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

HEALTH TECHNOLOGY ASSESSMENT

Adempas
0.5 mg film-coated x 42
1 mg film-coated x 42
1.5 mg film-coated x 42
2 mg film-coated x 42
2.5 mg film-coated x 42
riociguat

Therapeutic indication(s)	Pulmonary arterial hypertension (PAH) Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity. Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.
Start/end date of procedure	29.04.2019 – 07.05.2020
Final decision	Rejects inclusion in the Positive Drug List (PDL).

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

Health problem

Pulmonary arterial hypertension (PAH) is defined by the level of the mean pulmonary arterial pressure at rest being equal to or higher than 25 mmHg. This disorder often occurs against the background of various diseases, primarily associated with left heart disease or lung disease. The term pulmonary arterial hypertension is used for a rare subvariant of pulmonary hypertension (PH), characterized by angioproliferative vasculopathy at the level of mainly small pulmonary arteries, which in turn leads to progressive pulmonary vascular remodeling, increased pulmonary vascular resistance and eventually right-sided heart failure. Hemodynamically PH is classified as precapillary or postcapillary according to the left filling pressure or the values of the so-called pulmonary capillary pressure.

Pulmonary hypertension is considered a serious problem in clinical practice. Under conditions of increased pressure in A. pulmonalis, the right ventricle of the heart is overloaded, quickly leading to the development of right-sided congestive heart failure. Pulmonary arterial hypertension (PAH) is a variant of pulmonary hypertension (PH), with specific pathogenetic and pathophysiological characteristics. PAH and in particular PH are generally characterized as disease processes affecting the vessels of the lungs.

The etiological forms of PAH, which are very different, include the so-called chronic thromboembolic pulmonary hypertension (class 4 of the DANA classification, laid down in the Guidelines of the European Society of Cardiology). Chronic thromboembolic pulmonary hypertension is a rare disease that mainly affects the adults (3.2 cases per 1 million adults). The best treatment at the moment is surgical pulmonary endarterectomy, which is a highly specialized procedure. Not all patients are eligible for this surgery, and some patients, despite successful surgical treatment, remain with increased pressure in the system of A. pulmonalis.

PH based on chronic thromboembolic disease is defined clinically by the following hemodynamic parameters: increased mean pulmonary pressure above 25 mm Hg at rest, assessed by right cardiac catheterization, pulmonary capillary pressure less than 15 mm Hg and pulmonary vascular resistance over 3 Wood units.

Epidemiological data

PAH (including idiopathic PAH, familial PAH, connective tissue disease-associated PAH) is a rare form of BAH (6.6 - 26.0 cases per 1 million population according to European registers). The lowest reported frequency is 5.9 cases with idiopathic PAH per million population. According to European registers, the incidence of PAH is 5-10 cases per million

population identified per year. In the subgroup of patients with connective tissue disease-associated PAH, almost 50% of patients developed pulmonary hypertension, associated with systemic scleroderma.

The medical and social burden posed by the disease is serious, especially since it is associated with relatively high mortality and prevalence. On average, about 29% of patients with PAH die at year 5 since the diagnosis: 13.3% of the low-risk group, 28% of the intermediate risk group and 43.8% of the highest risk group. Despite improvements in diagnosis and the introduction of targeted therapies over the past 20 years, the disease continues to carry a poor prognosis over time. In Bulgaria, the mortality rate of patients with idiopathic PAH in 2017, treated and monitored in special centers, is 35%. The mortality of patients with idiopathic PAH in 2018 is 36%, and of patients with systemic sclerosis - 15%.

The clinical picture of PH is nonspecific and is primarily due to the gradual development of right-sided heart failure. In the early stages, symptoms appear with exertion and include shortness of breath, easy fatigability, angina and syncope. Dry cough and nausea and vomiting, caused by exertion are less common. The presence of symptoms at rest is characteristic of the advanced stages of the disease. With the development of heart failure, swelling of the abdomen and edema of the lower extremities are added. The guide to the treatment and diagnosis of pulmonary hypertension of the European Society of Cardiology, in association with the European Society of Pulmonary Society, identifies the most appropriate treatment strategies in clinical practice. The group of drugs defined as specific treatments for the disease includes calcium channel blockers, endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE-5), and guanylate cyclase stimulants (GCS), including riociguat. This guide defines the position of riociguat for monotherapy in patients with WHO II-III FC in class I/confidence level B and for WHO IV FC patients in class IIb / C. The guidance indicates a possible combination of riociguat with bosentan (ERA) in patients with FC II and III as class I/B and for patients with FC IV-IIa/C. The combination of riociguat with phosphodiesterase type 5 inhibitors (e.g. sildenafil) is contraindicated in all patients regardless of functional class; level of evidence B.

