SUMMARY

ibrutinib

IMBRUVICA 140, 280, 420 and 560 mg,

film-coated tablets

New indication

Original French opinion adopted by the Transparency Committee on 22 March 2023

The legally binding text is the original French opinion version

Key points

Favourable opinion on reimbursement, in combination with venetoclax, in the treatment of adult patients with chronic lymphocytic leukaemia (CLL) not previously treated and not presenting with a 17p deletion and/or a TP53 mutation, and ineligible for treatment with full-dose fludarabine.

Unfavourable opinion on reimbursement in the other situations of the MA extension namely, in combination with venetoclax, in the treatment of adult patients with CLL not previously treated presenting with a 17p deletion or a TP53 mutation and in patients not presenting with a 17p deletion or a TP53 mutation and eligible for treatment with fludarabine.

What therapeutic improvement?

Improvement in therapeutic strategy.

Role in the care pathway?

In the light of the data available from the GLOW study which demonstrated the superiority of the medicinal product IMBRUVICA (ibrutinib) in combination with venetoclax compared to the combination chlorambucil + obinutuzumab (O-Clb) in terms of progression-free survival, procurement of minimal residual disease and complete response rate, **IMBRUVICA (ibrutinib) in combination with venetoclax, is an additional first-line treatment option for CLL in patients not presenting with a 17p deletion or a TP53 mutation and ineligible for treatment with fludarabine**.

The current data do not allow IMBRUVICA (ibrutinib) in combination with venetoclax to be positioned relative to therapeutic alternatives such as IMBRUVICA (ibrutinib) in monotherapy, VENCLYXTO (venetoclax) in combination with obinutuzumab, and CALQUENCE (acalabrutinib) in combination or not with obinutuzumab in the absence of comparative data.

In patients with CLL not previously treated presenting with a 17p deletion or a TP53 mutation and in patients not presenting with a 17p deletion or a TP53 mutation and eligible for treatment with fludarabine, the role of IMBRUVICA (ibrutinib) in combination with venetoclax is not established, due to lack of data.

The Committee recalls that in compliance with the SmPC "appropriate clinical evaluation of cardiac history and cardiac function should be performed prior to initiating treatment with IMBRUVICA. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function, and clinically managed. Consider further evaluation (e.g. ECG, echocardiogram), as indicated, for patients in whom there are cardiovascular concerns" (see section 4.2 of the SmPC).

Specific recommendations

As a reminder, with regard to VENCLXYTO (venetoclax), the Committee recommends a systematic assessment of the risk of occurrence of tumour lysis syndrome (tumour mass best appraised by a CT scan, lymphocytosis, estimation of glomerular filtration), before beginning the treatment. Preventive measures such as the use of urate-lowering drugs, hyperhydration (oral or intravenous) and biological monitoring of patients during the first days of treatment must be implemented systematically. The appropriateness of hospitalisation must be assessed on a case-by-case basis according to the initial assessment of the risk of tumour lysis syndrome.

Conclusions of the Transparency Committee

Clinical benefit

- Chronic lymphocytic leukaemia (Binet stages B and C), characterised by the proliferation and accumulation of a malignant B-cell clone in the bone marrow, the blood and lymphatic organs, is life-threatening.
- The medicinal product IMBRUVICA (ibrutinib) in the context of its combination with venetoclax is a specific curative treatment for CLL.
- The efficacy/adverse effect ratio is significant in patients with CLL leukaemia not previously treated and not presenting with a del(17p) or a TP53 mutation and ineligible for treatment with full-dose fludarabine.
- There are medicinal alternatives (see section “Current management").
- IMBRUVICA (ibrutinib) in combination with venetoclax, is an additional first-line treatment option for CLL in patients not presenting with a 17p deletion or a TP53 mutation and ineligible for treatment with fludarabine.

