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

HEALTH TECHNOLOGY ASSESSMENT

Xospata

40 mg film-coated tablet x 84

gilteritinib

Therapeutic indication(s)	Xospata is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation.
Start/end date of procedure	26.05.2020 – 11.12.2020
Final decision	Inclusion 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 Xospata

Health problem

Acute myeloid leukemia (AML) is a malignant disease of hematopoiesis, which is characterized by uncontrolled proliferation of myeloid precursors in combination with differentiation and maturation block in the clonal cell line. It proceeds with blastic infiltration of the bone marrow, suppression of normal hematopoiesis and extramedullary expansion. A wide range of genetic abnormalities are responsible for the initiation of neoplastic growth, many of which have been described, confirmed and validated in large-scale cohorts of patients and constitute the "genomic terrain" of AML.

The modern classification of OML was developed based on the most common genetic abnormalities in AML. For example, the mutational status of FLT3 outlines a subtype of poor prognosis, higher recurrence rates, shorter remissions, reduced disease-free survival (DFS) and reduced five-year overall survival (OS). There are two major FLT3 mutations identified in patients with AML: FLT3-ITD and FLT3-TKD. They stratify patients with AML into prognostic risk groups due to their proven association with an increased risk of relapse or refractoriness to conventional treatment. Among the mutations of FLT3, those of class III receptor tyrosine kinase are among the most common with proven diagnostic and unfavorable prognostic value.

In clinical terms, the prognosis in AML is still among the most unfavorable in malignant diseases. The disease has a high risk of recurrence and low survival, especially in elderly patients with recurrent or refractory AML and unfavorable genetic profile. Patients with a second relapse, as well as patients resistant to the first rescue therapy have an extremely poor prognosis, with survival, measurable in weeks.

AML represents a significant burden for patients in somatic, psychological and social aspect. Patients with R/R AML have more severe emotional problems compared to newly diagnosed, as the prognosis is more pessimistic.

Targeting FLT-3 mutations is one of the most important goals in the treatment of AML. While for newly diagnosed patients with AML/FLT-3 + there is an effective drug for induction and maintenance treatment with very good clinical results, there is currently no generally accepted therapeutic standard for the treatment of patients with refractory or recurrent acute myeloid leukemia (R/R AML) with FLT3 mutations.

Epidemiological data

More than 16,000 new cases of AML are forecast in Europe annually. According to SEER the mean age is 67 years, with 54% of diagnosed patients over 65 years and one third over 74. In Bulgaria, the prevalence of leukemia is 15 per 100,000 people, of which 32% are patients with AML over 18 years of age, and the percentage of FLT3 mutations is 25%.

Efficacy data

Efficacy data are based on the main studies with Xospata (gilteritinib).

Main study: ADMIRAL, open multicenter randomized, phase 3 study of ASP2215 versus rescue chemotherapy in patients with R/R AML and FLT3 mutations. The results show that the frequency of complete remission or complete remission with partial haematological recovery (CR/CRh) was 34.0% in the gilteritinib arm and 15.3% in the rescue chemotherapy arm. The mean duration of CR/CRh was 11.0 months in gilteritinib arm and 1.8 months in the rescue chemotherapy arm, with a risk ratio (HR) of 0.480. The mean overall survival was 9.3 months vs 5.6 months and the 12-month overall survival was 37.1% vs 16.7%. The average event-free survival (EFS) was 2.8 months versus 0.7 months. The frequency of hematopoietic stem cell transplantation (HSCT) was 25.5% versus 15.3%. The mean time to remission with gilteritinib was longer in in numerical terms (but not statistically significant) than with rescue chemotherapy. The therapeutic response was also improved in patients with gilteritinib dose adjustment compared to the standard arm.

