MEDICAL UNIVERSITY
SOFIA

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BIOSIMILAR MEDICINAL PRODUCTS IN THE EU AND THE CHALLENGES IN PLACING THEM ON THE MARKET

A B S T R A C T

of a dissertation
for obtaining an educational and scientific degree
"Doctor"

Field of higher education: 7. Health care and sports;
Professional field: 7.4. Public Health;
Doctoral program: Social medicine and organization of healthcare and pharmacy

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Sofia, 2023

The dissertation contains **138** standard typewritten pages, and is illustrated with **12** tables, **27** figures and **6** appendices.

The bibliographic reference includes **106** titles, of which **37** are in Cyrillic and **69** are in Latin.

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The public defense will take place on July 11, 2023 at 1 p.m. in the hall of the Faculty of Public Health, UMBAL "Tsaritsa Joanna - ISUL" EAD, 8 "Byalo More" Str., Sofia.

Defense materials are available at the secretariat of the Dean's Office of the Faculty of Health Sciences, MU Sofia, UMBAL "Tsaritsa Joanna - ISUL" EAD, 8 Byalo More Str., Sofia and on the website of Medical University - Sofia.

C O N T E N T

Note: The numbering of the tables and figures in this abstract does not correspond to that in the dissertation.

LIST OF ABBREVIATIONS

ATC classification	Anatomical Therapeutic Chemical (ATC) Classification
VAT	Value Added Taxe
DLBCL	Diffuse large B-cell lymphoma
EC	European Commission
EU	European Union
PPA	Public Procurement Act
MP(s)	Medicinal product(s)
ICD code	Code of Disease from International Statistical Classification of Diseases and Related Health Problems, 10th Revision
Price Ordinance	Ordinance on terms, rules and procedure for regulation and registration of prices for medicinal products, adopted by Council of Ministers Decree No 97 of 19 April 2013
NCPRMP	National Council On Prices And Reimbursement Of Medicinal Products
NHIF	National Health Insurance Found
PDL	Positive Drug List
MAH	Marketing Authorization Holder
FL	Follicular lymphoma
CLL	Chronic lymphocytic leukemia
CPB	Central Purchasing Body in the Healthcare Sector
ESMO	European Society for Medical Oncology
EPR	External Price Referencing
INN	International non-proprietary name
NCCN	The National Comprehensive Cancer Network

INTRODUCTION

The development of medical science towards improving the methods of diagnosis and treatment of diseases determines the need to increase the funds required by the health insurance systems to ensure adequate health care of the population. This, in turn, determines the need for adequate regulation and optimization of the increasing costs for health care, including medicines, as well as for the efficient use of financial resources. A main tool for managing these resources is an effective drug policy, through which to achieve optimization of pharmaceutical costs on the one hand, and to ensure patients' access to the appropriate drug therapy on the other. A challenge for achieving this goal is to strike a balance between the interests and needs of the individual participants - patients, healthcare professionals, national health insurance institutions and the pharmaceutical industry in their capacity as consumers of health services, providers of health services, main payer of health services respectively and a partner that primarily determines progress and innovation in the healthcare sector.

The advantages and benefits of treatment with biological medicinal products in recent decades, and especially of the application of targeted therapy with monoclonal antibodies to a number of oncological diseases are undeniable. The patent protection expiration of these drugs predetermines the development of biosimilars, which defines the need for regulatory mechanisms with the relevant legislative framework ensuring market access to this group of drugs. Accessibility to the market should be considered as physical availability of the relevant MPs, on the one hand and as financial accessibility, guaranteed by a fair price and corresponding to the purchasing ability of the population and the national health system on the other.

The market placement of biosimilars is defined as a tool "to reduce drug costs and increase patient access to treatment". This can be considered as the ways to achieve one of the United Nations goals related to health well-being by 2030, namely "Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all ".

OBJECTIVE, TASKS, MATERIALS AND METHODS OF THE RESEARCH

1. Objective

This study aims to investigate and analyze the regulatory requirements for the market placement of biosimilars and how they affect access to therapy, as well as to analyze the impact of the market placement of biosimilars on drug therapy costs paid by the NHIF for treatment of oncohematological diseases - follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL).

2. Tasks

To achieve the set goal, the following tasks have been defined:

1) Determination of the main regulatory requirements regarding marketing authorization, principles of pricing and reimbursement, as well as the market placement of biosimilars in the EU and in Bulgaria.

The following sub-tasks are set to achieve the specified task:

✓ Overview of the general policy of the EU regarding marketing authorization, pricing and reimbursement of biosimilars, as well as the current regulatory requirements determining their release on the market in Bulgaria;

✓ Comparative analysis of the methods for pricing and market placement of biosimilars in Bulgaria and in the reference countries for Bulgaria;

2) Systematized review of the market of biosimilars in the EU and in Bulgaria through the following sub-tasks:

✓ Analysis of the biosimilars with valid marketing authorization and placed on the market in Bulgaria;

✓ Analysis of the impact of the launch of biosimilars in the reference countries on the price of drugs with INN Rituximab in Bulgaria for the period 2017-2021;

✓ Retrospective analysis of the reference value for MP with INN Rituximab for the period 2017-2021 as defined in Appendix No. 2 of the PDL.

3) Evaluation of the impact of biosimilars on the costs of the NHIF by:

✓ Analysis of the total costs of the NHIF for drug therapy of FL, DLBCL and CLL for the period 2018 – 2021;

✓ Analysis of the costs of the NHIF for drug therapy of FL, DLBCL and CLL with the reference MP and biosimilars for the period 2018 – 2021;

✓ Analysis of the biosimilars market share for the period 2018-2021.

4) Assessment of the impact of regulatory requirements on market access for biosimilars.

3. Materials

For the purposes of this dissertation, the used materials and data are from:

✓ regulatory framework in the field of medicinal products in human medicine - regulations, directives, EMA guidelines, laws and ordinancess;

✓ working documents and analyzes of international and national institutions, expert and professional organizations;

✓ articles and developments by leading authors and researchers in the field of drug policy in the EU;

✓ Union Register of medicinal products, public register of prices of MP maintained by NCPRMP;

✓ NHIF - costs reports for oncology drugs paid outside the cost of the relevant clinical pathways and outpatient procedures for the relevant diseases by ICD code.

4. Methods and methodology

4.1. Documentary analysis

Analysis of European regulations, directives and recommendations, concerning biosimilar marketing authorization and market placement.

Analysis of Bulgarian legislation regarding pricing and reimbursement of prescription drugs and payment of treatment with public funds.

International organizations and competent authorities reports for identifying specific challenges to the biosimilar market placement and patient access to drug therapy.

Internet check and review of the content of official websites indicated in the literature used.

4.2. Database analysis

Retrospective analysis of the public register of prices of MP maintained by NCPRMP, Annex No. 2 of the PDL.

Retrospective analysis of NHIF data concerning hospital MPs available under the Access to Public Information Act for the period 2016-2021.

Analysis of the Union Register of medicinal products.

4.3. System analysis

- in conducting regulatory studies through decomposition, synthesis and induction (at the EU level and Bulgaria).

4.4. General research methods

✓ Historical method - historical chronology, connectivity and upgrading of the information set were followed when reviewing the literature;

✓ A method of theoretical deductive analysis to reveal internal connections and interactions between different data and processes;

✓ Graphical analysis – to visualize the observed processes and the obtained results.

4.5. SWOT Analysis

– strengths and weaknesses, threats and opportunities in the biosimilars release to the market and patient access to drug therapy in Bulgaria.

5. Object of the research

The object of the study are:

✓ the regulatory requirements for the placing on market of biosimilars in Bulgaria and in the reference countries of Bulgaria,

✓ the NHIF costs for drug therapy of FL, DLBCL and CLL, and

✓ the impact of the launch of both biosimilar MPs and new therapeutic alternatives on drug therapy costs of FL, DLBCL and CLL.

6. Study period

The study covers the period 2017-2021 and has been prepared:

- analysis of the current regulatory framework for pricing, reimbursement and market placement in Bulgaria, and

- a retrospective analysis of the NHIF costs for drug therapy of the considered oncohematological diseases before and after the launch of the biosimilar medicinal products.

RESULTS AND DISCUSSION

The performed literature review clearly outlines the stages through which a biologic/biosimilar MPs should complete in order to reach the market. Insofar as the processes related to marketing authorization are strictly regulated and unified for the territory of the EU, a key moment of the market placement remains the pricing, reimbursement, supply, prescription and dispensing of drugs. The main approaches and methods for pricing and reimbursement, prescribing and dispensing are generally defined, with each country determining how and to what extent to apply them, which determines the challenges in placing biosimilars on the market.

The presented overview of the current legislation in Bulgaria indicates the regulatory requirements that are crucial for the market placement and on which the availability of biosimilars depends. Since the change of the Price Ordinance, which directly affects the pricing and reimbursement of biosimilars, is from 2019, accordingly the market analysis in this direction is very limited. An analysis is also necessary in connection with the start of the work of the CPB in January 2020, especially in the hospital market, to whether and to what extent this affects market access.