There are no published Bulgarian manuals on the administration of riociguat. According to a decision of the Bulgarian Society of Cardiology, the diagnostic and treatment strategies for patients with cardiac and vascular diseases are based on the guidelines of the European Society of Cardiology. According to this guide, the alternatives for the treatment of PH in Bulgaria are the following specific drugs, reimbursed by the NHIF: endothelin-receptor antagonists (bosentan, ambrisentan) and phosphodiesterase-type 5 inhibitors (sildenafil).

Target population

The target population of Adempas (INN Riociguat) is patients with pulmonary arterial hypertension (primarily patients with idiopathic pulmonary arterial hypertension, hereditary pulmonary hypertension, connective tissue disease-associated PAH), patients with thromboembolic disease and the presence of pulmonary hypertension, patients with pulmonary arterial hypertension associated with congenital heart disease. The distribution of patients in the above groups is based on the clinical classification of pulmonary hypertension adopted by the European Society of Cardiology.

The target population for Bulgaria is based on data from treatment for PAH in patients with: idiopathic pulmonary hypertension, systemic scleroderma, Eisenmenger's syndrome in connection with congenital heart malformations.

Efficacy data

Efficacy and safety of Adempas (riociguat) have been evaluated in several larger clinical trials.

PATENT - 1 study, published in 2013

The study is a 12-week, double-blind, randomized, placebo-controlled study at 124 centers. The patients included in the study had symptomatic pulmonary arterial hypertension (idiopathic, familial, associated with connective tissue disease, congenital heart malformations, portal hypertension). Dose titration lasted 8 weeks and the final dose was considered appropriate for the individual patient. The results showed that at 12 weeks of active treatment, the distance of the 6-minute walking test increased by an average of 30 m in patients in the group of riociguat 2.5 mg 3 times daily. The test distance decreased by an average of 6 m in placebo-treated patients. The statistical significance is $p < 0.001$. There was also a significant improvement in the values of pulmonary vascular resistance ($p<0.005$), in the decrease in the levels of NT-pro BNP ($p<0.001$) and in the WHO FC ($p < 0.003$). The improvement in the monitored indicators applies to both patients treated with ERA or prostanoids and to patients who had not received any prior treatment.

The study has several limitations: the employed 6-minute test is generally a surrogate marker that can lead to limitations in assessment; the majority of patients are in WHO FC II, which means less advanced disease, and therefore predetermine better outcomes; it is also not clear what the effect of riociguat is in patients previously treated with PDE5i (sildenafil or tadalafil) or intravenous prostanoids.

PATENT-2 study, published in 2015
The study was multicenter, open-label, single-group, with an 8-week double-blind dosing period of the studied drug up to 2.5 mg 3 times daily.

The results of the study show that the positive tendency for an increase in the distance of the 6-minute test is maintained in patients with PATENT - 2 until the end of 1 year of follow-up. At the end of the first year of treatment, the distance from the 6-minute test was increased by an average of 53 ± 70 m in patients treated in PATENT-1 with riociguat and by an average of 56 ± 88 m in patients receiving 1.5 mg riociguat. The absolute distance covered in the 6-minute test at the end of the first year was on average 419 ± 97 m compared to the beginning - 367 ± 67 m. The tendency for reduction in the values of NT-proBNP in the group of patients treated with riociguat in the study PATENT - 1 is also maintained in PATENT-2 patients until the end of the first year. Improvement was also observed in patients who were on placebo in PATENT-1 and already on active riociguat treatment in PATENT-2. At the end of the first year there is an improvement in FC. The trend for the dynamics of the EQ-5D Borg dyspnea index is similar.

PATENT - 2 data support PATENT - 1 data on the efficacy and safety of riociguat.

