

# Availability and reimbursement of biological products for severe asthma in Bulgaria

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## Abstract

**Objectives:** This study aims to analyze the reimbursement and cost of biological therapy for severe asthma in Bulgaria during 2014–2019 from the perspective of the National Health Insurance Fund.

**Methods:** It is a retrospective, Marco-costing, top-down study of the expenditures for biological products for severe asthma. The changes in the cost paid by the National Health Insurance Fund per year, per product, and per patient during 2015–2020 were systematized and calculated. The utilization of biologicals was analyzed by calculating the defined daily dose/1000inh/day. Three databases were searched—the European Medicines Agency for the date of marketing authorization of biological products, National Council of Prices and Reimbursement for the date of their respective inclusion in the positive drug list, and National Health Insurance Fund about the number of patients with asthma, reimbursed sum for all asthma patients, and number of packages sold of biological products.

**Results:** At the end of 2019, five international non-proprietary names of biologicals with indication for severe asthma had received European marketing authorization, and three of them were included in the Bulgarian positive drug list—omalizumab, mepolizumab, and benralizumab with a 75% reimbursement. Upon their introduction into the positive drug list, the reimbursed expenditures for asthma therapy started to increase from 27 million in 2014 to 33 million BGN in 2019 (€13.5–€16.5 million). The cost of therapy with biologicals rose from 16% to 24% of all anti-asthmatic medicines budget. The National Health Insurance Fund database reported that between 47,000 and 52,000 of patients with asthma, 466 are on biological therapy. The yearly cost of one asthma patient ranges between 512 and 615 BGN (€258–€307), and the yearly per-patient cost of severe asthma is 16,666 BGN (appr. €8333). Total utilization in defined daily dose/1000inh/day increases from 0.0199 to 0.0383 from 2015 to 2019.

**Conclusion:** The access to biological therapy through the reimbursement system has improved during the last 3 years. The cost of therapy is posing a high burden on the National Health Insurance Fund and on the patients and is expected to increase due to the small number of patients on biological therapy currently in comparison to all reimbursed asthmatics.

## Keywords

Asthma, biological therapy, cost study, reimbursement, Bulgaria

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## Introduction

Asthma is a common chronic disease that affects around 335 million people worldwide. It is a serious global health problem across all age groups, with increasing prevalence in many developing countries, increasing costs of treatment and increasing burden on patients and the community.<sup>1</sup> According to the Bulgarian Society of Lung Diseases, the number of asthma patients in the country is estimated to exceed 400,000 people with only 50% of asthmatics being diagnosed. Patients with severe asthma are estimated to comprise 5%–10% of them.<sup>2</sup>

Control of severe asthma presents a challenge because of the need for extensive diagnostic evaluation, complicated personalized therapy accompanied by very high direct, indirect, and intangible costs. In this regard, increasing consideration is being given to biological targeted therapies, which

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currently are applied to strictly selected patients because of their high costs.

According to Global Initiative for Asthma (GINA), 45.1% of patients have uncontrolled asthma, 83.7% of them consider their disease to be controlled, and 69.9% do not take it as serious. Patients with severe asthma are hospitalized twice as often as other asthma patients, and their care may be up to five times more expensive than patients with mild asthma.<sup>3</sup> For example, 14% of patients with severe asthma have 100% disability, and 38% are unable to perform their work properly due to their condition.<sup>4</sup>

There is no clear definition of severe asthma. The American Thoracic Society (ATS) and the European Network for Understanding the Mechanisms of Severe Asthma (ENFUMOSA) provide definitions based on criteria, among which corticosteroid use is a major factor in determining the severity.<sup>5,6</sup> The World Health Organization (WHO) uses the level of current clinical control and the associated risks to determine severe asthma; according to GINA, the definition of severe asthma is based on a retrospective assessment of the level of treatment required to control symptoms and exacerbations.

Several new biological products for the treatment of uncontrolled asthma recently received European marketing authorization, provoking our interest toward analyzing the local developments in the pharmacotherapy of severe asthma with biological products. There are published studies, which analyze the impact of biological therapy on the costs to the health insurance system, but in the case of asthma, such studies are not available at a national level.<sup>7,8</sup>

This study aims to analyze the reimbursement and cost of biological therapy for severe asthma in Bulgaria for the period 2015–2019, alongside estimating the level of patient access to therapy. The perspective is that of the National Health Insurance Fund (NHIF) for a 5-year time horizon. The study focuses on the question of availability of biological therapies on the national market as to how patient access is influenced by their level of reimbursement for the diagnosis of severe asthma, national guidelines for biological therapy and their concordance with the international recommendations, and the overall cost of therapy for the national system.

