Pharmacoeconomic Assessment of the Application of Dornase Alfa in the Treatment of Lung Generation in Patients with Cystic Fibrosis

Alla S. Nemchenko, Anna L. Panfilova, Maryna V. Podgaina, Yuliya L. Zaytzeva, Maryna V. Balynska

Abstract

Introduction: Cystic fibrosis (CF) is an important medical and pharmaceutical, social and economic problem both in the whole world and in Ukraine. Effective and safe, well-grounded health technology (HT) is needed to increase the availability of highly qualified medical and pharmaceutical care to patients with CF in Ukraine for the purpose of survival rate, recovery and life expectancy of patients increasing. Materials and Methods: Taking into account the aforementioned goal of our study, we have conducted a pharmacoeconomic assessment of the dornase alfa usage in the treatment of pulmonary exacerbations in patients with CF. We included data for this outcome from trials lasting 1 month, 6 months and 2 years (dornase alfa n = 575, control n = 576). This yielded a risk ratio of 0.78 (95% confidence interval 0.62–0.96) in favor of dornase alfa. Results: It has been established that in the inhalation use of the dornase alfa (2.5 mg 1 time a day) in adults and children over 5 years ago, the absolute risk of pulmonary exacerbations in patients with CF was 19.5%, without dornase alfa - 25.2%. That is, in 195 patients form a thousand of CF’ patients who took dornase alfa, there were pulmonary exacerbations. The frequency of pulmonary exacerbations in the treatment with dornase alfa per year was 1.25, and in non-dornase alfa – 3.13. Consequently, taking into account the data of the systematic review in the subsequent calculations, the annual period of use of the dornase alfa in the treatment of pulmonary exacerbations of patients with CF has been taken. It should be noted, that the total direct medical costs of the application of HT-1 (dornase alfa) in the treatment of pulmonary exacerbations in CF children aged 5–18 years have been in 2.7 times more comparing to the HT-2 (without dornase alfa). It has been established that the most cost-effective in the treatment of pulmonary exacerbations in children aged 5–18 years with CF is the use of HT-1. Direct medical costs for children aged 5–18 years with the use of HT-2 are 17% higher than with the use of HT-1. Thus, the use of HT-2 in children aged 5–18 years requires additional direct medical expenses of 245061.44 USD. Calculation of the coefficient of “lost opportunity” allowed to establish, in the course of the year, the use of dornase alfa in the treatment of patients with CF may additionally allows to treat almost 37 children diagnosed with CF. The BIA of direct medical expenses for the treatment of pulmonary exacerbations in patients with CF (for the predicted number of patients) for 2017–2021 has shown significant benefits of HT-1 (dornase alfa). Hence, in 2018, the total savings of budget funds will be 265 331.91 USD, in 2019–271 689.08 USD., in 2020–310,340.99 USD, and in 2021–310,340.99 USD (the average growth rate of budget savings for 2017–2021 will be 1.06). Discussion: There was not any study that describes pharmacoeconomic assessment of the application of dornase alfa in the treatment of lung generation in patients with CF for Ukraine’ conditions before. Conclusion: Consequently, pharmacoeconomic studies, conducted by us, allows to formulate a rational financial policy and promote the realization of the rights of the child patient with the CF for obtaining a pharmacotherapy that meets the modern international recommendations.

Keywords: Budget impact analysis, cystic fibrosis, dornase alfa, health technology assessment, pharmacoeconomic analysis

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INTRODUCTION

Cystic fibrosis (CF) is an important medical and pharmaceutical, social and economic problem both in the whole world and in Ukraine. This is due to the early disability of the patients, the need for the constant long-term use of expensive treatment regimens, active dispensary supervision. The comparative analysis of official epidemiological data has shown: In Britain, the average life expectancy of patients reaches 40–45 years, and in Ukraine - 12–15 years only.\(^1\) Thus, in European countries, due to the effective treatment, there is a tendency to increase the life expectancy of patients with CF. 90% of the causes of death and morbidity are caused by pulmonary disease, which is the result of chronic pulmonary infection.

