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

HEALTH TECHNOLOGY ASSESSMENT

Scemblix

20 mg film-coated tablet x 60 (blister PCTFE/PVC/Alu)

40 mg film-coated tablet x 60 (blister PCTFE/PVC/Alu)

INN Asciminib

Therapeutic indication(s)	Scemblix is indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase (Ph+ CML-HF) previously treated with two or more tyrosine kinase inhibitors.
Start/end date of procedure	11.05.2023 – 28.12.2023
Final decision	Inclusion in 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 clinical pathway.

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

Health problem

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease characterized by a reciprocal translocation between the long arms of chromosomes 9 (ch9) and 22 (ch22), called the Philadelphia chromosome (Ph). There are three distinct phases of the disease, including a latent phase called the chronic phase (CP), a more advanced accelerated phase (AP), and a very aggressive blast crisis phase (BP); most patients have CML in CP.

The disease mainly affects the elderly people. Approximately 50% of cases are diagnosed in people aged >65 years, and the average age at diagnosis is about 64 years. Risk factors predisposing to the development of CML include exposure to high doses of radiation, advanced age, and male gender.

Common signs and symptoms in most patients after the onset of CML are due to anemia and splenomegaly and include fatigue, weight loss, general malaise, rapid satiety, and left upper quadrant heaviness or pain. The spleen may fill most of the abdominal cavity, cause pain or heaviness, and present a significant clinical problem, or it may be only mildly enlarged. In about 10% of patients, the spleen is neither palpable nor enlarged on computed tomography (CT). Rare manifestations of the disease are bleeding (associated with decreased platelet count and/or dysfunction), thrombosis (associated with thrombocytosis and/or marked leukocytosis), gouty arthritis (due to elevated uric acid levels), priapism (usually with marked leukocytosis or thrombocytosis), retinal hemorrhages and ulcers, and upper gastrointestinal bleeding (due to increased histamine levels due to basophilia). Although the white blood cell count (WBC) exceeds 100 × 109/l, leukostatic symptoms (dyspnea, drowsiness, loss of coordination, confusion) due to the accumulation of leukemic cells in the pulmonary or cerebral vessels are not common in the chronic phase (CP). Splenomegaly is the most common physical sign and is found in 20-40% of patients with CML. The diagnosis is confirmed by detection of Philadelphia chromosome (Ph) (22q-) or BCR::ABL1 transcripts or both in peripheral blood or bone marrow cells.

Treatment for CML is determined based on the stage of the disease. Tyrosine kinase inhibitors (TKIs) are the treatment of choice in various lines of therapy along with consideration of stem cell transplantation. Imatinib, nilotinib, bosutinib, dasatinib, ponatinib, and asciminib are currently approved for the treatment of CML-CP in different lines of therapy and in certain patient populations (i.e. ponatinib in patients with the T315I mutation).

Asciminib is a potent inhibitor of ABL/BCR::ABL1 tyrosine kinase. Asciminib inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein by specifically targeting the ABL myristoyl pocket.

Epidemiological data

Annual incidence: 1-2 newly diagnosed patients per 100,000 inhabitants. Worldwide, the number of CML cases in 2019 was 65,800 (incidence 0.85 per 100,000 population).

According to data from the National Cancer Registry for 2017, 186 cases of myeloid leukemia were registered (109 men and 77 women; incidence - 2.6/100,000 people). In that year, a total of 235 deaths were registered, of which 124 were among men and 111 among women. For the period from 2000 to 2007 in Bulgaria, 328 cases of chronic myeloid leukemia were registered in men and 274 cases in women. The 5-year survival rate for this period was 33.4% for men and 37.7% for women.

Efficacy data

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

ASCEMBL Clinical Trial (NCT03106779) - Phase 3, multicenter, open-label, randomized trial to evaluate the safety and efficacy of asciminib in patients with chronic phase chronic myeloid leukemia (CML-CP) treated with ≥2 prior adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs) who have experienced treatment failure. 233 CML-CP patients treated with ≥2 prior TKIs were randomized to receive asciminib (n = 157) or bosutinib (n = 76).

The primary endpoint was the rate of major molecular response (MMR) (BCR-ABL1IS ≤0.1%) at week 24. The key secondary endpoint was to evaluate the efficacy of asciminib versus bosutinib at week 96 in CML-CP patients treated with ≥2 prior TKIs. Another key secondary endpoint was MMR rate at week 96. The MMR rate at week 96 was 37.6% with asciminib compared with 15.8% with bosutinib. The difference in MMR rate between the two arms, after adjustment for baseline MCyR status, was 21.74% (95% CI, 10.53-32.95; p = 0.001), which met the trial's key secondary endpoint. MMR rate at week 96 showed a consistent trend in favor of asciminib over bosutinib in all subgroups analyzed for demographic and prognostic factors of response, including baseline MCyR status, reason for discontinuation of last prior TKI, number of prior TKI lines, and BCR::ABL1 mutation status at baseline. Although the cumulative MMR rate increased in both arms, the increase was greater with asciminib. MMR was achieved early with asciminib, and the difference in cumulative MMR rates between arms was evident by week 12. By week 96, the probability of achieving MMR was 41.2% with asciminib and 22.6% with bosutinib. The rate of BCR::ABL1IS ≤1% at week 96 in patients with BCR::ABL1IS >1% at baseline was 45.1% with asciminib compared to 19.4% with bosutinib. Similarly, the cumulative incidence of BCR::ABL1IS ≤1% at week 96 was higher with asciminib (53.7%) than with bosutinib (33.7%), with differences apparent at week 8. The incidence of BCR::ABL1IS≤1% in patients receiving asciminib continued to increase after 48 weeks of treatment. The rate of complete cytogenetic response (CCyR) at week 96 in patients who did not have CCyR at baseline was 39.8% for

