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

HEALTH TECHNOLOGY ASSESSMENT

Venclyxto 100 mg film-coated tablet x 112 (4 x 28)

INN Venetoclax

Therapeutic indication(s)	Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
Start/end date of procedure	26.05.2020 – 18.12.2020
Final decision	To include a therapeutic indication in Annex 2 of the PDL for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF beyond the cost of the rendered medical services.

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

Health problem

Chronic lymphocytic leukemia (CLL) is a malignant haemopathy due to uncontrolled clonal proliferation and accumulation of relatively immature and immunologically imperfect lymphocytes in the peripheral blood, lymph nodes, spleen and bone marrow. They originate from the marginal zone of the lymph nodes, have a low proliferative index and longer survival due to evading apoptosis (programmed cell death). With its slow and long evolution, CLL is a classic example of indolent non-Hodgkin's lymphomas, which primary hematogenous forms it belongs to.

Pathogenetically, CLL is associated with disorders of BCR (B cell antigen receptor) signaling and activation of anti-apoptotic BCL-2 (B-cell lymphoma) proteins. BCR signaling includes a cascade of a number of kinase systems with a key intermediate point - the activation of Bruton-tyrosine kinase (BTK) and phosphoinositol-3-kinases (PI3Ks), which ensures survival, malignant cell migration and CLL progression. BCL-2 proteins evade the apotosis of the mutated cell pool, which practically guarantees its "immortality".

Natural course of the disease: CLL is characterized by indolent development of the clonal population and evolution of the disease. Most often, CLL is diagnosed accidentally due to the appearance of enlarged lymph nodes, leukocytosis during a control examination for another disease, left hypochondriac heaviness. Lymphadenopathy, leukocytosis, anemia, and constitutional symptoms progress slowly in standard variants of the condition. The consensus strategy for CLL is "watch and wait", and treatment begins only under strictly defined criteria.

Prognosis: CLL in standard cases has an average survival of patients in "0" or "A" stage of about 150 months (over 12-14 years); in stages I, II and B - 60 to 90 months and in stages III, IV and C 19 to 30 months.

The target population of Venclyxto (venetoclax) in combination with obinutuzumab are adult patients with untreated chronic lymphocytic leukemia.

Epidemiological data

CLL is one of the most common malignant blood diseases - 30% of all leukemias, and morbidity of 3-5/100,000 population. The disease mainly affects middle-aged and elderly people with the ratio of men:women 2:1. CLL is the most common chronic leukemia in Europe and America.

According to data from the National Cancer Registry, a total of 786 patients (460 men and 326 women) have been registered in Bulgaria.

Efficacy data

The therapeutic efficacy and safety profile of venetoclax in patients with untreated chronic lymphocytic leukemia were analyzed in two clinical studies.

Clinical study GP28331 to evaluate the maximum tolerated dose (MTD) of venetoclax (Ven) when used in combination with obinutuzumab (G), and its tolerability and safety in patients with recurrent/refractory (R/R) CLL or no previous treatment (1L) for CLL. The results of the study for 1L only are presented in the following table:

	Genaral population with CLL/1L (N=32)	Patients with CrCL ≥ 70 ml/min and ECOG 0 or 1 (N=22)
ORR, best response (95% CI), investigator-assessed	100% (89%, 100%)	100%
CR/Cri (95% CI), investigator-assessed	78% (60%, 91%)	73%
DOR	NR	NR
PFS at month 24 (95% CI)	90.6% (80.5%, 100%)	86.4% (70%, 100%)
PB MRD - ≥3 months after last dose Ven	72%	68%

1L – first line ; CRR – complete response rate ; Cri – complete remission with incomplete blood count recovery DoR – duration of response ; MRD – minimal residual disease ; NR - not reached ORR – overall response rate

CLL14 clinical study compared the efficacy of venetoclax + obinutuzumab (VenG) with obinutuzumab + chlorambucil (GClb) in patients with untreated CLL and comorbidities. The results show:

• Significantly higher progression-free survival (PFS), 24 months, VenG vs GClb - 88.2% vs 64.1%;
• PFS (36 months) VenG (81.9%) vs GClb (49.5%);
• 69% reduction in the risk of progression and death (at 24 months) in the VenG vs GClb arm;
• 67% reduction in the risk of progression and death after treatment discontinuation (29 months) in the VenG vs GClb arm;
• PFS by subgroups, depending on genetic abnormalities, is significantly higher in the VenG vs GClb arm;
• undetectable minimum residual disease (MRD) 10-4 (<1 cell in 10,000 leukocytes at the end of therapy significantly better in the VenG vs GClb arm);
• undetectable MRD persists after cessation of treatment with a significant duration in the VenG vs GClb arm:
• patients with undetectable MRD in the peripheral blood have better PFS than detectable MRD at the end of therapy;
• Overall survival (OS) (28.1 months median time without treatment): median OS was not reached in either arm;

