HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
OPINION
20 MARCH 2020

ibrutinib
IMBRUVICA 140 mg hard capsules

New indication

Key points

Unfavourable opinion for reimbursement for IMBRUVICA in combination with obinutuzumab in the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Role in the care pathway?

The therapeutic indications are 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 of CLL treatment depends on several factors: the presence of del17p deletion and/or TP53 mutation (associated with an unfavourable prognosis due to a low response rate and a short duration of response to standard chemo-immunotherapy treatments), the patient's general condition and the presence or otherwise of comorbidities.

- In the absence of a del17p mutation or TP53 mutations:

o In patients without significant comorbidities: as first-line therapy for CLL, a rituximab + fludarabine + cyclophosphamide combination (R-FC protocol) is the reference treatment,

o In elderly patients and/or those with comorbidities making them ineligible for "full-dose" standard R-FC protocols, the options are as follows:

- IMBRUVICA (ibrutinib), orally, as a single agent.

- Anti-CD20 monoclonal antibody and chemotherapy combinations:
- GAZYVARO (obinutuzumab) + chlorambucil (G-Clb protocol)
- MABTHERA (rituximab) + chlorambucil or bendamustine (B+R protocol).

- In the presence of a del17p mutation or TP53 mutations, IMBRUVICA as a single agent is the reference treatment.

Role of the medicinal product in the care pathway

Given the methodological limitations of the ILLUMINATE trial, and in the absence of comparative data versus ibrutinib as a single agent, the Committee deems that IMBRUVICA in combination with obinutuzumab has no role in the care pathway.

01 COMMITTEE'S CONCLUSIONS

01.1 Clinical benefit

◗ Chronic lymphocytic leukaemia (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;
◗ This is a specific curative treatment for CLL;
◗ The efficacy/adverse effects ratio of the IMBRUVICA (ibrutinib) and obinutuzumab combination has not been adequately established (see section "08.6 summary and discussion");
◗ There are medicinal alternatives;
◗ IMBRUVICA (ibrutinib) in combination with obinutuzumab has no role in the current care pathway for the treatment of CLL (see section "09 Role in the care pathway");

◗ **Public health impact**.
Considering:
- the seriousness of CLL (Binet stages B and C), which is a life-threatening disease,
- the low prevalence of CLL with comorbidities,
- the partially met medical need,
- the absence of response to the identified medical need provided by IMBRUVICA (ibrutinib) in combination with obinutuzumab,
- the potentially negative impact in terms of safety and quality of life of patients compared to monotherapy with ibrutinib due to the addition of an injectable antiCD20, and without a demonstrated advantage in terms of efficacy,

IMBRUVICA (ibrutinib) in combination with obinutuzumab is unlikely to have an impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of IMBRUVICA (ibrutinib) in combination with obinutuzumab is insufficient to justify its funding by the French national health insurance system in the indication extension "IMBRUVICA in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)".

The Committee issues an unfavourable opinion for inclusion of IMBRUVICA (ibrutinib) in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indication extension "IMBRUVICA in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)".

01.2 Clinical Added Value

Not applicable.