The difficulties in performing this type of analysis originate from the structure and completeness of the available information, as well as from the difficult access to it. The lack of disease registries, as well as information on the actual number of patients who received a specific drug therapy, especially in hospital settings, makes forecasts of the necessary resources uncertain. This, in turn, determines the impossibility of guaranteeing stability in the drug supply system.

1. Comparative analysis of the methods for pricing and market placement of biosimilars in Bulgaria and in the reference countries for Bulgaria.

In the literature review of the legislative framework regarding the pricing and reimbursement of pharmaceuticals in Bulgaria, the regulatory requirements directly concerning biosimilar pharmaceuticals has been presented.

The presented milestones for placing an MP to the market as a comparative analysis of a reference MP and biosimilar outline the main differences affecting the inclusion of a MP in the PDL as follows:

- For biosimilars, the main parameter that is subject to regulation is the manufacturer's stated price - it applies in addition to EPR , as well as a normatively determined ratio (80:20%) compared to the price of the reference MP. In the absence of a price for the same medicinal

product in the reference countries, a comparison with the manufacturer's price for the same dosage form, concentration, but in a different package of the manufacturer entered in the marketing authorization is also applied. If such a price is also missing, then the requested price is compared with that of the reference drug, included in the PDL with the same dosage form and concentration.

- Clinical and pharmacoeconomic data are not evaluated for biosimilars. A pharmacoeconomic evaluation can only be done if the candidate drug is in a dosage form and concentration that is not included in the PDL, as in this case evidence of reimbursement in 5 of the reference countries is not required.

- The timeframe for inclusion of MP in PDL is significantly shorter – 30 days or 60 days, if pharmacoeconomic assessment required.

- An application to the NHIF can be submitted at any time, and inclusion in the NHIF list occurs on the 1st or 16th of the month update.

- A discount on the value of a package for the benefit of the NHIF or for the benefit of patients is voluntary.

For biosimilars, as well as for other prescription medicines, the following applies:

- The same principle of internal price referencing of the reference value paid by the NHIF,

- The mechanism guaranteeing sustainability and predictability of the NHIF budget,

- The tender procedures of the CPB and medical establishments for MPs for hospital treatment.

The regulatory requirements applicable in Bulgaria to the prices of biosimilars are comparable to those in the reference countries.

In all reference countries, the prices of biosimilars are subject to regulation. A valid marketing authorization is required to start the pricing and reimbursement procedures in all countries, only Italy allows the pricing procedure to be started before the marketing authorization is granted, but ends after the MP is approved.

EPR is implemented in 6/10 countries, the comparison being to manufacturer’s price. Countries implementing EPR can be divided into 3 groups depending on the number of reference countries used:

- countries with small reference baskets - Slovenia and Spain are compared with 3 countries only,

- countries with medium reference baskets – Latvia (7 reference countries) and Romania (12 reference countries),

- with large reference baskets - Greece and Slovakia use all EU member states for reference.

Bulgaria refers to the countries with average reference baskets with the 10 countries used.

In terms of the methodology used in EPR, Bulgaria`s reference countries are divided into those using:

- the lowest manufacturer's price – applies in 2/6 reference countries: Romania and Slovenia,

- average of the three lowest manufacturer's prices – applied in 2/6 countries: Greece and Slovakia, as these are the countries with the largest reference baskets,

- the third lowest price – Latvia and

- negotiation based on the price of the biosimilar MP in the reference countries and the agreed price of the reference MP from the hospital tender - Spain.

Bulgaria ranks among the group of Romania and Slovenia using the lowest manufacturer's price.

In 8/10 countries (excluding Greece and Latvia) there is a normatively determined ratio between the manufacturer's price of the biosimilar and the reference MP. It should be noted that countries that apply both approaches in 3/4 countries EPR is the main criterion in setting the price. In France, the price is set by negotiation between the MAH and the regulatory body (Economic Committee for Medicinal Products (CEPS)) based on the price of the reference drug, the price in other countries, as well as forecasts for sales volume.

In 2/8 countries (Slovakia and Latvia), this normatively determined ratio between the price of the biosimilar and the reference drug is applied not only to the first biosimilar placed on the market. In Slovakia, the price of the first biosimilar MP shoud be 25% lower than the price of the reference MP, the second - by another 5%, and the third - by another 5%. In Latvia, the first biosimilar is -30% of the price of the reference, the second and third - by -10% and each subsequent one - by -5%.

Internal price referencing is applicable in 6/10 countries, and of those that apply it only in Greece it is at the ATC-4 level. In addition, 4 of these countries also implement EPR.

An essential point to be addressed is the obligation to periodically declare the manufacturer's prices of MPs. All countries that implement the EPR principle require periodic

verification of the manufacturer's price after initial registration. The timeframe for this check is different:

- 6 months - in Slovakia, Slovenia and Greece, in which countries EPR is used as the main pricing criterion,

- 12 months – in Romania EPR is also used as the main criterion in pricing,

- 24 months – in Latvia and Spain, which use EPR as an additional pricing criterion.

In Bulgaria, this period is 24 months, when internal price referencing is applicable, in case of available MPs on different MAHs.

The review of the EPR usage shows its multi-component impact on prices not only of biosimilars. In practice, cross-referencing occurs, where prices are affected not only directly, but also indirectly by countries that are not included in the main reference basket of the given country. In reality, prices in Bulgaria can be influenced by all EU member states through Greece and Slovakia, which refer to the prices of all member states. The greatest likelihood of indirect price influencing in Bulgaria can be expected from Austria (via Romania, Greece, Slovakia and Slovenia), the Czech Republic (via Romania, Greece, Slovakia and Latvia), Germany (via Romania, Greece, Slovakia and Slovenia), Hungary (via Romania, Greece, Slovakia and Latvia), Denmark and Estonia (via Greece, Slovakia and Latvia), Poland (via Romania, Greece and Slovakia) and Portugal (via Greece, Slovakia and Spain).

To determine which of the reference countries have the greatest impact on the prices of MP in Bulgaria, the Annual Reports on the activity of the NCPRMP for the period 2013 - 2021 were used. The reports clearly show that the most lower prices were found in Romania, Greece, Slovakia and France. In total for the whole considered period in Romania are found 932 lower prices, in Greece - 912, in Slovakia - 857 and in France – 533. Accordingly, 64% of all established lower prices (5,014) for the period 2013-2021 are from these four countries.

The most frequently changed prices were for MPs with 100% reimbursement, both paid by the NHIF for home treatment (29% on average of MPs with a changed price) and for hospital use (30% on average). Thus, the prices of biosimilars, such as mainly 100% reimbursement medicines in Bulgaria, can be assumed to be highly dependent on EPR .

From the data presented, it is clear that the countries that have the largest reference basket and in EPR refer to the average of the 3 lowest manufacturer’s prices - Greece and Slovakia, are most often the cause of price changes in Bulgaria. Slovakia can be expected to have a greater impact on biosimilar prices due to the implementation of a 3-tier scheme of the legally determined ratio between the price of the biosimilar and the reference medicine (25% lower price for the first and for each subsequent biosimilar that enters the market – an additional

5% lower price) and the short period for periodic price verification – every 6 months. Practice shows that there is no problem in terms of changing the RON/Euro/BGN exchange rate, since for the purposes of pricing of MPs, a fixed RON/Euro rate is applicable, which is relatively constant. Rather, the problem is the availability of information about a change that has occurred, however infrequent it may be.

Although the EPR as a main tool has proven its effectiveness in terms of the regulation of drug prices and hence on drug therapy costs, its application should be carefully considered, especially in drugs for which there are therapeutic analogs, in order to be minimized the negative impact on the patient's access to medicines. Consideration should also be given to the requirement for periodic reference to the manufacturer's price in the reference countries, which obligation occurs at different times for individual MPs, given the date of the last registered price. This leads to a more frequent change of the reference value in the PDL than the legally defined period of 24 months and to a possible change in the sales prices by all MAHs, especially for MPs included in Annex No. 1 of the PDL. In some cases, such an administratively imposed change may be unacceptable or unaffordable for a given MAH considering the size of the market and the possibility of affecting other markets through EPR. Thus, the administrative maintenance of low registered prices of MP may result in limited access to drug therapy because of the impossibility to meet the needs of the country`s necessary quantities due to the parallel export or withdrawal of the product from the market. In the case of more than one biosimilar MP on the market, competitive market mechanisms should prevail over regulation through statutory requirements when setting prices.

2. Analysis of the biosimilars with valid marketing authorization and placed on the market in Bulgaria

In order to obtain a complete picture of the volume of the market of biosimilars, an analysis of biosimilars that have been centrally authorized by EC and, accordingly, those placed on the Bulgarian market was prepared. The data has been updated as of December 2022 for completeness and objective presentation of the information.

