BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

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

Moderate improvement in chronic lymphocytic leukaemia in second-line and subsequent therapy, and in the first line in case of 17p deletion or TP53 mutation.

Minor improvement in patients with relapsed or refractory mantle cell lymphoma

Main points

- IMBRUVICA has Marketing Authorisation in two indications:
  - treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy;
  - treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).
- In the second-line and subsequent treatment of CLL, IMBRUVICA showed an improvement in progression-free survival and overall survival by comparison with ARZERRA (ofatumumab). In 1st-line treatment of patients with a 17p deletion (del17p) or TP53 mutation, efficacy data are limited.
- In relapsed or refractory MCL, the therapeutic contribution was observed in a non-comparative study based on the overall response rate, after two or more failures. IMBRUVICA as monotherapy is a next-line treatment in patients with relapsed or refractory MCL.

Therapeutic use

In CLL

- The decision on whether to treat a CLL patient depends on the patient’s general condition (age and comorbidities) and on the stage of the disease and the presence or lack of factors pointing to a poor prognosis (time for doubling of peripheral lymphocytes less than 12 months, TP53 mutation or del17p, etc.). The most common forms of the disease, i.e. Binet stage A or Rai stages 0, I and II, are asymptomatic and do not justify any specific treatment. The existence of a del17p mutation confers poor sensitivity to chemotherapies, particularly purine analogues. The first-line treatment is therefore alemtuzumab (MABCAMPATH), available under a temporary usage authorisation. The conventional therapies for CLL in second-line treatment are ofatumumab (ARZERRA) and chemo-immunotherapies (bendamustine-rituximab, fludarabine-cyclophosphamide-rituximab). Autologous stem cell transplantation is a treatment option, especially for young patients. ZYDELIG (idelalisib), in combination with rituximab, has an indication identical to that of IMBRUVICA in CLL.

- Role of the medicinal product in the therapeutic strategy
  IMBRUVICA as monotherapy is a first-line treatment of CLL in cases of 17p deletion or TP53 mutation, as is idelalisib in combination with rituximab.
  In other forms of CLL, IMBRUVICA as monotherapy is a second-line and subsequent treatment, as is idelalisib in combination with rituximab.

In MCL

- The management of MCL depends on how aggressive it is. At present there is no real consensus on patients in relapse. TORISEL is a treatment alternative after the failure of at least two prior treatments.

- Role of the medicinal product in the therapeutic strategy
  IMBRUVICA as monotherapy is a next-line treatment in patients with relapsed or refractory mantle cell lymphoma.
Clinical data

In CLL
A randomised open study compared ibrutinib with ofatumumab in 391 patients with relapsed or refractory CLL. Median progression-free survival (primary efficacy endpoint) was 8.1 months in the group treated with ofatumumab and was not reached in the group treated with ibrutinib after a median follow up of 9.4 months. In the subgroup of patients with del17p where the number was low (n=127), median progression-free survival was 5.8 months in the ofatumumab group and was not reached in the ibrutinib group (HR=0.247 (95% CI [0.136; 0.450])). Median overall survival was not reached in either of the two groups due to the small number of events. The analysis of overall survival showed a 57% reduced risk of death for patients in the ibrutinib group compared with those in the ofatumumab group (HR=0.434, (95% CI [0.24; 0.79], p=0.0049).

The efficacy data for ibrutinib in 1st-line treatment of CLL with 17p deletion or TP53 mutation are very limited (n=2) and from a non-comparative phase II study.

Discontinuations of treatment were rare (<10%).

The adverse events of grade ≥3 most commonly reported in all clinical studies were haematological in nature (neutropenia between 13 and 16%, thrombocytopenia between 5 and 10%, anaemia between 5 and 10% and haemorrhages), gastrointestinal (diarrhoea between 2 and 5%) and cardiac (arterial hypertension between 2 and 8% and atrial fibrillation between 3 and 5%).

In MCL
A non-comparative study evaluated ibrutinib in 115 patients with relapsed or refractory MCL. The overall response rate (primary efficacy endpoint) was 67.6%, of which 20.7% with complete response and 46.8% with a partial response after a median follow-up of 15.3 months. The median duration of the response (complete or partial) was 17.5 months. After median follow-up of 26.7 months, the benefit was also observed in terms of the overall response rate (66.7% of which 22.5% with complete response). Median progression-free survival was 13 months and median overall survival was 22.5 months.

Although it is a relevant comparator, there are no comparative data versus TORISEL (temsirolimus).

Benefit of the medicinal product

- The actual benefit of IMBRUVICA is substantial.
- IMBRUVICA in monotherapy, like ZYDELIG in combination with rituximab, provides moderate clinical added value** (CAV III) in the therapeutic strategy for adult patients with CLL who have received at least one prior treatment, or in the first line in patients with a 17p deletion or a TP53 mutation and who are unsuitable for chemo-immunotherapy.
- IMBRUVICA as monotherapy provides minor clinical added value** (CAV IV) in patients with relapsed or refractory mantle cell lymphoma.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

---

1. The actual benefit (AB) of a proprietary 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 AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

2. 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".

© Haute Autorité de Santé 2015