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

HEALTH TECHNOLOGY ASSESSMENT

Alunbrig 30 mg film-coated tablets x 28

Alunbrig 90 mg film-coated tablets x 7

Alunbrig 90 mg film-coated tablets x 28

Alunbrig 180 mg film-coated tablets x 28

Alunbrig 90 mg + 180 mg film-coated tablets initiation pack x 28 (7 x 90 mg + 21 x 180 mg)

INN Brigatinib

Therapeutic indication(s)	Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.
Start/end date of procedure	06.07.2020 – 27.11.2020
Final decision	Addition of 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 and payment by the 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 Alunbrig

Health problem

Lung cancer is the most commonly diagnosed cancer worldwide. The early stages of the disease are usually asymptomatic. Clinical manifestations are non-specific and include chest pain, protracted cough, haemoptysis, fatigue, loss of appetite and weight, shortness of breath, wheezing. Lung cancer is classified according to histology, with the two main forms being small cell and non-small cell lung cancer (NSCLC). Non-small cell lung cancer accounts for about 85% of all lung cancer cases. Most patients (over 70%) are diagnosed with advanced disease (stage IIIB/IV). The estimated 5-year survival in patients with stage IV NSCLC is about 5%. Approximately 3%-5% of patients with NSCLC adenocarcinoma are positive for anaplastic lymphoma kinase (ALK) advanced non-small cell lung cancer (ALK+ NSCLC). ALK+ NSCLC is most commonly seen in young nonsmokers.

Patients with ALK-positive NSCLC at the time of diagnosis are often at a more advanced stage of the disease with metastases at different sites compared to other subtypes of NSCLC. Lung cancer metastasizes rapidly to the brain, liver, bones and adrenal glands through the blood and lymph. The development of CNS metastases in patients with advanced NSCLC is associated with a significant reduction in health-related quality of life and life expectancy compared to other metastatic sites. Brain metastases and CNS metastases are usually accompanied by many complications, can significantly reduce neurocognitive function, and are associated with poor prognosis.

Epidemiological data

Lung cancer is the most frequently diagnosed cancer worldwide, with 2 million new cases diagnosed each year. This represents 12% of the total number of cancer diagnoses. Survival is extremely poor globally - about 13% to 19% over a period of 5 years after diagnosis. Approximately 1.8 million people die from lung cancer each year, accounting for 18% of cancer deaths.

The incidence of NSCLC in Bulgaria is increasing. Patients in advanced stage (stage III and IV) comprise about 63.7%. Of these, patients with NSCLC are about 78.4%, with adenocarcinoma about 46.6%. About 90% of first-line treatment are tested for EGFRs. About 88.2% of them are EGFR-negative. Patients with ALK-positive NSCLC comprise about 3.8%.

Efficacy data

The efficacy and safety of Alunbrig were evaluated in a randomized (1:1), open-label, multicenter study (ALTA 1L) in 275 adult patients with advanced ALK-positive NSCLC who

had not previously received ALK-targeted therapy. Patients were randomized 1:1 to receive Alunbrig 180 mg once daily with a 7-day lead-in at 90 mg once daily or crizotinib 250 mg orally twice daily.

The major outcome measure was progression-free survival (PFS) according to RECIST v 1.1. Additional outcome measures include confirmed objective response rate (ORR), response duration (DOR), time to response, disease control rate (DCR), intracranial ORR, intracranial PFS, and intracranial DOR. The results evaluated by the investigators included PFS and overall survival.

The ALTA 1L study achieved its main endpoint, showing a statistically significant improvement in PFS. Brigatinib demonstrated early and sustained overall improvement in PFS vs Crizotinib, more than doubling the median PFS (24.0 months vs. 11.0 months). Brigatinib significantly improved PFS in patients with brain metastases at baseline compared to Crizotinib (median 24 months versus 5.6 months). Brigatinib is associated with an intracranial ORR of 78% versus 26% for Crizotinib in patients with brain metastases at baseline, significantly improving intracranial PFS in patients with brain metastases at baseline relative to Crizotinib (median: 24.0 months vs. 5.6 months), the median PFS is similar in patients with and without brain metastases at baseline. Brigatinib has been shown to be effective in patients who have received previous chemotherapy as well as in patients without previous treatment. It is associated with improved ORR versus Crizotinib (confirmed ORR: 74% vs. 62%) and longer DOR. Brigatinib is the only ALK tyrosine kinase inhibitor to show a significant difference in the health-related quality of life (HRQOL) compared to Crizotinib, with delayed deterioration and longer duration of improvement in HRQOL compared to Crizotinib, as well as clinically significant improvement in HRQOL and function from baseline.

