HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
3 FEBRUARY 2021

The legally binding text is the original French opinion version

ibrutinib

IMBRUVICA 140 mg hard capsules
IMBRUVICA 140 mg film-coated tablets
IMBRUVICA 280 mg film-coated tablets
IMBRUVICA 420 mg film-coated tablets
IMBRUVICA 560 mg film-coated tablets

New indication

Key points

Favourable opinion for reimbursement in combination with rituximab for the first-line treatment of chronic lymphocytic leukaemia (CLL), only in patients eligible for full-dose fludarabine treatment and not presenting a del17p deletion or a TP53 mutation.

Unfavourable opinion for reimbursement in combination with rituximab for the first-line treatment of chronic lymphocytic leukaemia (CLL) in patients ineligible for full-dose fludarabine treatment and/or presenting a del17p deletion and/or a TP53 mutation.

What therapeutic improvement?

Therapeutic improvement compared to the FCR (fludarabine, cyclophosphamide, rituximab) immunochemotherapy protocol in the therapeutic strategy.

◗ Role in the care pathway?

In patients requiring treatment, the choice depends on several parameters: the patient's age and general condition, the presence or otherwise of comorbidities and the cytogenetic status (presence of the del17p deletion and/or the TP53 mutation, IgVH mutation status):
- In the presence of a TP53 mutation or a del17p deletion, IMBRUVICA (ibrutinib) as monotherapy is currently the reference treatment.
- In the absence of a TP53 mutation or del17p deletion, in patients without significant comorbidities, immunochemotherapy with rituximab + fludarabine + cyclophosphamide (FCR protocol) is the reference treatment. In these patients, in the event of a non-mutated IgVH status (currently recognised as being a factor for a poor response to immunochemotherapy), ibrutinib is recommended internationally, with the FCR protocol remaining an available alternative. It should be noted, however, that in France, IMBRUVICA (ibrutinib) as monotherapy does not currently have a reimbursed indication for the first-line treatment of patients eligible for the FCR protocol and not presenting a TP53 mutation or del17p deletion. In elderly patients and/or those with comorbidities making them ineligible for the FCR protocol, the options are as follows: GAZYVARO (obinutuzumab) + chlorambucil (G-Clb protocol), MABTHERA (rituximab) + bendamustine (BR), VENCLYXTO (venetoclax) + GAZYVARO (obinutuzumab) (G-VEN) or IMBRUVICA (ibrutinib) as monotherapy.

Role of the medicinal product in the care pathway

IMBRUVICA (ibrutinib) in combination with rituximab is a first-line treatment for chronic lymphocytic leukaemia (CLL) in patients eligible for full-dose fludarabine treatment and not presenting a del17p deletion or a TP53 mutation.
Considering the distinct medical need, the latest international guidelines and the exploratory subgroup analyses of the E1912 study suggesting a benefit of the ibrutinib + rituximab combination compared to the FCR protocol only in patients with a non-mutated IgVH status, it is necessary to adapt the care pathway based on the patient's IgVH status:

- In patients with a non-mutated IgVH status, the ibrutinib (administered continuously) + rituximab (administered over 6 months) combination is the first-line treatment.
- In patients with a mutated IgVH status, the choice between targeted therapy (ibrutinib administered continuously + rituximab over 6 months) and immunochemotherapy (FCR protocol administered over 6 months) must be discussed, taking into account the safety, the extent of the response expected, the administration conditions (duration and administration routes), and the patient's preferences.

As a reminder, in the E1912 study, exploratory results suggested a response to treatment that was rarely extensive in the ibrutinib + rituximab group (8% negative MRD versus 59% in the FCR group).
As regards toxicity, the ibrutinib + rituximab combination presents a cardiovascular and haemorrhagic safety profile while the FCR protocol is associated with a risk of myelodysplasia and acute leukaemia.

In patients ineligible for full-dose fludarabine treatment and/or presenting a del17p deletion and/or a TP53 mutation, the role of the ibrutinib + rituximab combination is not established, in the absence of data. In these patients, it is highlighted that IMBRUVICA (ibrutinib) as monotherapy is a first-line treatment (Committee's opinions of 17 June 2015 and 20 March 2020).

COMMITTEE'S CONCLUSIONS

Clinical benefit

For the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), eligible for full-dose fludarabine treatment and not presenting a del17p deletion or a TP53 mutation

◗ 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.