Effective and safe, well-grounded health technology (HT) is needed to increase the availability of highly qualified medical and pharmaceutical care to patients with CF in Ukraine for the purpose of survival rate, recovery and life expectancy of patients increasing. It is worth noting that the costs of an additional year of life are reduced if effective preventive strategies for delaying the development of infections caused by Pseudomonas aeruginosa and other infections are introduced in the country, as well as supporting respiratory basis therapy is used.\(^2\) For example, in the United Kingdom, preventing of the development of a 1-year-old Pseudomonas aeruginosa infection allows to save more than € 25,000 per patient, which is equivalent to the difference in the average annual medical costs between chronically infected and uninfected patients.\(^3\) In Ukraine, the solution of this problem complicates the substantially limited financing of the health system. To optimize pharmaceutical provision under these conditions, rational use of pharmacoeconomically substantiated HTs are necessary.

Taking into account the aforementioned goal of our study, we have conducted a pharmacoeconomic assessment of the dornase alfa usage in the treatment of pulmonary exacerbations in patients with CF.

To achieve this goal, it was been necessary to solve the following tasks:

- To analyze the Cochrane database to determine the effectiveness of the use of dornase alfa in the treatment of pulmonary exacerbations in patients with CF;
- To carry out a pharmacoeconomic analysis using the “cost-effectiveness” method based on the results of a systematic reviews of the trials;
- To calculate the “lost opportunity” rate;
- To analyze the impact on the budget subject to HTA applying.

MATERIALS AND METHODS

For pharmacoeconomic analysis, we have analyzed the data of the Cochrane systematic review of the use of dornase alfa in the treatment of pulmonary exacerbations in patients with CF.\(^4-7\)

Recent studies in young children with CF identified neutrophil elastase as a key risk factor for the onset and early progression of CF lung disease. Several studies demonstrated that neutrophil elastase is implicated in several key features of CF lung disease such as neutrophilic airway inflammation, mucus hypersecretion, and structural lung damage in vivo. Furthermore, these studies identified macrophage elastase (matrix metalloproteinase 12 [MMP12]) as an additional protease contributing to early lung damage. Understanding of CF pathogenesis, in our pharmacoeconomic assessment as the selected clinical efficacy indexes absolute risk of pulmonary exacerbation (%) (Fuchs 1994; Brody et al. 2001) and the frequency of such exacerbations in patients were used.\(^8-13\) The trials included participants with stable lung disease. None of the included trials reported respiratory exacerbations expressed as a mean number per period of follow-up. However, three trials reported either the risk ratio (RR) or the number of people experiencing respiratory exacerbations; therefore, these data have been included within the review (Fuchs 1994; Brody et al. 2001).\(^8-10,13\)

The definition of a respiratory (pulmonary) exacerbation varied in the trials. Fuchs defined an exacerbation as the need for parenteral antibiotics because of any four of the following 12 signs or symptoms: Change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical exam of the chest; decrease in pulmonary function by 10% or more from previously recorded value; or radiographic changes indicative of pulmonary infection (Fuchs 1994).\(^10\) Quan defined an exacerbation as respiratory symptoms requiring IV antibiotics (Brody et al. 2001)\(^12,5,7,9\). The remaining two trials did not include a specific definition for pulmonary exacerbations.\(^8,14\) The Amin trial planned to withdraw participants who had a pulmonary exacerbation requiring IV antibiotics and one participant was withdrawn for this reason, but it was not reported which treatment used. We included data for this outcome from trials lasting 1 month, 6 months (Fuchs 1994), and 2 years (Brody et al. 2001) (dornase alfa \(n = 575\), control \(n = 576\)). This yielded a RR of 0.78 (95% CI 0.62–0.96) in favor of dornase alfa.\(^4,5\)

Thus, it has been established that in the inhalation use of the dornase alfa (2.5 mg 1 time a day) in adults and children over 5 years ago, the absolute risk of pulmonary exacerbations in patients with CF was 19.5%, without dornase alfa - 25.2%. That is, in 195 patients form a thousand of CF patients who took dornase alfa, there were pulmonary exacerbations.\(^4,8,10\)

