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2023031557

National Health Care Institute
Care
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Contact
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Our reference
2023031557

Date 31 August 2023
Re: Package advice for the lock procedure medicinal product zanubrutinib (Brukinsa®) for the treatment of chronic lymphocytic leukaemia

Dear Mr Kuipers,

This is a corrected version of the letter already sent on 4 August 2023 (reference 20230315577), in which the phrasing 'statistically significant' has been replaced by 'numerical'. This correction has been implemented in the pharmacotherapeutic report that has been attached.

The National Health Care Institute advises you on the assessment of zanubrutinib (Brukinsa®) in the treatment of chronic lymphocytic leukaemia (CLL; a type of blood cancer). The reason for this advice was the placement of zanubrutinib for this indication, among others, in the lock procedure for expensive medicinal products.

Zanubrutinib is, after ibrutinib and acalabrutinib, the third Bruton's tyrosine kinase (BTK) inhibitor assessed for CLL by the National Health Care Institute.

The National Health Care Institute has concluded that zanubrutinib as a monotherapy meets the legal criterion of 'established medical science and medical practice'. The National Health Care Institute has determined that zanubrutinib has an equal value to ibrutinib for this indication.

The National Health Care Institute advises you to include zanubrutinib in the basic health insurance package for the stated indication, provided that the price negotiations with the marketing authorisation holder successfully deliver a net price that does not exceed that of the existing treatments ibrutinib or acalabrutinib. We would like to point out that the Insured Package Advisory Committee has recommended that the price for a treatment should be reduced when several drugs are available for the same indication.
We would like to explain our findings and final conclusion below.

General
At your request, the National Health Care Institute assesses whether new care should be part of the standard health insurance package from the perspective of the health insurance package paid from joint premiums.

National Health Care Institute
Care
Medicinal Products

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We consider this both in the scientific sense and in terms of public support. We also review the aspects of efficiency and transparency.

The National Health Care Institute assessed zanubrutinib on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. The National Health Care Institute is advised by the Scientific Advisory Board (WAR) for the review of data according to established medical science and medical practice. We also consulted stakeholders during the assessment process.

Comprehensive weighting of package criteria
Zanubrutinib has been studied as secondary healthcare treatment in adult patients with relapsed refractory CLL (R/R CLL) in the ALPINE study. In this randomised study, the treatment with zanubrutinib was directly compared to ibrutinib. In this study, 48 of 327 patients in the zanubrutinib arm and 60 of 325 patients in the ibrutinib arm had died at the latest analysis. At a median follow-up duration of 29.6 months, the hazard ratio (HR) for overall survival *(*OS) was 0.76 (95% confidence interval (CI) [0.51, 1.11]). The median OS was not yet achieved in both groups. The researcher-assessed progression-free survival (PFS) was significantly higher with zanubrutinib than with ibrutinib. In the zanubrutinib arm, 87 out of 327 patients had disease progression, compared to 118 out of 325 patients in the ibrutinib arm. This gives an HR of 0.65 (95% CI [0.49; 0.86]). Median PFS was not achieved in the zanubrutinib arm and was 34.2 months (95% CI [33.3; inestimable [NS]]) in the ibrutinib arm.

Zanubrutinib as monotherapy has not been directly compared to ibrutinib in studies with adult patients who had not been previously treated for CLL. Therefore, an indirect comparison was used in the assessment. A naive indirect comparison was made based on the SEQUOIA and ALLIANCE studies. in the SEQUOIA study, zanubrutinib was directly compared to bendamustine rituximab (BR). In the ALLIANCE study, ibrutinib was also directly compared to BR. In both studies, no statistically significant difference in OS compared to BR was found. Treatment with zanubrutinib showed a statistically significant improvement in PFS, compared to treatment with BR. When comparing ibrutinib and BR, a statistically significant and possibly also clinically relevant difference in PFS was seen in favour of ibrutinib.

The ALPINE study in patients with R/R CLL shows that treatment with ibrutinib results in a higher incidence of both undesirable effects and discontinuation due to undesirable effects, compared to zanubrutinib. When looking at the intervention-related grade ≥3 undesirable effects, the two treatments appear to be at least non-inferior.

In adult patients with previously untreated CLL, treatment with zanubrutinib results in a numerical improvement over BR in both the intervention-related serious undesirable effects and the discontinuation rate due to intervention-related undesirable effects. Ibrutinib provides a numerical improvement in the incidence of grade ≥3 undesirable effects compared to BR.

[1] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[2] Established medical science and medical practice assessment: updated version (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

[3] Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

National Health Care Institute
Care
Medicinal Products

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Conclusion
Looking at the results of the direct comparison between zanubrutinib and ibrutinib in patients with R/R CLL, it can be concluded that zanubrutinib is at least non-inferior to ibrutinib for both desirable and undesirable effects. As the National Health Care Institute previously concluded that ibrutinib meets the established medical science and medical practice for both R/R CLL and primary healthcare CLL treatment, and treatment-naïve patients generally have a better prognosis than patients with R/R CLL, the National Health Care Institute states that extrapolation of zanubrutinib evidence for R/R CLL to primary healthcare is warranted. The results of the naïve indirect comparison between zanubrutinib and ibrutinib in treatment-naïve patients support this extrapolation.

Established medical science and medical practice
The National Health Care Institute concludes that based on current scientific evidence and additional arguments, zanubrutinib in CLL meets the established medical science and medical practice, and that there is an equal value to the standard treatment, in this case ibrutinib.

Budget impact analysis
Inclusion in the basic health care package of the lock procedure medicinal product zanubrutinib (Brukinsa®) for the treatment of adult patients with R/R/ CLL is not expected to lead to substantial additional costs for medicinal products.
There is some uncertainty about the actual number of adult patients with treatment-naïve and R/R CLL in Dutch practice who are eligible for treatment with zanubrutinib. In addition, the marketing authorisation holder and other consulted parties indicate that the applied market penetration rates lead to an overestimation of the absolute costs of zanubrutinib. However, the occupational group was unable, for now, to provide an estimate of the actual market penetration of zanubrutinib. The National Health Care Institute has calculated a number of scenario analyses with lower market penetration rates to investigate the impact of this.

Cost-effectiveness
Because of the similarity in effectiveness (equal therapeutic value) of zanubrutinib compared to the already reimbursed treatment with ibrutinib for this indication, a cost-effectiveness analysis has not been considered here.

Package advice
The National Health Care Institute advises you to include zanubrutinib in the basic health insurance package for the stated indication, provided that the price negotiations with the marketing authorisation holder successfully deliver a net price that does not exceed that of the existing treatments ibrutinib or acalabrutinib. We would like to point out that the Insured Package Advisory Committee has advised the National Health Care Institute in general terms that the price for a treatment should be reduced when several medicinal products are available for the same indication.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board