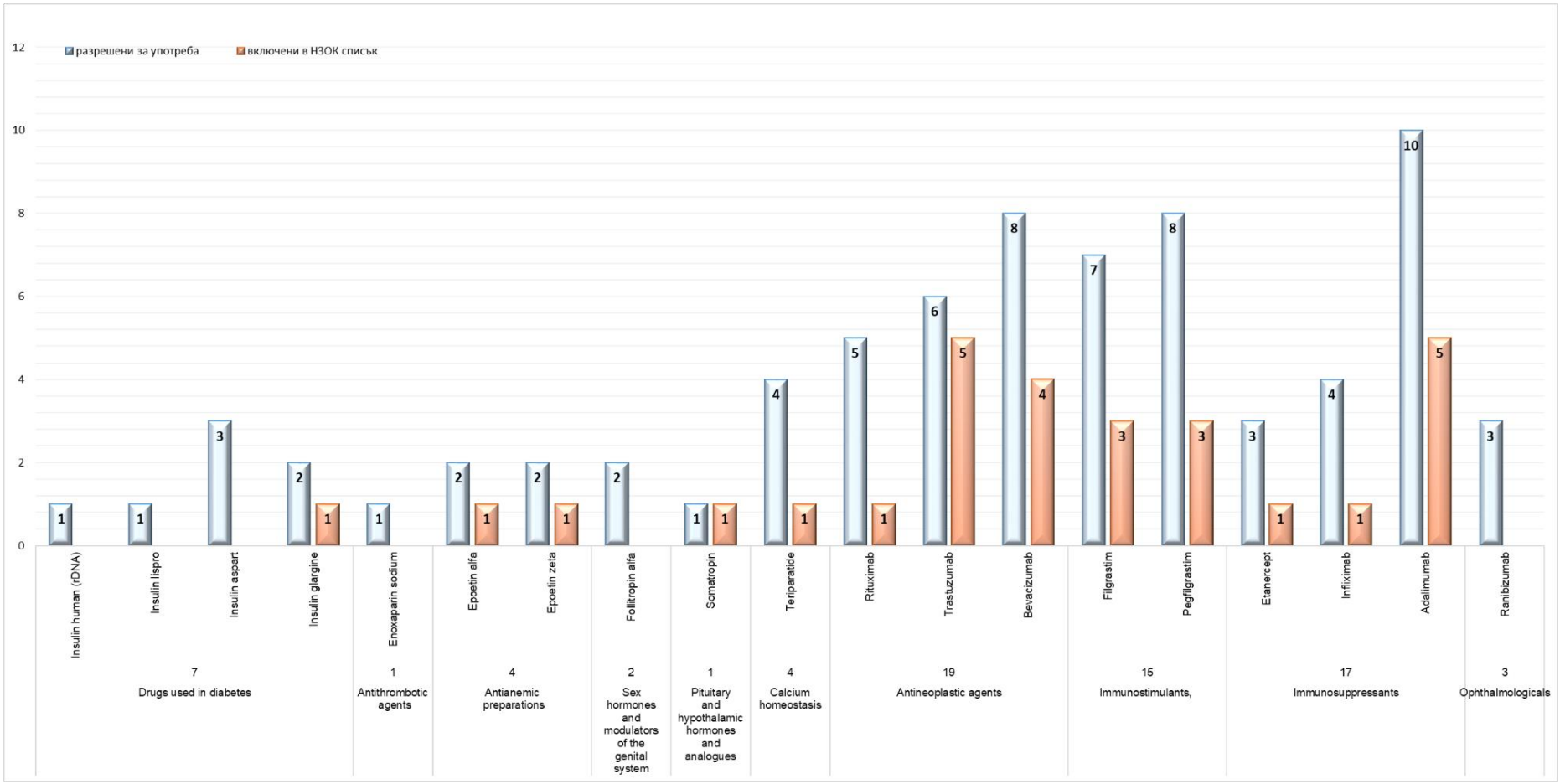
As of December 2022, 73 biosimilar MPs with 19 INNs belonging to 10 pharmacotherapeutic groups have been authorized for use in the EU under a centralized procedure (Fig. 1). The group of antineoplastic agents has the highest number of authorized products (19 MPs belonging to 3 INNs), followed by immunomodulating agents - immunosuppressants (17 MPs with 3 INN) and immunostimulants (15 MP with 2 INN).

Correspondingly, of these groups account for the largest number of medicines released on the market in Bulgaria (23/28).

In Annex No. 1 of the PDL, 24 biological MPs are included, authorized for use under a centralized procedure, of which 13 are biosimilar MPs with a reimbursement level between 50 and 100%.

In Annex No. 2 of the PDL - included 43 biological medicines, of which 29 are biosimilars, of which 22 biological and 18 biosimilar drugs are paid by the NHIF, outside the value of the medical activity provided.

Figure 1Distribution of biosimilars authorized for use and marketed in Bulgaria by pharmacotherapeutic groups



Monoclonal antibodies are of interest. Since their inception in 1975, monoclonal antibodies have been developed and used for diagnostic purposes as well as for the treatment and palliative care of oncological and autoimmune diseases, cardiovascular diseases, respiratory diseases, rare diseases, neurological diseases, infections and more. With the development of biotechnology and medical science, the number of monoclonal antibodies approved for use is constantly growing. Biologics account for half of the pharmaceutical market in oncology.

To the monoclonal antibodies Rituximab, Trastuzumab, Bevacizumab, Infliximab, Adalimumab and Ranibizumab belong 49% (36/73) of the authorized biosimilar MPs. Logically, 68% (19/28) of the biosimilars placement on the market in Bulgaria are with these INNs.

MP with INN Infliximab and Adalimumab are included in Annex No. 1 of the PDL. With INN Infliximab, the reference and 1 biosimilar MP were placed on the market and paid accordingly by the NHIF, and 2 biosimilar MPs were deleted from the list. With INN Adalimumab, 5 biosimilars (50% of those authorized for use) and the reference drug are included in Annex No. 1 of the PDL. Annex No. 1 also includes the products with the INN Rituximab (1 biosimilar and the reference drug) for the treatment of rheumatoid diseases.

Treatment with MPs with INN Rituximab (for oncohematological indications), Trastuzumab and Bevacizumab is paid by NHIF beyond the value of medical activities and, accordingly, MPs are included in Annex No. 2 of the PDL.

With INN Rituximab has 2 MPs available (1 biosimilar and the reference MP).

With INN Trastuzumab out of all 6 biosimilars authorized for use, only 1 is not included in Annexx No. 2 of the PDL, respectively, in the NHIF list with medicines used in hospital care. The reference Trastuzumab in the dosage form for which there are biosimilar drugs authorized for use is excluded from Annex No. 2 of the PDL.

With the INN Bevacizumab 4/8 biosimilars are included in the NHIF list with medicines used in hospital care, as well as the reference drug.

In Bulgaria, there is still no MP with INN Ranibizumab on the market.

The average time from the marketing authorization to the inclusion in the PDL varies widely – from 2.6 to 27.9 months. However, it should be kept in mind that whether and when a product will be placed on the market is entirely up to the MAH – it is his decision to start the relevant procedures. This is confirmed by the fact that not all authorized biosimilars are included in the PDL in Bulgaria.

Monoclonal antibodies compose a substantial part of the NHIF's expenditure on drug therapy. For the period 2016 - 2020, for home treatment with monoclonal antibodies (MPs with 23 INN), the NHIF paid BGN 580,502,407, with an increase over a 5-year period of 56% (BGN 88,410,381 in 2016 to BGN 138,267,272 in 2020). Only for a 3-year period (2018 – 2020) for monoclonal antibodies (MPs with 21 INN), paid outside the value of the medical activity provided, the costs of the NHIF are BGN 785,832,447, and in 2020 (BGN 330,197,894) the increase is 65% compared to 2018 (BGN 200,263,776). Thus, on average, the NHIF paid BGN 116,100,482 annually for MPs with 23 INN for home treatment, and BGN 261,944,149 for MPs with 21 INN for hospital use, or the costs of monoclonal antibodies drug therapy for hospital treatment are 2.2 times more than the cost of monoclonal antibody drug therapy for home treatment.

In addition, the cost of medicines represents a significant part of the budget of medical establishments and depends on their type – lowest in state psychiatric hospitals, followed by municipal and regional multidisciplinary hospitals for active treatment, university hospitals and logically highest in specialized hospitals and oncology centers.

Given the above, as well as taking into account the timing of the market placement of biosimilars monoclonal antibodies, the changes in the regulatory requirements directly related to the market access of biosimilars, for the purposes of the present development, monoclonal antibodies for the treatment of oncological diseases are examined in more detail.

The first biosimilar monoclonal antibody included in Annex No. 2 of the PDL is with INN Rituximab. The reference drug was approved for use in the EU on June 2, 1998. Rituximab is indicated for the treatment of patients with oncohematological and rheumatological diseases. The subject of this work are the oncohematological indications:

- ✓ treatment of adult patients with follicular lymphoma (ICD code C82);
- ✓ treatment of adult patients with CD20 positive diffuse large B-cell non-Hodgkin lymphoma (ICD code C83.2, C83.3);
- ✓ treatment of adult patients with chronic lymphocytic leukemia (ICD code C91.1).

Rituximab therapy has been accepted as the standard of care for FL, DLBCL and CLL, although depending on the specific case it is not always the first choice of treatment, given the availability of other specific medicinal alternatives. Rituximab is included in the main regimens of immunotherapy with or without concomitant chemotherapy, or in combination with other targeted agents, for the first as well as for second and subsequent lines of treatment according to the NCPRMP Pharmacotherapeutic Guideline in Clinical Hematology, the guidelines of the European Society for Medical Oncology (ESMO) for diagnosis, treatment and follow-up of FL,

DLBCL, and CLL, and the guidelines of the National Comprehensive Cancer Network (NCCN) for FL and DBECL, and CLL.