Again, there are some limitations, similar to those in studies with identical design. The lack of placebo group and the fact that about 50% of patients receive concomitant treatment with added specific therapy that also targets the pathogenesis of PAH, largely renders the benefit of riociguat treatment ambiguous. The withdrawal of some patients could also lead to conflicting conclusions about the benefit of the drug, such as overestimating the improvement in efficacy parameters.

A study for the treatment of connective tissue disease-associated PAH was published in 2017
The study included a population of patients who participated in PATENT-1 and PATENT-2. A prospective analysis of the safety and efficacy of riociguat in a subgroup of patients with connective tissue disease-associated PAH was used. Patients in this subgroup were subsequently subdivided (post hoc) into a group with PAH with systemic sclerosis and patients with PAH and other connective disease. The results show that when administered to patients with connective tissue disease and PAH, riociguat causes an increase in the distance from the 6-minute walking test, WHO FC, reduces pulmonary vascular resistance and increases the cardiac index. The observed positive changes persisted over the next 2 years of the follow-up. The two-year survival of patients is the same as the survival of patients with idiopathic PAH (93%). The safety profile did not change compared to other patient groups.

CHEST I study, published in 2013

The study was a phase III, 16-week, multicenter, randomized, double-blind, placebo-controlled, at 89 centers.

The results show that by week 16, patients treated with riociguat had an increased covered distance by an average of 39 m, while placebo patients had a decreased distance by an average of 6 m. This difference is statistically significant with $p < 0.001$. Pulmonary vascular resistance decreased in the riociguat-treated group by 226 dyn-sec-cm -5 while in placebo patients it increased by 23 dyn-sec-cm -5. Riociguat resulted in significant improvement in NT-proBNP values ($p < 0.001$). There was no statistical difference in the frequency of clinical deterioration between the two groups of patients ($p = 0.17$).

The main limitations of the CHEST-1 study are: the lack of monitoring of efficacy parameters in patients who withdraw from the study; the study is of relatively short duration and its design does not allow morbidity and mortality to be adequately assessed; the positive dynamics observed in patients treated with riociguat is based mainly on surrogate markers.

CHEST-2 study, published in 2015

The study was a multicenter, open, single group, conducted in 71 centers participating in CHEST - 1. The study included an 8-week double-blind period, followed by an open phase. Patients participating in CHEST-1 on riociguat treatment started CHEST-2 with the same dose of the drug, and patients in the placebo group of CHEST-1 started treatment in CHEST-2 with riociguat 1 mg 3 times daily.

Of the 243 patients who completed the CHEST-1 study, 237 continued to participate in CHEST-2. Thus, the average duration of riociguat treatment was a total of 83 weeks (mean 75 weeks). 73% of patients had inoperable chronic thromboembolic pulmonary hypertension and 27% had persistent/recurrent PH after pulmonary endarterectomy.

The results show that the decrease in NT-proBNP values in patients from the riociguat group of CHEST-1 was maintained until the end of the first year in CHEST-2. FC of patients in the riociguat group in CHEST-1 during and until the end of CHEST-2 improved, stabilized or worsened in 50%, 45% and 4%, respectively. A total of 16% of all follow-up patients at the end of the first year showed deterioration in clinical status. A drawback of CHEST - 2 is the lack of hemodynamic assessment.

PATENT PLUS study, published in 2015

The study was randomized, double-blind, placebo-controlled, multicenter. The majority of patients have idiopathic PAH (50%) in FC II and III. The results of the study did not reveal a difference in the maximum change in systolic blood pressure (SBP) between the two groups

of patients. However, there is a tendency for lower systolic blood pressure (approximately 10 mm Hg) in patients treated with riociguat + sildenafil. Combination therapy (riociguat + sildenafil) however, did not show beneficial effects on clinical parameters, haemodynamics and exercise capacity. In the group of patients on combination therapy, a higher frequency of treatment discontinuation due to hypotension was observed. The investigators believe that there are potentially more safety-related adverse effects in the group of patients treated with riociguat + sildenafil, and that there is no evidence of a positive benefit/risk balance. No improvements were reported in FC, in NT pro-BNP values, and in the distance from the 6-minute walking test. A drawback of the study is the relatively small number of patients, which in turn led to limitations in the evaluation of efficacy.

