HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
OPINION
20 MARCH 2020

ibrutinib
IMBRUVICA 140 mg hard capsules

Reevaluation

Key points

Maintenance of the favourable opinion for reimbursement **as a single agent**, for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), **only in patients not eligible for treatment with full-dose fludarabine**.

What therapeutic improvement?

Therapeutic improvement compared to the bendamustine / rituximab combination.

Role in the care pathway?

Strategy

Treatment initiation is defined on the basis of the presence of symptoms and progression of the disease, in accordance with the existing Binet and Rai classifications. According to the most recent guidelines (IWCLL 2018), in general practice, patients with asymptomatic early-stage disease (Rai 0, Binet A) should be monitored without therapy unless they have evidence of disease progression or disease-related symptoms.

In patients requiring treatment, the choice depends on several factors, in particular the presence of del17p deletion and/or TP53 mutation, the patient's general condition and the presence or otherwise of comorbidities.

In the first-line treatment of CLL, in previously untreated patients and in the absence of 17p deletion or TP53 mutation, the therapeutic strategy is as follows:

- in patients without significant comorbidities: the rituximab + fludarabine + cyclophosphamide combination (R-FC protocol) is the reference treatment.
- in patients aged over 65 years and/or those with comorbidities making them ineligible for the standard R-FC protocol, the options are ibrutinib (IMBRUVICA) as a single agent, obinutuzumab (GAZYVARO) in combination with chlorambucil (CHLORAMINOPHENE) or bendamustine (LEVACT) in combination with rituximab.

Role of the medicinal product in the care pathway

IMBRUVICA (ibrutinib) as a single agent remains a first-line therapy for CLL in patients aged over 65 years and/or those with comorbidities making them ineligible for treatment with full-dose fludarabine.

As a reminder, IMBRUVICA (ibrutinib) has no role in the management of patients eligible for fludarabine.

In the presence of a 17p deletion or TP53 mutations, IMBRUVICA (ibrutinib) as a single agent remains a first-line treatment.

01 COMMITTEE'S CONCLUSIONS

01.1 Clinical benefit

◗ Chronic lymphocytic leukaemia (LLC) (Binet stages B and C), characterised by the proliferation and accumulation of a malignant clone of mature B lymphocytes in the bone marrow, blood and lymphoid organs, is a life-threatening disease.
◗ IMBRUVICA (ibrutinib) is a specific curative treatment for CLL.
◗ The efficacy/adverse effects ratio remains high.
◗ The medicinal alternatives are the medicinal products cited in chapter 05. "Clinically relevant comparators"
◗ IMBRUVICA (ibrutinib) as a single agent is a first-line therapy for CLL in patients ineligible for treatment with full-dose fludarabine. As a reminder, IMBRUVICA has no role in the care pathway for patients eligible for full-dose fludarabine (Committee opinion of 8 February 2017). The role of IMBRUVICA as a single agent in the presence of a 17p deletion or TP53 mutation is unchanged (Committee opinion of 17 June 2015).

◗ **Public health impact**
Considering:
- the seriousness of CLL (Binet stages B and C), which is a life-threatening disease,
- its incidence in patients not eligible for full-dose fludarabine,
- the partially met medical need,
- the partial response to the identified need with respect to the morbidity and mortality of previously untreated patients not eligible for full-dose fludarabine,
- the absence of a demonstrated impact on patients' quality of life,
- and the potential impact on the organisation of care (follow-up consultations) due to administration via the oral route, in view of the alternatives,

IMBRUVICA is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of IMBRUVICA remains substantial as a single agent, for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia, only in patients not eligible for treatment with full-dose fludarabine.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication to "as a single agent, for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia", only in patients not eligible for treatment with full-dose fludarabine and at the MA dosages.

01.2 Clinical Added Value

Considering:

- **new available data from the ALLIANCE study**
  - **demonstrating the superiority of ibrutinib as a single agent compared to the bendamustine/rituximab combination, a clinically relevant comparator,**
  - **with a demonstrated improvement for progression-free survival (HR = 0.39; 95% CI: 0.26 – 0.58) evaluated on an open-label basis by the investigators, in patients aged more than 65 years, making them ineligible for full-dose fludarabine treatment,**
  - **without any demonstrated improvement in overall survival (secondary endpoint considered to be exploratory),**
  - **and in the absence of collection of quality of life data,**
- **initial data having demonstrated the superiority of ibrutinib compared to chlorambucil, in terms of progression-free survival and overall survival,**
- **the more favourable haematological safety profile of ibrutinib compared to the bendamustine/rituximab combination, although ibrutinib presents other types of adverse events, in particular atrial fibrillation and hypertension,**
- **and the benefit of the administration route of ibrutinib (oral route) compared to the available alternatives,**

the Committee considers that IMBRUVICA (ibrutinib) as a single agent provides a minor clinical added value (CAV IV) compared to the bendamustine/rituximab combination in patients not eligible for treatment with full-dose fludarabine.