HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
March 2017

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

REVLIMID (lenalidomide), immunosuppressant

No clinical benefit demonstrated in patients with relapsed or refractory mantle cell lymphoma compared to monochemotherapy.

Main points

- REVLIMID now has Marketing Authorisation in the treatment of relapsed or refractory mantle cell lymphoma (MCL).
- As a monotherapy, it improved progression-free survival modestly relative to monochemotherapy (cytarabine, gemcitabine, fludarabine, rituximab and chlorambucil) which are no longer involved in current management of relapsed or refractory MCL. No improvement in overall survival was demonstrated compared to these types of monochemotherapy.
- In patients with relapsed or refractory MCL and presenting high tumour burden, the use of REVLIMID is to be considered only in the absence of available therapeutic alternative and with close monitoring, following the observation of a high proportion of early deaths occurring in the 20 weeks after initiation of lenalidomide treatment in these patients.

Pre-existing indications*

- REVLIMID already has Marketing Authorisation for the treatment of multiple myeloma and transfusion-dependent anaemia in patients due to myelodysplastic syndrome.

Therapeutic use

- In patients with relapsed or refractory MCL, there is no standard treatment.
  Intensive chemotherapy, with haematopoietic stem cell transplant, is offered to eligible patients. When it is not possible, alternatives are polychemotherapy, more or less combined with rituximab, as well as bortezomib (off-label), ibrutinib, lenalidomide and temsirolimus.
- **Role of the proprietary medicinal product in the therapeutic strategy**
  REVLIMID, as a monotherapy, is a treatment option in the management of patients with relapsed or refractory MCL and who are not eligible for transplant (conforming to the pivot study exclusion criteria). In patients with a high tumour burden, its use is recommended only in the absence of available alternative therapy and with close monitoring. A high tumour burden was defined as the presence of at least one lesion ≥ 5 cm in diameter or at least 3 lesions ≥ 3 cm. In the absence of comparative data, its role in relation to ibrutinib is unknown.

Clinical data

- The treatment data in relapsed or refractory MCL result from a phase II, randomised, open-label study that compared lenalidomide administered orally until progression or unacceptable toxicity to monochemotherapy left to the discretion of the investigator. The 6 predefined types of monochemotherapy were: cytarabine IV, gemcitabine IV, fludarabine (oral or IV), rituximab IV and chlorambucil (oral).

* This summary does not cover these indications

After a median follow up of 15.9 months, the median progression-free survival (primary endpoint) was longer in the lenalidomide arm (37.6 weeks) than the monochemotherapy arm based on investigator assessment (22.7 weeks), with an absolute difference of +15 weeks (+3.5 months) (HR = 0.63; 95% CI [0.4; 0.9] p=0.012).
No statistically significant difference was observed on overall survival : 27.9 months (2.3 years) in the lenalidomide arm versus 21.2 months (1.8 years) in the control arm. These medians were observed while 46.4% of patients of the control arm in progression changed treatment arm, such as provided in the protocol (crossover).
A high proportion of early deaths occurring within 20 weeks after initiation of treatment with lenalidomide was observed in the subgroup of patients with a high tumour burden compared to the control arm (20% versus 7%).

- The most common grades 3-4 adverse events (AEs) considered to be treatment-related were: neutropenia (43.7% versus 33.7%), thrombocytopenia (18% versus 27.7%), pulmonary embolism (4.2% versus 0%) and episodes of diarrhea (3.6% versus 0%). One new type of AE associated with REVLIMID was demonstrated, these were tumour growth reactions observed in 16 patients (9.6%) in the lenalidomide arm versus none in the control arm. Furthermore, lenalidomide is structurally similar to thalidomide; the inherent precautions for use of thalidomide should be applied to lenalidomide: pregnancy prevention, etc.
- The types of chemotherapy administered as a monotherapy in the control arm (cytarabine, gemcitabine, fludarabine, rituximab and chlorambucil) were considered to be a non-optimal treatment that no longer reflects current management, and which do not ensure transposability of the study results to French practice.

Special prescribing conditions

- Medicine for hospital prescription, restricted to oncology or haematology specialists or doctors with cancer or blood disease training.
- Medicinal product requiring special monitoring during treatment.

Benefit of the medicinal product

- The actual clinical benefit* of REVLIMID, as a monotherapy, is substantial.
- REVLIMID, as a monotherapy, does not provide clinical added value** (CAV V) compared to monochemotherapy (cytarabine, gemcitabine, fludarabine, rituximab and chlorambucil)
- Recommends inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 08 March 2017 (CT-15734) and is available at **www.has-sante.fr**

* 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. The HAS Transparency Committee assesses the ACB, 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”.