RIVER study published in 2018

The clinical trial was conducted as a retrospective analysis using data from previous prospective, randomized, double-blind, multicenter, parallel-group, placebo-controlled trials (PATENT-1, PATENT plus, CHEST – 1, Early Access Study), as well as from other long-term studies during which echocardiography was performed.

Several echocardiographic parameters were monitored. After 12 months from the start of the study, the results showed that patients on active treatment with riociguat had a significant reduction in right atrial volume as well as right ventricular volume ($p < 0.001$).

Drawbacks of the study are related to the technical side of the echocardiographic examination - low sensitivity of the method for repeatability of results and echocardiographic measurements, especially after 12 months of follow-up, which can lead to conflicting data. Another important limitation is the retrospective nature of the study, and the small number of patients, especially patients in the placebo group.

EAS (Early access study) published in 2017

The study was open, uncontrolled, one arm, conducted after phase III of CHEST-1. The study was conducted in three phases: an 8-week phase to determine the dose of riociguat, a maintenance phase in which riociguat is expected to be included in the country authorization lists, and a third phase for safety assessment. The starting dose is 1 mg 3 times a day to a maximum dose of 2.5 mg 3 times a day. Included were patients with chronic thromboembolic pulmonary hypertension who are defined as inoperable or have been operated on, but the pulmonary artery pressure did not reach target values.

The results show that side effects were observed in 273 of the monitored patients (91%). The most common serious side effect was syncope (6%).

Network meta-analysis

To assess the comparative efficacy of adempas, a network meta-analysis was performed, the end point of which was the identification of clinical deterioration (death, lung transplantation, interatrial communication, hospitalization associated with deterioration of HF). The comparative analysis includes the following classes of drugs: endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE5), prostacyclins and sGCS (represented by adempas). The comparison was done versus placebo. For the network meta-analysis, 7 randomized trials evaluating the efficacy of ERA (bosentan, ambrisentan, macisentan), three studies evaluating the efficacy of sildenafil, tadalafil and vardenafil (PDE-5 group), five studies evaluating prostanoids were included (beraprost and treptostenil) and one study involving riociguat (PATENT-1). 15 comparisons were made - 5 direct and 10 indirect. The results based on a model of direct comparison between the groups of patients on active treatment and placebo show a statistically significant difference. In general, the heterogeneity is low. The obtained histogram of the ranking based on Bayesian probability analysis showed the highest efficacy for riociguat, EPA, PDE-5. Data obtained from the network meta-analysis, although encouraging, should be considered critically. In the context of the needs of Bulgarian patients, greater interest is focused on evaluating the efficacy of riociguat in patients with idiopathic PAH. There is no doubt that compared to placebo, each of the specific groups of drugs leads to an improvement in the clinical condition. However, evidence based on a head-to-head risk analysis is lacking. In addition, in the PATENT-1 study, the change in the 6-minute test was smaller than the change seen during treatment with sildenafil (PDE-5) in the SUPER study. At the same time, the improvement in the 5-minute test from PATENT-1 was close to that seen in tadalafil patients in the PHIRST study. Inclusion of additional clinical trials with riociguat in such a meta-analysis is essential in order to obtain more convincing results, as well as to monitor various variable parameters.

In general, clinical trials related to the treatment of patients with PAH, especially in the early stages when eligible patients are identified, are generally short-term, involving a relatively small population. Their design and duration do not allow mortality and morbidity to be assessed. Quality of life assessment was performed in two of the larger clinical trials, CHEST-1 and PATENT-1. There was a nominal improvement in quality of life in patients treated with riociguat 2.5 mg 3 times daily.

Summary of the results of the PATENT-1, CHEST-1 and other smaller studies show that side effects were more common in the riocciguat-treated groups than in placebo groups. These are headache (27%), dyspepsia/gastritis (21%), dizziness (20%), hypotension (10%), vomiting (10%). The most commonly reported side effects are those in the groups treated with riociguat - syncope and manifestations of right-sided heart failure. The serious adverse reaction, bleeding, was more common in patients treated with riociguat than in patients with placebo.

