health and comorbidities (presence or absence of neuropathy or renal failure). Generally speaking, if the initial response duration is high, first-line treatment can be reused. For young patients, after salvage therapy, autologous, or allogeneic haematopoietic stem cell transplantation is proposed. In other cases, several combinations are used: VELCADE (off-label) in combinations, particularly with immunomodulators (lenalidomide or thalidomide) and with cyclophosphamide. Lenalidomide (REVLIMID) is used in combination with dexamethasone only. It is common to administer an immunomodulator to patients who received bortezomib as first-line treatment. Carfilzomib in combination with lenalidomide and dexamethasone is also to be preferred compared to the lenalidomide/dexamethasone combination, in adults having received at least one prior line. This treatment requires monitoring of heart function, in particular in patients with a history of heart condition.
- From the second relapse, the choice depends on the same parameters, particularly the efficacy and safety of previous treatments. Combinations including immunomodulators (lenalinomide or thalidomide), corticosteroids, anthracyclines or alkylating agents can still be used in patients who received 2 or 3 lines of treatment.
- Beyond this, for heavily pre-treated and resistant patients at very advanced stages, therapeutic options are limited and the patients are most frequently at a therapeutic dead end. Pomalidomide is an alternative, in patients having already been treated with bortezomib and lenalidomide. Panobinostat, combined with bortezomib and dexamethosone, represents a last resort treatment option for patients with recurrent and/or resistant myeloma, having previously received two lines of treatment, including bortezomib and an immunomodulator.
- Two drugs have MA in the treatment of multiple myeloma in adults who have received at least one prior therapy:
    - DARZALEX (daratumumab) in tritherapy, in combination with lenalidomide and dexamethasone, or with bortezomib and dexamethasone;
    - KYPROLIS (carfilzomib) in combination with dexamethasone.

  DARZALEX also has MA in adults with relapse and refractory multiple myeloma, for whom previous treatments included a proteasome inhibitor and an immunomodulating agent, and whose disease progressed during the last treatment, which was the third treatment line.

- **Role of the medicinal product in the therapeutic strategy**
  NINLARO, combined with lenalidomide and dexamethasone, is a second-line treatment in adults with relapsing multiple myeloma.

Clinical data

- A randomised, double-blind study assessed the efficacy and safety of the ixazomib/lenalidomide/dexamethasone combination (ixazomib/LenDex) versus placebo/lenalidomide/dexamethasone (placebo/LenDex) in 722 patients with multiple myeloma, who have received between 1 and 3 treatment lines and treated until disease progression. During final analysis of progression-free survival (primary endpoint) by the independent data monitoring board (median follow-up 14.8 months in the ixazomib/LenDex group and 14.6 months in the placebo/LenDex group), median survival-free progression was 20.6 months in the ixazomib/LenDex group and 14.7 months in the placebo/LenDex group, therefore an absolute difference of 5.9 months in favour of the ixazomib/LenDex group (HR = 0.742; $CI_{95\ \%}$ [0.587; 0.939]; p=0.012).
  However, the results on this endpoint as assessed by the investigators did not show statistical difference between the two groups: HR = 0.827 [0.653; 1.047]. Also, in an additional analysis of progression-free survival over a longer follow-up period (around 9 additional months), not scheduled in the protocol, a reduced difference in progression-free survival between arms was observed.
- The safety data after median follow-up of around one year showed a similar percentage of treatment-related adverse events between the groups (93%). More severe toxicity was reported in the ixazomib/LenDex group for gastrointestinal disorders (diarrhoea, nausea, vomiting), blood disorders (especially thrombocytopenia), neurological disorders (peripheral neuropathy) and cutaneous disorders (rash).
- The quality-of-life scores (EORTC QLQ-30 and MY-20) were generally similar between the 2 groups.

Special prescription requirements

- Medicine for hospital prescription.
- Prescription restricted to oncology or haematology specialists or physicians with expertise in oncology or blood disorders.

Benefit of the medicinal product

- The actual clinical benefit* of NINLARO is substantial.
- NINLARO, in combination with lenalidomide and dexamethasone, does not provide an improvement of actual clinical benefit** (IACB V) compared to lenalidomide and dexamethasone combination, for patients with multiple myeloma who have received at least one prior therapy.
- Recommends inclusion on the list of reimbursable products for supply by pharmacist and for hospital use.

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This document was drafted on the basis of the Transparency Committee opinion dated 05 July 2017, 22 November 2017 and 21 February 2018 (CT-15988, CT-16587 and CT-16714) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product 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 substantial, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"