Thus, Rituximab appears to be a suitable example for a practical evaluation of the effect of a market placement of biosimilar in terms of legislative requirements and as well as in terms of the possibility of optimizing the drug therapy costs with biologically equivalent drugs and freeing up resources for new therapies.

On the other hand, the choice of Rituximab is consistent with the way of reporting the costs of MPs for hospital treatment by the NHIF and, accordingly, with the possibility of providing information, which is essential for the fulfillment of the set goal.

3. Analysis of the impact of the launch of biosimilars in the reference countries on the established price of Rituximab, as well as on the reference value paid by the NHIF in Bulgaria

As noted, the decision as to whether and when an MP will be released to a given market is entirely up to the MAH. To confirm this, a report was prepared for the considered biosimilar drugs with INN Rituximab and authorized for use in the EU under a centralized procedure. It was found that not all biosimilar MPs were marketed in all EU countries, and this was not linked to the reference MP, as it was found to be priced in all countries except the Netherlands.

Truxima, the first authorized biosimilar, has a registered price in 16/24 countries in the EU (excluding Estonia, Portugal and Malta, for which no information is available). At the same time, Blitzima on the same MAH, has a price in only 5/24 countries.

The situation is similar with Rixathon with an established price in 22/24 and Riximyo – with a price in 4/24 countries. For the last licensed biosimilar, Ruxience, the price has been registered in 18/24 countries.

It should be noted that all approved biosimilar drugs with INN Rituximab, except for Blitzima , are approved for the same therapeutic indications as the reference drug. The reference MP is approved for the treatment of non-Hodgkin's disease lymphomas (FL and DLBCL), chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener 's granulomatosis) and microscopic polyangiitis, pemphigus vulgaris . Blitzima is not indicated for the treatment of rheumatoid arthritis.

In addition, the time from the marketing authorization to the first price registration was evaluated, as the first condition for the market placement of a given drug. For this purpose, the biosimilars with INN Rituximab, which have been placed on the market in Bulgaria, as well as in the reference countries for Bulgaria for pricing purposes, were taken into account.

Thus, the price of the first biosimilar Rituximab - Truxima has been registered between 4.6 and 12.6 months after marketing authorization, with some markets still lacking. For Truxima, a registered price was found in 5/10 reference countries, with the fastest occurring in Slovenia, followed by Italy and France, and the slowest in Greece - more than 1 year after authorisation. In Bulgaria, the price was registered 8 months after the marketing authorization, which puts the country in the middle. In Slovakia and Romania, instead of Truxima, the other biosimilar MP of the same MAH Blitzima is available.

For the second biosimilar Rituximab - Rixathon, despite being authorized for use only 4 months later, the price has been registered much later - in 7/10, as well as in Bulgaria, it took more than 1 year. In Italy and France, again this happened the fastest - 5.8 and 5.7 months, respectively. Registration took the longest in Romania - 29.5 months, where Blitzima is available instead of Truxima. Another Rituximab biosimilar, Ruxience is also available in Lithuania, which may be the explanation for the longer time from marketing authorization to registration at a price - 18 months. In Slovakia, the price registration also took 15.5 months, but 3 biosimilars are available – Riximyo, Blitzima and Ruxience. But this cannot be said for Latvia, where no other biosimilar Rituximab has been released and time to price is 19.6 months.

The registration of the price of biosimilars in the reference countries has an impact on the Bulgarian market, both through the EPR principle and through internal price referencing. To assess this impact, the manufacturer's price dynamics of the reference and biosimilar medicines with the INN Rituximab - Mabthera, Truxima and Rixathon were analyzed in Bulgaria (fig. 2) and in the reference countries for the period 2017 - 2021, as well as how this change affects the calculated reference value in Annex No. 2 of the PDL (fig. 3). For full trend tracking, information is also presented up to March 2022, when the estimated reference value in PDL was last changed for the INN Rituximab for intravenous administration (Fig. 3).

The price of the reference MP Mabthera changes even before the registration of the first biosimilar MP, because of the periodic EPR every 6 months (Fig. 2). With Mabthera, there is a more frequent change in the registered price, because it remains to submit a declaration every 6 months, regardless of the introduction of biosimilars, which is due to the fact that there are indications of the drug for which, when calculating the reference value in the PDL does not include MPs of other MAHs. These indications are Wegener's Granulomatosis and Pemphigus vulgaris, for which indications the reference drug is included in Annex No. 1 of the PDL and for which biosimilars are not included in the calculation of the reference value. These indications are not listed in Annex No. 1 of the PDL for Rixathon, although it is indicated for treatment according to the marketing authorization. However, in the relevant Annex of the PDL,

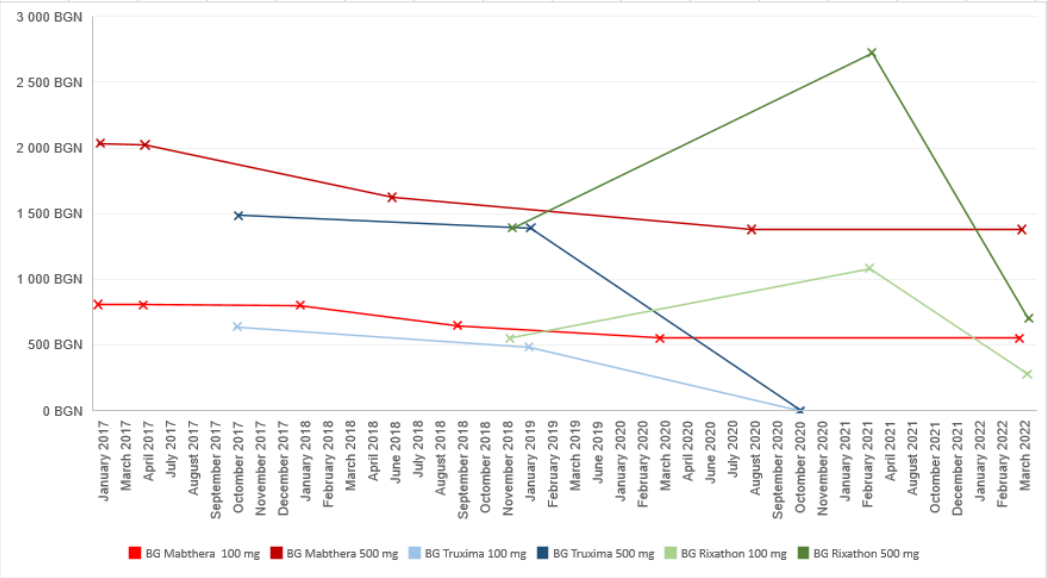
the indications for which the MAH has submitted an application in accordance with the provisions of the Price Ordinance are entered.

For the period 2017 - 2021, there was a 3, respectively 4 times change in the registered price of individual Mabthera packages, resulting in a -32% reduction in the registered price in total. Thus, the price of Mabthera 100 mg was changed from BGN 809.54 in January 2017 to BGN 552.31 in March 2020, and the price of Mabthera 500 mg was BGN 2,035.39 in January 2017 to BGN 1,380.78 BGN in August 2020 (Fig. 2). Accordingly, the price at wholesaler level including VAT as of August 2020 is BGN 674.77 for Mabthera 100 mg and BGN 1,668.94 for Mabthera 500 mg .

This is due to price change in Slovakia (5 times) by -32% total, Slovenia (4 times) with -51% total and Greece (4 times) with -15% overall.

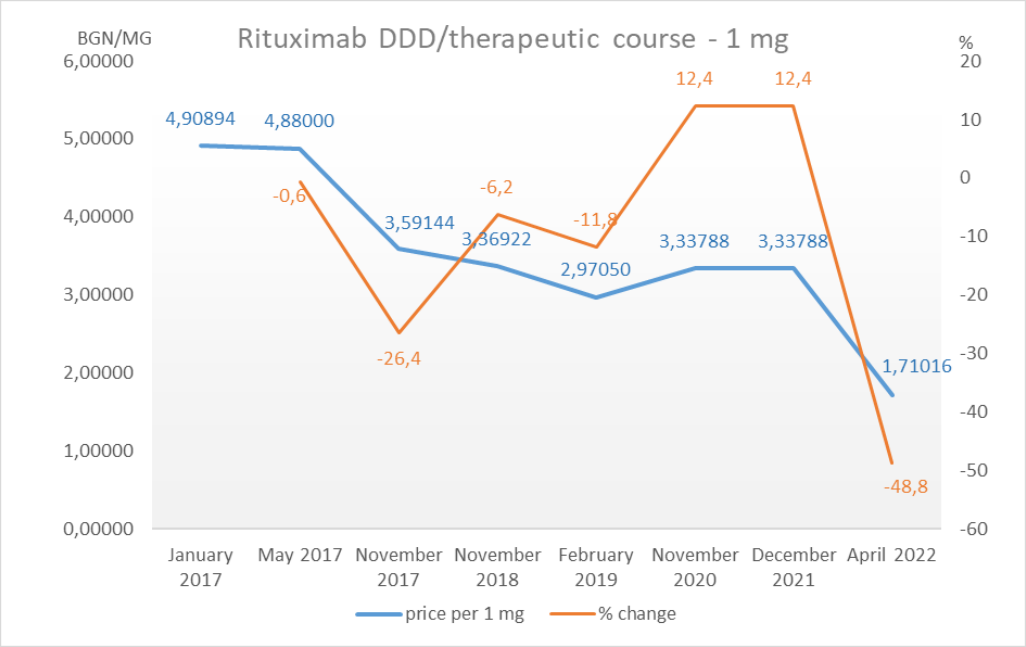
However, this change in the registered price does not lead to a change in the calculated reference value after the inclusion of biosimilar Rituximab in the PDL (Fig. 3). As of August 2020, the calculated reference value in Annex No. 2 of the PDL is BGN 2.97050/ mg Rituximab (price at wholesaler level with VAT), and the price of Mabthera after the change of the registered price is BGN 3.33788/mg (price at wholesaler level with VAT).

