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Recommendation Letter

18 May, 2021

To Whom It May Concern,

I am writing to strongly advocate for the inclusion of zanubrutinib (Brukinsa®)) capsules on the WHO Essential Medicine List and I am in full support of the submitted application.

I am a member of the European Hematology Association (EHA), American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO) and Australasian Leukemia & Lymphoma Group (ALLG). As the leading PI of the zanubrutinib BGB-3111-AU003 study and member of multiple Study Steering Committee (SSC) for protocols using zanubrutinib, including the zanubrutinib BGB-3111-305 study, I recommend zanubrutinib for the reasons below.

As the majority of patients with B-cell malignancies are elderly (≥65 years old) and have an increased incidence of hypertension, coronary heart disease and atrial premature beats, safer drugs are urgently needed. For patients treated with BTK-inhibitor monotherapy which requires treatment until disease progression or unacceptable toxicity, more efficacious therapies with superior safety profiles are warranted. With better safety and tolerability, zanubrutinib can reduce treatment-related adverse reactions in patients, improve the quality of life, and reduce the burden of long-term management of patients by doctors and medical institutions.

Bruton kinase inhibitors (BTKi) have transformed the therapeutic landscape for indolent B-cell lymphoid malignancies such as for chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL) and Waldenstrom's macroglobulinemia (WM). Ibrutinib was the first available BTKi in 2013, first in US by the Food and drug Administration (FDA) for MCL. Since then a next generation BTKi, zanubrutinib (Brukinsa®), has been internationally recognized and has been approved in several countries and indications:

1. In November 2019, zanubrutinib was approved in the United States by FDA for the treatment of MCL in adult patients who have received at least one prior therapy; During the approval process, it received FDA "Breakthrough Therapy" designation and "Accelerated Approval".
2. In June 2020, zanubrutinib was approved in China for the treatment of MCL in adult patients who have received at least one prior therapy, and CLL/SLL in adult patients who have received at least one prior therapy.
3. In February 2021, zanubrutinib was approved in the United Arab Emirates for the treatment of relapsed or refractory MCL.
4. In March 2021, zanubrutinib was approved in Canada for the treatment of Waldenstrom's macroglobulinemia (WM) in adult patients.

The activity and tolerability of zanubrutinib have been demonstrated in early and late phase clinical trials in several B-cell malignancies:

1. For the treatment of relapsed/refractory (R/R) CLL/SLL patients pooled from BGB-3111-AU003, BGB-3111-205 and BGB-3111-1005 trials, the objective response rate (ORR) of zanubrutinib monotherapy was as high as 92.1%, including a 6.7% rate of complete response (CR), with good safety, low incidence of grade ≥3 atrial fibrillation and other adverse events, and a low rate of treatment discontinuation.
2. In the treatment of R/R MCL patients, the CR rate of zanubrutinib monotherapy was 78%, and the PFS was 22.1 months; The efficacy data were significantly better than the historical data of other BTK inhibitors and drugs in R/R MCL

3. In the treatment of WM patients on Study BGB-3111-AU-003, the ORR for zanubrutinib was 95.9%, and the very good partial response (VGPR)/CR rate was 45.2%, and estimated 3-year PFS rate was 80.5%, with an acceptable safety profile. The long-term treatment with zanubrutinib monotherapy resulted in deep and durable responses in patients with WM.
4. In BGB-3111-302, a large global phase 3 head-to-head study against ibrutinib, 28.4% of zanubrutinib patients and 19% of ibrutinib patients achieved a VGPR. A total of 84% of zanubrutinib and 85% of ibrutinib patients were progression free at 18 months. Compared to ibrutinib, zanubrutinib was shown to have a superior safety profile compared to ibrutinib, especially for cardiac events including atrial fibrillation (3.0% vs 18.4%), and was shown to have lower treatment discontinuation rates due to adverse events (4.0% vs 14.3%).
5. In an interim analysis of a global head-to-head phase 3 trial, BGB-3111-305, for R/R CLL/SLL patients treated with zanubrutinib vs. ibrutinib, zanubrutinib met its primary endpoint of objective overall response by investigator and demonstrated a superior response rate that was statistically significant (ORR: 78.3% vs. 62.5%, superiority p-value=0.0006 compared to two-sided stringent statistical boundary of p-value<0.0099 set for the interim analysis) and a pre-specified statistically significant lower rate of atrial fibrillation/flutter compared to ibrutinib (rate of atrial fibrillation/flutter: 2.5% vs 10.1%, p-value=0.0014 compared to two-sided stringent statistical boundary of p-value<0.0099). The interim analysis from this fully-enrolled, ongoing trial is based on 415 of 652 patients followed for a minimum of 12 months. The descriptive summaries of PFS showed an early trend favoring zanubrutinib.

With better safety and efficacy, zanubrutinib can reduce treatment-related adverse reactions in patients, improve the quality of life, and reduce the burden of long-term management of patients by doctors and medical institutions.

In terms of cost-effectiveness, the 2020 ASH study confirmed the cost-effectiveness advantage of zanubrutinib over ibrutinib in the treatment of R/R MCL, with an incremental PFS LYs of 0.98 and incremental PFS QALYs of 0.77 compared to ibrutinib. In probability analysis, the ICER and ICUR of zanubrutinib were lower than the WTP threshold in the United States. At $100,000 WTP, the cost-effectiveness acceptability curve showed that the probability of Zanubrutinib and Ibrutinib being cost-effective was 34% and 16%, respectively, suggesting that zanubrutinib, was more cost-effective than ibrutinib in the treatment of R/R MCL.

From March 1st, 2021, zanubrutinib has been officially included in National Medical Care Insurance Medicine Catalogue, with the new price of 6,336 yuan/box. The monthly treatment cost of Brukinsa® for CLL and MCL is only 11,880 yuan. From the perspective of the Chinese healthcare system, the long-term (patient lifetime) economics of zanubrutinib vs ibrutinib in the treatment of R/R MCL were compared, and each patient in the zanubrutinib group could obtain 3.043 QALYs and 4.164 LYs in a lifetime - 1.228 more QALYs and 1.721 more LYs per patient than the ibrutinib group, respectively. The total cost of Zanubrutinib group was 612,956.5 yuan, which was 75,947.3 yuan higher than 537,009.2 yuan in Ibrutinib group, and the incremental cost-effectiveness ratio (ICER) of the two groups was 61,848.6 yuan /QALY, lower than China's GDP per capita of 70,892.0 yuan in 2019.

Based on the above, I strongly support the inclusion of zanubrutinib in the WHO Model List of Essential Medicines. Thank you for your time and consideration. Please feel free to contact me with any questions.

Yours sincerely,

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