HAUTE AUTORITÉ DE SANTÉ

HAEMATOLOGY
New medicinal product
July 2017

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

VENCLYXTO (venetoclax), BCL-2 inhibitor

High clinical benefit but no proven clinical added value for the therapeutic strategy only for the treatment of CLL:
- in the presence of 17p deletion or TP53 mutation for adults for whom B-cell antigen receptor inhibitor therapy has failed (second-line and subsequent treatments);
- in the absence of 17p deletion or TP53 mutation for adults for whom both chemoimmunotherapy and B-cell antigen receptor inhibitor therapy have failed (third-line and subsequent treatments)

Insufficient clinical benefit to justify reimbursement by public funding for the treatment of CLL in the presence of 17p deletion or TP53 mutation for adults ineligible for B-cell antigen receptor inhibitor therapy (first-line treatment).

Main points

- VENCLYXTO has been granted a marketing authorisation for monotherapy treatment of chronic lymphocytic leukaemia (CLL):

- in the presence of 17p deletion or TP53 mutation for adults ineligible for B-cell antigen receptor inhibitor therapy or for whom this therapy has failed.
- in the absence of 17p deletion or TP53 mutation for adults for whom both chemoimmunotherapy and B-cell antigen receptor inhibitor therapy have failed.

- In CLL patients, not carrying the 17p deletion or TP53 mutation, for whom both chemo-immunotherapy and B-cell antigen receptor inhibitor therapy had failed, a non-comparative study demonstrated high overall response rates, with no robust data in respect of clinically relevant criteria (survival) in exchange for toxicity, particularly haematological, and a risk of tumour lysis syndrome on commencement of treatment resulting in patient hospitalisation,
- In CLL patients in the presence of 17p deletion or TP53 mutation for whom B-cell antigen receptor inhibitor therapy had failed, a non-comparative study demonstrated high overall response rates, with no robust data in respect of clinically relevant criteria (survival) in exchange for toxicity, particularly haematological, and a risk of tumour lysis syndrome on commencement of treatment resulting in patient hospitalisation,
- In CLL patients in the presence of 17p deletion or TP53 mutation ineligible for B-cell antigen receptor inhibitor therapy, sufficient data are not available to document the benefit and clinical added value of this medicinal product (n=5 patients).

Therapeutic strategy

- For the first-line treatment of CLL (previously untreated CLL):
  - in cases of 17p deletion/TP53 mutation: the therapeutic strategy is based on ibrutinib. The idelalisib + rituximab combination may be proposed for cases ineligible for ibrutinib (see marketing authorisation). Based on expert opinions, patients ineligible for ibrutinib are in particular patients presenting with a haemorrhagic risk. Allogeneic stem cell transplantation is also a therapeutic option based on eligibility.
  - in the absence of 17p deletion/TP53 mutation, and based on the presence of comorbidities or not, the therapeutic strategy is based on chemoimmunotherapy (rituximab + fludarabine + cyclophosphamide [R-FC], rituximab + chlorambucil [R- Clb], rituximab + bendamustine [RB], obinutuzumab + chlorambucil) or ibrutinib.

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- After the failure of a first-line treatment, for relapsed or refractory patients, the initiation of a second-line treatment is based on the same criteria as those used for the first-line treatment. The choice of treatment is dependent on a number of factors, such as comorbidities, existence of 17p deletion/TP53 mutation (to be retested), the nature of the previous treatment(s) and the duration of the latest response.
- As per the European guidelines updated in 2017, second-line and subsequent treatments are based on chemoimmunotherapy (in the absence of 17p deletion/TP53 mutation), ibrutinib, idelalisib + rituximab, venetoclax. There is no ranking among these treatments. The first-line treatment used may be resumed if the relapse or progression occurs after 24 months to 36 months in the absence of 17p deletion. Allogeneic stem cell transplantation may be offered to patients in remission. As per the U.S. NCCN 2017 guidelines, second-line and subsequent treatments are based, in order of preference, on:
  - in cases of 17p deletion or TP53 mutation: ibrutinib, venetoclax, idelalisib + rituximab
  - in the absence of 17p deletion or TP53 mutation: ibrutinib, idelalisib + rituximab, venetoclax, etc.
- **Role of the medicinal product in the therapeutic strategy**

  For previously untreated CLL with 17p deletion or TP53 mutation (first-line) and for patients ineligible for B-cell antigen receptor inhibitor therapy, venetoclax monotherapy has no role in this indication.
  For CLL with 17p deletion or TP53 mutation for patients for whom B-cell antigen receptor inhibitor therapy has failed (second-line and subsequent treatments), venetoclax monotherapy is an alternative therapeutic option.
  For CLL in the absence of 17p deletion or TP53 mutation for patients for whom both chemoimmunotherapy and B-cell antigen receptor inhibitor therapy have failed (third-line and subsequent treatments), venetoclax monotherapy is an alternative therapeutic option.