Figure 2 Dynamics of established manufacturer`s prices in BGN of MPs with INN Rituximab in Bulgaria



Source: Registers, NCPRMP

Figure 3 Change in reference value (at wholesaler level with VAT) of Rituximab in Annex No. 2 of the PDL



Source: Registers, NCPRMP

The first biosimilar drug - Truxima was included in the PDL 8 months after marketing authorization, as Bulgaria being the fourth country after France, Italy and Slovenia. In Latvia, Lithuania, Romania and Slovakia Truxima has no registered price.

In October 2017, Truxima was listed in the PDL with the following manufacturer's prices: BGN 641.47 for Truxima 100 mg and BGN 1,486.43 for Truxima 500 mg (Fig. 2).

The registration of the price of Truxima determines a reduction of the calculated reference value in Annex No. 2 of the PDL by 26.4% (fig. 3) - from 4.88000 to 3.59144 BGN/mg (price at wholesaler level with VAT).

The approved price in Bulgaria is lower than the prices available in other reference countries. It should be noted that the drug Truxima was included in the PDL before the requirement that the price of the biosimilar drug should not be more than 80% of the price of the reference medicine came into force. Thus, when requesting a price for Bulgaria, MP has to take into account only the price in the reference countries - in this case the prices in France, Italy, and Slovenia, which are on average 34.5% higher than those registered in Bulgaria. This can only be explained by the price policy of the MAH or in the reference countries there is a registered price, which is not publicly available and therefore cannot be analyzed in this case.

For the period 2017 – 2020, the price was changed only once - in January 2019, respectively to BGN 485.08 for Truxima 100 mg and BGN 1,393.84 for Truxima 500 mg , or a reduction of -24% for Truxima 100 mg and -6% for Truxima 500 mg (Fig. 2). This change in

the registered price is also associated with a decrease in the reference value in the PDL from 3.36922 to 2.97050 BGN/ mg (price at wholesaler level including VAT) or by – 11.8% (Fig. 3).

For the same period, the price was most often changed in Belgium (2 times) with -6% in total, France (2 times) with -41 % in total and Slovenia (3 times) with an average of -24%.

Truxima was excluded from the PDL and accordingly the price was deleted in October 2020, resulting in an increase of the reference value by 12.4% from BGN 2.97050 to BGN 3.33788/mg (price at wholesaler level with VAT) (Fig. 3). This change does not lead to an increase in the value paid by the NHIF, as the medicines for hospital treatment is supplied on the basis of a concluded contract after negotiation in accordance with the PPA.

The second biosimilar Rituximab – Rixathon has been included in the PDL in Bulgaria 16.6 months after receiving marketing authorization, and only in Latvia, Lithuania and Romania price registered after the one in Bulgaria.

The prices listed in Annex No. 2 of the PDL are BGN 553.89 for Rixathon 100 mg and BGN 1,393.84 for Rixathon 500 mg, respectively. Rixathon's approved prices correspond to the lowest manufacturer's price in the reference countries, in this case Slovakia. The prices were also established before the requirement for the legally determined ratio to the price of the reference MP came into force.

Although the manufacturer's price of Rixathon is 14% lower than that of the reference MP Mabthera, the inclusion of Rixathon in the PDL determines a reduction of the reference value by an additional 6.2% - from 3.59144 to 3.36922 BGN/mg (price at wholesaler level with VAT) (Fig. 3).

In February 2021, a significant price increase was approved for Rixathon in Bulgaria, which does not correspond to affordable manufacturer's prices in the reference countries. The price of Rixathon 100 mg is BGN 1,083.31 and BGN 2,725.76 BGN for Rixathon 500 mg (fig. 2). This does not change the reference value calculated in Annex No. 2 of the PDL (Fig. 3).

Basically, the manufacturer's price of Rixathon was changed once after registration in the reference countries except Greece - 3 times with -26% until the end of 2021.

The inclusion of the biosimilars with the INN Rituximab in Annex No. 2 of the PDL determines a reduction of the reference value for the period 2017-2021 by 32% in total. The calculated reference value in Annex No. 2 of the PDL was changed from 4.90894 to 3.33788 BGN/mg (price at wholesaler level with VAT) (Fig. 3).

Given the different times of inclusion of the individual MPs in the PDL, a change in the calculated reference value is observed more often, since the periodic EPR occurs at different times and, accordingly, the MAH submits a declaration regarding the absence or not of a change in the manufacturer's price in the reference countries. Although such declaration for MPs with INN Rituximab is submitted every 24 months (with the exception of the reference MP), MAHs should revise their selling prices more frequently due to internal price referencing. This mainly affects the MPs included in Annex No. 1 of the PDL, since the value that the NHIF pays for drug therapy in hospital conditions is the result of the negotiation conducted according to the PPA.

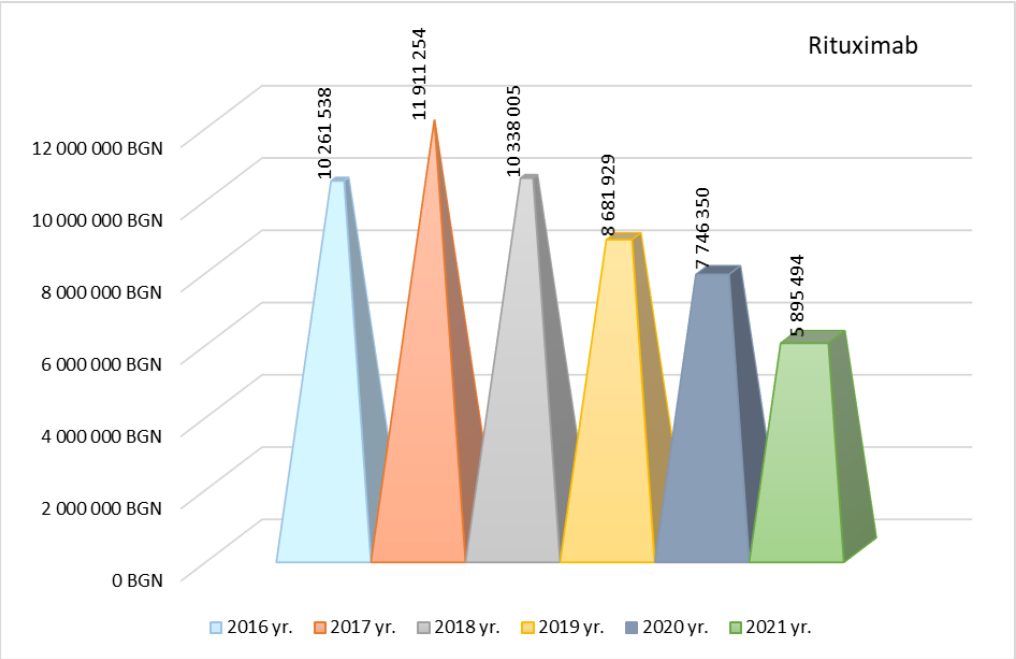
In the case of medicines with 100% reimbursement, the entry of biosimilars leads to an immediate reduction in the value of drug therapy paid by the NHIF, and for MPs from Annex No. 2 of the PDL, in practice, this reduction initially only affects the reference product before the actual biosimilar MP is available in the medical establishments. In the case of MPs included in Annex No. 1 of the PDL and partially paid by the NHIF for home treatment, the reduction of the reference value can only be at the expense of the patient, if the MAH does not cover the difference in co-payment. An additional problem arises when, after the inclusion of the biosimilar MP, there is no real market placement or this launch takes a long time. Thus, in practice, conditions are created for unfair competition.

4. Analysis of the NHIF costs for drug therapy of oncohematological diseases after the biosimilars market placement

To assess the impact of the placement of biosimilars on the market, the NHIF expenditure for drug therapy for the treatment of adult patients with oncohematological diseases (FL, DLBCL and CLL) were analyzed in accordance with the approved summary of product characteristics of MPs with INN Rituximab. The current analysis did not comment on the cost-effectiveness of the therapeutic alternatives used.

