HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
30 MARCH 2022

The legally binding text is the original French opinion version

zanubrutinib
BRUKINSA 80 mg hard capsules

First assessment

Key points

Unfavourable opinion for reimbursement as monotherapy for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.

Role in the care pathway?

The initiation of treatment is guided by the disease symptoms (cytopenia, hyperviscosity, moderate to severe peripheral neuropathy, amyloidosis, symptomatic cryoglobulinemia, cold agglutinins).

At present, there is no curative treatment for this disease, which can be life-threatening. The objective of treatment is primarily to correct the symptoms of WM and to prevent progression of the disease. Plasma exchange is recommended only in the event of symptomatic hyperviscosity associated with high IgM levels.

In some cases, stem cell transplantation may also be an option for young patients in good general condition, following the failure of prior therapy.

According to the 2018 ESMO (European Society for Medical Oncology) guidelines and the NCCN (National Comprehensive Cancer Network) guidelines updated in June 2021, first-line treatment (in treatment-naïve patients) is based on:

- Firstly, a combination of rituximab and an alkylator (cyclophosphamide or bendamustine) or a proteasome inhibitor (bortezomib);

- Secondly, in patients with comorbidities making them unsuitable for combined and more intensive chemo-immunotherapy, an alkylator or nucleoside analogue (for example fludarabine) or rituximab.

Considering the existing treatment options with different profiles (safety, response rate, etc.), the situations in which patients may not be able to receive a chemo-immunotherapy protocol as first-line treatment are rare, and the clinician's decision-making process should take into consideration the improvement or, at the very least, the absence of any deterioration in the patient's quality of life, and their eligibility for systemic therapy.

Salvage therapies may involve the use of the initial products or products belonging to a different class, either alone or in combination.

Second or later-line treatment depends on the time to relapse and is based on IMBRUVICA (ibrutinib) as monotherapy or on rituximab-based chemo-immunotherapy identical to the first cycle or another rituximab-based chemo-immunotherapy.

IMBRUVICA (ibrutinib) also has an MA as a single-agent in the first-line treatment of patients unsuitable for chemo-immunotherapy or in combination with rituximab for the treatment of adult patients with WM but the Committee considered that its clinical benefit is insufficient to justify public funding cover in these indications.

It should be noted that the American NCCN guidelines recommend the preferential use of zanubrutinib or ibrutinib ± rituximab as second or later-line therapy.

Role of the medicinal product in the care pathway

Considering:

- the inclusion of a heterogeneous population of patients in the study in terms of prognosis, with mainly relapsed or refractory patients (82%), and only 18% de patients receiving first-line therapy;

- the absence of demonstrated superiority in terms of complete response or very good partial response compared to ibrutinib, the relevance of which as a primary endpoint is also debatable;

- the impossibility of reaching a conclusion with respect to the contribution of zanubrutinib compared to ibrutinib in terms of progression-free survival and overall survival, which are more relevant outcome measures but were exploratory unranked secondary endpoints;

- the safety profile of zanubrutinib, which appears to differ from that of ibrutinib in terms of the frequency of occurrence of adverse events of interest, which were less frequently reported with zanubrutinib concerning atrial fibrillation/flutter, hypertension and bleeding events, and more frequently reported with zanubrutinib concerning the development of neutropenia during the phase 3 study. However, the open-label nature of the study and the more limited experience of use of zanubrutinib compared to ibrutinib should be taken into consideration, and the results of the phase 3 study do not eliminate the uncertainties concerning the safety profile of BRUKINSA (zanubrutinib);

the Committee considers that BRUKINSA (zanubrutinib) as monotherapy has no role in the treatment of adult patients with Waldenström's macroglobulinaemia (WM), as first-line treatment for patients unsuitable for chemo-immunotherapy, or as second-line treatment in patients who have received at least one prior therapy.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Waldenström's macroglobulinaemia (WM) is a rare disease that is life-threatening, particularly following the failure of several treatment lines.

◗ The proprietary medicinal product BRUKINSA (zanubrutinib) is a curative medicinal product.

◗ Due to the lack of demonstration of any superiority of BRUKINSA (zanubrutinib) compared to IMBRUVICA (ibrutinib) in terms of very good partial response (primary endpoint), the absence of robust data on progression-free survival and overall survival and uncertainties with respect to the safety profile of BRUKINSA (zanubrutinib), the efficacy/adverse effects ratio of BRUKINSA (zanubrutinib) is inadequately established.

◗ In the first-line treatment of patients unsuitable for chemo-immunotherapy, there are no medicinal alternatives with an MA in this indication. However, the current guidelines recommend the use of other medicinal products, as specified in section 05 "clinically relevant comparators". For second and later-line therapy, there is an alternative with an MA -, IMBRUVICA (ibrutinib) - and recommended alternatives (see section 05 "clinically relevant comparators").

◗ BRUKINSA (zanubrutinib) as monotherapy has no role in the care pathway for the treatment of adult patients with Waldenström's macroglobulinaemia (WM), as first-line treatment for patients unsuitable for chemo-immunotherapy, or as second-line treatment in patients who have received at least one prior therapy.

Public health impact

Considering:

- the seriousness of the disease and its prevalence/incidence,
- the partially met medical need,
  the lack of response to the identified need with the absence of any demonstrated additional impact of BRUKINSA (zanubrutinib) on morbidity and mortality or on quality of life, given the exploratory nature of the results for these endpoints in the phase 3 study,
- the absence of any demonstrated additional impact on the organisation of care in the absence of data.

BRUKINSA (zanubrutinib) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BRUKINSA (zanubrutinib) is insufficient in the marketing authorisation indication to justify public funding cover.

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 MA indication and dosages.