Clinical data

- Two non-comparative phase II studies assessed the overall response rate (primary endpoint) defined as the proportion of patients obtaining a complete response (CR), complete response with incomplete marrow recovery (CRi), partial response (PR) or nodular partial response (nPR). In these 2 studies, the patients received venetoclax monotherapy, as per the dose titration schedule recommended by the marketing authorisation over 5 weeks.
- The study M13-982 was conducted on 107 CLL patients with 17p deletion or TP53 mutation and treated on average with 3 prior treatments (main cohort). A safety cohort of 51 patients was added, in which 5 previously untreated CLL patients with 17p deletion or TP53 mutation were included. Insofar as:
  - 2 patients (2/107) from the main cohort had previously been treated with one of the B-cell antigen receptor inhibitors (ibrutinib),
  - 5 patients (5/51), from the safety cohort, were treatment-naive and none of these were probably "ineligible" for idelalisib + rituximab or ibrutinib as per the inclusion/non-inclusion criteria,
  - 45.5% (35/107) of the patients from the main cohort had Binet diagnostic stage A CLL, whereas this stage, in the absence of objective active disease criteria, is not treated in French practice,

  the findings of this study cannot be used to quantify the clinical added value of the medicinal product in the presence of 17p deletion or TP53 mutation for adult patients ineligible for B-cell antigen receptor inhibitor therapy or for whom this therapy has failed.
- The study M14-032 was conducted on 64 CLL patients, carrying 17p deletion or TP53 mutation or not, subject to relapse or refractory (R/R) to treatment with:
  - ibrutinib (group A): 43 patients of whom 24/43 (55.8%) carried the 17p deletion and/or TP53 mutation
  - idelalisib (group B): 21 patients of whom 5/21 (23.8%) carried the 17p deletion and/or TP53 mutation

  The overall response rates were 69.8% (30/43; 95% CI [53.9; 82.8]) in group A and 61.9% (13/21; 95% CI [38.4; 81.9]) in group B with CR/CRi in group A and none in group B, according to the independent review committee. The findings were very similar in the subgroup of patients with 17p deletion and/or TP53 mutation.
- The median progression-free survival and overall survival were not reached after a median of 12.4 months of treatment in group A and 9.3 months in group B.
- The most frequently reported adverse events were essentially: neutropoenia (45 to 55% and a large majority of grade 3 or 4), anaemia, infections (20 to 50%), digestive disorders (40%), persistent biological or clinical tumour lysis syndrome despite preventive measures.

Benefit of the medicinal product

- The actual clinical benefit* of VENCLYXTO is high only for the treatment of CLL:
  - in the presence of 17p deletion or TP53 mutation for adult patients for whom B-cell antigen receptor inhibitor therapy has failed;
  - in the absence of 17p deletion or TP53 mutation for adult patients for whom both chemoimmunotherapy and B-cell antigen receptor inhibitor therapy have failed.

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The actual clinical benefit* of VENCLYXTO is insufficient to justify publicly funded cover for the treatment of CLL in the presence of 17p deletion or TP53 mutation for adult patients ineligible for B-cell antigen receptor inhibitor therapy.

- VENCLYXTO monotherapy does not provide any clinical added value** (CAL V) for the therapeutic strategy of CLL in the absence of 17p deletion or TP53 mutation for adult patients for whom both chemoimmunotherapy and B-cell antigen receptor inhibitor therapy have failed and in the presence of 17p deletion or TP53 mutation for adult patients for whom B-cell antigen receptor inhibitor therapy has failed.

- Approval for non-hospital pharmacy reimbursement and for hospital treatment only for cases with a high actual clinical benefit.

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This document was drafted on the basis of the Transparency Committee opinion dated 07 February 2018 (CT-16439) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement".

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