The presented analysis of the change in the registered prices of medicines with INN Rituximab in Bulgaria and the corresponding change of the reference value in Annex No. 2 of the PDL also implies a reduction in the NHIF costs for drug therapy with MPs with INN Rituximab. From fig. 4 it is evident that the amount paid by the NHIF for drug therapy with INN Rituximab significantly decreases - from BGN 10,261,538 in 2016 to BGN 5,895,494 in 2021, or - 42.5%.

Figure 4 NHIF expenditure for MPs with INN Rituximab



In order to assess the factors that determine this reduction, a detailed analysis was made for the concrete diseases - FL, DLBCL and CLL and for the individual medicinal alternatives used for the treatment of the specified diseases. The analysis was prepared on the basis of information from the NHIF, received in accordance with the procedure for access to public information, as well as available on the NHIF website.

The costs of drug therapy were analyzed for the following medicines from Annex No. 2 of the PDL, included in the NHIF list with medicines, paid outside the value of the performed medical activity and providing the main treatment of the diseases under consideration:

✓ In addition to the drug with INN Rituximab for intravenous administration, in Annex No. 2 of the PDL the drug with INN Rituximab in pharmaceutical form for subcutaneous administration is also included. For both pharmaceutical forms of Rituximab in Annex No. 2 of the PDL, no internal price referencing was applied when determining the reference value paid by the NHIF. The Rituximab in pharmaceutical form for subcutaneous administration has been paid by the NHIF outside the value of the medical activity since 2016 for the treatment of DLBCL and FL and since 2019 for the treatment of CLL.

✓ The medicine with INN Obinutuzumab is indicated for the treatment of adult patients with FL as well as patients with untreated CLL and comorbidities. The NHIF has paid for CLL treatment with Obinutuzumab since 2018 and for FL treatment since 2019.

✓ Medicines with INN Ibrutinib and with INN Venetoclax are indicated for the treatment of adult patients with CLL. Treatment with INN Ibrutinib has been publicly funded since 2017 and Venetoclax since 2018.

Thus, for the treatment of DLBCL, the NHIF has paid immunotherapy with MPs with INN Rituximab with or without combination with chemotherapy. For the treatment of FL, another alternative also has been applied – treatment with Obinutuzumab, while for CLL has the most therapeutic alternatives available - Obinutuzumab, Ibrutinib and Venetoclax.

Taking into account the time of inclusion in the PDL of alternative therapies for the specific diseases under consideration, the logical period for evaluating the effect of the entry of biosimilar drugs into the market is 2016-2021. Given the information available from the NHIF, such a report was prepared for the period 2018-2021. For 2016 and 2017 yr., the information is incomplete and not available in a form that meets the task, therefore it was not used.

When evaluating the factors determining the drug therapy costs, it should be taken into mind that the considered oncohematological diseases (FL, DLBCL and CLL) are defined as rare diseases, and as such no increase in incidence is observed or expected, which determines relatively permanent patient population in need of drug therapy.

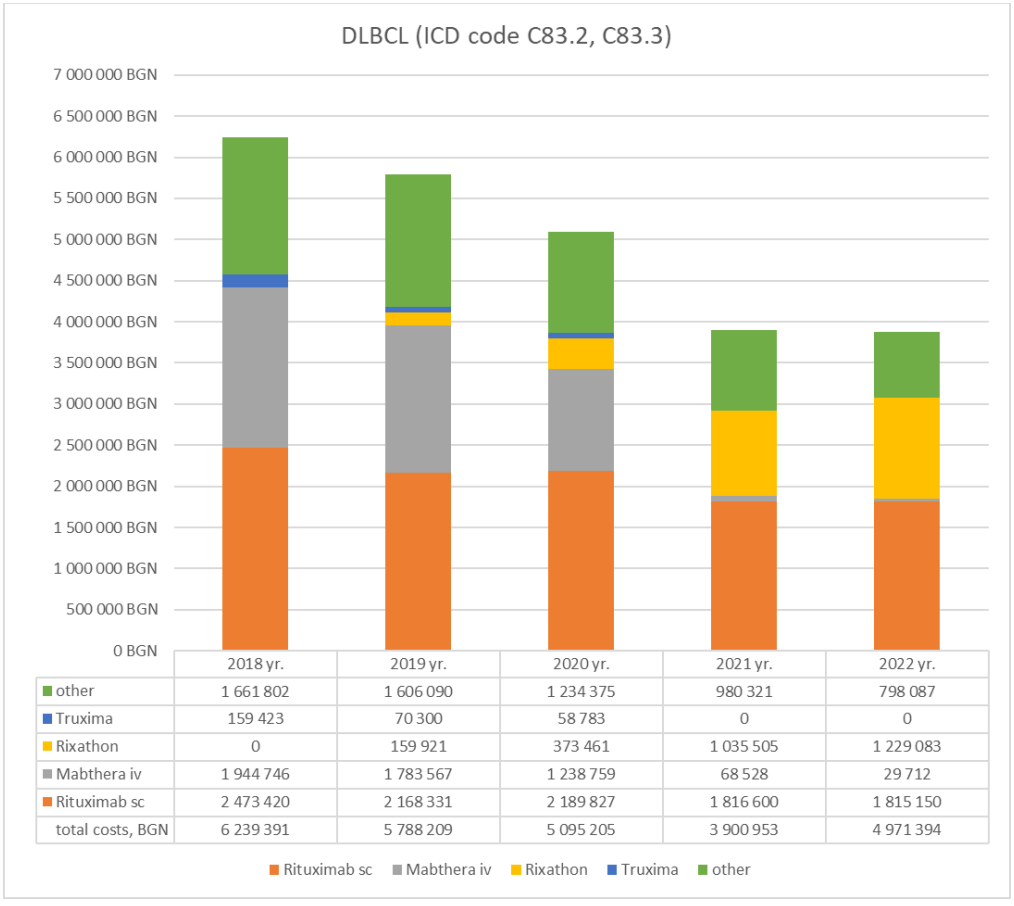
NHIF costs for drug therapy of DLBCL

The assessment of the total costs for drug therapy of DLBCL for the period 2018-2021 shows a decrease by 37% of the funds paid by the NHIF - from BGN 6,239,391 in 2018 to BGN 3,900,953 in 2021 (Fig. 5). The relative share of chemotherapy used in combination, as well as of medicines for control of adverse drug reactions, remains relatively constant - on average 26% of the total drug therapy expenditure - 26.6% in 2018 and 25.1% in 2021 (Fig. 6). This determines a major impact on total drug therapy costs from Rituximab spending.

Since the main drug therapy of DLBCL is Rituximab-based immunotherapy, it is logical that the reduction of the reference value paid by the NHIF after the launch of biosimilars should also lead to a decrease in the funds paid by the NHIF. The ratio of the pharmaceutical form for subcutaneous administration of Rituximab to the total costs of drug therapy also remains relatively constant - an average of 42% (Fig. 6). A slight increase in the relative share was observed in 2020-2021 (up to 47% in 2021), which can be explained by the preferred more convenient and faster way of administration of the subcutaneous form, correspondingly requiring fewer hospital stays during a pandemic. However, over the period considered, spending on subcutaneous Rituximab decreased by 27% (from 2,473,420 in 2018 to 1,816,600 in 2021).

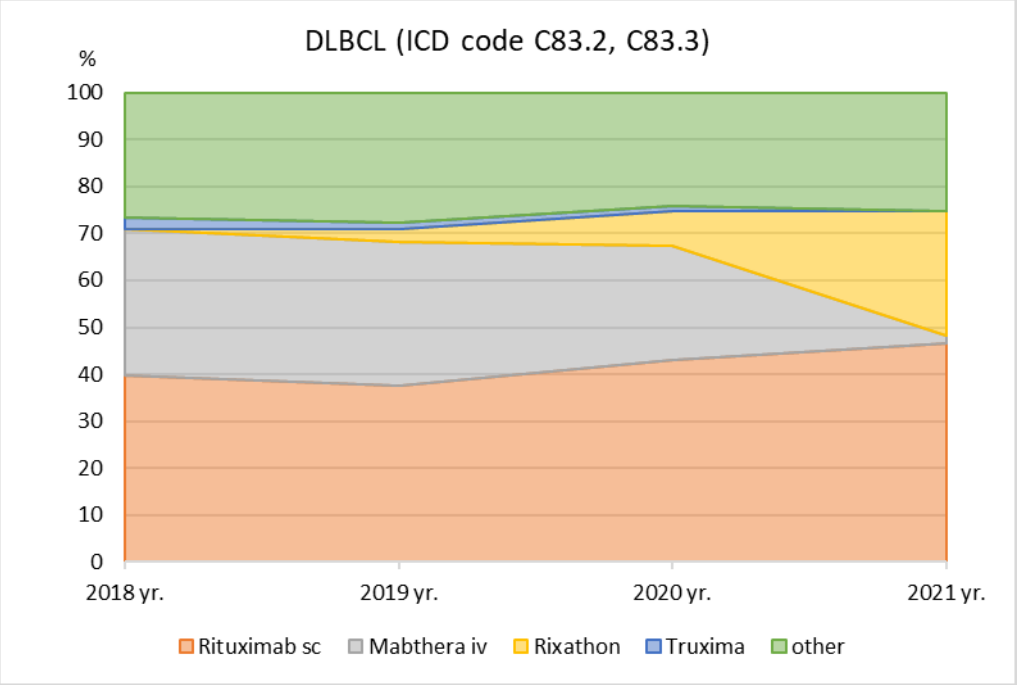
With regard to the drug therapy costs with Rituximab for intravenous administration, the largest reduction in funds paid by the NHIF was observed - from BGN 2,104,169 in 2018 to BGN 1,104,033 in 2021, or -48%. This decrease is mainly due to the introduction of biosimilars, respectively, from EPR , as well as from the internal price referencing. Last but not least, the mandatory hospital tendering for drug supply is also important, which leads to further price reduction on a purely competitive basis in the presence of more than one MP with INN Rituximab. The conditions for conducting tender procedures predetermine the observed shift of the reference MP from the biosimilar. For the considered 4-year period the NHIF paid 96% less for the reference MP - from BGN 1,944,746 in 2018 to BGN 68,528 in 2021. Thus, in 2018, of the NHIF costs paid for Rituximab for intravenous administration, 92% were due to the reference MP, and in 2021 - only 6% of the NHIF costs for Rituximab for intravenous administration were due to the reference MP.