• DOR (duration of response) - median not reached; DOR is larger in the VEN + G arm and lasts longer;
• Event-free survival (EFS): significantly longer in the VenG arm;
• Time to next treatment (TTNT). The risk of starting a new treatment was reduced in the VenG arm compared to patients in the GClb arm.
• Patient-reported outcomes are comparable in both arms. VenG did not adversely affect health-related quality of life (HRQoL) in 1L treatment of CLL patients and no deterioration in general health status or increase in severity of symptoms was reported.

An indirect comparison was made with 8 randomized clinical trials involving almost all treatment regimens for CLL. The CLL14 study showed a tendency for improved efficacy between therapies with respect to PFS in patients in poor physical condition. Compared to VEN + G, IBR + G only demonstrates greater efficacy with respect to PFS. No numerical differences in efficacy were observed compared to VEN + G vs IBR, IBR + G and IBR + R. The results for OS show that all therapies have comparable efficacy with CrI overlap. The inclusion of patients in good physical condition in the analysis does not lead to numerical differences in efficacy compared to the analysis in only participants with poor physical condition. The OS results do not show a difference in the efficacy between VEN + G and other comparators.

Safety data

The safety analysis is presented as a summary of data from 758 CLL patients, treated in venetoclax clinical trials in combination with obinutuzumab or rituximab or as monotherapy. The most frequent adverse reactions (≥ 20%) of any grade in patients receiving venetoclax in the studies with combined treatment with obinutuzumab or rituximab were neutropenia, diarrhea and upper respiratory tract infection. The most common side effects with monotherapy are neutropenia, diarrhea, nausea, anemia, fatigue and upper respiratory tract infection. The most common serious adverse reactions (≥ 2%) with venetoclax in combination with obinutuzumab or rituximab were pneumonia, sepsis, febrile neutropenia and tumor lysis syndrome (TLS).

Data on comparators

The following were chosen as comparators: FCR (fludarabine, cyclophosphamide, rituximab), chlorambucil + rituximab, chlorambucil + obinutuzumab, bendamustine + rituximab, ibrutinib and chlorambucil monotherapy.

Pharmacoeconomic indicators

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

TLV recommends Venclyxto in patient access shemes for expensive treatment.

Applied analysis

Two pharmacoeconomic analyses were applied - cost-benefit and cost-effectiveness. The health benefits for patients in the attached model were measured as years of life gained (LYG), quality adjusted life years (QALY) and annual survival. The perspective of the analysis is that of the paying institution - the National Health Insurance Fund (NHIF). The chosen time horizon in the model is lifelong. Health benefits and results are discounted with an annual discount factor of 3.5%. A partitioned survival model is presented with three mutually exclusive health conditions - pre-progression (PFS), post-progression (PPS) and absorbing state - death. The results show that the inclusion of venetoclax in combination with obinutuzumab in the therapeutic algorithm demonstrates a cost-saving approach for the entire course of treatment. The cost savings compared to the comparator regimens is a result of a smaller proportion of patients who had progressed switching to subsequent therapy. Venetoclax + obinutuzumab dominates all comparators. With a pre-set threshold of favorable cost-effectiveness of 3 times GDP per capita, venetoclax + obinutuzumab therapy is defined as the optimal treatment option for the target group of patients. Sensitivity analysis was performed, which includes a Monte Carlo simulation.

Subgroup analyses

Not attached.

Cost of the assessed health technology

Calculated were: the cost of venetoclax + obinutuzumab therapy, cost of therapy with comparators, cost of medical services, cost of adverse events management, cost of drug therapy in subsequent treatment.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the paying institution - the National Health Insurance Fund. The time horizon in the budget impact analysis is 5 years. The expected number of patients in the first year is 10, and in the fifth it reaches 33. The inclusion of the health technology in the PDL will generate additional cost for the NHIF, which increases each year, not taking into account risk sharing agreements and patient access schemes.

Conclusion

Venclyxto is a specific pathogenetic agent that selectively inhibits BCL-2 antiapoptotic proteins, significantly expressed by malignant lymphocytes in CLL. In the long term, with venetoclax + obinutuzumab therapy, the duration of the progression-free period is prolonged in contrast to alternatives. The combination of venetoclax + obinutuzumab demonstrates a

cost-saving approach for the entire course of treatment and therapeutic superiority, expressed in prolonging life and improving its quality. Inclusion of the health technology in the PDL will generate additional cost for the entire period of the analysis.