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 systemic sclerosis associated interstitial lung disease (SSc-ILD).
Start/end date of procedure	28.09.2020 - 18.12.2020
Final decision	Addition of therapeutic indication in Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF).

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

Health problem

Scleroderma is a systemic autoimmune disease characterized by endothelial dysfunction that causes small vessel disease, fibroblast dysfunction with excessive collagen production and fibrosis, as well as immune dysfunction. Depending on the spread of skin changes, two forms of the disease are distinguished - systemic scleroderma and localized scleroderma. Lung involvement in scleroderma may be due to direct lung damage, indirect lung complications, a combination of direct and indirect damage, other lung diseases not related to systemic sclerosis - COPD/emphysema, asthma, lung nodules and others. Direct lung damage is of two main types - interstitial lung disease (ILD) and pulmonary hypertension (PH).

About 25% of patients develop clinically significant lung disease within 3 years of detection of physical and radiographic changes or abnormalities in bronchoalveolar lavage (BAL). The clinical picture of SSc-ILD most often includes symptoms of shortness of breath, fatigue and unproductive cough, but early ILD is often asymptomatic.

The standard for non-invasive diagnosis of SSc-ILD is high-resolution computed tomography (HRCT). Depending on the changes detected by the HRCT, as well as the FVC values, the SSc-ILD is classified as having extensive (HRCT>20%; FVC <70%) or limited (HRCT <20%; FVC>70%) lung engagement. It was found that patients that fall in the group of those with more extensive involvement have a higher mortality rate than those with limited involvement. The fastest decline in FVC values is reported in the first three years after the onset of the disease.

Epidemiological data

The overall incidence of scleroderma worldwide is about one in 10,000. The ratio of women/men according to various literature data is from 2.6 to 4:1, with the main age group involved in the disease being 45-55 years. According to literature data, about 35% of patients with systemic sclerosis in Europe and 52% of those in the United States have interstitial lung disease. The two forms, ILD and PH, together account for about 60% of scleroderma-related mortality.

Efficacy data

The SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) study, a randomized, double-blind, placebo-controlled clinical trial, has been analyzed. The primary endpoint is the annual reduction in FVC over a period of 52 weeks.

Key secondary endpoints were the absolute change from baseline in the modified Rodnan Skin Score (mRSS) at week 52 and the absolute change from baseline in the overall score from the St. George's Hospital Respiratory Questionnaire (SGRQ) per week 52.

Pulmonary function results: annual decrease in FVC over a period of 52 weeks (primary endpoint), is significantly reduced in patients treated with nintedanib: -52.4 ml compared to placebo -93.3 ml.

Mortality-related results: during the study period death was reported in 10 patients (3.5%) in the nintedanib group and 9 patients (3.1%) in the placebo group.

Analysis of patient-reported data
The SENSCIS study used the St. George's Respiratory Questionnaire (SGRQ), the Health Assessment Questionnaire-Disability Index (HAQ-DI) and the Functional Assessment of Chronic Illness Therapy – Dyspnea; FACIT - D. The results of the study did not show a significant difference between patients on placebo and nintedanib in terms of SGRQ at the end of the study.

The primary results of the FACIT-Dyspnoea questionnaire range from 0 to 30, and the scaled result from 27.7 to 75.9. Higher scores indicate more pronounced dyspnea.

Safety data

Adverse drug reactions, associated with nintedanib are: diarrhea, nausea, abdominal pain, vomiting, decreased appetite, weight loss, hypertension, bleeding, elevated liver enzymes - aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma glutamyl transferase (GGT), alkaline phosphatase (AF); headache. Dehydration, myocardial infarction, aneurysms and arterial dissections, pancreatitis, alopecia are observed with unknown frequency.

The percentage of patients with an adverse event/serious adverse event were similar in the nintedanib and placebo groups. The percentage of patients who had an adverse event leading to discontinuation of the prescribed intervention was higher in the nintedanib group than in placebo group (16.0% vs. 8.7%). The most common adverse reaction was diarrhea, which was reported in 75.7% of patients in the nintedanib group and in 31.6% of patients in the placebo group. Elevations in alanine aminotransferase, aspartate aminotransferase, or both up to at least three times the upper limit of normal have been reported in 4.9% of patients in the nintedanib group and in 0.7% of placebo patients.

In clinical trials, the incidence of bleeding was slightly higher in patients treated with Ofev or comparable between treatment groups (Ofev 11.1% versus placebo 8.3% in SENSCIS). The

most commonly reported bleeding event is epistaxis, which is not serious. Serious bleeding events occurred at low frequencies in both treatment groups (Ofev 1.4% versus placebo 0.7% in SENSCIS). Post-marketing bleeding events include, but are not limited to, gastrointestinal, respiratory and central nervous system events, with gastrointestinal events being the most frequent.

Data on comparators

There is no reimbursed therapy for SSc-ILD in Bulgaria.

Pharmacoeconomic indicators

Applied analysis

In the analysis, the pharmacoeconomic methods cost-utility with the main outcome measure quality adjusted life years (QALY) and cost-effectiveness with the main outcome measure years of life gained (LYG) have been employed. The perspective of the analysis is that of the paying institution – the NHIF. The time horizon of the analysis is lifelong (50 years). All costs and results are discounted by 3.5% per year. The conducted pharmacoeconomic analysis is based on a microsimulation model that assesses the cost and effects in individual patients for the time horizon of the analysis. A comparator in the analysis is the standard therapy. According to clinical guidelines, the standard clinical practice in Bulgaria includes the administration of methotrexate, cyclophosphamide, azathioprine, mycophenolate and corticosteroids. The values of the incremental cost-utility ratio (ICUR) and the incremental cost-effectiveness ratio (ICER) are above the breakeven point set by the WHO within 3 times the gross domestic product per capita.

Cost of the assessed health technology

Medication cost has been estimated. Other costs included in the model are ADR treatment cost and hospitalization cost.

Subgroup analysis

Not applicable.

Budget impact analysis

The analysis of the budget impact is conducted from the perspective of the paying institution – the NHIF. The time horizon is 5 years. The estimated number of patients in the first year is 15 and in the last year it is 104. The reimbursement of the therapeutic indication of the medicinal product Ofev for treatment of patients with SSc-ILD will lead to additional cost for the paying institution, not taking into account risk sharing agreements and patient access schemes.

Conclusion

Ofev (nintendanib) is a medicinal product, indicated for the treatment of adult patients with systemic sclerosis associated interstitial lung disease SSc-ILD. There is currently no other reimbursed therapy for this disease. The medicinal product slows the progression and improves survival in patients with SSc-ILD, is well tolerated and has a manageable adverse events profile. The value of the incremental cost-utility ratio (ICUR) and the incremental cost-effectiveness ratio (ICER) is above the cost-effectiveness threshold. The addition of the therapeutic indication for the medicinal product Ofev will lead to additional cost for the NHIF, without taking into account risk-sharing agreements and patient access schemes.