The discontinuation rate due to adverse events associated with the medicinal product was 2.9%.
The most important parameter - clinical deterioration in patients compared with placebo decreased in patients treated with riociguat (14.5% in the placebo group and 2.8 in the riociguat group). Clinical deterioration was reported in 3.9% of patients treated with ERA + PDE5i and in 5.7% treated with PDE5i alone. However, it should be emphasized that patients included in the studies with riociguat represent for the most part a lower risk group (a larger number are in FC II). Improvement in FC (for example, transition to a lower class) is observed in 23% of patients (for comparison, this percentage for intravenous prostanoid is 81%, for ERA + PDE5i is 28%). Due to the heterogeneous etiology of PAH, the results have been considered according to each subtype. In general, the analyses show an increase in the average difference in distance from the 6-minute test by an average of 30 meters. Patients with idiopathic pulmonary hypertension did not show a significant increase in this distance, compared with those with chronic pulmonary thromboembolic hypertension. Secondary data showed a one-way increase in the functional class, assessed clinically, in all riociguat studies. In summary, riociguat is effective in reducing the incidence of clinical deterioration and improving exercise capacity.

The differences in mortality and morbidity, as already mentioned, cannot be estimated due to the relatively short duration of the studies and the small number of patients. However, studies with other groups of drugs recommended for the treatment of PAH have shown a reduction in mortality from PDE5i and ERA.

Safety data

Important identified risks are: hypotension; disorders of the upper gastrointestinal tract (dyspepsia, gastroesophageal reflux, dysphagia, gastritis); deterioration of one of the forms of PH - veno-occlusive disease; severe haemoptysis (bleeding from the lungs).
Important potential risks are: bleeding; embryo-fetal toxicity; dosing errors; renal failure; use of Adempas (riociguat) off-label in patients under 18 years of age (no clinical data are available for this age group); bone changes and fractures; treatment of patients with previous atrial fibrillation (treatment to restore sinus rhythm is a key to improving the prognosis in patients with PAH); smoking (induction of CYP1A1) - in smokers treated with Adempas (riociguat), 50% -60% lower levels were observed compared to non-smokers. Dose titration is therefore extremely important as regards smokers.

Data on comparators

The current goal for patients with PAH is primarily achieving low-risk status according to international guidelines. Treatment of PAH can be started as monotherapy or as a

combination therapy with drugs targeted at different pathogenetic pathways. Modern therapeutic options allow to control the three main pathways associated with the genesis of PAH: prostacyclin pathway, endothelin pathway and pathway of nitric oxide synthesis (NO). There are three main therapeutic options for controlling nitric oxide synthesis: 2 drugs (sildenafil and tadalafil), known as phosphodiesterase-5 inhibitors (PDE5i) and the so-called sGC stimulator (NO-sGC-cGM pathway stimulator) - riociguat (Adempas). From a global perspective, PDE5i (sildenafil and tadalafil) are the most commonly used drugs for the treatment of PAH, as mono- or as combination therapy with ERA. Riociguat and the PDE5i group have the same target of action, but through different pathogenetic molecules. Therefore, riociguat and PDE5i have different molecular targets at the level of the same pathogenetic pathway. Due to this fact, the simultaneous use of sildenafil and riociguat is not allowed (data from the PATENT-PLUS study). It is hypothesized that in patients without a sustained response to PDE5i there is a biological basis for switching to treatment with sGC stimulants (riociguat). Based on differences in mode of action, it can be assumed that riociguat would be beneficial in patients with an insufficient response to PDE5i.

Pharmacoeconomic indicators

Description of published health technology assessments performed by governmental institutions, intended for the health care systems of other countries

Riociguat was evaluated as monotherapy or in combination with endothelial receptor antagonists (ERAs), indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH), with WHO functional class (FC) II to III to improve physical capacity. Positive evaluations were given by France (HAS), Canada - CADTH Canadian Drug Expert Review Committee (CDEC), and Great Britain (NHS England), with the latter two countries imposing certain restrictions on the inclusion in their lists and dispensing of the medicinal product. IQWiG's assessment refers to riociguat as being authorized for use as an orphan medicine and following a decision by the G-BA in October 2014, a subject to authorization for use as a medicinal product for the treatment of a rare disease.

Applied analysis

A cost-minimisation analysis was used, and the choice of method is based on a published indirect comparison of riociguat, done by a network meta-analysis involving 5 classes of drugs in adult patients with pulmonary arterial hypertension.