## Methods

### *Design of the study*

It is a retrospective, Marco-costing, top-down study of the expenditures for biological products for severe asthma. The study was performed in two steps. First, we identified current biological products for severe asthma therapy authorized at the European level and reimbursed at the national level. We analyzed the international therapy guidelines alongside the requirements of the NHIF. The NHIF defines certain criteria that need to be met in order to initiate patients on biological products with the option of reimbursement.

The comparison between national and international processes was done in order to estimate the level of concordance between both sets of guidelines, as well as to elucidate and review the criteria set by the NHIF, which can limit access to therapy on a national level.

Second, macro-costing was done by summarizing information available in the officially published data resources by the NHIF regarding all reimbursed expenditures for biological products for severe asthma. The changes in the cost paid by the NHIF per year, per product, and per patient during 2015–2020 were systematized and calculated. The cost of pharmacotherapy is presented in national currency (BGN) at the exchange rate of €1=1.9558 BGN in 2019. The exchange rate has been fixed since 1998.

### *Sources of data*

Information was collected from three different official databases. The three databases were freely available with open public access. Due to the public availability of databases, no requirement for ethics approval was necessary.

The European Medicines Agency (EMA) database was analyzed for the precise date of marketing authorization of biological products indicated for severe asthma therapy to clarify the date of their placement on the European market.<sup>9</sup> The products for severe asthma therapy were identified after a revision of their summary of product characteristics (SPC). By origin, they should be monoclonal antibodies and as indication should be approved for severe asthma therapy in order to be included in the study. The search period encompassed the latest 20 years (2000–2020).

National Pricing and Reimbursement Committee (NPRC) database was searched for the date of inclusion of the respective biologicals in the positive drug list (PDL) and its level of reimbursement. This was done to establish the date of the patient access to reimbursed biological therapy and define the time lag if any.<sup>10</sup> The National Council of Pricing and Reimbursement (NCPR) regularly publishes information about the newly included international non-proprietary names (INNs) of products in the PDL, their approved prices, level of reimbursement, and indications for reimbursement by International Classification of Diseases (ICD) code. There are three lists of medicines: for outpatient, inpatient, vaccines, and infectious diseases which are updated monthly. Those lists were revised since the date of European marketing authorization for the date of inclusion of a respective biological therapy.

Then, from the database of the NHIF, we extracted information about the number of patients with asthma, patients with severe asthma, reimbursed sum for all asthma patients, reimbursed sum for biological therapy, and number of packages sold of biological products.<sup>11</sup> This information was extracted after a review of the tables with reimbursed INNs, trade names of products, and reimbursed sum which are published every month on the web page of

the NHIF. The information was summarized on a yearly basis. Patients with asthma were sub-categorized after a revision of the official tables with number of health-insured patients who received their prescription every month for a particular ICD code.

### Statistical analysis

The utilization of biologicals for every year was analyzed by calculating the DDD/1000inh/day using the modified WHO formula as follows<sup>12</sup>

$$\text{DDD} / 1000\text{inh} / \text{day} = \left( \frac{\text{Utilization in BGN} / \text{reference DDD}}{n \text{ population} / 365} \right) \times 1000$$

The World Health Organization<sup>12</sup> defined daily dose (DDD) is fixed for the country at the lowest DDD among all available alternatives with the same INN in the PDL. In addition, for the years 2018–2019, we obtained data on the number of packages sold and calculated the number of treatment patient months, by dividing the number of packages on the average recommended prescribing dose, according to the summary of product characteristic (SPC) of the observed INNs of medicines.

