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

HEALTH TECHNOLOGY ASSESSMENT

Lenvima

4 mg capsule, hard x 30

lenvatinib

Therapeutic indication(s)	Indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.
Start/end date of procedure	29.05.2020 – 30.09.2020
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.

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

Health problem

Hepatocellular carcinoma (HCC) is the most common histological subtype of liver cancer (90% of cases). The risk of developing HCC is 2.4 times higher in men than in women, increasing with age - the average age of onset of HCC is 63-65 years. In 80% of cases hepatocellular carcinoma is caused by chronic liver disease. Risk factors include viral infection with hepatitis B or C, excessive alcohol consumption, obesity and aflatoxins. The majority of cases of HCC are diagnosed at an advanced stage in the presence of regional and distant metastases. Patients with advanced HCC (BCLC stage C and D) account for 56% of all HCC patients.

Late diagnosis implies significant tumor volume and an increased likelihood of advanced disease. The diagnosis of HCC is made on the basis of non-invasive criteria or after a biopsy.

The symptoms of HCC are similar to those of chronic hepatitis, in the former there is pain in the right hypochondrium, increased abdominal circumference and increased fatigue. In advanced HCC, there may be mood swings, leg swelling, abdominal swelling due to ascites, rapid onset or worsening of portal hypertension with esophageal or rectal varices, as well as hemorrhoids or bleeding. Over 80% of patients with HCC have cirrhosis. Cirrhosis can lead to the development of signs of hepatic decompensation and/or complications, such as esophageal or gastric varices, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome (HRS) and hepatic encephalopathy. Acute decompensated diabetes is also a sign of advanced HCC.

The most important prognostic factors as regards survival are elevated alpha fetoprotein (AFP) levels, the presence of macrovascular invasion, the number and sites of metastases, Child-Pugh class, and the stage of the disease. AFP levels in adult patients with HCC are directly proportional to tumor size and increase in parallel with tumor doubling time.

Early stages of HCC can be treated surgically by percutaneous radiofrequency or thermal ablation; patients, however, are often at a very advanced stage and are treated with locoregional therapy or systemic therapy. Transarterial chemoembolization (TACE) is recommended for patients with unresectable HCC in BCLC stage B. Systemic therapy is recommended for patients with BCLC stage C.

Lenvatinib is a new tyrosine kinase receptor inhibitor (TKI) for the first-line treatment of unresectable hepatocellular carcinoma, leading to increased survival, rapid and clinically significant tumor reduction, and a manageable safety profile.

Epidemiological data

In Bulgaria, mortality from carcinoma of the liver and intrahepatic tract in men occupies the 7th place in frequency. The incidence of HCC in Bulgaria is 531 new cases - 335 new cases in men and 196 new cases in women. Similar to global statistics, patients with HCC are usually detected at an advanced stage of the disease according to the National Cancer Registry.

Efficacy data

The REFLECT study was a multicenter, phase III, open-label, randomized study comparing the efficacy and safety of lenvatinib and sorafenib as first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). Patients were selected in 154 centers in 20 countries in the Asia-Pacific, European and North American regions. All tumor assessments were performed at the research center by suitably qualified personnel.

- Lenvatinib is taken orally as capsules, once daily for continuous 28-day cycles. The dose of lenvatinib is determined based on the patient's baseline body weight.
- Sorafenib (NEXAVAR) is taken orally at a dose of 400 mg twice a day.

The REFLECT study demonstrated non-inferiority of lenvatinib to sorafenib - the current standard of care for hepatocellular carcinoma - in terms of overall survival, with a median duration of overall survival of 13.6 months, compared with 12.3 months in the sorafenib group. The effect of lenvatinib and sorafenib on the median overall survival was generally similar in the different subgroups based on baseline characteristics.

- The baseline level of AFP is not a stratification factor and is not the same in both treatment groups. Patients with baseline AFP levels < 200 ng/ml had a longer overall survival than those with ≥ 200 ng/ml in both arms. More patients had baseline AFP levels of ≤ 200 ng/mL in the sorafenib arm compared to the lenvatinib arm. Pre-planned OS analyses, adapted for baseline AFP, provide a nominal risk ratio (HR) advantage for lenvatinib OS versus sorafenib.
- The application of post-therapeutic antitumor therapy is not the same in the two treatment groups. Patients receiving post-therapeutic antitumor therapy during the follow-up of survival had a longer median OS than those who did not receive such therapy. A higher percentage of patients in the sorafenib arm received post-therapeutic antitumor therapy compared to those in the lenvatinib arm: 51.1% vs. 43.1%, respectively. Adapted for post-therapeutic antitumor therapy, the risk factor (HR) for lenvatinib versus sorafenib was 0.87.