In Shah PL, 2001, trial 38 patients were matched. Slopes of median changes in FEV1 were \(-2.19 (~3.32, –1.06)\) in the control group and \(-0.75 (~1.87, 0.36)\) in the dornase alfa-treated group (\(P = 0.076\)). There were more infective
exacerbations per patient-year in the control group (3.13 [1.25–4.25]) in comparison to the dornase alfa group (1.25 [0.63–3.0], p = 0.035) over the 4-year treatment period. Antibiotic requirements were also greater with a median 43.75 (17.5–60.0) days of intravenous antibiotic use per patient-year in the control group and 16.25 (8.5–44.0) days in the dornase alfa group (P = 0.034). Consequently, the frequency of pulmonary exacerbations in the treatment with dornase alfa per year was 1.25, and in non-dornase alfa – 3.13.[15]

Consequently, taking into account the data of the systematic review in the subsequent calculations, the annual period of use of the dornase alfa in the treatment of pulmonary exacerbations of patients with CF has been taken.[2,7,16,17]

In Ukraine, the medical and pharmaceutical providing of patients suffering from CF have been determined by the current unified clinical protocol (UCP) of primary, secondary (specialized), and tertiary (highly specialized) medical care: CF, approved by the order of the Ministry of Health of Ukraine dated July 15, 2016, No. 723, as well as the appendix to the order is “Adapted Clinical Guidelines based on evidence (CF), 2016.” According to the data of clinical protocols, the treatment regimens for pulmonary exacerbations of patients with CF have been selected. They have included Mycolytic therapy; physiotherapeutic measures for the purification of respiratory tract from sputum; antibiotic therapy, namely, the use of antibiotics for Pseudomonas aeruginosa [Table 1].[9]

It is noted in the UCP hat physicians should appoint a dornase alfa to patients with CF from the age of 5 years and older in combination with standard therapy of CF with an indicator of forced vital capacity of the lungs at least 40% of the norm to improve the function of the lungs. It is worth noting that the CF Foundation (USA) recommends the continued use of dornase alfa for patients with CF from 6 years and older to improve lung function, quality of life and reduce the frequency of exacerbations strongly:

- From moderate to severe lung disease (Level of evidence: A. Benefit from use: high. Strength of recommendation: A [strongly recommended for routine use]);
- For asymptomatic or mild lung disease (Level of evidence: A. Benefit from use: Moderate. Recommendation strength: B [recommended for routine use]).

A pharmacoeconomic analysis of the treatment of pulmonary exacerbations in patients with pulmonary arterial hypertrophy with the use of alfa toxin (HT-1) and without the use of alfa dornase (HT-2) based on Cochrane systematic review data and clinical protocols has been conducted. The direct medical costs have been compared in the study, namely, the cost of treatment regimens and bed-days for inpatient treatment. Information processing was carried out using special software (Microsoft Office Excel 2010).

The cost of HTs for pulmonary exacerbations in patients with CF treatment has been calculated on the basis of selected trade names of medicines and medical products that had the lowest declared wholesale price until 21.09.2017.[8,18,19] That is, certain indicators reflect the lowest cost threshold for the use of any of treatment of any of HTs for CF treatment within a specified period of time. In accordance with the Order of the Ministry of Health of Ukraine dated September 25, № 829, planning and calculation of needs for medications for antibiotic therapy is based on the average weight of the child’s body (30 kg).

The calculation of direct medical costs also takes into account the cost of bed-days for inpatient treatment (length of stay in a hospital, in days). Due to the lack of the official information about the cost of bed-days in public health-care facilities, prices from private health centers have been analyzed. As a result, it is established that the minimum cost of bed-day of staying in a hospital is $ 100 USA (the average length of stay in a hospital is 14 days). Recalculation of the national currency in the USD index has been calculated in accordance with the rate of the National Bank of Ukraine as of 20.11.2017.

The cost of the HTs of treatment of the pulmonary exacerbations in patients with CF has been calculated on the basis of selected trade names of medicines and medical products that had the lowest declared wholesale price until 21.09.2017.[19] That is, certain indicators reflect the lowest cost threshold for the use of one or another HT of treatment of CF within a specified period of time. In accordance with the Order of the Ministry of Health of Ukraine dated September 25, № 829, planning and calculation of needs for medications for antibiotic therapy is based on the average weight of the child’s body (30 kg).