Figure 5 Costs NHIF expenditures for drug therapy of DLBCL



	2018 yr.	2019 yr.	2020 yr.	2021 yr.	2022 yr.
other	1 661 802	1 606 090	1 234 375	980 321	798 087
Truxima	159 423	70 300	58 783	0	0
Rixathon	0	159 921	373 461	1 035 505	1 229 083
Mabthera iv	1 944 746	1 783 567	1 238 759	68 528	29 712
Rituximab sc	2 473 420	2 168 331	2 189 827	1 816 600	1 815 150
total costs, BGN	6 239 391	5 788 209	5 095 205	3 900 953	4 971 394

Figure 6 Percentage ratio of the individual alternatives to the total costs of DBECL drug therapy



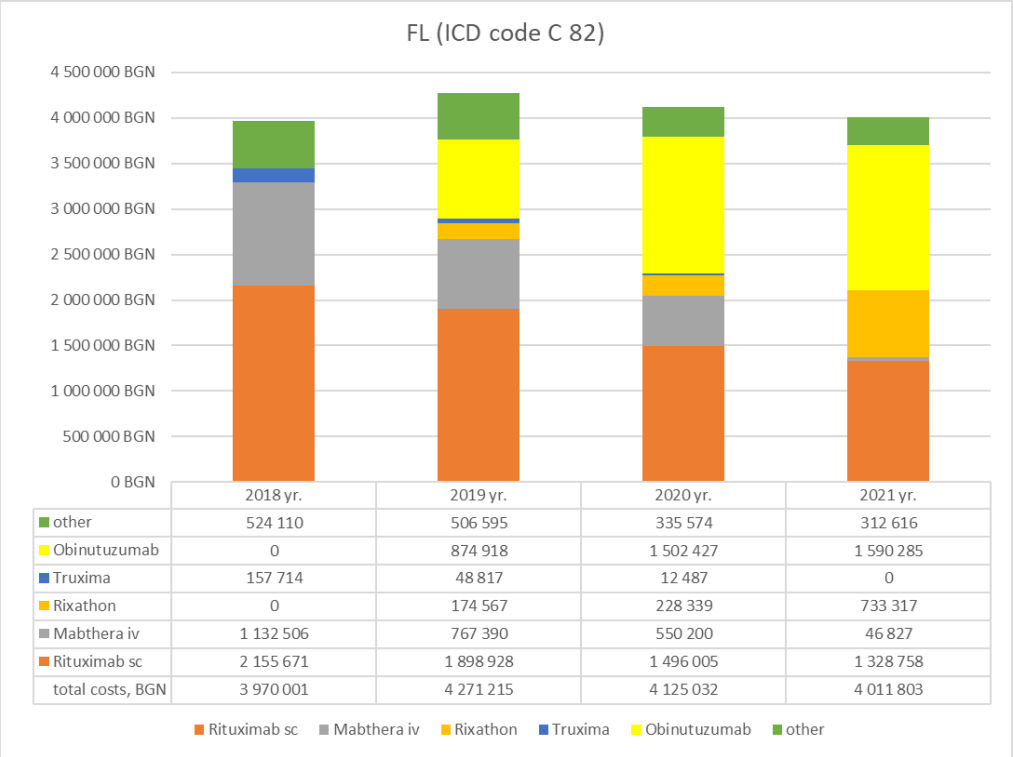
NHIF costs for drug therapy of FL

The analysis of the total costs of FL drug therapy shows relative stability, as the average cost over a 4-year period is BGN 4,094,513, respectively, the increase in 2018 compared to 2021 is 1% - from BGN 3,970,001 to BGN 4,011,803 (Fig. 7). A more significant change (+8%) was observed in 2018 compared to 2019 (BGN 3,970,001 to BGN 4,271,215), when medicine with a new INN for the treatment of FL was included (Fig. 7). At the same time, there was a decrease in the relative share of chemotherapy used in combination, as well as of medicines to control adverse drug reactions - from 13.2% in 2018 to 7.8% in 2021 (Fig. 8), which respectively is associated with a reduction of these costs from BGN 524,110 in 2018 to BGN 312,616 in 2021, or -40% (Fig. 7).

The market entry of the new medicines determined a decrease in the use of MPs with INN Rituximab (Fig. 8). In 2018, 87% of the total costs for drug therapy of FL were costs for INN Rituximab (BGN 3,445,891), reaching in 2021 to 53% (BGN 2,108,902). A decrease was observed not only in the cost of therapy, but also a decrease in the use of MPs with INN Rituximab. Thus, the costs of Rituximab for intravenous administration were reduced by -40% (from BGN 1,290,220 in 2018 to BGN 780,144 in 2021), as well as the costs of Rituximab for subcutaneous administration by -62% (from 2 155,671 BGN in 2018 to 1,328,758 BGN in 2021) (Fig. 7). Changing the drug therapy cost with the biosimilars provides an opportunity to offset the increased expenditures with the new therapeutic alternative.

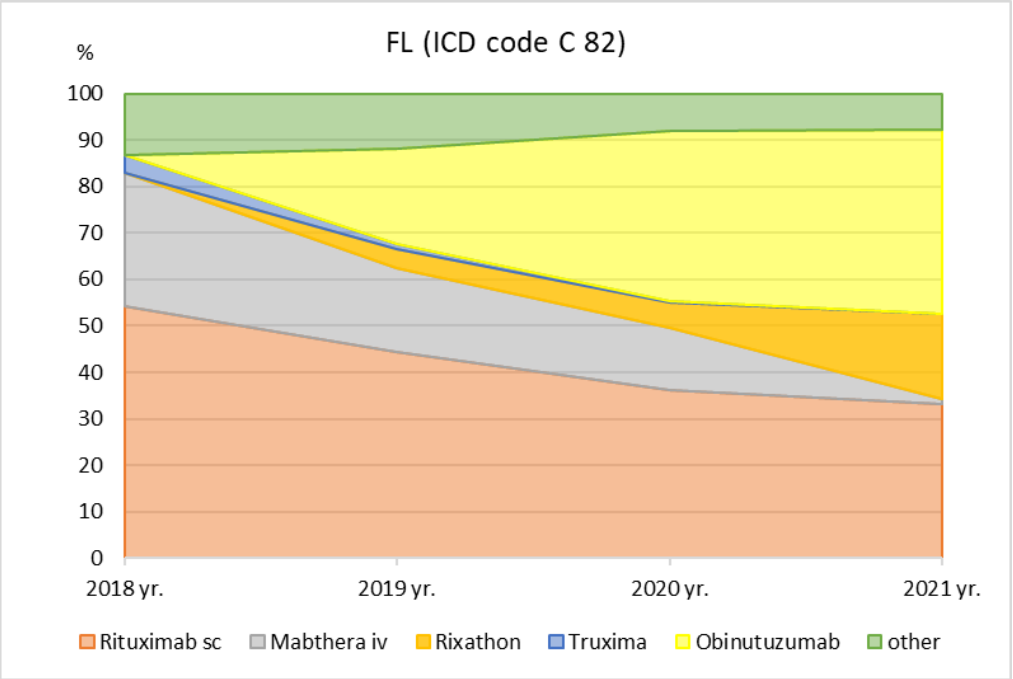
Analogous to DLBCL, the reference Rituximab has been replaced by the biosimilars following procurement in accordance with the PPA. Costs for the reference Rituximab have decreased by 96% (from BGN 1,132,506 in 2018 to BGN 46,827 in 2021). If in 2018 the costs of the reference Rituximab were 29% of the total costs of FL therapy, then in 2021 the costs of the reference Rituximab were only 1% of the total costs of therapy.

