



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



HEALTH TECHNOLOGY ASSESSMENT

Polivy

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

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

INN polatuzumab vedotin

Therapeutic indication	Polivy in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).
Start-end of the procedure	15.08.2022 – 14.12.2022
Final decision	Addition of a therapeutic indication to 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.



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



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

Health problem

Diffuse large B-cell lymphomas (DLBCL) are a heterogeneous group of aggressive lymphomas, morphologically consisting of large, transformed B-cells. They have a diffuse growth pattern. DLBCL arises from centroblasts or immunoblasts and contains genetic abnormalities that are relatively specific to the disease. DLBCL often arises de novo, but may also represent a malignant progression or transformation of a less aggressive lymphoma (e.g., follicular lymphoma, chronic lymphocytic leukemia, small cell lymphocytic lymphoma, and MALT lymphoma). The average age at onset of the disease is 67 years, with a predominance in men. About 40% of patients have extranodal affected areas - most often the gastrointestinal tract and bone marrow. In patients with DLBCL, the extent of the disease is assessed by staging, which is extremely important in determining the best therapeutic option and the prognosis. The Ann Arbor staging classification is routinely used to classify the extent of disease based on the spread and number of affected sites, as well as the presence or absence of extranodal involvement and constitutional symptoms. Fludeoxyglucose positron emission tomography - computed tomography (PET-CT) is the gold standard for staging patients with DLBCL. The stage of the disease (based on IPI) and the age of the patient are significant factors affecting survival. Most patients with DLBCL are successfully treated with standard immunochemotherapy. Approximately 10-15% of DLBCL cases are primary refractory, and 20-30% - recurrent.

Although DLBCL is often asymptomatic, it may be associated with constitutional symptoms, for example, nonspecific “B-symptoms” that include fever, recurrent night sweats, and weight loss in approximately 30% of patients, and/or local effects associated with enlargement of lymph nodes, and bone marrow insufficiency. It is characterized by rapidly growing tumors in the lymph nodes, spleen, liver, bone marrow or other organs. Patients with DLBCL usually develop rapidly growing masses within or outside the lymph nodes, which damage the affected and surrounding tissues and organs and require immediate treatment. When treating patients with DLBCL, the ultimate therapeutic goal is to cure the disease. However, in about 40% of patients, cure is not achieved and the goal is to control the disease.

Currently, the standard first-line treatment for DLBCL is R-CHOP, with treatment administered every 3 weeks for six to eight cycles. Second-line treatment includes rituximab (if relapse occurs after > 6 months and biopsy shows continued CD20 expression), followed by autologous stem cell transplantation. For patients who are not eligible for transplantation, treatment options include participation in clinical trials, gemcitabine-based regimens with or without rituximab, and Polivy in combination with BR. The treatment strategy depends on the patient’s age, IPI risk and the presence of cardiac dysfunction in older patients.



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



Polivy is the first product in this drug class and the first antibody-drug conjugate product for the treatment of DLBCL that has been developed specifically for B-cell malignancies that express CD79b, a component of the B-cell receptor.

Epidemiological data

The GLOBOCAN database provides a forecast for Bulgaria that the number of newly diagnosed patients with non-Hodgkin's lymphoma for the period 2020-2030 will decrease from 647 (in 2020) to 641 (in 2025) to 633 (in 2030). The incidence data in Bulgaria for the various types of diffuse non-Hodgkin's lymphoma (C83) show that the most common are C83.3 (Large cell [diffuse]) and C83.9 (Diffuse non-Hodgkin's lymphoma, unspecified). Without treatment, the natural course of DLBCL is aggressive and the outcome is fatal, with a median survival of approximately 6 months.

Efficacy data

The therapeutic efficacy and safety profile of polatuzumab vedotin in adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) were evaluated in two clinical trials.

The POLARIX clinical trial compared the efficacy, safety, pharmacokinetics and patient-reported outcomes of polatuzumab vedotin (pola) + rituximab with cyclophosphamide, doxorubicin and prednisone (R-CHP) versus rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in patients with previously untreated DLBCL. As of the final date of data analysis, June 28, 2021, 1,063 patients were screened and 879 were randomized. Endpoints: The primary endpoint is progression-free survival (PFS) as assessed by the investigator. Secondary endpoints are event-free survival for reasons related to efficacy (EFSeff), complete response (CR) rate at the end of treatment, OS measured by positron emission tomography (PET) and assessed by blinded independent central review. The primary endpoint (PFS) was achieved with a 27% reduction in the risk of disease progression or death in the pola+R-CHP arm compared to the R-CHOP arm.

In the pola-R-CHP arm, a greater proportion of patients were alive and progression-free at year 1 and year 2 compared to the control arm. The observed increase in the proportion of patients without PFS events for the pola+R-CHP arm versus the R-CHOP arm was 4.14% at year 1 and 6.50% at year 2.

A statistically significant 25% reduction in the risk of an EFSeff event (progression of disease, relapse, death, biopsy positive for residual disease, after end of treatment or initiation of new anti-lymphoma therapy for efficacy-related reasons) was observed in the pola+R-CHP arm compared to the R-CHOP arm.

Clinical trial GO29044 to evaluate the safety, tolerability and antitumor activity of pola in combination with rituximab or obinutuzumab, cyclophosphamide, doxorubicin and prednisone (chemotherapy CHP) in patients with B-cell non-Hodgkin's lymphoma (NHL).



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



The primary endpoint was the frequency, type and severity of adverse events (AEs) to determine the maximum tolerated dose and dosing regimen of polatuzumab in combination with R-CHP or G-CHP. All efficacy endpoints are secondary. In treatment-naïve patients with B-cell NHL, pola+R-CHP or pola+G-CHP led to a high CR rate (78.0% and 80.0%, respectively).