The calculation of direct medical costs also takes into account the cost of bed-days in inpatient treatment (length of stay in a hospital, in days). Due to the lack of official information about the cost of bed-day in public health-care facilities, prices from private health centers have been analyzed. As a result, it is established that the minimum cost of bed-day of staying in a hospital was 100 USD (the average length of stay in a hospital is 14 days). Recalculation of the national currency in the USA has been carried out in accordance with the rate of the National Bank of Ukraine as of 20.11.2017.

**RESULTS**

The results of calculation of direct medical costs for the treatment of pulmonary exacerbations in children from 5 to 18 years with CF are given in Table 2.

It should be noted, that the total direct medical costs of the application of HT-1 in the treatment of pulmonary exacerbations in CF children aged 5–18 years have been in 2.7 times more comparing to the HT-2.

Cost-effectiveness analysis

To obtain more accurate results from pharmacoeconomic studies, it is necessary to take into account clinical effectiveness indicators and to model (to plan) direct medical costs for the official quantity of patients with CF in Ukraine. Further, calculations have included direct medical costs on the basis of the absolute risk of pulmonary exacerbations (%) and frequency of exacerbations of the pulmonary system in patients per year, which had been presented in a systematic review of the use of dornase alfa in the treatment of pulmonary exacerbations in CF patients.

In Ukraine, according to the UCP “CF”, 920 patients diagnosed with CF have been registered in 2017, of which 495 (70% of patients) were children aged 5–18 years. Hence, in the case of

Table 1: Health technologies of treatment of pulmonary exacerbations in patients with CF

<table>
<thead>
<tr>
<th>HT of treatment of pulmonary exacerbations in patients with CF (dornase alfa)</th>
<th>HT of treatment of pulmonary exacerbations in patients with CF (without dornase alfa)</th>
</tr>
</thead>
</table>
| **Mucolytic therapy**  
Dornase alfa 2.5 mg inhalation 1 time per day with a nebulizer system (1 year)  
Acetylcysteine 1 ampoule inhalation 1-2 times a day (14 days)  
Physiotherapeutic measures to clean the airways (respiratory tract) from sputum  
Therapeutic physical training+breathing exercises for children (14 days)  
chest massage (14 days)  
Antibacterial therapy  
Ceftazidime 50 mg/kg 3 times a day (maximum dose 9 g a day) (intravenously 14 days)  
Obromicin 10 mg/kg/day in a single dose (maximum dose 660 mg/day) (intravenously 14 days)  
Colistin 2,000,000 units twice a day (inhalation for 90 days) | **HT of treatment of pulmonary exacerbations in patients with CF (without dornase alfa)**  
Acetylcysteine 1 ampoule inhalation 1-2 times a day (14 days)  
Ceftazidime 50 mg/kg 3 times a day (maximum dose 9 g a day) (intravenously 14 days)  
Obromicin 10 mg/kg/day in a single dose (maximum dose 660 mg/day) (intravenously 14 days)  
Colistin 2,000,000 units twice a day (inhalation for 90 days) |

CF: Cystic fibrosis, HT: Health technology

Table 2: Direct medical costs for the treatment of pulmonary exacerbations in children with CF

<table>
<thead>
<tr>
<th>Indexes</th>
<th>HT - 1 (dornase alfa)</th>
<th>HT - 2 (without dornase alfa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of HT of treatment of the pulmonary exacerbations for one child in age from 5 to 18 years old, USD</td>
<td>8975,03</td>
<td>2441,62</td>
</tr>
<tr>
<td>Cost of bed-days (14 days), USD</td>
<td>1400,00</td>
<td>1400,00</td>
</tr>
<tr>
<td>Total direct medical costs for one child with CF from 5 to 18 years old, USD</td>
<td>10375,03</td>
<td>3841,62</td>
</tr>
</tbody>
</table>

CF: Cystic fibrosis, HT: Health technology

Table 3: Pharmacoeconomic analysis of HTs for the treatment of pulmonary exacerbations in CF patients

