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

HEALTH TECHNOLOGY ASSESSMENT

Ayvakyt

50 mg film-coated tablet x 30 (bottle)

100 mg film-coated tablet x 30 (bottle)

INN avapritinib

Therapeutic indication(s)	Monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukemia (MCL), after at least one systemic therapy.
Start/end date of procedure	30.05.2023 – 20.12.2023
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 Ayvakyt

Health problem

Advanced systemic mastocytosis (AdvSM) is a debilitating and life-threatening disease associated with a high burden for patients due to the multiple symptoms that can affect different organs. AdvSM includes the most severe forms of systemic mastocytosis (SM), which is a rare, heterogeneous disease characterized by the accumulation of neoplastic mast cells in the bone marrow and also in other organs and tissues. There are also non-advanced forms of systemic mastocytosis such as indolent (ISM) and smoldering (SSM) systemic mastocytosis. AdvSM accounts for only 5%–10% of SM cases, but comprises the most aggressive and life-threatening forms and is subdivided into aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL). The most common triggers include, but are not limited to, insect stings, physical stress (heat, cold, mechanical skin irritation, exercise), emotional stress, alcohol, spicy foods and medications, including aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), narcotic substances, muscle relaxants, contrast agents and others.

Avapritinib is the only targeted therapy designed for highly effective and selective inhibition of KIT D816V. Avapritinib is a kinase type 1 inhibitor that exhibits in vitro biochemical activity against PDGFRA D842V and KIT D816V mutants associated with resistance to imatinib, sunitinib and regorafenib, with half-maximal inhibitory concentrations (IC50) of 0.24 nM and 0.27 nM, respectively, and greater activity against the clinically relevant KIT Exon, KIT Exon 11/17, and KIT Exon 17 mutants than against the KIT wild-type enzyme. In cellular assays, avapritinib inhibited the autophosphorylation of KIT D816V and PDGFRA D842V with an IC50 of 4 nM and 30 nM, respectively. Avapritinib also showed 19 growth inhibitory activity in a mouse mastocytoma xenograft model with a KIT Exon 17 mutation.

Health Technology avapritinib is the first therapy to use the mIWG-MRT-ECNM (International Working Group-Study of Myeloproliferative Neoplasms and European Mastocytosis Expert Network) criteria as a primary efficacy endpoint in a clinical trial in AdvSM. An overall response rate (ORR) of ~75% was demonstrated with avapritinib in patients who can be evaluated according to the mIWGMRT-ECNM criteria. The target population for Ayvakyt is persons aged ≥18 years.

Efficacy data

The efficacy and safety of avapritinib have been demonstrated in two single-arm trials **(EXPLORER and PATHFINDER)** and in a retrospective trial in which pooled results from EXPLORER and PATHFINDER were compared with BAT (best available therapy) (BLU-285-2405). In total, trial BLU-285-2405 included data from 176 patients who received avapritinib in

EXPLORER or PATHFINDER and 141 patients with AdvSM who had previously been treated with BAT.

Avapritinib and midostaurin were compared using indirect treatment comparison (ITC).

Results from the EXPLORER trial showed that the ORR for patients who received avapritinib was 75%. Furthermore, the ORR was consistently high (~60% or more) in patients who had received prior therapy, including midostaurin. Complete remission (CR) was observed in 15% of patients who received avapritinib, and complete remission with partial normalization of peripheral blood counts (CRh) was observed in 21% of patients, indicating that a significant number of patients (36%) have shown a response to treatment with avapritinib. In 92% of patients, bone marrow mast cells were reduced by ≥50%, including complete elimination of bone marrow mast cell aggregates in 77% of patients; in 99% of patients, serum tryptase was reduced by ≥50% and reduced to levels below 20 ng/ml in 74% of patients, and in 86% of patients, spleen volume was reduced by ≥35%.

The results of the PATHFINDER trial showed that ORR was achieved by 75%, including six patients who achieved complete remission with partial CRh. The response rate has also been demonstrated to be consistently high in patients who have received prior treatment, including midostaurin. Responses have also been shown to occur rapidly, with a median duration of response of 2 months (range: 0.3 to 12.2 months). Reduction of bone marrow mast cells by ≥50% in 88% of patients; 60% of patients showed complete elimination of mast cell aggregates in the bone marrow; in 93% of patients, serum tryptase decreased by ≥50%, including to levels below 20 ng/ml in 43% of patients, and in 66% of patients, spleen volume decreased by ≥35%.