In the PFS analyses, the proportion of patients without an event in year 1 was comparable in the pola+R-CHP arm and the pola+G-CHP arm (90.0% and 91.8%, respectively); in year 2 it was 80.0% and 87.7% in the pola+R-CHP arm and the pola+G-CHP arm, respectively. In the EFSall analyses, the proportion of patients without an event in year 2 was 70.0% and 80.0% in the pola+R-CHP arm and the pola+G-CHP arm, respectively. The DOR rate is numerically higher in the pola+G-CHP arm compared to the pola+R-CHP arm (95.5% and 85.0%, respectively). The frequency of OS is numerically higher in the pola+R-CHP arm compared to the pola+G-CHP arm (94.0% and 87.8%, respectively).

Safety data

The most frequently reported ($\geq 30\%$) ADRs are peripheral neuropathy (52.9%), nausea (41.6%), neutropenia (38.4%) and diarrhea (30.8%). Serious adverse reactions were reported in 24.1%. The most common serious adverse reactions reported in $\geq 5\%$ of patients are febrile neutropenia (10.6%) and pneumonia (5.3%). The ADR leading to discontinuation of the therapeutic regimen in $> 1\%$ of patients was pneumonia (1.1%).

Data on comparators

The choice of a comparative alternative was made according to the following criteria:

- Therapeutic indication according to SPC - untreated diffuse large B-cell lymphoma;
- Recommendations for treatment in accordance with the Pharmacotherapeutic Guidance for Clinical Hematology of NCPR;
- Listed in Annex 2 of the Positive Drug List;
- Reimbursed by the NHIF for the the indication under consideration.

The standard first-line treatment (1L) is R-CHOP, a combination of the following medicinal products: Rituximab: 375 mg/m; Cyclophosphamide: 750 mg/m; Doxorubicin: 50 mg/m; Vincristine: 1.4 mg/m and Prednisone: 100 mg.

Pharmacoeconomic indicators

Applied analysis

The chosen method for comparative evaluation of health technology is cost-utility analysis (CUA). In addition, data are also presented for a cost-effectiveness analysis (CEA), where the final result is presented in the form of cost per life year gained (LYG) and progression-free survival (PFS) for the compared technologies. The comparative alternative R-CHOP is a combination of the



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



following medicinal products: Rituximab: 375 mg/m; Cyclophosphamide: 750 mg/m; Doxorubicin: 50 mg/m; Vincristine: 1.4 mg/m and Prednisone: 100 mg. The perspective of the analysis is that of the paying institution - NHIF. The chosen time horizon in the model is lifetime (60 years), which is consistent with recommendations for setting the time horizon in cost-effectiveness models—the time horizon should be long enough to capture any important differences in costs or clinical outcomes between the technologies being compared. Costs and results are discounted at an annual discount rate of 3.5%.

To evaluate the cost-effectiveness of Pola+R-CHP versus R-CHOP as first-line treatment (1L) in diffuse large B-cell lymphoma (DLBCL) a partitioned survival model was used – two models were developed as the following approaches were used: (1) standard parametric survival model; (2) a mixture-cure model. In a distributed survival model, time-to-event data are used to model the percentage of patients who are “progression-free”, “post-progression” and “death” depending on the time since the start of the trial. Mixture-cure models are an approach to modeling cancer therapies for which there is evidence to support that a proportion of treated patients enter long-term remission and subsequently have mortality equal to that of the general population.

The analysis of the results shows that the inclusion of Polatuzumab in the therapeutic practice for the first-line treatment of DLBCL is associated with both improved health benefits (when starting treatment with polatuzumab vedotin in combination with R-CHP, patient survival is improved - one year of progression-free survival, years of life, and years of life in full health were added - compared to R-CHOP, and with additional costs. The incremental ratios ICER, BGN/PFS, ICER, BGN/LYG and ICUR, BGN/QALY are available above the conditionally accepted threshold of favorable cost-effectiveness (3 times GDP per capita).

Costs for the assessed health technology

Costs included in the analysis are direct medical costs related to drug therapy and administration, costs of managing adverse events, costs of follow-up treatment, costs of medical activities in monitoring the disease by health conditions, and costs of palliative care.

Subgroup analysis

Not attached.

Budget impact analysis

The analysis of the budget impact was conducted from the perspective of a paying institution - NHIF. The time horizon is 5 years. A model is presented with projected data on the number of patients with previously untreated diffuse large B-cell lymphoma who are expected to be treated with Polivy in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) over a 5-year period. The expected number of patients in the first year is 42, and at the end of the fifth year – 66. Two scenarios are considered: "World without" and "World with" the new technology. The budget impact analysis shows that paying for the treatment of adult patients with untreated diffuse large B-cell lymphoma, with the medicinal product Polivy (polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone), results in



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



additional costs for the NHIF throughout the entire analysis period, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Polivy in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma, the first antibody-drug conjugate product for the treatment of DLBCL. The benefits of Polivy in combination with R -CHP per 1L for treatment of DLBCL have been demonstrated in the main trial POLARIX and the confirmatory trial GO29044. Patients treated with Polivy +CHP had a 27% reduction in the risk of progression, relapse, or death compared to patients treated with R-CHOP. The inclusion of the health technology provides additional benefits in terms of improved survival, prolongation of the disease progression-free period, and reduction of the risk of recurrence and death, covering the unmet need for first-line treatment of diffuse large B-cell lymphoma. With the inclusion of Polivy in clinical practice, an increase in costs for the paying institution NHIF is expected for the entire period of the analysis.