◗ IMBRUVICA (ibrutinib) in combination with rituximab is a specific curative treatment for CLL.

◗ The efficacy/adverse effects ratio is high.

◗ There are medicinal alternatives.

◗ IMBRUVICA (ibrutinib) in combination with rituximab is a first-line treatment for chronic lymphocytic leukaemia (CLL) in patients eligible for full-dose fludarabine treatment and not presenting a del17p deletion or a TP53 mutation (see 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,
- its prevalence in patients eligible for full-dose fludarabine treatment,
- the partially met medical need,
- the partial response to the identified need, with
    - an additional impact on morbidity and mortality, without any impact on quality of life,
    - a potential impact on the care pathway due to the oral administration of ibrutinib combined with rituximab treatment by injection,

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

Considering all these elements, the Committee deems that the clinical benefit of IMBRUVICA (ibrutinib) in combination with rituximab is substantial in the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), eligible for full-dose fludarabine treatment and not presenting a del17p deletion or a TP53 mutation.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), eligible for full-dose fludarabine treatment and not presenting a del17p deletion or a TP53 mutation and at the MA dosages.

◗ **Recommended reimbursement rate: 100%**

For the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), ineligible for full-dose fludarabine treatment and/or presenting a del17p deletion and/or a TP53 mutation

◗ 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.

◗ IMBRUVICA (ibrutinib) in combination with rituximab is a specific curative treatment for CLL.

◗ The efficacy/adverse effects ratio has not been established, in the absence of data.

◗ There are medicinal alternatives, in particular ibrutinib as monotherapy.

◗ In adult patients with previously untreated chronic lymphocytic leukaemia (CLL), ineligible for full-dose fludarabine treatment and/or presenting a del17p deletion and/or a TP53 mutation, the role of the ibrutinib + rituximab combination is not established, in the absence of data.

Public health impact

Considering:

- the seriousness of CLL (Binet stages B and C), which is a life-threatening disease,
- its prevalence in patients ineligible for full-dose fludarabine treatment,
- the medical need partially met by ibrutinib as monotherapy, in particular,
- the absence of a response to the identified medical need, in the absence of data in patients ineligible for full-dose fludarabine treatment and/or presenting a del17p deletion and/or a TP53 mutation,

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

Considering all these elements, the Committee deems that the clinical benefit of IMBRUVICA (ibrutinib) in combination with rituximab is insufficient in the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), ineligible for full-dose fludarabine treatment and/or presenting a del17p deletion and/or a TP53 mutation.

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), ineligible for full-dose fludarabine treatment and/or presenting a del17p deletion or a TP53 mutation.

◗ **Recommended reimbursement rate: 0%**

Clinical Added Value

For the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), eligible for full-dose fludarabine treatment and not presenting a del17p deletion or a TP53 mutation

Considering:

- **demonstration of the superiority of the ibrutinib + rituximab combination compared to the FCR protocol (fludarabine + cyclophosphamide + rituximab), a clinically relevant comparator, in an open-label randomised study having included predominantly high-risk patients (59%) in terms of progression-free survival (HR = 0.34; CI95%: [0.222; 0.522]) and overall survival (HR = 0.170; CI95% [0.053; 0.541]) after a median follow-up**

of 36.6 months and non-quantifiable absolute improvements (medians not reached) at this stage,

and despite:

- **the safety profile of the ibrutinib + rituximab combination marked by cardiovascular toxicity (in particular hypertension and atrial fibrillation) and haemorrhagic toxicity, with a cumulative risk associated with the long-term administration of ibrutinib, in a context in which the treatment durations differ since ibrutinib is administered continuously until progression and the FCR protocol is administered over 6 months,**
- **the absence of improvement in quality of life compared to the FCR protocol, in a context in which this relevant endpoint was a ranked secondary endpoint, which needs to be highlighted despite the fact that the open-label nature of the study significantly limited interpretation,**

the Committee considers that the ibrutinib + rituximab combination provides a moderate clinical added value (CAV III) compared to the FCR (fludarabine + cyclophosphamide + rituximab) protocol in the first-line treatment of chronic lymphocytic leukaemia (CLL) in patients eligible for full-dose fludarabine treatment and not presenting a del17p deletion or a TP53 mutation.

For the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), ineligible for full-dose fludarabine treatment and/or presenting a del17p deletion and/or a TP53 mutation