## SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

# **ZYDELIG** (idelalisib), antineoplastic

**High clinical benefit, in combination with rituximab, for the treatment of chronic lymphocytic leukaemia for patients who are not eligible for any other treatment but no proven clinical added value for the therapeutic strategy in respect of these patients**

## Main points

- ZYDELIG has been granted a marketing authorisation, in combination with rituximab, for the first-line treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation for patients who are not eligible for any other treatment.
- The efficacy of the idelalisib + rituximab combination is based on very limited data (n=9 patients) in exchange for high toxicity: risk of infections and neutropoenia.
- *Pneumocystis jiroveci* pneumonia prophylaxis and regular clinical and pathological cytomegalovirus infection and blood count monitoring are recommended.

## Therapeutic strategy

- The choice of CLL treatment is dependent on the patient's age, comorbidities, cytogenetic status, general health and prior treatments. The most common cases of the disease, i.e. stages A (Binet) or 0, I, II (Rai), are asymptomatic and do not justify specific treatment.
- The existence of 17p deletion/TP53 mutation induces a modest susceptibility to chemotherapies, particularly to purine analogues.
- For the first-line treatment of CLL (previously untreated CLL) and in cases of 17p deletion, in 2012, the French Haematology Society (SFH) recommended alemtuzumab (MABCAMPATH), in combination with high-dose corticosteroids, as well as allogeneic haematopoietic stem cell transplantation for responding eligible patients. Neither ibrutinib nor idelalisib + rituximab had been granted a marketing authorisation on the date of publication of these guidelines.
- In 2015, ESMO recommended BCR inhibitors (ibrutinib or idelalisib + rituximab) or allogeneic stem cell transplantation for patients in good general health and responding to treatments.
- The U.S. NCCN guidelines in 2017 recommend, in order of preference, ibrutinib, chemoimmunotherapy and alemtuzumab. The idelalisib + rituximab combination is not mentioned since this indication has not been FDA-approved.
- Venetoclax (VENCLYXTO) has been granted a marketing authorisation since late 2016 for CLL 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.
- **Role of the medicinal product in the therapeutic strategy**
  ZYDELIG, in combination with rituximab, must be reserved for the rare patients presenting with previously untreated CLL (first-line) with 17p deletion or TP53 mutation and who are unable to receive ibrutinib i.e. those presenting with a haemorrhagic risk (in particular cardiac rhythm disorders such as atrial fibrillation, deep thrombocytopoenia, anticoagulant co-treatments, etc.) based on expert opinion and as per the U.S. NCCN 2017 guidelines.

## Clinical data

- Within the scope of a review of ZYDELIG following amendments to the wording of its marketing authorisation for previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion or TP53 mutation, the laboratory

furnished the findings of a follow-up phase of patients treated with idelalisib, conducted on an open-label basis, particularly including patients from the study 101-08.

- The study 101-08 is a non-comparative phase II assessing the efficacy of the idelalisib + rituximab combination on 64 patients with previously untreated CLL or lymphocytic lymphoma. Only 9 patients (n=9, 14.1%) had a 17p deletion and/or TP53 mutation. The overall response rate was 96.9% (62/64; 95% CI [89.2; 99.6]) including 12 complete responses (18.8%) and 50 partial responses (78.1%). Of the 9 patients with a 17p deletion and/or TP53 mutation, all obtained an overall response (95% CI [66.4; 100]), 3 patients having obtained a complete response and 6 a partial response. The inclusion/non-inclusion criteria cannot be used to determine whether the 9 patients falling within the indication under review (previously untreated CLL with 17p deletion/TP53 mutation) were ineligible for ibrutinib.
- A total of 41 patients from the study 101-08 were included in the follow-up study, of which 7 patients (12%) with a 17p deletion and/or TP53 mutation. During the extension phase, they were treated with idelalisib monotherapy consisting of 150 mg twice daily until progression or the observation of toxicity incompatible with retaining treatment.
  On the date of the intermediate analysis (1 August 2014), 23 patients (56.1%) were receiving treatment. The median duration of response and the median overall survival had not been reached. At 36 months, 90.1% (95% CI [82%; 99%]) of the patients were alive and none of the 9 patients presenting with a 17p deletion and/or TP53 mutation were deceased.
- Almost 90% of the patients presented with at least one grade ≥ 3 treatment-related adverse event with primarily: diarrhoea (n=18; 28,1%), colitis (n=16; 25%), increased ALAT (n=15, 23.4%), increased ASAT (n=12; 18.8%) and pneumonia (n=12; 18.8%). Further infection risk reduction measures have been added to incorporate guidelines in respect of *Pneumocystis jiroveci* pneumonia prophylaxis and regular clinical and pathological cytomegalovirus infection and blood count monitoring.

## Special prescription requirements

- Hospital-prescribed medicinal product
- Medicinal product subject to prescription reserved for haematology specialists or physicians with expertise in blood disorders.
- Medicinal product requiring special monitoring during treatment

## Benefit of the medicinal product

- The actual clinical benefit* of ZYDELIG is high
- Given the lack of efficacy data for patients ineligible for ibrutinib and in view of the safety warnings in particular in respect of the risk of neutropoenia and severe infections, ZYDELIG, in combination with rituximab, does not provide any clinical added value (CAV V) for the therapeutic management strategy for previously untreated CLL, in the presence of 17p deletion or TP53 mutation, for patients who are not eligible for any other treatment.
- Approval for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 7 June 2017 (CT-15973) 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".