The analyzed endpoint is the time to onset of clinical deterioration, and the results are presented as odds ratio, with a 95% confidence interval. The applied cost-minimisation analysis compares riociguat with the available therapies for pulmonary arterial hypertension

(PAH) - sildenafil, bosentan and ambrisentan, reflecting the Bulgarian therapeutic practice and standards for treatment of PAH.

The analysis includes possible alternatives - endothelial receptor antagonists (ERAs) - bosentan and ambrisentan, and phosphodiesterase type 5 inhibitors (PDE5 inhibitors) - sildenafil, which are used to treat PAH and are included in the PDL. Riociguat would be beneficial in patients with an inadequate response to PDE5i and therefore ambrisentan and bosentan are not direct alternatives to the applicant medicinal product. Sildenafil may to some extent be considered as a direct alternative. The perspective of the analysis is that of the paying institution – the NHIF, only the direct costs are calculated. The selected time horizon is 1 year, due to which discounting has not been applied.

The comparison of the alternatives was made only in terms of costs, as equivalence of the therapeutic outcomes is assumed, based on the indirect comparison of the therapies.

The presented cost-minimisation analysis has drawbacks: the chosen measure of therapeutic outcome is not a long-term one, and other therapies have long-term follow-up with measures of long-term results, while riociguat has no long-term clinical trials and no measure of long-term therapeutic effect. There are no data on the impact on the quality of life, which is an important condition for the evaluation of orphan drugs.

No analysis was performed for individual subgroups of patients.

The presented analysis shows that the applied health technology is not value-effective for the cohort of patients with PAH, compared to the therapies used thus far in Bulgaria.

The analysis includes costs for treatment with riociguat health technology and therapeutic alternatives, calculated on an annual basis and according to a defined daily dose (DDD). For the applicant medicinal product, the dose is titrated according to the individual response and tolerability, therefore the cost of monthly and annual therapy is calculated on the basis of a maximum dose of 3 x 2.5 mg daily. The cost of hospitalization associated with riociguat dose titration, as well as the cost of specialist visits twice a year for all alternatives, have not been included.
The difference in annual treatment value for the compared alternatives indicated that riociguat therapy resulted in an additional annual cost per patient compared to sildenafil, bosentan and ambrisentan, at a riociguat dose of 4.5 mg daily and 7.5 mg daily.

Budget impact analysis

The perspective of the budget impact analysis is of the paying institution – the NHIF. The time horizon of the analysis is 5 years. The estimated number of patients is 16 patients in the first year, increasing to 20 patients by the fifth year, which will increase the NHIF budget over the next five years. The inclusion of the new health technology is associated with an increase in the NHIF budget for a five-year period depending on the number of patients and the dose regimen, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

There is insufficient evidence from studies and meta-analyses regarding long-term survival and quality of life outcomes in patients taking riociguat compared to established therapeutic practice alternatives.

Most studies with the applicant technology used a surrogate marker - the 6-minute exercise test as an end point, the comparative analyses were performed with placebo groups. In most cases, indirect comparisons were done between riociguat vs. bosentan, ambrisentan and macitentan to evaluate the effectiveness of a regimen such as monotherapy and other classes of drugs through the 6-minute test. The comparison with bosentan did not show a significant difference in all other parameters used (pulmonary vascular resistance, WHO FC deterioration, improvement of FC, BORG CR 10 and clinical deterioration) except for stabilization of FC; the results of the comparison with ambrisentan were identical. The results of a relatively large meta-analysis (NMA) demonstrate through Bucher's indirect comparisons that there is a similar efficacy and safety of Adempas vs. bosentan, ambrisentan and macitentan in terms of treatment outcome. The results of studies, including meta-analyses, show that the efficacy of riociguat is not higher than that of PDE-5 inhibitors and endothelin-receptor antagonists already in clinical practice. One of the main goals of treatment in patients with PAH is to improve the quality of life by increasing functional capacity. The improvement of FC by riociguat is moderate compared to other specific types of medicinal products and only about 20% of patients move to a lower grade.

The presented cost-minimisation analysis does not show advantages of the applicant health technology in comparison with the alternative medicinal products reimbursed for treatment of PAH. Taking into account the comparisons between riociguat and existing medicinal products for the treatment of PAH, its inclusion in PDL is not expected to reduce the costs of the NHIF for the treatment of the disease, moreover, costs are likely to increase significantly depending on the number of patients and the administered dose.