An indirect comparison of Brigatinib treatment with other ALK TKIs in 1L therapy was performed. A systematic literature review (SLR) has been conducted to identify relevant clinical trials and publications for inclusion. The results of these analyses show that Brigatinib is at least as effective as Alectinib in improving PFS and better than Ceritinib as 1L ALK TKI in patients with advanced ALK + NSCLC.

Analysis of patient- reported data

A secondary endpoint of the ALTA-1L study was to assess patient-reported symptoms and health-related quality of life. Analysis of the data from the patient reported outcomes show that patients treated with Brigatinib had a clinically significant and longer-lasting improvement in HRQoL compared with patients treated with Crizotinib. Brigatinib also significantly improved baseline results compared to Crisotinib for emotional and cognitive functioning, fatigue, nausea and vomiting, loss of appetite, constipation.

Safety data

The most common adverse reactions (≥ 25%) were increased AST, hyperglycaemia, hyperinsulinemia, anemia, increased CPK, nausea, increased lipase, decreased lymphocyte count, increased ALT, diarrhea, increased amylase, fatigue, cough, headache, increased alkaline phosphatasee, hypophosphatemia, increased APTT, rash, vomiting, dyspnoea, hypertension, decreased white blood cell count, myalgia and peripheral neuropathy. The most common serious adverse reactions (≥ 2%) reported in patients treated with Alunbrig, other than events related to neoplasm progression were pneumonitis, pneumonia and dyspnoea.

Data on comparators

The available therapeutic alternatives for first-line treatment of adult patients with ALK + advanced non-small cell lung cancer in Bulgaria are Crizotinib, Ceritinib and Alectinib.

Pharmacoeconomic indicators

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

An assessment of Alunbrig health technology from the Swedish state institution TLV is presented for the indication: treatment of anaplastic lymphoma kinase (ALK) positive, advanced NSCLC, previously not treated with an ALK inhibitor. The assessment is positive and the assessed health technology is reimbursed.

Applied analysis

The chosen method for comparative evaluation of the health technology is of the cost-effectiveness type (CEA). Long-term outcomes - life expectancy (LYG) and quality-adjusted life years (QALY) were used. The perspective of the analysis is that of the paying institution - NHIF. The chosen time horizon is 30 years. Health benefits and costs are discounted at an annual discount rate of 3.5%. A model with four possible health conditions was applied: before disease progression, no CNS progression, CNS disease progression, and absorbent state - death. The selected comparators are Crizotinib and Alectinib. The results show that Brigatinib as first-line therapy demonstrates therapeutic superiority in terms of increased life expectancy and quality adjusted life years gained vs Crizotinib. A similar efficacy was found compared to the comparator Alectnib. Brigatinib therapy was associated with a higher cost per patient and a higher QALY value than Crizotinib therapy. Brigatinib therapy can be defined as cost-effective compared to Crizotinib, and compared to Alectnib, Brigatinib is dominant as it demonstrates similar efficacy data and lower treatment costs.

Subgroup analyses

No subgroup analysis was performed.

Costs of the assessed health technology

The costs of brigatinib therapy and alternative drug therapy have been estimated. Additional cost for establishing diagnosis and cost associated with the administration of the medicinal product are not included in the analysis as they are identical for the alternatives.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the paying institution – the NHIF. The time horizon of the analysis is 5 years. The estimated number of patients eligible for treatment with the assessed technology is 8 in the first year, reaching 20 in the fifth year. The introduction of the new health technology for first-line treatment will reduce the cost of the paying institution - NHIF, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The results of the cost-effectiveness analysis show that therapy with Brigatinib is dominant over Alectinib therapy, as it demonstrates similar efficacy data but lower treatment costs. Compared to therapy with Crizotinib, the new health technology leads to more health benefits, but also higher treatment cost. In terms of the budget impact, the reimbursement of brigatinib as a first-line treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC), previously untreated with ALK inhibitor, will lead to cost savings for the NHIF.