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

HEALTH TECHNOLOGY ASSESSMENT

Inrebic

100 mg capsule, hard x 120

INN Fedratinib

Therapeutic indication(s)	Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis who have been treated with ruxolitinib.
Start/end date of procedure	24.02.2023 - 21.12.2023
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 provided medical services.

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

Health problem

Osteomyelofibrosis (OMF) results from stem cell mutations with initial overactivation of myeloid progenitors, autonomous proliferation of all three blood lineages, followed by gradual but progressive development of bone marrow fibrosis and extramedullary ineffective hematopoiesis. OMF belongs to the group of chronic myeloproliferative neoplasias, where two types are distinguished:

• Primary myelofibrosis - myelofibrosis that occurs independently in 70% of cases.
• Secondary myelofibrosis - occurs in the evolution of other chronic myeloproliferative neoplasias - essential thrombocythemia and polycythemia vera. Secondary myelofibrosis accounts for about 10% to 20% of cases.

Myelofibrosis is a rare hematologic disease characterized by peripheral and bone marrow tricytopenia, bone marrow fibrosis, and extramedullary hematopoiesis. The evolution of the disease is characterized by huge splenomegaly, constitutional symptoms and reduced survival. It can either occur de novo as primary myelofibrosis or after previously diagnosed polycythemia vera (PV) and essential thrombocythemia (ET). The disease results from mutations in a number of genes encoding JAK2, calreticulin (CALR) and myeloproliferative leukemia (MPL) with subsequent pathological activation of JAK/STAT signaling.

The clinical picture is associated with debilitating symptoms steadily progressing with the evolution of the disease: splenomegaly in over 80% of patients, cytopenias (e.g. anemia, 35% of patients; neutropenia - 10%, thrombocytopenia), constitutional symptoms (night sweats, fever, unmotivated pruritus and weight loss to the extent of cachexia in one third, progressive fatigue in > 90% of patients as a result of abnormal cytokine production. The splenomegaly causes abdominal pain, early satiety, weight loss associated with lack of appetite. The treatment strategies depend on the prognostic category of the disease, as well as the presence and type of symptoms.

Fedratinib (Inrebic) is an oral kinase inhibitor with activity against wild-type and mutationally activated JAK2, a key component of the JAK/STAT pathway, and FMS-like tyrosine kinase 3 (FLT3). Fedratinib reduces the effects of constitutive activation of JAK2, which plays a key role in the pathogenesis of MF. This leads to relief of the main symptoms associated with MF, including

splenomegaly. Fedratinib binds to both the peptide substrate binding site and the adenosine triphosphate (ATP) binding site of JAK2, thereby providing a low risk of occurrence of fedratinib-resistant clones. Fedratinib is an alternative to ruxolitinib as first-line of treatment, especially in patients with platelet levels 50–100 x10⁹/l. Patients with platelet counts 50–100 x10⁹/l generally received low-dose ruxolitinib (5–10 mg vs. 20 mg bid) or HU (which was used in approximately 30% of these patients) and achieved less benefit than patients, who may receive higher doses of ruxolitinib.

Efficacy data

The therapeutic efficacy and safety profile of fedratinib was analyzed in one clinical trial:

JAKARTA (NCT01437787) is a clinical trial to assess the safety and efficacy of fedratinib 400 mg or 500 mg compared with placebo in reducing spleen volume in patients with primary or secondary myelofibrosis. The primary endpoint was splenic response, defined as the proportion of patients with at least a 35% SVR - decrease in spleen volume (measured by MRI) from baseline at the end of cycle 6 and confirmed by follow-up scan 4 weeks later. Splenic response rate at the end of cycle 6 (no follow-up scan 4 weeks later) was also assessed. Total symptom score (TSS) response, defined as the proportion of patients with at least a 50% reduction in TSS (assessed by the modified MF-SAF v2.0) from baseline to the end of cycle 6, was included as a key secondary endpoint. Safety assessments included AE incidence, clinical and laboratory parameters, body weight, ECOG PS and ECG.