For omalizumab, the recommended dose is administered by subcutaneous injection every 4 weeks—three vials for every 70 kg weight of the patient. Therefore, the number of packages was divided by 36 (12 months per three vials).<sup>13</sup> For mepolizumab, the recommended dose is 100 mg administered subcutaneously once every 4 weeks. The number of packages sold was divided by 12 yearly doses.<sup>14</sup> For benralizumab, the recommended dose is 30 mg injected every 4 weeks for the first three doses, and every 8 weeks afterwards. Therefore, the number of packages sold was divided by an average of 7.5 yearly doses.<sup>15</sup>

## Results

### Review of the national criteria for severe asthma therapy

In Bulgaria, the criteria for treating severe asthma are based on the GINA step approach and are included in the Pharmacotherapeutic Guide to Pneumology and Phthysiology.<sup>2</sup> Severe asthma requires treatment with high-dose inhaled corticosteroid (ICS) and additional control drug (long-acting inhaled beta-2 agonist (LABA), montelukast, and theophylline), and/or the use of oral corticosteroid over 6 months in the last year, step 4 or 5 according to GINA, to prevent loss of control or remain uncontrolled nonetheless treatment. If despite application of steps 4 and 5 patients with exacerbations remain poorly controlled, step 6 of GINA recommends the inclusion of biological targeted therapy in patients who have eosinophilic or allergic biomarkers or need oral corticosteroid support.

NHIF has a list with 10 criteria for starting a course of treatment with omalizumab for severe allergic asthma as well as for starting a course with mepolizumab or benralizumab for severe refractory asthma. GINA's recommendations are included in the requirements of the NHIF for initiation of biological therapy. For omalizumab, along with GINA's recommendations for specific serum IgE, high level of total serum IgE, frequent severe exacerbations, and hospitalization in the previous year, the health insurance fund has additional requirements to start the treatment—patients should demonstrate reduction of forced expiratory volume (FEV) below 60%, Asthma Control Test (ACT) result below 20, have had a visit to an emergency room in the last 6 months, and are currently using high daily doses of ICS. If the patient meets the criteria, therapy with omalizumab could be initiated—the first course is within 16 weeks, and after assessment of the therapeutic efficacy, the treatment could be extended for another 24 weeks. For mepolizumab and benralizumab, the NHIF considers GINA's recommendations for peripheral eosinophilia  $\geq 300/\mu\text{L}$  and applies additional requirements for ACT result below 20—administration of two or more courses with systemic corticosteroids due to exacerbations in the last 12 months, FEV below 60%, and hospitalization or visit of emergency room in the last 6 months. If the criteria are met, the patient is included in the therapy for 6 months, and after assessment of the efficacy the course could be extended. NHIF applies exclusion criteria like pregnancy and breastfeeding, age restriction, lack of efficacy after 16 weeks for omalizumab, smoking, systemic autoimmune diseases, impaired liver, and kidney function.

### Reimbursed biologicals in Bulgaria with European marketing authorization

At the end of 2019, five INNs of biological monoclonal antibody medicines with indication severe asthma—omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab had received European Marketing authorization (Table 1). They differ in respect with their mechanism of action—anti-immunoglobulin E (anti IgE), used for the treatment of severe persistent allergic asthma, anti-interleukin 5 (anti-IL-5), and anti-interleukin 5 receptor (anti-IL-5R), used for the treatment of severe refractory eosinophilic asthma, and anti-interleukin 4 receptor (anti-IL-4) monoclonal antibodies. All are indicated for treatment of severe, persistent asthma, either allergic or eosinophilic type that is uncontrollable with oral or injectable corticosteroids.

The first product in the group was omalizumab which began to be reimbursed in Bulgaria nearly 9 years after its European marketing authorization, while the two other approved products received reimbursement status within 2 year after their European marketing authorization. All products are reimbursed at 75%. Dupilumab and reslizumab were not present in the PDL at the end of 2019.

**Table 1.** Biologicals for severe asthma therapy with EU marketing authorization, reimbursed in Bulgaria.

INNs	Therapeutic group	Marketing authorization by EMA	Inclusion into PDL in Bulgaria	Level of reimbursement
Omalizumab	anti IgE	October 2005	November 2014	75%
Mepolizumab	anti-IL-5	December 2015	December 2017	75%
Benralizumab	anti-IL-5R	August 2016	December 2018	75%
Dupilumab	anti-IL-4R	September 2017	Not included at the end of 2019	
Reslizumab	anti-IL-5	January 2018	Not included at the end of 2019	

EU: European Union; INN: international non-proprietary names; EMA: European Medicines Agency; PDL: positive drug list.