<table>
<thead>
<tr>
<th>Indexes</th>
<th>HT - 1 (dornase alfa)</th>
<th>HT - 2 (without dornase alfa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct medical costs per child from 5 to 18 years, USD</td>
<td>10375,03</td>
<td>3841,62</td>
</tr>
<tr>
<td>Absolute risk of pulmonary exacerbations, %</td>
<td>19,50</td>
<td>25,20</td>
</tr>
<tr>
<td>The number of patients with CF (from 5 to 18 years), taking into account the risk, persons</td>
<td>97</td>
<td>125</td>
</tr>
<tr>
<td>Direct medical costs taking into account the risk of pulmonary exacerbations, USD</td>
<td>1006377,91</td>
<td>480202,50</td>
</tr>
<tr>
<td>Frequency of cases of exacerbations of the pulmonary system per year, cases</td>
<td>1,25</td>
<td>3,13</td>
</tr>
<tr>
<td>Direct medical costs taking into account the incidence of pulmonary exacerbations, USD</td>
<td>1257972,39</td>
<td>1503033,83</td>
</tr>
<tr>
<td>Additional direct medical costs, USD</td>
<td>-</td>
<td>245061,44</td>
</tr>
</tbody>
</table>

CF: Cystic fibrosis, HT: Health technology
HT-1 (dornase alfa), the number of children aged 5–18 years will be $495 \times 19.5\% = 97$ patients. The generalized results of the pharmacoeconomic analysis of HTs in the treatment of pulmonary exacerbations in children aged 5–18 years with CF, using “cost-effectiveness method,” are presented in Table 3.

It has been established that the most expedient in the treatment of pulmonary exacerbations in children aged 5–18 years with CF is the use of HT-1 (dornase alfa). Direct medical costs for children aged 5–18 years with the use of HT-2 are 17% higher than with the use of HT-1 (dornase alfa).

Thus, the use of HT-2 in children aged 5–18 years requires additional direct medical expenses of 245061.44 USD.

Next, we calculated the “lost opportunity” coefficient (Q), which allows to calculate the number of patients who can be treated further by saving money using more rational technology during the year of treatment. The coefficient of “lost opportunity” was calculated by the formula:

\[
Q = \frac{aDMC}{Clow}
\]

where:

- \(aDMC\) - coefficient of “lost opportunity,”
- \(aDMCx\) - difference in the cost of compared HTs (HT-1 and HT-2) (additional direct medical costs);
- \(Clow\) - the cost of the course of pharmacotherapy with the use of alfa dornase.

That is, the “lost opportunity” coefficient has shown the number of patients who could additionally receive the dornase alfa, which will further reduce the risk of pulmonary exacerbations, improve the quality of life of patients with CF.

The “lost opportunity” rate when HT-2 is used in children aged 5–18 years versus the HT-1 (dornase alfa) (the cost of treatment per year was $6533.41) was calculated as follows:

\[
Q = \frac{aDMC}{Clow}
\]

That is, in the course of the year, the use of dornase alfa in the treatment of patients with CF may additionally allow to treat almost 37 children diagnosed with CF.

**Budget impact analysis**

In the context of the resource deficit in the modern health system, the budget impact analysis (BIA) has a significant social and economic role in the application of HTs, which enables us to determine the financial implications of using the new technology in certain situations or in the context of the system, taking into account resource constraints. This method is an important part of a comprehensive economic assessment of the HTs. Consequently, the next stage of the study was an analysis of the impact on the budget in the use of HTs for the treatment of pulmonary exacerbations in children aged 5–18 years with CF. In calculations of the impact on the budget, the number of patients with CF (aged–18 years and adults) for the 2017–2021 has been estimated (average annual growth rate of 1.05).

Furthermore, structuring of the predicted number of patients at the risk of pulmonary exacerbations was carried out (use of dornase alfa in children over 5 years of age determines the absolute risk of pulmonary exacerbations as 19.5%, without dornase alfa - 25.2%); calculated direct medical costs associated with the use of one or another technology for the treatment of pulmonary exacerbations in patients with CF, taking into account the frequency of exacerbations per year. The results of the calculations are presented in Table 4.