Lenvatinib showed a statistically and clinically significant improvement in all endpoints of efficacy (progression-free survival, time to progression and objective response) in the individual subgroups, as well as in terms of slowing the deterioration of quality of life.

Lenvatinib treatment demonstrated superiority as it doubled the median progression-free survival (PFS) compared to sorafenib (median: 7.4 versus 3.7 months) and the median time to progression (TTP) in the lenvatinib arm was more than twice as high as that found with sorafenib (8.9 versus 3.7 months). The objective response rate (ORR) is also higher, being more than twice as high in the lenvatinib arm as in the sorafenib arm; 24.1% vs. 9.2%.

Data reported by patients

Patients treated with lenvatinib had a clinically significant delay in deterioration in daily function (work/leisure), pain, diarrhea, body sensation and nutrition compared to patients treated with sorafenib.

Safety data

During treatment, fatal adverse events with similar frequencies occurred in both arms. Fatal adverse events identified by the investigator as related to lenvatinib treatment occurred in 2.3% of patients and included hepatic failure, cerebral haemorrhage, and respiratory failure. Fatal adverse events during treatment occurred in 0.8% of patients in the sorafenib group and included tumor haemorrhage, ischemic stroke, respiratory failure, and sudden death.

The most common treatment-related adverse events (TRAE) are hypertension, diarrhea, decreased appetite and weight loss. Lenvatinib resulted in fewer cases of palmar-plantar erythrodysaesthesia (PPE), diarrhea and alopecia, and more cases of hypertension, proteinuria, dysphonia and hypothyroidism compared to patients taking sorafenib.

Data on comparators

Sorafenib is the main alternative for comparing the efficacy and safety of Lenvatinib. Sorafenib is the only medicinal product with similar indications and was comparator in clinical trials.
At present, patients with advanced HCC are treated with sorafenib.

Pharmacoeconomic indicators

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

Assessments from NICE (UK), IQWIG (Germany), SMC (Scotland) have been presented, with NICE and SMC recommending reimbursement of the assessed technology.

Applied analysis

Two pharmacoeconomic analyses were employed - cost-effectiveness with incremental ratio (ICER) of additional costs and results for the year of life gained (LYG), and cost-benefit with incremental ratio (ICUR) of costs for added QALY. The perspective of the analysis is that of the paying institution - NHIF. The time horizon of the model is 20 years and it covers all costs and results that are associated with the treatment for the rest of the lives of patients with hepatocellular carcinoma. A 3.5% discount on costs and results is applied. A Markov model is employed with three states included - progression free time, progression and death. The alternative used for comparison is sorafenib as the only currently available alternative drug recommended as first-line therapy for unresectable hepatocellular carcinoma. The results of the applied model show that Lenvima prolongs patients' life compared to sorafenib, improves the quality of life and results in additional costs for the paying institution. The incremental ratio for a quality adjusted life years is over 3 times GDP per capita.

Deterministic and probabilistic sensitivity analyses have been performed. Factors that markedly affect the incremental ratio are progression free survival and the cost of both products.
Subgroup analysis has not been applied.

Costs for the assessed health technology

Only direct medical costs are included in the analysis - for medication, for treatment of adverse reactions and for medical services.

Budget impact analysis

The budget impact analysis was conducted from the perspective of the paying institution - NHIF, the time horizon is 5 years. The estimated number of patients eligible for treatment with the assessed technology is 29 in the first year, reaching 136 in the fifth year. The results of the analysis show that the reimbursement of the new Lenvima (lenvatinib) health technology generates additional costs for the first year, increasing in each subsequent year, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Hepatocellular carcinoma is detected late and is associated with many complications, a severe course and low quality of life. Lenvatinib health technology results in prolonged time to progression, prolongs survival and improves quality of life, while generating a higher cost of a therapeutic outcome. The reimbursement of the new Lenvima health technology (lenvatinib) is associated with an increase in the NHIF budget, without taking into account risk-sharing agreements and patient access schemes.