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

HEALTH TECHNOLOGY ASSESSMENT

Ofev

100 mg soft capsules

150 mg soft capsules

Nintedanib

Therapeutic indication(s)	Ofev is indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.
Start/end date of procedure	28.09.2019 - 30.12.2020
Final decision	Rejects inclusion of a therapeutic indication of the medicinal product in the Positive Drug List (PDL).

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

Health problem

The term interstitial lung disease (ILD) refers to a group of more than 200 chronic lung diseases, characterized by inflammation of the pulmonary interstitium, often leading to the formation of pulmonary fibrosis. Fibrosis can gradually cause lung rigidity, reducing the gas exchange properties of the alveoli and the ability to transfer oxygen. According to the current classification, ILD is divided into four major groups: Interstitial lung disease of known etiology; Idiopathic interstitial lung disease; Granulomatosis and Others.

ILD with progressive fibrosing phenotype (PF-ILD) is defined as a disease in which, despite treatment, there is an increase in fibrotic changes, decreased lung function, worsening symptoms and deteriorating health-related quality of life. About 20% -30% of patients with ILD are defined as having a progressive phenotype.

Acute exacerbations of PF-ILD, defined as episodes of rapid respiratory deterioration, accompanied by evidence of new ground-glass opacity changes on HRCT, are a common feature of the natural course of the disease, thought to occur in 5-10% of patients per year.

Epidemiological data
Scleroderma - related ILD is associated with increased mortality. The reported percentage of scleroderma patients who develop ILD range from 35% to 90%. Although scleroderma can occur at any age, patients are usually between the ages of 30 and 60, and women are more likely to develop the disease than men.

Idiopathic interstitial pneumonia (IIP): One variant of IIP is NSIP, the overall incidence of which (regardless of the progressive fibrosing phenotype) is lower than in idiopathic pulmonary fibrosis (IPF), with retrospective data from mixed cohorts of patients with IPF and NSIPs, estimating the prevalence of NSIP at 1–9 per 100,000, compared to 2–20 per 100,000 for IPF. A small subgroup (15–25%) of all IIP patients remains unclassifiable.

Hypersensitivity pneumonitis (HP): up to 25% of patients meet the criteria for a progressive fibrosing phenotype of HP (prevalence ranges from 0.41-0.80 per 100,000 individuals), associated with higher mortality.

The global prevalence of sarcoidosis is estimated at 4.7 - 64 per 100,000 with a rate of 1.0 - 35.5 per 100,000 per year.

Efficacy data

Ofev (nintedanib) slows progression and improves survival in patients with idiopathic pulmonary fibrosis.

The INBUILD study (Efficacy and Safety of Nintedanib in Patients with Progressive Fibrosing Interstitial Lung Disease) is a prospective, randomized, double-blind, placebo-controlled multinational phase III clinical trial.

The primary endpoint is the annual decline in forced vital capacity (FVC) (in ml) over a period of 52 weeks. The annual decline in FVC (in ml) was significant in patients treated with nintedanib -80.8 ml compared to placebo -187.8 ml. The adjusted difference between the two groups was 107.0 ml per year. In the subgroup of patients with usual interstitial pneumonia, the annual decline in FVC (in ml) was -82.9 ml in patients treated with nintedanib compared to -211.1 ml per year in those treated with placebo. The adjusted difference between the two groups was 128.2 ml per year. In patients with fibrotic changes other than usual interstitial pneumonia, the annual decline in FVC (in ml) was -79.0 ml in patients treated with nintedanib compared to placebo - 154.2 ml per year (intergroup difference of 75.3 ml). In the INBUILD study, the percentage of patients who died or received acute exacerbation of IBD during the 52-week study period was 7.8% in the nintedanib group, compared with 9.7% in the placebo group in the overall population and 8.3% versus 12.1%, respectively in the group of patients with fibrotic changes characteristic of usual interstitial pneumonia. The mortality rate for the 52-week period was 4.8% for nintedanib versus 5.1% for placebo for the overall population and 5.3% versus 7.8% for patients with usual interstitial pneumonia.

Analysis of patient-reported data
The INBUILD study utilized *King's Brief Interstitial Lung Disease (K-BILD) questionnaire.* At week 52, the adjusted mean absolute change from baseline in overall score (activity, psychological factors, and chest symptoms) was 0.55 points for nintedanib group and −0.79 points for the placebo group for the overall population and 0.75 points for −0.78 points for patients in the subgroup with signs of usual interstitial pneumonia.

Safety data

Very common side effects with nintedanib are diarrhea, nausea, abdominal pain, vomiting, and elevated liver enzymes. Hepatic adverse events were more significant in nintedanib patients than in placebo. Elevations in AST or ALT, or both transaminases, at least three times the upper limit of normal were seen in 13.0% of patients treated with nintedanib compared to 1.8% of placebo over the 52-week study period. Adverse events were similar in patients with fibrous scars characteristic of usual interstitial pneumonia, compared to those with other types of fibrosis.

Data on comparators

There is no reimbursed therapy for PF-ILD in Bulgaria, the alternative is the best supportive care.

Pharmacoeconomic indicators

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

No assessments by governmental institutions in France, Sweden or Germany have been found.

Applied analysis

The pharmacoeconomic methods cost-utility and cost-effectiveness were used in the analysis. The perspective of the analysis is of the paying institution - the National Health Insurance Fund. The time horizon of the analysis is lifelong and the costs and results are discounted by 3.5% per year. The value of the incremental cost-utility ratio (ICUR) and the incremental cost-effectiveness ratio (ICER) is above the threshold for value efficiency 3 times GDP per capita.

Costs of the assessed health technology

Direct medical costs are included in the analysis.

Analysis of subgroups

Not applicable.

Budget impact analysis

The analysis was conducted from the perspective of the paying institution - NHIF, and the time horizon is 5 years. The estimated number of patients eligible for treatment with the assessed technology is 52 in the first year, reaching 169 in the fifth year. The reimbursement of the assessed health technology will lead to additional costs for the paying institution, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Ofev is the only approved medicinal product for the treatment of patients with fibrotic interstitial lung disease - progressive phenotype, characterized by rapid progression, poor quality of life and high mortality. The medicinal product slows progression and improves survival in patients with PF-ILD, it is well tolerated and has a manageable safety profile. The reimbursement of the assessed health technology will lead to additional costs for the paying institution, without taking into account risk-sharing agreements and patient access schemes.