CHRYSALIS study, an open-label, first-in-human dose escalation study in patients with R/R AML, with concomitant multi-dose expansion cohort shows that the frequency of combined complete remission CRc is 30%, the median for total survival (OS) is 25 weeks and the median duration of response (DOR) is 17 weeks. The incidence of CRc in the subgroup of patients with FLT3 mutations was 37%, the median for OS is 30 weeks and the median duration of response (DOR) is 20 weeks. The frequency of CRc in the subgroup with FLT3 mutations treated with doses of 80 mg daily was 41%. The median for OS in this subgroup is 31 weeks and DOR is 20 weeks, 32% of patients achieved incomplete haematological recovery (CRi).

<u>Event-free survival progression and duration of response</u>

In the ADMIRAL study, the mean EFS was 2.8 months versus 0.7 months in the rescue chemotherapy arm. The EFS endpoint does not meet the criteria for statistical significance (HR: 0.793). In the CHRYSALIS study, the median for response time (DOR) was 17 weeks, and in the FLT-3 + subgroup it was 20 weeks.

Dependence on blood transfusions

The frequency of transfusion independence conversion was 38.2% of patients who became independent of transfusions after baseline.

Analysis of patient-reported data

The ADMIRAL study assessed the health related quality of life of patients (HRQOL). The gilteritinib PRO arm has shown that quality of life (HRQOL) remained good during therapy. No clinically relevant changes were reported in symptoms of fatigue, dizziness and stomatitis compared to baseline at the first day of the second treatment cycle. Patients in the gilteritinib arm frequently reported symptoms of dizziness at the end of treatment, which is in line with the known adverse drug reactions profile of gilteritinib.

Safety data

Gilteritinib is a medicinal product with an acceptable and manageable toxicity profile.

In the ADMIRAL study, in the gilteritinib arm, the most common non-haematological treatment-related adverse events (TRAE) are: pyrexia (42.7%), increased ALT (41.9%), increased AST (40.2%), diarrhea (32.9%), nausea (32.1%) and constipation (30.9%). The most common hematological adverse events associated with treatment in the ADMIRAL/gilteritinib study were anemia (47.2%), febrile neutropenia (46.7%), thrombocytopenia (25.6%) and decreased platelets (22.8%).

Data on comparators

There is no medicinal product that constitutes a therapeutic alternative. The alternative is rescue chemotherapy.

Pharmacoeconomic indicators

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

The health technology Xospata (gilteritinib) has received a positive evaluation from G-BA (Germany), NICE (UK) and HAS (France).

Applied analysis

A cost-effectiveness pharmacoeconomic analysis was used. The perspective of the analysis is of the paying institution – the NHIF. The time horizon is one year. No discounting has been applied due to the 1-year time horizon. A comparator is rescue chemotherapy. Xospata (gilteritinib) is an orphan drug intended for use in a rare malignant disease. Orphan drugs are characterized by the inability to fall into the traditional pharmacoeconomic efficacy

indicators. Gilteritinib therapy shows better results - leads to more years of life gained than rescue chemotherapy at a higher therapy cost.

Cost of the assessed health technology
Attached are cost for the medicinal product acquisition, cost for treatment administration, cost of diagnosis before and during therapy and cost of adverse drug reactions therapy.

Analysis of subgroups
Not attached.

Budget impact analysis
The analysis of the budget impact was conducted from the perspective of the public payer - the National Health Insurance Fund. The time horizon of the analysis is 5 years. The expected number of patients for the first year is 13, and for the fifth 18. Reimbursement of the health technology will generate additional costs for the payer in the first year, increasing over each following year, not taking into account risk-sharing agreements and patient access schemes.

Conclusion

Xospata is indicated as monotherapy for the treatment of adults who have recurrent or refractory acute myeloid leukemia (AML) with FLT3 mutation. Gilteritinib is an innovative health technology with an orphan drug status and is not cost-effective at a profitability threshold of 3 times GDP per capita. The results of the budget impact analysis show that the reimbursement of the health technology will lead to additional cost for the National Health Insurance Fund.