### Reimbursed cost of therapy

The reference price per package for omalizumab is 747 BGN (appr. €374), for mepolizumab is 2189 BGN (appr. €1095), and for benralizumab is 5140 BGN (appr. €2570). With the introduction of the biological products, the reimbursed expenditures for asthma therapy began to increase from 27 to 33 million BGN (€13.5–€16.5 million)—Table 2. The cost of therapy with biologicals rose from 16% to 24% of all anti-asthmatic medicines budget.

During the observed period the reimbursed sum for omalizumab increased from 4.2 million BGN (€2.1 million) to nearly 7 million BGN (€3.5 million) in 2019, respectively. In the first quarter of 2018, mepolizumab reimbursed expenditures accounted for 34,000 BGN (€17,000), but at the end fourth quarter of 2019, they had increased to 546,000 of BGN (€273,000). Benralizumab was still in the beginning of its reimbursement but with 70 reimbursed packages it accounts for 270,000 of BGN (€135,000).

Recalculating the reimbursed expenditures in DDD/1000inh/day confirms that utilization of biologicals increases not only in monetary units. Total utilization in DDD/1000inh/day increases from 0.0199 to 0.0383 from 2015 to 2019. In addition to utilization per INNs increased and total utilization for all biologicals.

The NHIF database reported that on average 51,892 (standard deviation (SD): 275.11) of patients with asthma are reimbursed for their medicines annually, and out of them, 466 patients are on biological therapy. Thus, the yearly cost of one asthma patient accounts from 512 to 615 BGN (€258–€307). The yearly per-patient cost of severe asthma is 16,666 BGN (appr. €8333). The information about the reimbursed packages shows permanent increase (Table 3).

When recalculating the number of packages sold in number of treatment months by following the SPC average daily dose, we confirmed that nearly 400 patients are receiving therapy with minimum 1-year length of treatment.

### Discussion

Asthma is widespread chronic disease affecting nearly 300 million people worldwide.<sup>16</sup> Out of them, about 5%–10% suffer from severe or uncontrolled asthma, which is

associated with increased mortality and hospitalization, reduced quality of life (QOL), and increased health care costs.<sup>17</sup> Understanding the cost of severe asthma therapy and availability of medicines on the national markets could orientate physicians toward possible therapeutic options and careful selection of suitable patients, including also the cost of therapy as a determinant. For the health insurance institutions, such an analysis provides an important information about the scope of coverage for crucial patients and tendencies in cost changes.

We consider the access to biological products for severe asthma therapy in Bulgaria at the end of 2018 to be relatively good, because out of five INNs with centralized marketing authorization in European Union (EU), three (60%) are reimbursed by national authorities. Comparison between the EMA date for marketing authorization and entrance on the national markets is an important indicator for patients' access to innovative therapies. Other studies in the field show that Bulgarian patients have a relatively delayed access to innovative medicines as only 5% of centrally authorized medicinal products (MPs) in 2017 are available in the PDL, 16% of all in 2016, and 18%—in 2015. Other authors have offered explanations for the reasons behind this relatively long procedure for innovative products appraisal in Bulgaria before their inclusion into the PDL.<sup>18</sup> It is also worth commenting that the period for local approval has shortened, allowing for improved access to medicines—from 9 years for omalizumab to 2 years for the others. Factors that might influence the slow penetration of biological anti-asthmatic products on the national market could be the regulatory barriers and companies' policy for market entrance.<sup>13–15</sup>

Regarding the affordability, the level of reimbursement of 75% is a barrier to individual patients, having in mind also the high prices of all biologicals. For example, the average monthly salary in 2019 was €500 while the prices of mepolizumab and benralizumab were two to four times higher.<sup>9</sup> We should note that patients probably received other additional anti-asthmatic medicines, which increases the cost burden on individuals. Such a conclusion is also supported by the calculations of the average cost per patient being between 512 and 615 BGN (€258–€307), which is almost equal to the average per-patient cost of pharmacotherapy in the country for 2019 for all reimbursed medicines. The average yearly

