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

HEALTH TECHNOLOGY ASSESSMENT

Rydapt

25 mg soft capsules x 112

Midostaurin

Therapeutic indication(s)	Rydapt is indicatedas monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).
Start/end date of procedure	31.03.2020 – 11.11.2020
Final decision	Rejects inclusion of a new therapeutic indication in Annex 2 of the Positive Drug List (PDL) for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act for payment by the National Health Insurance Fund (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 Rydapt

Health problem

Mastocytosis is a myeloproliferative clonal disease of the bone marrow progenitors with uncontrolled proliferation and accumulation of mast cells, with the formation of focal and/or diffuse infiltrates in the liver, spleen, gastrointestinal tract, skin, bones, soft tissue, leading to organ dysfunction. The pathological process includes skin lesions (pruritus, urticaria), symptoms associated with the release of mediators (angioedema, redness, nausea, vomiting, abdominal pain, diarrhea, episodic anaphylaxis), organ dysfunction caused by direct mastocytic infiltration (hypersplenism, pathologic fractures, ineffective hematopoiesis).

The more aggressive forms of systemic mastocytosis (SM) are associated with a higher degree of visceral organopathy and lower degree of skin involvement. Individual symptoms in SM show a frequency of 31% for musculoskeletal symptoms through 65% for gastrointestinal symptoms.

In indolent SM, the median survival (MS) is similar to that of the respective age and sex of the general population; aggressive SM - MS of 3.5 years; SM, associated with hematological diseases - MS 2 years; mast cell leukemia (MCL) - MS 2 months.

Mastocytosis poses a significant medical and social burden. Progressive disability occurs in 60-80% of patients, and in 28% it is severe or intolerable. The severity of disability is independent of SM forms, D816V kit mutation status, or serum tryptase levels. Only 14% of patients report that the disease does not affect their quality of life.

The target population of midostaurin as monotherapy includes adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukemia (MCL). As a targeted therapy, midostaurin is the optimal option in patients with SM/ASM with a KIT mutation in progenitor cells and old age, a mutation in exon 17 (including the D816V point mutation), which occurs in one third of the cases.

Epidemiological data

The prevalence in Europe is 3.75/100,000 population, the annual incidence is 0.9/100,000. The disease affects both sexes with a slight predilection for older women, regardless of ethnicity and age distribution. In Bulgaria, the expected number of patients with systemic mastocytosis with associated haematological neoplasia (20-35%) is about 10. The total number of cases of aggressive systemic mastocytosis is expected to be about 12 (almost entirely of adults without skin involvement with an unfavorable prognosis of 2 to 4 years).

Expected number with mast cell leukemia - less than 1% of all cases or 1 patient with a rapid lethal outcome.

The stated epidemiological data for Bulgaria are provisional, coming from reports from single studies, mainly from the medical societies of hematology and allergology.

Efficacy data

The therapeutic efficacy and safety profile of midostaurin were analyzed in three clinical trials.

General characteristics of the studies
The studies were prospective with a follow-up period of 60, 89 and 32 months, respectively, with the same goal: efficacy of midostaurin in the most aggressive forms of the disease - ASM or MCL +/- AHNMD (systemic mastocytosis with clonal hematological disease with non-mast cell lineage disease) and identical endpoints. The primary endpoint was the overall response rate (ORR), which included a significant and partial response after 6 days and confirmed over the next 56 days. Secondary endpoints were duration of response (DOR), time to response (TTR), progression-free survival (PFS), overall survival (OS), safety. The average follow-up duration (from inclusion to the end date for data analysis) is 45-70 months.

The results of the studies show an ORR of 59.6%, 73.1% and 42.7%, respectively; DOR: 31.4 months, in others it was not achieved; OS -26.8 months; 40 months; wasn't determined in the third study.

Patient reported outcomes in clinical trial D2201
Patients reported a reduced incidence of 30 of 32 symptoms during the study (assessed by the Total Memorial Symptom Assessment Scale - TMSAS).

Safety data

The safety of midostaurin 100 mg twice daily in patients with ASM, SM-AHN and MCL was evaluated in 142 patients in two open-label, single-arm, multicenter studies. The median duration of midostaurin exposure was 11.4 months.