Public health benefit

In view of:

- the gravity of the CLL (Binet stages B and C) which is life- threatening and its incidence,
- the partially met medical need,
- the partial response to the partially met medical need identified due to:
  - an additional expected impact on morbidity in view of the results of the phase III, randomised, controlled, open study (GLOW), which demonstrated the superiority of the combination ibrutinib and venetoclax compared to chlorambucil + obinutuzumab in terms of progression-free survival, minimal residual disease (MRD) negative results in the bone marrow and of the complete response rate but in view:
    - of the absence of proven impact on overall survival or quality of life;
    - of the debatable relevance of the comparator used and of the absence of comparison with other clinically relative comparators;
    - of the tolerance profile of IMBRUVICA (ibrutinib) associated with a rise in cardiovascular toxicity with two early deaths in the study.
- the absence of proven impact on the care pathway and life course, although the administration of the combination of the medicinal product IMBRUVICA (ibrutinib) for a fixed time period (15 cycles) with VENCLYXTO (venetoclax) orally may represent an advantage compared to long-term ibrutinib monotherapy,

IMBRUVICA (ibrutinib), in combination with venetoclax is not liable to have an additional impact on public health.

In view of all of these elements, the Committee considers that the clinical benefit provided by IMBRUVICA (ibrutinib) in combination with VENCLYXTO (venetoclax) is:

- **significant in first-line treatment of CLL in patients not presenting with a 17p deletion or TP53 mutation and ineligible for treatment with fludarabine.**

- **insufficient in first-line treatment of CLL in patients presenting with a 17p deletion or a TP53 mutation and in patients not presenting with a 17p deletion or TP53 mutation and eligible for treatment with fludarabine.**

The Committee gives an opinion:

- **favourable to inclusion on the list of medicinal products reimbursable to persons insured under social security schemes and on the list of medicinal products approved for the use of communities as first-line treatment of CLL in patients not presenting with a 17p deletion or a TP53 mutation and ineligible for treatment with fludarabine and at the MA doses.**
- **unfavourable to inclusion on the list of medicinal products reimbursable to persons insured under social security schemes and on the list of medicinal products approved for the use of communities as first-line treatment of CLL in patients presenting with a 17p deletion or a TP53 mutation and in patients not presenting with a 17p deletion or a TP53 mutation and eligible for treatment with fludarabine.**

Recommended reimbursement rate for inclusion on the list of medicinal products reimbursable under social insurance: 100 %

Clinical Added Value

In patients not presenting with a 17p deletion or a TP53 mutation and ineligible for treatment with fludarabine, in view of:

- the demonstration of the superiority of IMBRUVICA (ibrutinib) in combination with venetoclax compared to the combination chlorambucil + obinutuzumab (O-Clb), demonstrated in the GLOW study with a median follow-up of 27.7 months in 211 elderly patients (> 65 years) or persons with comorbidities with CLL, not previously treated, in terms of progression-free survival (primary endpoint; HR = 0.216; $_{95\%}$ CI [0.131; 0.357]; p<0,0001), and the procurement of minimal residual disease in the bone marrow and the overall response rate (hierarchical secondary endpoints);
- the absence of superiority demonstrated in terms of overall survival, an endpoint that will remain exploratory due to the interruption of the hierarchical sequence upstream;
- the exploratory nature of the quality of life analyses;
- the tolerance profile of IMBRUVICA (ibrutinib) marked by cardiovascular toxicity (arterial hypertension, atrial fibrillation and haemorrhage);
- the absence of direct comparison and the absence of, demonstration of difference in efficacy in terms of progression-free survival and overall survival of the indirect comparison analyses versus ibrutinib monotherapy. The clinical benefit of the combination compared to monotherapy is therefore not supported**.** In addition, this combination could be associated with more marked toxicity, particularly infectious, compared to monotherapy in view of the addition of venetoclax;
- the absence of direct comparison and the absence of demonstration of difference in efficacy in terms of progression-free survival and overall survival of the indirect comparison analyses versus the venetoclax combination with obinutuzumab and acalabrutinib in combination or not with obinutuzumab;

the Committee considers that IMBRUVICA (ibrutinib) in combination with venetoclax, in the same way as venetoclax in combination with obinutuzumab, provides minor clinical added value (CAV IV) compared to the combination obinutuzumab + chlorambucil in the current therapeutic strategy for first-line treatment of CLL in patients not presenting with a 17p deletion or TP53 mutation and ineligible for treatment with fludarabine.