HAUTE AUTORITÉ DE SANTÉ

**ASSESS** HEALTH TECHNOLOGIES

**OPINION ON MEDICINAL PRODUCTS**

venetoclax

# VENCLYXTO 10, 50 and 100 mg

**film-coated tablet**

New indication

**Adopted by the Transparency Committee on 29 June 2022**

**SUMMARY**

**The legally binding text is the original French opinion version**

- **Chronic lymphocytic leukaemia**
- **Sectors: Community and Hospital**

## Key points

Approval of reimbursement, in association with obinutuzumab, for the treatment of previously untreated patients with chronic lymphocytic leukaemia (CLL), only in the presence of a 17p deletion and/or TP53 mutation or for patients with no 17p deletion or TP53 mutation and ineligible for fludarabine-based treatment.

Disapproval of reimbursement in the other marketing authorisation contexts, namely for patients with no 17p deletion or TP53 mutation and eligible for fludarabine-based treatment.

## Therapeutic improvement?

Therapeutic improvement with respect to the chlorambucil + obinutuzumab association for treatment.

## Role in therapeutic strategy?

According to ESMO 2021 guidelines, the French group FILO's 2020 guidelines, and IWCLL 2018 guidelines, the therapeutic indications are defined according to the presence of symptoms and progressive nature of the disease (as per the existing Binet and Rai classifications). In routine practice, patients with asymptomatic early-stage (Rai 0, Binet A) disease should be monitored without any treatment, unless they have signs of disease progression or disease-related symptoms. In cases of psychological impact or complications from the disease, particularly tumoral syndrome and/or cytopenia, treatment is required.

For patients requiring a first-line treatment, the choice of this treatment is dependent on a number of parameters: age, health state of the patient, presence of comorbidities or not, and cytogenetic status (presence of del(17p) and/or TP53 mutation, IGVH mutation status):

- In the presence of a TP53 mutation and/or del(17p),
  - IMBRUVICA (ibrutinib) monotherapy is currently the conventional treatment
  - CALQUENCE (acalabrutinib), as monotherapy or in association with obinutuzumab, is a therapeutic option
- In the absence of TP53 mutation and/or del(17p),
  - For patients with no significant comorbidities, the Transparency Committee has deemed that the therapeutic strategy should be adapted according to the patient's IGVH mutation status.
    - For patients with a mutated IGVH status, the choice between rituximab + fludarabine + cyclophosphamide immunochemotherapy (FCR regimen) and targeted therapy with the IMBRUVICA (ibrutinib) + rituximab association may be discussed.
    - In cases of non-mutated IGVH status (currently recognised as a factor in poor immunochemotherapy response), the IMBRUVICA (ibrutinib) + rituximab association is the first-line treatment.
    - Note that, in France, IMBRUVICA (ibrutinib) monotherapy currently has no reimbursed indication for the first-line treatment of FCR regimen-eligible patients with no TP53 mutation or del(17p).
  - For patients who are older and/or have comorbidities, meaning that they are not eligible for the "full-dose" standard FCR regimen, the options are:
    - Associations of anti-CD20 monoclonal antibody and chemotherapy:
      - GAZYVARO (obinutuzumab) + chlorambucil (G-Clb regimen)
      - MABTHERA (rituximab) + bendamustine (BR)
    - Targeted therapies:
      - VENCLYXTO (venetoclax) + GAZYVARO (obinutuzumab) (G-VEN)
      - IMBRUVICA (ibrutinib) monotherapy.
      - CALQUENCE (acalabrutinib) +/- GAZYVARO (obinutuzumab)

### Role of VENCLYXTO (venetoclax) in the therapeutic strategy:

In view of the data available from the CLL14 study demonstrating the superiority of VENCLYXTO (venetoclax) associated with obinutuzumab with respect to the chlorambucil + obinutuzumab (O-

Clb) association in terms of progression-free survival, haematological response rate, and minimal residual disease outcomes, **VENCLYXTO (venetoclax) in association with obinutuzumab, is an additional first-line CLL treatment option for patients with no 17p deletion or TP53 mutation and ineligible for fludarabine-based treatment, and for patients with a 17p deletion or a TP53 mutation.**

**The Committee points out that, although this treatment is preferable over the immunochemotherapy regimens for cases ineligible for ibrutinib, failing comparative data, it is not possible to determine its role with respect to BTK inhibitors.**

# Committee's conclusions

## Actual 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 life-threatening.

- The proprietary medicinal product VENCLYXTO (venetoclax) is a specific curative CLL treatment.