The most common adverse reactions (ADRs) were nausea (82%), vomiting (68%), diarrhea (51%), peripheral edema (35%) and fatigue (31%). The most common grade 3/4 ADRs were fatigue (8.5%), sepsis (7.7), pneumonia (7%), febrile neutropenia (7%), and diarrhea (6.3%). The most common non-haematological laboratory abnormalities were hyperglycaemia (93.7%), increase in total bilirubin (40.1%), increase in lipase (39.4%), increase in aspartate aminotransferase (AST) (33.8%) and increase in alanine aminotransferase (ALT) (33.1%).

The most common haematological laboratory abnormalities were decreased absolute lymphocyte count (73.2%) and decreased ANC (absolute neutrophil count) (58.5%). The most common grade 3/4 laboratory abnormalities were a decrease in absolute lymphocyte count (45.8%), a decrease in ANC (26.8%), hyperglycemia (19%), and an increase in lipase (17.6%).

Change in the dosage (interruption or adjustment) due to ADRs was reported in 31% of patients.

ADRs leading to treatment discontinuation were reported in 9.2% of patients. The most common (≥1%) were febrile neutropenia, nausea, vomiting and pleural effusion.

Data on comparators

The assessed health technology has not been compared to other treatments due to the lack of an alternative paid for with public funds.

Pharmacoeconomic indicators

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

Two positive evaluations of midostaurin were retrieved for the treatment of aggressive systemic mastocytosis, systemic mastocytosis associated with hematological neoplasm, mast cell leukemia. The assessments were intended for the health systems of France (HAS) and Germany (G-BA).

Applied analysis

The objective of the analysis was to assess the cost effectiveness of midostaurin health technology compared to standard care of treatment of adult patients with aggressive systemic mastocytosis, systemic mastocytosis associated with haematological neoplasm, or mast cell leukemia. The main therapeutic alternatives of midostaurin in the treatment of aggressive mastocytosis, systemic mastocytosis associated with hematological neoplasm, or mast cell leukemia are Interferon-α, corticosteroids, cladribine (administered as infusion), antihistamines, imatinib, belonging to the standard of care. As these therapies are not included in a positive drug list and/or are not indicated for the respective indication, midostaurin health technology has not been compared with other active treatments, only the impact of medical services and adverse events on the costs and benefits in both arms of treatment (midostaurin and SoC) were considered. The perspective of the analysis is that of the payer - the National Health Insurance Fund. A pharmacoeconomic cost-utility analysis (CUA) was employed to evaluate the midostaurin health technology.

Costs of the assessed health technology

The analysis considers the following costs:

- Cost of drug therapy with midostaurin
- Alternatives (Standard of Care - SoC) cost
- Cost of ADR management

The analysis showed that compared to SoC, midostaurin therapy demonstrated a higher value of acquired health benefits at a higher direct cost per patient. Midostaurin demonstrates therapeutic superiority, expressed in more years of life gained. The results of the cost-benefit analysis did not identify midostaurin as a cost-effective therapy against SoC.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the paying public institution, the time horizon is 5 years.

There are 3 patients eligible for treatment with Rydapt in the first year rising to 7 in the fifth year.

The reimbursement of the new technology will lead to added cost for the payer, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Rydapt is an orphan medicine used to treat a rare disease with a prevalence of 3.75/100,000 population or 0.9/100,000 per year. The evaluated medicinal product is a pathogenetic targeted therapy for cases of aggressive systemic mastocytosis (ASM), systemic mastocytosis associated with haematological neoplasm (SM-AHN), or mast cell leukemia (MCL) with optimal option - the presence of kit mutation in the progenitor cells, exon 17 mutation (including the point mutation D816V). Midostaurin (Rydapt) covers the unmet medical need for AFM and D816V (+).

Treatment with midostaurin in ASM results in a high rate of sustained response and significant improvement in OS. The treatment is usually well tolerated and has a manageable toxicity profile, mainly gastrointestinal. In more than 40% of patients, the recovery of organ damage after treatment with midostaurin resulted in a significant improvement in ASM symptoms and quality of life and elimination of transfusion dependence.

Midostaurin is not a cost-effective therapy vs SoC, although it results in more years of life gained. The inclusion of the health technology in the Positive Drug List will lead to increased cost for the National Health Insurance Fund.