The BIA of direct medical expenses for the treatment of pulmonary exacerbations in patients with CF (for the predicted number of patients) for 2017–2021 has shown significant benefits of HT-1 (dornase alfa). The results of the calculations convincingly suggest that the use of dornase alfa should be defined as the dominant in the treatment of pulmonary exacerbations in children patients with CF from 5 to 18 years old.

As can been seen from Table 4, while applying HT-1, there is a tendency of growth of saving of budget funds in comparison with HT-2.

Hence, in 2018, the total savings of budget funds will be 265 331.91 USD, in 2019 - 271 689.08 USD., in 2020 - 291 015.04 USD., and in 2021 - 310,340.99 USD (the average growth rate of budget savings for 2017-2021 is 1.06).

**DISCUSSION**

There are at least 54 trials that include analysis of dornase alfa for CF, of which three additional papers examined the healthcare cost from one of the clinical trials. 15 trials compared dornase alfa to placebo or no dornase alfa treatment; two compared dornase to hypertonic saline; one compared daily dornase alfa with hypertonic saline and alternate day dornase alfa; one compared dornase alfa to mannitol and the combination of both drugs. Trial duration varied from 6 days to 3 years.[4-5,8-10,14,21]

The results for trials comparing dornase alfa to other medications that improve airway clearance. Evidence of dornase alfa compared to other medications was limited,
Table 4: The results of the “BIA” of the HTs for treatment of pulmonary exacerbations in children with CF

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</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with CF from 5 to 18 years old, persons</td>
<td></td>
<td>495</td>
<td>520</td>
<td>546</td>
<td>573</td>
<td>602</td>
<td></td>
<td>495</td>
<td>520</td>
<td>546</td>
<td>573</td>
<td>602</td>
</tr>
<tr>
<td>Absolute risk of pulmonary exacerbations, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19,5</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>The number of patients with CF from 5 to 18 years old, taking into account the absolute risk, persons</td>
<td></td>
<td>97</td>
<td>101</td>
<td>107</td>
<td>112</td>
<td>117</td>
<td></td>
<td>125</td>
<td>131</td>
<td>138</td>
<td>145</td>
<td>152</td>
</tr>
<tr>
<td>Direct medical costs taking into account the risk of pulmonary exacerbations, USD</td>
<td></td>
<td>1006377,91</td>
<td>1047878,03</td>
<td>1110128,21</td>
<td>1162003,36</td>
<td>1213878,51</td>
<td></td>
<td>480202,50</td>
<td>503252,22</td>
<td>530143,56</td>
<td>557034,90</td>
<td>583926,24</td>
</tr>
<tr>
<td>Frequency of pulmonary exacerbations for a year, cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,25</td>
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</tr>
<tr>
<td>Direct medical cost, taking into account the frequency of exacerbations, USD</td>
<td></td>
<td>1257972,39</td>
<td>1309847,54</td>
<td>1387660,26</td>
<td>1452504,20</td>
<td>1517348,14</td>
<td></td>
<td>1503033,83</td>
<td>1575179,45</td>
<td>1659349,34</td>
<td>1743519,24</td>
<td>1827689,13</td>
</tr>
<tr>
<td>Savings of budget funds, USD</td>
<td></td>
<td>245061,44</td>
<td>265331,91</td>
<td>271689,08</td>
<td>291015,04</td>
<td>310340,99</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

BIA: Budget impact analysis, CF: Cystic fibrosis, HT: Health technology
and the open-label design of the trials may have induced bias; therefore, the quality of the evidence was judged to be low.

However, there was not any study that describes pharmacoeconomic assessment of the application of dornase alfa in the treatment of lung generation in patients with CF for Ukraine’ conditions before.

**CONCLUSION**

Consequently, taking into account the medical, pharmaceutical and socioeconomic importance of organizing of effective pharmaceutical providing for the patients with CF, conducted by us pharmacoeconomic studies allows us to formulate a rational financial policy and promote the realization of the rights of the child patient with the CF for obtaining an affordable, high-quality, effective pharmacotherapy that meets the modern requirements, UCP, and international recommendations.

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