HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

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

No proven clinical advantage in the management of patients with chronic lymphocytic leukaemia who have not received prior therapy and are not eligible for fludarabine-based therapy

Main points

- IMBRUVICA has marketing authorisation in the treatment of chronic lymphocytic leukaemia (CLL) as a single agent in patients who have not received prior therapy.
- In a study including patients who were not eligible for full-dose fludarabine, progression-free survival was improved with IMBRUVICA (median duration not reached) versus a non-relevant comparator, chlorambucil used as a single agent (median duration 18.9 months).
- A network meta-analysis did not allow IMBRUVICA to be positioned in relation to its clinically relevant comparators.
- The main characteristics of IMBRUVICA safety profile of are haemorrhagic events and diarrhoea.

Pre-existing indications*

- IMBRUVICA already has marketing authorisation in the treatment of adult patients with CLL who have received at least one prior therapy, or as 1st-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy, as well as in relapsed or refractory mantle cell lymphoma and in Waldenström's macroglobulinaemia.

Therapeutic use

- In 1st-line treatment of CLL in patients with no significant comorbidity, the combination of fludarabine + cyclophosphamide + rituximab (FCR regimen) is the standard of care.
- Patients with comorbidities (severe renal impairment or frail patients whose comorbidities would affect their ability to tolerate a severe infection) are not eligible for the standard FCR regimen (with "full dose" fludarabine). For these patients, one treatment option is rituximab + chlorambucil combination (RClb regimen), or an alternative is a reduced-dose purine-based combination (fludarabine + cyclophosphamide + rituximab [FCR] or pentostatin + cyclophosphamide + rituximab). Obinutuzumab in combination with chlorambucil, ofatumumab in combination with chlorambucil or bendamustine, and bendamustine in combination with rituximab are the 1st-line treatment options for patients with CLL who are not eligible for full-dose fludarabine regimen.
- **Role of the medicinal product in the therapeutic strategy**
  IMBRUVICA as a single agent is a 1st-line treatment option for CLL in adults who are not eligible for full-dose fludarabine regimen, namely:
  - patients aged over 70 years;
  - patients aged 65 to 70 years with one of the following comorbidities:
    - estimated creatinine clearance using the Cockcroft-Gault equation of < 70 ml/min;
    - clinically apparent autoimmune cytopenia (autoimmune haemolytic anaemia or immune thrombocytopenia).

* This summary does not cover these indications.

Clinical data

- A study evaluated the efficacy of ibrutinib versus chlorambucil in 269 patients who had not had prior therapy and were ineligible for full-dose fludarabine regimen. After a median follow-up of 18.4 months (final analysis), ibrutinib was found to have better progression-free survival (PFS) as measured by an independent review committee (primary endpoint); there was a statistically significant reduction in the risk of progression or death in the ibrutinib group (11.0%) compared with the chlorambucil group (48.1%, HR 0.161; 95% CI [0.091; 0.283], p<0.0001). The median PFS was not yet reached in the ibrutinib group and was 18.9 months in the chlorambucil group. This result was confirmed after a median follow-up of 28.1 months. The median PFS was still not reached in the ibrutinib group, and was 15.2 months in the chlorambucil group. The PFS rate at 24 months was estimated to be 88.7% and 35.8%, respectively.
- The proportion of treatment discontinuations due to adverse events (AEs) was lower in the ibrutinib group (10.4%) than in the chlorambucil group (22.7%). The most common AEs in the two treatment groups (incidence ≥ 20% in one group) were diarrhoea, fatigue, cough, nausea, neutropenia, anaemia and vomiting. Haemorrhagic events (47.4% in the ibrutinib group and 15.2% in the chlorambucil group), diarrhoea (42.2% and 16.7% respectively) and cough (22.2% and 15.2% respectively) were more common in the ibrutinib group, with a majority of grade 1 and 2 events.

Special prescribing conditions

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

Benefit of the medicinal product

- The actual clinical benefit* of IMBRUVICA is substantial in patients who are not eligible for full-dose fludarabine regimen and is insufficient for patients who are eligible for full-dose fludarabine regimen.
- IMBRUVICA does not provide clinical added value** (CAV V) in the treatment of patients with CLL who have not had prior therapy and are not eligible for full-dose fludarabine-based regimen.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use only in the treatment of patients who are not eligible for full-dose fludarabine-based regimen.

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This document was created on the basis of the Transparency Committee Opinion of 08 February 2017 (CT-15633) and is available at **www.has-sante.fr**

* The actual clinical benefit (ACB) 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 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”.