**Table 2.** Reimbursed cost of therapy per INN (BGN).

	2015		2016		2017		2018		2019	
	Reimbursed cost (BGN)	DDD/1000inh/day	Reimbursed cost (BGN)	DDD/1000inh/day	Reimbursed cost (BGN)	DDD/1000inh/day	Reimbursed cost (BGN)	DDD/1000inh/day	Reimbursed cost (BGN)	DDD/1000inh/day
Omalizumab	4,164,646	0.01994923	4,715,945	0.02274903	4,963,536	0.02411891	5,961,124	0.02917633	6,949,841	0.03425582
Mepolizumab							34,447	0.00017049	546,528	0.00272401
Benralizumab									269,845	0.00135799
Total DDD/1000inh/day		0.01994923		0.02274903		0.02411891		0.02934682		0.03833782
Total for all biologicals (BGN)	4,164,646		4,715,945		4,963,536		5,995,571		7,766,214	
Total for all asthma patients (BGN)	26,610,291		29,574,804		30,390,164		32,200,000		33,000,000	

INN: international non-proprietary names; DDD: defined daily dose.

cost per patient with severe asthma is even higher. No official policy focusing on the reimbursement of biological products for different diseases as well as distinguishing biologicals from the rest of the products exists in the country. Having in mind the targeted mechanism of action of biologicals that could benefit only carefully selected patients such a policy might be an important cost containment measure. The argument supports the performance of cost studies of the biologicals.

Our macro-costing study revealed that biological therapy led to substantial increases in the reimbursed cost. Similar studies in Bulgaria reported such an increase in the area of rheumatoid arthritis where the cost of therapy can sometimes be higher than that of some malignant diseases.<sup>10,11</sup> The fact that cost of biologicals already comprises 24% of total asthma pharmacotherapy costs. This is a serious concern for ensuring the future affordability of medicines for patients. Despite the limitations set by the NHIF, other cost-containment measures might be necessary.

The NHIF database shows a very low number of reimbursed asthma patients, which is smaller in comparison with the estimation of the Bulgarian Society of Lung Diseases. Other authors also have reported threefold differences, from 3.6% to 9.5% in asthma prevalence depending on the diseases definitions.<sup>16</sup> We cannot evaluate the estimation of the Bulgarian Society of Lung Diseases but can assume that official data reflect the real number of asthma patients applying for therapy. The official number of patients is also the major reimbursement cost-driving factor; therefore, it is the only one component of the analyzed cost. On the contrary, only 0.9% of asthmatics receive biological therapy, which is a relatively small percentage, having in mind the global prevalence reports of 5%–10% of severe asthma. Therefore, the cost for severe asthma therapy should be expected to increase further.

Similar studies are quite limited, especially in Central and Eastern Europe. In 2018, the Midwest Comparative Effectiveness Public Advisory Council reported an assessment of the comparative cost-effectiveness of omalizumab, mepolizumab, reslizumab, ebenralizumab, and dupilumab for the United States and found an incremental cost-effectiveness ratio for biologicals ranging from US\$325,000 to US\$391,000 (2018 dollars) per QALY gained. It is far above the accepted threshold between US\$100,000 and US\$150,000 per quality-adjusted life year (QALY) gained and confirms the high cost of biological asthma therapy.<sup>17</sup> Similar to our study, a systematic review of cost-effectiveness analyses found that biological therapy should be carefully targeted to specific populations such as responders in order to further improve value.<sup>18</sup>

This macro-costing approach possess some limitations because it focuses only on the pharmacotherapy cost and does not include any other costs, due to their unavailability in the country of such an information at central level.<sup>19–26</sup> The other limitation is the lack of data at patient level, as well number of

**Table 3.** Reimbursed number of packages of biological products.

INNs	2018	No. of treatment months	2019	No. of treatment months
Omalizumab	10,613	295 patients for 12 months	12,457	346 patients for 12 months
Mepolizumab	21	2 patients for 11 months	333	28 patients for 12 months
Benralizumab			70 (fourth quarter)	22.5 patients for 3 months

INN: international non-proprietary names.

packages sold for the whole period. This limits some of the calculations. More detailed per-patient micro cost analysis is necessary to evaluate the actual changes in the cost of therapy after the switch to biologicals and resulting disease control.

## Conclusion

The access to biological therapy through the reimbursement system has improved during the last 3 years as number of reimbursed products and the NHIF pose additional criteria restricting all eligible patients' access. The cost of therapy is posing a high burden on the NHIF and on the patients and is expected to increase due to the small number of patients on biological therapy currently in comparison to all reimbursed asthmatics.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Ethical approval was not sought for this study because the study uses officially published and accessible information about the cost and prescribing at national level. No work with human subject or their individual data was performed. The databases used for the study were freely available and there is no need of approval from ethical committee.

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## Supplemental material

Supplemental material for this article is available online.

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