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

HEALTH TECHNOLOGY ASSESSMENT

Pemazyre

4.5 mg, tablet x 14 blister

INN Pemigatinib

Therapeutic indication	Monotherapy for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.
Start-end of the procedure	18.07.2023 – 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 Pemazyre

Health problem

Biliary tract cancer (Cholangiocarcinoma; CCA) is a malignant disease of epithelial origin with a high mortality rate that can occur anywhere in the biliary tree. CCA is characterized by cholangiocytic differentiation and probably arises primarily from the epithelial cells lining the bile ducts, which are called cholangiocytes. CCA accounts for <1% of all human cancers and is the second most common primary liver cancer after hepatocellular carcinoma (HCC), accounting for 10%-15% of all primary liver cancers. Depending on the site of tumor origin, CCA can be classified as intrahepatic (iCCA) or extrahepatic (eCCA). Recurrent pathological features in almost all subtypes CCA involves chronic inflammation and/or cholestasis. The symptoms associated with CCA are usually nonspecific and appear in the advanced stages of the disease. The most common symptoms in CCA are jaundice and associated pruritus. Emotional functioning and fatigue worsen during the first 6 months after diagnosis. Jaundice is very common in patients with eCCA because tumor localization often leads to blockage of bile drainage. However, jaundice is rarely seen in iCCA, which usually presents with abdominal pain and weight loss. Abdominal pain or dyspepsia, fatigue, and lack of appetite were found to be the most troublesome for CCA patients compared to other symptoms.

Surgery is the only curative treatment option for patients with CCA, but less than 1/2 of patients are resectable at diagnosis. Furthermore, 10-45% of patients considered resectable are found to be unresectable at exploratory laparotomy, and the recurrence rate in the minority of patients who undergo surgery is 50-60% .

Pemazyre is a small molecule kinase inhibitor of FGFR1, 2, and 3. Pemazyre inhibits FGFR phosphorylation and signaling, selectively reducing cell viability in cancer cell lines with FGFR-activating genetic alterations, including point mutations, amplifications, and fusions/rearrangements. Treatment with Pemazyre continues to progression or unacceptable toxicity. In clinically stable patients with initial evidence of disease progression, it is recommended that treatment be continued until disease progression is confirmed.

Efficacy data

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

Clinical trial **FIGHT-202** is a phase 2, open-label, international, single-arm trial to evaluate the efficacy and safety of pemigatinib in patients with advanced/metastatic or surgically unresectable CCA, including FGFR2 rearrangements or fusions, other FGF/FGFR alterations, or negative for any FGF/FGFR alterations that have progressed on at least 1 line of prior systemic therapy.

Primary endpoint was overall response rate (ORR) to pemigatinib in subjects with FGFR2 rearrangements or fusions based on central genomic laboratory results who had progressed on at least 1 prior treatment (Cohort A).

Secondary endpoints - ORR in participants with FGF/FGFR alterations other than FGFR2 fusions or rearrangements (Cohort B), ORR in all participants with FGF/FGFR alterations (Cohorts A and B), ORR in participants with negative alterations of FGF/FGFR (cohort B [US only]), progression-free survival PFS (from first dose to progressive disease (PD) or death; all cohorts), duration of response (DOR, time to complete response (CR) or partial response (PR); all cohorts) to progressive disease (PD); all cohorts), disease control rate (DCR, complete response (CR) + partial response (PR) + stable disease (SD); all cohorts), overall survival (from first dose to death for any cause; all cohorts), safety and tolerability were assessed by assessing the frequency, duration and severity of adverse events (AEs); by reviewing the results of physical examinations, changes in vital signs, and electrocardiograms; and by clinical laboratory evaluations of blood and urine samples (all cohorts) and population pharmacokinetics (all cohorts).

The results of the clinical trial showed that objective response was 35.5%, confirmed complete response - 2.8%, confirmed partial response - 32.7%, stable disease: 46.7%, median duration of response - 9.13 months and PFS - 6.93 months.

Safety data

The most common side effects were hyperphosphatemia (60.5%), alopecia (49.7%), diarrhea (47.6%), nail toxicity (44.9%), fatigue (43.5%), nausea (41.5%), stomatitis (38.1%), constipation (36.7%), dysgeusia (36.1%), dry mouth (34.0%), arthralgia (29.9%), dry eye (27.9%), hypophosphatemia (23.8%), dry skin (21.8%), and palmar-plantar erythrodysesthesia syndrome (16.3%).

Data on comparators

The chemotherapy regimen mFOLFOX (5-fluorouracil, oxaliplatin, calcium folinate) was chosen as a comparative alternative.

Pharmacoeconomic indicators

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

Three assessments have been published by other state institutions - The National Institute for Health and Care Excellence - NICE (Great Britain), Haute Autorité de santé - HAS (France) and The Federal Joint Committee - G-BA (Germany). As NICE opinion and G-BA recommend

reimbursement of pemigatinib indicated as monotherapy for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement who has progressed after at least one previous line of systemic therapy. HAS also gives a positive opinion.

Applied analysis
A cost-effectiveness pharmacoeconomic analysis (CEA) was applied, in which the final result in terms of health benefits is presented in the form of life years gained (LYG) as well as a cost-utility analysis (CUA), in which the final outcome in terms of health benefits is expressed as a quality-adjusted life years (QALY) gained. mFOLFOX was selected as a comparative alternative. The perspective of the analysis is that of the paying institution - the National Health Insurance Fund (NHIF). The chosen time horizon is lifetime (45 years). Costs and outcomes were discounted at an annual discount rate of 3.5%. A model with 5 health states was used: "No progression, on treatment", "No progression, off treatment", "With progressive disease on treatment", "Progressed illness, discontinued treatment" and death.

The results of the analysis show that Pemazyre therapy is above the favorable cost-effectiveness threshold of BGN 60,636 (3xGDP per capita), which defines the therapy as cost-ineffective.

Costs for the assessed health technology
Included in the model were costs for Pemazyre drug therapy, costs for acquiring pemigatinib, costs for therapeutic alternatives, administration costs, follow-up costs, adverse event costs, and palliative care 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 all patients with locally advanced or metastatic cholangiocarcinoma, with a fusion or rearrangement of the fibroblast growth factor receptor 2 (FGFR2) that has progressed after at least one prior line of systemic therapy. The estimated number of patients during the first year is 1, and in the fifth year – 4. The budget impact analysis considers two scenarios: "World without" and "World with" the new technology.

The analysis projected increases in costs over a five-year period to NHIFs, excluding risk-sharing agreements and patient access schemes.

Conclusion

Treatment options for unresectable or advanced/metastatic patients are limited to palliative care, chemotherapy and best supportive care (BSC), including biliary stenting. Pemazyre is a selective,

potent, oral FGFR inhibitor that offers a valuable non-chemotherapy option for patients with cholangiocarcinoma with FGFR2 fusions or rearrangements. The analysis forecasts increased costs over a five-year period to the NHIF.