BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

GAZYVARO (obinutuzumab), type II humanised anti-CD20 recombinant monoclonal antibody

Moderate improvement in the treatment of previously untreated chronic lymphocytic leukaemia in patients with comorbidities making them unsuitable for full-dose fludarabine-based therapy.

Main points

- GAZYVARO in combination with chlorambucil has Marketing Authorisation for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have not previously been treated and have comorbidities making them unsuitable for full-dose fludarabine-based therapy.
- Its efficacy has been shown in a study versus rituximab plus chlorambucil (R-Clb) and chlorambucil alone in terms of progression-free survival and the rate of residual disease, but without there being any demonstrated gain in overall survival.
- In combination with chlorambucil, the toxicity of the dual therapy containing GAZYVARO was greater than that containing rituximab. This toxicity was mainly haematological or infusion-related reactions.

Therapeutic use

The therapeutic options for the first-line treatment of CLL are:

- In patients with no significant comorbidity, the combination of rituximab + fludarabine + cyclophosphamide (R-FC protocol) is the conventional treatment.
- In patients with comorbidities, treatment with chlorambucil (Clb) as monotherapy was historically regarded as the usual first-line therapy. Although this medicinal product is less myelotoxic than the other available first-line medicines, the complete response rate remains low (<10%). Thus, the addition of rituximab to Clb (R-Clb protocol) is recommended; this combination showed an improvement in results by comparison with chlorambucil alone, although with a complete response rate of only 12%.

The available alternatives are:

- reduced-dose purine-based treatments (rituximab + fludarabine + cyclophosphamide [R-FC], or pentostatin + cyclophosphamide + rituximab). However, data on patients with comorbidities are limited for these combinations and the results in terms of response and overlall survival are mixed.
- bendamustine.

The 2011 European guidelines recommend the use of chlorambucil or bendamustine for patients with comorbidities. In this situation, the 2014 US guidelines recommend one of the following options:

- obinutuzumab + chlorambucil
- ofatumumab + chlorambucil
- rituximab + chlorambucil
- bendamustine +/- rituximab.

GAZYVARO is a first-line treatment for patients with CLL who are unsuitable for high-dose fludarabine treatment.

Clinical data

- An open, randomised, two-stage study with 3 parallel groups evaluated the efficacy and safety of GAZYVARO plus chlorambucil (G-Clb) versus rituximab plus chlorambucil (R-Clb) or chlorambucil (Clb) alone in patients with chronic lymphocytic leukaemia who had not previously been treated and had comorbidities.
  The first stage consisted of a comparison of each of the two groups, G-Clb or R-Clb, with chlorambucil monotherapy in 589 patients. Once superiority had been demonstrated, the second stage consisted of comparing GAZYVARO with rituximab, both combined with chlorambucil, in 663 patients.

At the end of a median patient follow-up period of 14.5 months for the G-Clb group and 13.6 months for the Clb month (stage 1), median progression-free survival (primary efficacy endpoint) was 23 months in the G-Clb group and 10.9 months in the Clb alone group, i.e. a gain in absolute terms of 12.1 months in favour of the G-Clb group ($p < 0.0001$) (stratified HR = 0.14; 95% CI: [0.10; 0.21]. An interim analysis of the comparison of G-Clb versus R-Clb (stage 2, cut-off date 9 May 2013) was carried out with a median follow-up period of 18.7 months. It showed a median progression-free survival of 26.7 months for the G-Clb group versus 15.2 months in the R-Clb group, i.e. a gain in absolute terms of 11.5 months in favour of the G-Clb group (stratified HR = 0.39; 95% CI: [0.31; 0.49]).
On the date of this analysis, there was no difference in overall survival between the two, and median overall survival was not reached in either of the two groups.
With an additional follow-up period of about 10 months (total median follow-up of 27.3 months), overall survival did not differ between the two groups.
The proportion of patients showing a response at the end of treatment (complete response [CR], complete response with incomplete recovery of the bone marrow [iRC], partial response [PR] and partial nodular response [pNR]) was 78.4% in the G-Clb group versus 65% in the R-Clb group ($p = 0.0001$).
Given the substantial quantity of missing data, no conclusion can be drawn from the assessment of quality of life in this study.

- The main adverse events of grade >3 noted in the comparison of GAZYVARO dual therapy versus chlorambucil alone were haematological disorders (neutropenia: 35% versus 16%; thrombocytopenia: 11% versus 6%) and infusion-related reactions (21% versus no cases).
- Compared with rituximab, the incidence of adverse events was of grade ≥3 higher in the G-Clb group than in the R-Clb group (70% versus 55%). The difference between the two groups was due mainly to haematological disorders (neutropenia: 33% versus 28% and thrombocytopenia: 10% versus 3%) and infusion-related reactions (20% versus 4%).

Prescribing conditions

Reserved for hospital use. Medicine restricted to haematologists and haematology departments or doctors trained in blood diseases.

Benefit of the medicinal product

- The actual benefit* of GAZYARO is substantial.
  GAZYVARO + chlorambucil provides moderate clinical added value** (CAV III) in the treatment of patients with previously untreated CLL who have comorbidities making them unsuitable for full-dose fludarabine-based treatment.

- Recommends inclusion on the list of reimbursable products for hospital use.

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* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".