REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Minjuvi

200 mg powder for concentrate for solution for infusion x 1 vial

INN Tafasitamab

Therapeutic indication	Minjuvi is indicated in combination with lenalidomide followed by Minjuvi monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplantation (ASCT).
Start - end of the procedure	18.07.2023 – 21.12.2023
Final decision	Inclusion Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act, and reimbursement by the NHIF beyond the value of the provided medical services.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Minjuvi

Health problem

Diffuse large B-cell lymphoma (DLBCL) is an aggressive type of non-Hodgkin's lymphoma (NHL), which accounts for about 25-40% of all NHL cases. The reason is the occurrence of mutations in mature B-lymphocytes, which leads to their uncontrolled proliferation and loss of functionality. Like all other malignancies, DLBCL results from genetic alterations affecting proto-oncogenes and tumor suppressor genes, with the involvement of the lymph node microenvironment. DLBCL can develop as a primary disease de novo or as a consequence of progression of an indolent lymphoma. Most patients with DLBCL have rapidly enlarging lymphadenopathy in one or more lymph nodes, and 40% have extranodal involvement. Primary DLBCL can develop in any organ. Symptoms of extranodal origin of the disease depend on the organs or tissues in which the tumor spreads. About 30% of people with DLBCL have systemic symptoms such as fever, weight loss, and night sweats.

The therapeutic standard for first-line treatment in Bulgaria is chemoimmunotherapy R-CHOP and it coincides with the treatment guidelines of the European Society of Medical Oncology (ESMO) and the American National Cancer Network (NCCN). Half of patients undergoing this therapy are resistant to it or relapse: about 10% of patients have primary refractory disease, and 40% are likely to relapse after initial response. For patients with relapsed or refractory lymphoma who are not suitable for autologous stem cell transplantation, there is no standard therapy and there is an unmet need for an effective treatment.

Health technology tafasitamab is a first-in-class monoclonal anti-CD19 IgG antibody with an optimized Fc region. Modifications in the constant region enhance the binding of the antibody to the Fc receptors of immune cells and thus stimulate effector mechanisms of the immune system such as cytotoxicity and phagocytosis. The immunomodulator lenalidomide helps tafasitamab activate the immune system. The synergistic effect of the combination of tafasitamab and lenalidomide leads to a good therapeutic antitumor effect.

Efficacy data

The therapeutic efficacy and safety profile of tafasitamab was analyzed in one clinical trial.

The clinical trial **L-MIND** is a single-arm, multicenter, open-label phase 2 trial of tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy in adult patients with DLBCL who have relapsed or are refractory to at least one but no more than three prior systemic regimen, and who are not candidates for high-dose chemotherapy (HDCT) and subsequent ASCT. Tafasitamab in combination with lenalidomide was administered for up to 12 cycles (28 days

each), followed by tafasitamab monotherapy until progression in patients with an SD or better response. The primary endpoint was objective response rate (ORR) (complete response + partial response [CR+PR]). Key secondary endpoints included disease control rate (DCR; CR+PR+stable disease [SD]); duration of response (DoR); survival after progression (PFS); overall survival (OS), time to progression (TTP); time to subsequent treatment (TTNT); and safety, assessed as frequency and severity of AEs.

The results of the L-MIND clinical trial showed that the primary endpoint of the trial (ORR; defined as CR+PR) was achieved. Of the 46 responding patients, 13 patients progressed, two patients died, and another 31 patients were censored. Of the 32 patients with the best objective CR response, five patients progressed, one patient died, and another 26 patients were censored. Median DoR for patients with the best objective response CR was not reached. Of the 14 patients with PR, the median DoR was 5.6 months, eight patients progressed, one patient died, and another five patients were censored. The Kaplan-Meier estimate of median overall survival was 33.5 months with a median follow-up time of 42.7 months.

Safety data

The most common side effects were: infections (73%), neutropenia (51%), asthenia (38%), anemia (36%), diarrhea (36%), thrombocytopenia (31%), cough (26%), peripheral edema (24%), pyrexia (24%), decreased appetite (22%). The most common serious adverse reactions were infections (26%), including pneumonia (7%), and febrile neutropenia (6%).

Data on comparators

The comparator chosen for the main pharmacoeconomic analysis was Pola-BR (polatuzumab vedotin + bendamustine + rituximab). The therapeutic regimens R-GemOx (rituximab + gemcitabine + oxaliplatin) and BR (bendamustine + rituximab) were included as comparative alternatives in an additional scenario of the pharmacoeconomic analysis.

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions intended for the health care systems of other countries

Three positive evaluations have been published by other governmental institutions - The National Institute for Health and Care Excellence - NICE (Great Britain), Haute Autorité de santé - HAS (France) and The Federal Joint Committee - G-BA (Germany).

Applied analysis
The cost-effectiveness pharmacoeconomic analysis (CEA) was applied, in which the final result in terms of health benefits is presented in the form of life year gained (LYG) as well as a cost-utility analysis (CUA), where the final outcome in terms of health benefits is expressed as a quality-adjusted life year (QALY) gained. As comparative alternatives for the main scenarios, the therapeutic regimen Pola-BR (polatuzumab vedotin + bendamustine + rituximab) was selected. The therapeutic regimens R-GemOx (rituximab + gemcitabine + oxaliplatin) and BR (bendamustine + rituximab) were included as comparative alternatives in an additional scenario. The perspective of the analysis is that of the paying institution - the National Health Insurance Fund (NHIF). The chosen time horizon in the model for both populations evaluated is lifetime (31 years). The model includes three health states: progression free (PF), progressed disease (PD), and death.

The incremental ratio of Minjuvi's costs and results to the compared alternative is above the established profitability threshold of 3x GDP/capita, which according to NSI data for 2022 is EUR 12,400 (BGN 24,253.29 and BGN 72,756.88 upper limit of 3xGDP) .

Costs for the assessed health technology
The model includes costs of Minjuvi health technology, costs of the alternatives used, costs for administration and patient follow-up, costs for adverse event monitoring, costs for follow-up therapy and costs for palliative care.

Subgroup analysis
Not attached.

Budget impact analysis
The budget impact analysis was conducted from the perspective of a paying institution - NHIF. The time horizon is 5 years. The target population includes patients who have refractory or relapsed disease (numbers based on morbidity data). The estimated number of patients in the first year is 3, and in the fifth year – 9. The budget impact analysis considers two scenarios: "World without" and "World with" the new technology.

The analysis forecasts an increase in the NHIF expnditures over a five-year period, excluding risk-sharing agreements and patient access schemes.

Conclusion

Minjuvi (Tafasitamab) in combination with lenalidomide provides a new treatment option for patients with refractory or relapsed DLBCL who have a limited choice of available therapies. Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy is a chemotherapy-free treatment option with a manageable short- and long-term safety profile. Compared to other second- and subsequent-line therapies, it has demonstrated high and sustained

clinical efficacy with prolongation of overall survival and improvement of quality of life, including in difficult-to-treat R/R patients not eligible for transplantation. The budget impact analysis forecasts an increase in the NHIF expenditure over a five-year period.