asciminib and 16.1% for bosutinib. The difference in CCyR rate between the two arms, after adjusting for baseline MCyR status, was 23.9%. At the end date, fewer patients receiving asciminib (51.0%) than bosutinib (82.9%) experienced treatment failure. The median time to treatment failure was much longer with asciminib (24 months) than with bosutinib (6 months). The 2-year progression-free survival estimate (95% CI) was 94.4% (88.6–97.3) with asciminib and 91.1% (79.5–96.3) with bosutinib; the 2-year overall survival estimate (95% CI) was 97.3% (92.9–99.0) with asciminib and 98.6% (90.2–99.8) with bosutinib.

The percentage of patients with new-onset mutations at the end of treatment was 25.6% for asciminib and 6.7% for bosutinib. However, a greater proportion of patients who discontinued due to lack of efficacy or disease progression had no BCR::ABL1 mutations detected at their end-of-treatment visit in both arms: 56.4% (22/39) with asciminib and 66.7% (20/30) with bosutinib.

Safety data

The most common adverse reactions of any grade (incidence ≥20%) in patients receiving asciminib were musculoskeletal pain (37.1%), upper respiratory tract infections (28.1%), thrombocytopenia (27.5%), fatigue (27.2%), headache (24.2%), arthralgia (21.6%), increased pancreatic enzymes (21.3%), abdominal pain (21.3%), diarrhea (20, 5%) and nausea (20.2%).

The most common grade ≥ 3 adverse reactions (incidence ≥5%) in patients receiving asciminib were thrombocytopenia (18.5%), neutropenia (15.7%), elevated pancreatic enzymes (12.4%), hypertension (8.7%) and anemia (5.3%). Serious adverse events occurred in 12.4% of patients receiving asciminib. The most common serious adverse reactions (incidence ≥1%) were pleural effusion (2.5%), lower respiratory tract infection (2.2%), thrombocytopenia (1.7%), pyrexia (1.4%), pancreatitis (1.1%), noncardiac chest pain (1.1%), and recovery (1.1%).

Data on comparators

In view of the clinical practice in Bulgaria, the medicinal products available in the PDL and the Pharmacotherapeutic Guidance for Clinical Hematology, the tyrosine kinase inhibitors - bosutinib, dasatinib, nilotinib and ponatinib - were chosen as comparative alternatives to Scemblix (asciminib) in the target group of patients.

Pharmacoeconomic indicators

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

Three positive evaluations are presented, under certain conditions, by HTA agencies of other countries - HAS (France), NICE (Great Britain) and CADTH (Canada).

Applied analysis
A pharmacoeconomic cost-utility analysis (CUA) assessing the cost-effectiveness of the health technology in terms of improvement in patient quality of life (QALY) and an additional cost-effectiveness analysis assessing the cost-effectiveness in terms of life years gained (LYG) were applied. The point of view is of the paying institution - NHIF, the time horizon is for life (50 years).

The comparative alternatives used in the analysis are the tyrosine kinase inhibitors - bosutinib, dasatinib, nilotinib and ponatinib. Costs and results are discounted at 3.5% per annum. The model has a partitioned survival model structure. The pharmacoeconomic analysis performed shows that Scemblix (asciminib) is not a cost-effective therapy compared to the comparative alternatives, as the significantly better outcomes related to LYs and QALYs (compared to bosutinib, dasatinib and nilotinib) have an ICER of over 3xGDP per capita. Compared to ponatinib, the candidate health technology has lower total treatment costs, but also lower values for health benefits - LY and QALY.

Subgroup analyses
No subgroup analyzes were performed.

Costs for the assessed health technology
The analysis includes costs of drug therapy with the candidate health technology and with the comparative alternatives, costs of medical services and patient follow-up, and costs of treatment-related adverse events and palliative care.

Budget impact analysis
The analysis of the budget impact was conducted from the point of view of the paying institution - NHIF. The time horizon of the analysis is 5 years. The expected number of patients to be treated with asciminib is 13 in the first year and reached 61 in the fifth year. Two scenarios were developed: "A world without the new health technology" and "A world with the new health technology".

The budget impact analysis performed shows that the inclusion of the Scemblix drug therapy in Annex 2 of the PDL for the treatment of adult patients with CLL in chronic phase after failure of two or more tyrosine kinase inhibitors will result in an additional cost in Year 1, but from Year 2 to Year 5 of the analyzed period, cost savings can be expected, excluding risk-sharing agreements and patient access schemes.

Conclusion

Scemblix (asciminib) provides a new treatment option for patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase (Ph+ CML-CF) previously treated with two or more tyrosine kinase inhibitors. These are patients who have gone through two transitional lines of treatment, where treatment options have been drastically reduced, and who have a large unmet need for treatment.

The pharmacoeconomic analysis showed that Scemblix (asciminib) was not a cost-effective therapy relative to comparator alternatives, as the incremental ratios were above the favorable cost-effectiveness threshold for significantly better LY and QALY-related outcomes. Compared to ponatinib, the candidate health technology has lower total treatment costs, but also lower LY and QALY values. The budget impact analysis shows that health technology reimbursement will result in cost savings over the period of the analysis.