The EXPLORER and PATHFINDER clinical trials demonstrated the efficacy of avapritinib for the treatment of patients with AdvSM. Patients with all subtypes of advanced systemic mastocytosis (ASM, SM-AHN and MCL) demonstrated a high response rate to treatment. The efficacy of avapritinib is supported by its targeted mechanism of action, which provides the highest efficacy against the active conformation of KIT D816V. This specificity results in a significant decrease in mast cells in AdvSM patients, including a decrease in organ mast cell infiltration, mast cell mediators, and KIT D816V-containing cells in the blood. Avapritinib produced significant benefits in terms of HRQoL (health-related quality of life) in AdvSM patients as determined by assessments based on the patient's perspective, namely the EORTC–QLQ–C30, a questionnaire designed to determine the ability to perform important activities of daily living in cancer patients, and the AdvSM-SAF, a symptom-focused questionnaire for patients with AdvSM.

In an indirect comparison of midostaurin and avapritinib treatments, avapritinib was found to increase the probability of survival, best response and complete remission in patients with AdvSM.

Safety data

Serious adverse events occurred in 12% of patients receiving avapritinib. The most common serious adverse events during treatment with avapritinib were subdural hematoma (2%), anemia (2%), and hemorrhage (2%). In AdvSM patients treated with 200 mg, 7.1% had adverse reactions leading to permanent discontinuation. Two patients (1.6%) had a subdural hematoma. One patient experienced cognitive impairment, depressed mood, diarrhea, impaired attention, decreased hemoglobin, hair color change, decreased libido, nausea, neutropenia, premature menopause and thrombocytopenia (0.8% for each symptom).

Data on comparators

In observation of the clinical practice in Bulgaria, the best available therapy (BAT), which includes a set of medical activities, was chosen as a comparative alternative to Ayvakyt (avapritinib). In addition, avapritinib and midostaurin were compared.

Pharmacoeconomic indicators

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

Two positive evaluations have been published by other state institutions - Haute Autorité de santé - HAS (France) and GBA (Gemeinsamer Bundesausschuss), Germany.

Applied analysis

The cost-utility pharmaco-economic analysis (CUA) was applied, where the final result in terms of health benefits was presented in the form of added quality life years (QALYs), and cost-effectiveness (CEA), where the final health benefit outcome is presented in terms of life years added (LYs). The perspective of the analysis is that of the paying institution - the National Health Insurance Fund (NHIF). A time horizon of 28 years was chosen, which is consistent with all medical-diagnostic studies, as well as the recommended period of medical-diagnostic activities within the total duration of the observation according to APr #7. Discounting with an annual discount factor of 3.5% has been applied to both costs and results. Alternatives compared in the analysis were midostaurin and best available therapy (BAT).

The health benefit results showed a significant increase in life years (LY) and good quality life years (QALY) with avapritinib therapy compared to the alternatives. The incremental ratios for cost efficiency are placed above the threshold for favorable cost efficiency of BGN 60,636 (3 times GDP/capita).

Subgroup analyses
No subgroup analyzes were performed.

Costs for the assessed health technology
Included in the model are avapritinib healthcare technology costs, therapy administration costs, adverse drug reaction costs and palliative care costs.

Budget impact analysis
The analysis of the budget impact was carried out from the point of view of the paying public institution - NHIF. The time horizon of the budget impact analysis is 5 years. It is assumed that for the first 5 years, the number of patients who will need treatment with avapritinib will increase from 3 to 15 people at the end of the period.

The budget impact analysis of avapritinib projected increased costs without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Ayvakyt (avapritinib) represents an effective new treatment option for advanced systemic mastocytosis (AdvSM) and results in significant improvements in patient survival and quality of life. Currently, no other pharmacotherapy for AdvSM is reimbursed in Bulgaria. Ayvakyt is a rescue treatment for patients whose disease has progressed on previous systemic therapy.

The budget impact analysis of avapritinib projected an increase in costs to the paying institution.