- The efficacy/adverse effect ratio is significant for previously untreated CLL patients with no del(17p) or TP53 mutation and ineligible for a full-dose fludarabine-based treatment, or for adults patients with a cytogenetic status associated with poor prognosis (17p deletion or TP53 mutation).

- Alternative medications are available (see Section "05. Clinically relevant comparator").

- VENCLYXTO (venetoclax) in association with obinutuzumab, is an additional first-line CLL treatment option for patients with no 17p deletion or TP53 mutation and ineligible for fludarabine-based treatment, and for patients with a 17p deletion or a TP53 mutation (see Section 09 of this opinion)

- **Public health benefit**

Considering:

- the severity of CLL (Binet stages B and C), which is life-threatening, and its incidence,
- the partially met medical need,
- the partial response to the identified partially met medical need due to:
  - an expected additional impact on morbidity among previously untreated CLL patients, with comorbidities meaning that they are ineligible for fludarabine, considering the findings of the CLL14 phase III randomised, controlled open-label study, demonstrating the superiority of the venetoclax + obinutuzumab association with respect to chlorambucil + obinutuzumab in terms of progression-free survival, haematological response rate, and minimal residual disease outcomes;

- but considering:
  - the lack of statistically significant difference in terms of overall survival;
  - the lack of demonstrated impact on quality of life considering the exploratory nature of the analyses;
- the lack of comparison to BCR inhibitors (ibrutinib considered as the conventional treatment and acalabrutinib);
- the lack of demonstrated impact on the care and life pathway, even though oral administration of venetoclax over a defined period may be a benefit;

**VENCLYXTO (venetoclax), in association with obinutuzumab, is not likely to have an additional impact on public health.**

**Considering all of these elements, the Committee deems that the actual clinical benefit of VENCLYXTO (venetoclax) is:**

- **SIGNIFICANT, in association with obinutuzumab, for the treatment of previously untreated patients with chronic lymphocytic leukaemia (CLL), only in the presence of a 17p deletion and/or TP53 mutation or for patients with no 17p deletion or TP53 mutation and ineligible for fludarabine-based treatment;**
- **INSUFFICIENT to justify public funding in the other marketing authorisation contexts, namely for patients with no 17p deletion and/or TP53 mutation and eligible for fludarabine-based treatment.**

**The Committee approves inclusion in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary products approved for community use for the indication "in association with obinutuzumab, for the treatment of previously untreated patients with chronic lymphocytic leukaemia (CLL), only in the presence of a 17p deletion and/or TP53 mutation or for patients with no 17p deletion or TP53 mutation and ineligible for fludarabine-based treatment" and at the dosages of the marketing authorisation.**

**The Committee disapproves inclusion in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary products approved for community use for the indication "in association with obinutuzumab, for the treatment of previously untreated patients with chronic lymphocytic leukaemia (CLL), with no 17p deletion or TP53 mutation and eligible for fludarabine-based treatment".**

Recommended reimbursement rate: 100%

## Clinical Added Value

**For patients with 17p deletion or a TP53 deletion and for patients with no 17p deletion or TP53 mutation and ineligible for fludarabine-based treatment**

Considering:

- the evidence of the superiority of venetoclax associated with obinutuzumab with respect to the chlorambucil + obinutuzumab (O-Clb) association, demonstrated in the CLL14 study with a median follow-up of 28.1 months in 432 previously untreated CLL patients, with comorbidities, in terms of progression-free survival (primary outcome measure; HR = 0.35; CI95% [0.23; 0.53]; p<0.0001), and haematological response, and minimal residual disease outcomes (ranked secondary outcome measures);
- the limitations of the CLL14 study (primary outcome measure assessed by the investigator in an open-label study, low number of patients with del17p/TP53 mutation [12%], lack of stratification on this measure, etc.);
- the lack of demonstrated superiority in terms of overall survival (ranked secondary outcome measure);
- the exploratory nature of the quality-of-life analyses;
- and the lack of comparison (direct or indirect) to ibrutinib, which is the conventional treatment, and was developed concomitantly;

the Committee deems that VENCLYXTO (venetoclax), in association with obinutuzumab, provides **minor clinical added value (CAV IV) with respect to the chlorambucil + obinutuzumab association** for previously untreated LLC patients with a 17p deletion or a TP53 mutation or for patients **with no 17p deletion or TP53 mutation and** ineligible for fludarabine-based treatment.

**For patients with no 17p deletion and/or TP53 mutation and eligible for fludarabine-based treatment**