BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

IMBRUVICA (ibrutinib), Bruton’s tyrosine kinase (BTK) inhibitor

Moderate clinical added value compared to TORISEL in terms of progression-free survival and safety profile in the treatment of relapsed or refractory mantle cell lymphoma.

Main points

- IMBRUVICA has Marketing Authorisation in the treatment of adult patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL).
- In one study, IMBRUVICA shows benefit in terms of progression-free survival compared to temsirolimus, without any difference in terms of overall survival between the IMBRUVICA and temsirolimus arms, in this disease where the medical need is partially covered.
- IMBRUVICA has shown a less unfavourable safety profile compared to temsirolimus in terms of grade ≥3 adverse events (67.6% versus 87.1%, respectively).

Pre-existing indications

IMBRUVICA is also indicated in the treatment of chronic lymphocytic leukaemia and Waldenström macroglobulinaemia.

Therapeutic use

- In relapsing patients, there is no standard treatment for the disease. Intensive chemotherapy, with haematopoietic stem cell transplant, is used in eligible patients. In patients who are not eligible, 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**
  IMBRUVICA, as a single agent, is a treatment option preferred to temsirolimus in the management of patients with relapsed or refractory mantle cell lymphoma, within constraints related to its safety profile, especially for patients on antiplatelet or anticoagulant treatment.
  The available data do not answer the question of the success rate of a possible haematopoietic stem cell transplant after treatment with IMBRUVICA.
  The occurrence of bleeding events and the fact that vitamin K antagonists should not be administered concomitantly with IMBRUVICA are impediments to its use, especially in the elderly. The concomitant use of IMBRUVICA with strong or moderate inhibitors or inducers of CYP3A4 should be avoided.

Clinical data

- One study compared the efficacy and safety of ibrutinib compared to temsirolimus (clinically relevant comparator seldom used in France) in patients with R/R MCL who received a median number of prior treatments of 2.0 [1.0; 9.0]. The study randomised 280 patients (1:1 ratio) between the 2 arms. At the date of the main analysis, the median progression-free survival (the primary efficacy endpoint) was 14.6 months in the ibrutinib arm versus 6.2 months in the temsirolimus arm, an absolute difference of 8.4 months in favour of the ibrutinib arm (HR = 0.43, 95% CI [0.32; 0.58]; p < 0.0001). Analysis of the secondary efficacy endpoints showed an improvement in the overall response rate (71.9% in the ibrutinib arm versus 40.4% in the temsirolimus arm, p <0.0001), and an

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*This summary does not cover these indications.*

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absence of a statistically significant difference in overall survival with median overall survival not reached in the ibrutinib arm versus 21.3 months in the temsirolimus arm with a median follow-up of 20 months.

The rate of patients who reported an adverse effect (AE) was of the same magnitude in both arms. The most common AEs (≥20% of patients) in the ibrutinib arm were diarrhoea, cough and fatigue and in the temsirolimus arm: thrombocytopenia, anaemia, diarrhoea, fatigue, neutropenia, epistaxis, cough, peripheral oedema, nausea, fever and stomatitis. The percentage of patients who reported grade ≥3 AEs was lower in the ibrutinib arm (67.6%) compared to the temsirolimus arm (87.1%). The main grade ≥3 AEs (more than 10% of patients of one of the treatment arms) were haematological.

Special prescribing conditions

- Hospital prescription restricted to haematologists or doctors trained in blood diseases
- Medicine requiring special monitoring during treatment

Benefit of the medicinal product

- The actual benefit* of IMBRUVICA is substantial.
- IMBRUVICA provides moderate clinical added value** (CAV III) compared to temsirolimus.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and 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. The HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement of the medicinal product 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 (equivalent to “no CAV”) means “no clinical added value”.

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