The results of the clinical trial showed that the primary endpoint was met and a greater proportion of patients in the fedratinib group achieved a splenic response at the end of cycle 6 (confirmed by a follow-up scan 4 weeks later) compared to placebo: 36.5% vs. 1.0% ($p<0.0001$). At the end of cycle 6 (no follow-up confirmation), the response rate was 46.9% for fedratinib vs. 1.0% for placebo ($p<0.0001$). The improvements in spleen size were rapid, with a reduction of ≥50% from baseline occurring at the end of cycle 2 in 29% of patients receiving fedratinib compared with 3% of patients in the placebo group. The median size reduction at this time point was - 40% with fedratinib versus 0% with placebo. The improvement in SVR at the end of cycle 6 with confirmation 4 weeks later was similar for all subgroups considered regardless of the administered therapy. Almost all (96%) patients in the fedratinib group achieved SVR after the sixth treatment cycle, while three-quarters of patients (76%) in the placebo group had an increase in spleen volume. At the end of the 6th cycle, a TSS response was achieved in 40.4% of patients in the fedratinib group versus 8.6% in the placebo group ($p<0.0001$). In a greater proportion (79%) of patients the fedratinib group had symptom improvement (i.e., TSS percent change >0) at the end

of cycle 6 compared with 51% in the placebo group. The median time to final symptom improvement (defined as ≥50% improvement of TSS for at least two consecutive visits) following fedratinib was 16.1 weeks. Clinically significant and statistically significant intergroup differences in favor of fedratinib were observed for all individual MFSAF symptoms at all visits (>0.50) for night sweats, abdominal discomfort, rapid satiety, pain under the ribs on the left side. After the sixth cycle of treatment, almost one-third (31%) of patients receiving a dose of 400 mg fedratinib once daily experienced both decreased spleen volume and symptom response.

Safety data

The most common non-hematological adverse reactions were diarrhea (67.5%), nausea (61.6%) and vomiting (44.8%). The most common hematologic adverse reactions were anemia (99.0%) and thrombocytopenia (68.5%) based on laboratory values.

Data on comparators

A comparable alternative is ruxolitinib.

Pharmacoeconomic indicators

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

Two opinions have been published by other governmental institutions – HAS (France) and SMC (Scotland), NICE (Great Britain), with HAS giving a positive opinion.

Applied analysis
A cost-utility analysis (CUA) was applied, in which the final result in terms of health benefits was presented in a quality-adjusted life year (QALY) and in addition a cost effectiveness analysis (CEA) was carried out, where the final result in terms of health benefits is presented in a life year gained (LYG). Ruxolitinib therapy was chosen as a comparative alternative. The perspective of the analysis is that of the paying institution - the National Health Insurance Fund (NHIF). Health benefits and costs are discounted with an annual discount factor of 3.5%. The time horizon is 33 years. A discrete event simulation (DES) was used for modeling, covering both JAKi-naive and JAKi-exposed populations. The type of model resembles the approach taken in previous evaluations of Jakavi (ruxolitinib), the first JAK inhibitor approved for myelofibrosis. As the

discrete event simulation (DES) model structure is not accepted by all health authorities, a partitioned survival model (AUC) has been developed.

Fedratinib therapy increases patient health benefits in terms of additional years of good-quality life. The value of the incremental cost-effectiveness ratio is above the break-even point of 3xGDP/capita.

Costs for the assessed health technology
The costs included in the model are health technology costs, health technology alternative costs, follow-up costs, and adverse event control costs.

Subgroup analysis
Not attached.

Budget impact analysis
The analysis of the budget impact was conducted from the perspective of the paying institution - NHIF. The time horizon is 5 years. The target population includes elderly patients with primary myelofibrosis, myelofibrosis after polycythemia vera, or myelofibrosis after essential thrombocythemia who were treated with ruxolitinib. The estimated number of patients in the first year is 11 and in the fifth year - 14. The budget impact analysis is based on two scenarios - "World without Inrebic" and "World with Inrebic". Option 1 presents costs at a reported 100% dose intensity (according to SPC) of the candidate therapy, and Option 2 presents the relative dose intensity (RDI) derived from clinical trial data. The analysis predicts an increase in costs over a five-year period for the NHIF, excluding risk-sharing agreements and patient access schemes.

Conclusion

Health technology Inrebic (fedratinib) is an oral kinase inhibitor that suppresses the key pathogenetic factor - activated Janus-associated kinase 2 (JAK2) - in patients with primary and secondary osteomyelofibrosis. This leads to relief of the main symptoms associated with myelofibrosis, including splenomegaly.

The pharmacoeconomic results show that fedratinib therapy increases the health benefits for the patients, expressed in additional years of good quality life. The budget impact analysis predicts an increase in costs for the paying institution.