Figure 7 NHIF expenditures for drug therapy of FL



	2018 yr.	2019 yr.	2020 yr.	2021 yr.
other	524 110	506 595	335 574	312 616
Obinutuzumab	0	874 918	1 502 427	1 590 285
Truxima	157 714	48 817	12 487	0
Rixathon	0	174 567	228 339	733 317
Mabthera iv	1 132 506	767 390	550 200	46 827
Rituximab sc	2 155 671	1 898 928	1 496 005	1 328 758
total costs, BGN	3 970 001	4 271 215	4 125 032	4 011 803

Figure 8 Percentage ratio of the individual alternatives to the total costs of drug therapy of FL



NHIF costs for drug therapy of CLL

For patients with CLL, there are the most therapeutic alternatives for drug therapy, which accordingly has a significant impact on the NHIF expenditures for drug therapy. The Obinutuzumab, Ibrutinib, and Venetoclax spending accounted for between 61% in 2018 and 96% in 2021 of total CLL drug therapy spending (Fig. 10). This accordingly determines an increase in total costs more than 3.5 times for the considered 4-year period - from BGN 7,809,656 in 2018 to BGN 25,096,427 in 2021 (Fig. 9).

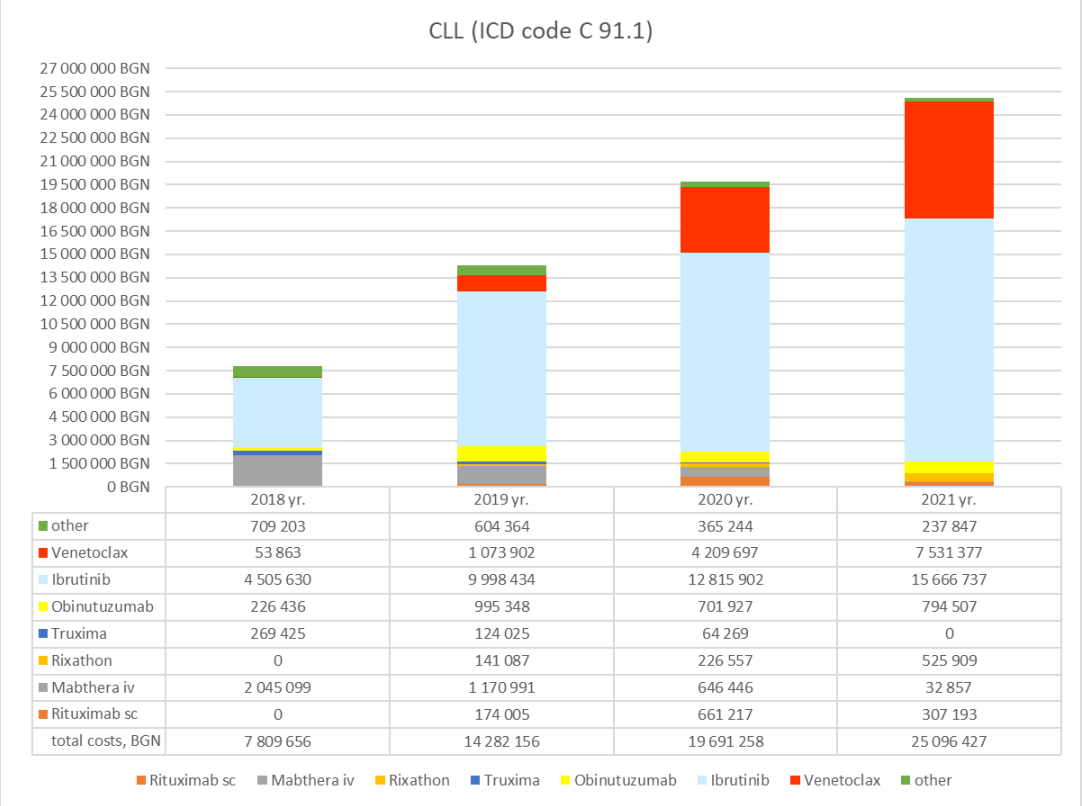
There was a decrease in the relative share of chemotherapy used in combination, as well as of medicines to control adverse drug reactions - from 9% in 2018 to 0.9% in 2021, which is also associated with a decrease in the costs of these medicines from BGN 709,203 in 2018 to BGN 237,847 in 2021 or -66%.

The inclusion of new therapeutic alternatives, correspondingly reduces the use of MPs with INN Rituximab, as well as the costs of drug therapy with Rituximab (regardless of the administered pharmaceutical form). The relative share of Rituximab drug therapy expenditures (regardless of the administered pharmaceutical form) of the total cost of drug therapy decreased from 30% in 2018 to 3% of the total costs in 2021 (Fig. 10). Thus, the costs for MPs with INN Rituximab from BGN 2,314,524 in 2018 will decrease to BGN 865,959 in 2021 or -63%.

The inclusion of the biosimilars in the PDL defines an additional reduction in the costs of the used Rituximab for intravenous administration - from BGN 2,314,524 in 2018 to BGN 558,767 in 2021 or -76% (Fig. 9), which also determines reduction of the relative share to the total costs from 29.6% in 2018 to 2.2% in 2021. In this case, the change in the value of drug therapy with the biosimilars does not allow to compensate the increased drug therapy costs with the new therapeutic alternatives.

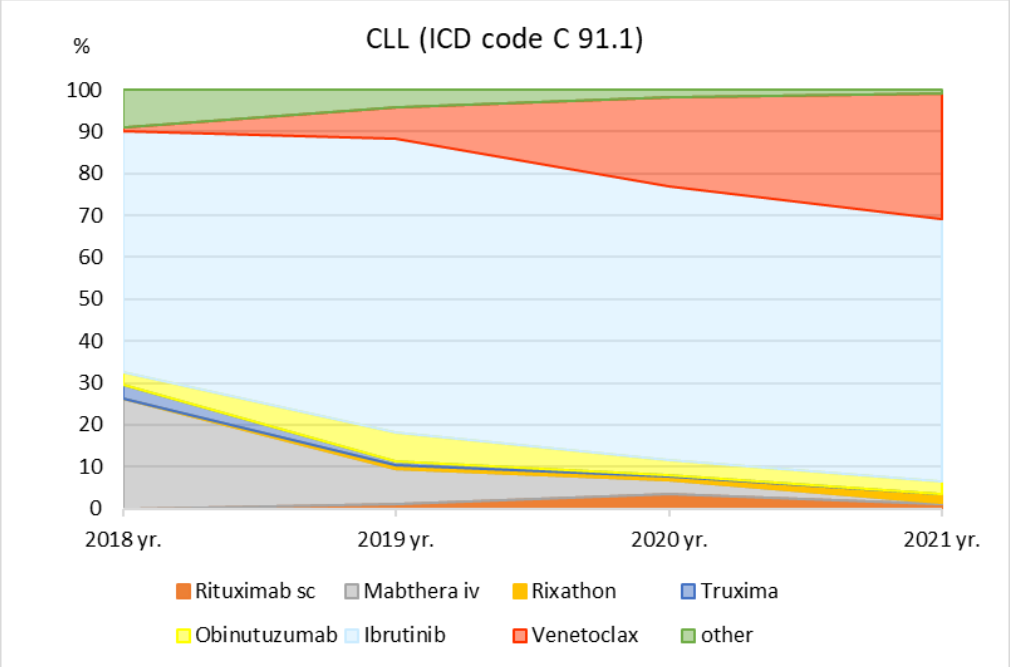
Again, the biosimilar Rituximab replaces the reference drug after the tender procedures under PPA. The relative share of the costs of drug therapy with the reference Rituximab (Mabthera iv) decreased from BGN 2,045,099 in 2018 to BGN 32,857 in 2021 and, accordingly, the relative share of these costs from the total costs of CLL drug therapy are 26% in 2018 and reach 0.1% in 2021.

Figure 9 NHIF expenditures for drug therapy of CLL



	2018 yr.	2019 yr.	2020 yr.	2021 yr.
other	709 203	604 364	365 244	237 847
Venetoclax	53 863	1 073 902	4 209 697	7 531 377
Ibrutinib	4 505 630	9 998 434	12 815 902	15 666 737
Obinutuzumab	226 436	995 348	701 927	794 507
Truxima	269 425	124 025	64 269	0
Rixathon	0	141 087	226 557	525 909
Mabthera iv	2 045 099	1 170 991	646 446	32 857
Rituximab sc	0	174 005	661 217	307 193
total costs, BGN	7 809 656	14 282 156	19 691 258	25 096 427

Figure 10 Percentage ratio of individual alternatives to total CLL drug therapy costs



5. Analysis of the biosimilars market share

For the period 2018 – 2021, the market share of biosimilars and the time to reach it respectively were analyzed.

We can talk about effective reimbursement when all the conditions that determine its availability in the relevant pharmacy (regardless of whether it is a hospital pharmacy or not) have already been met for a given medicine. When it comes to medicines for hospital treatment, it became clear that a tender procedure is necessary in advance to determine the MPs that will be supplied to the specific medical establishment. It is the time required for this tender procedure that determines when the relevant biosimilar drug will be available in the medical establishment after its inclusion in Annex No. 2 of the PDL and, accordingly, in the NHIF list of medicines paid beyond the value of the medical activity provided and patients will have access to drug therapy with biosimilar.

On the other hand, the conduct of tender procedures and therefore their outcome directly predetermines the market share of MPs. The conduct of a centralized electronic tender and, subsequently, hospital tenders respectively determine the supply of only one MP, which logically predetermines that the market share of the winning MP is guaranteed for the duration of the concluded contract.

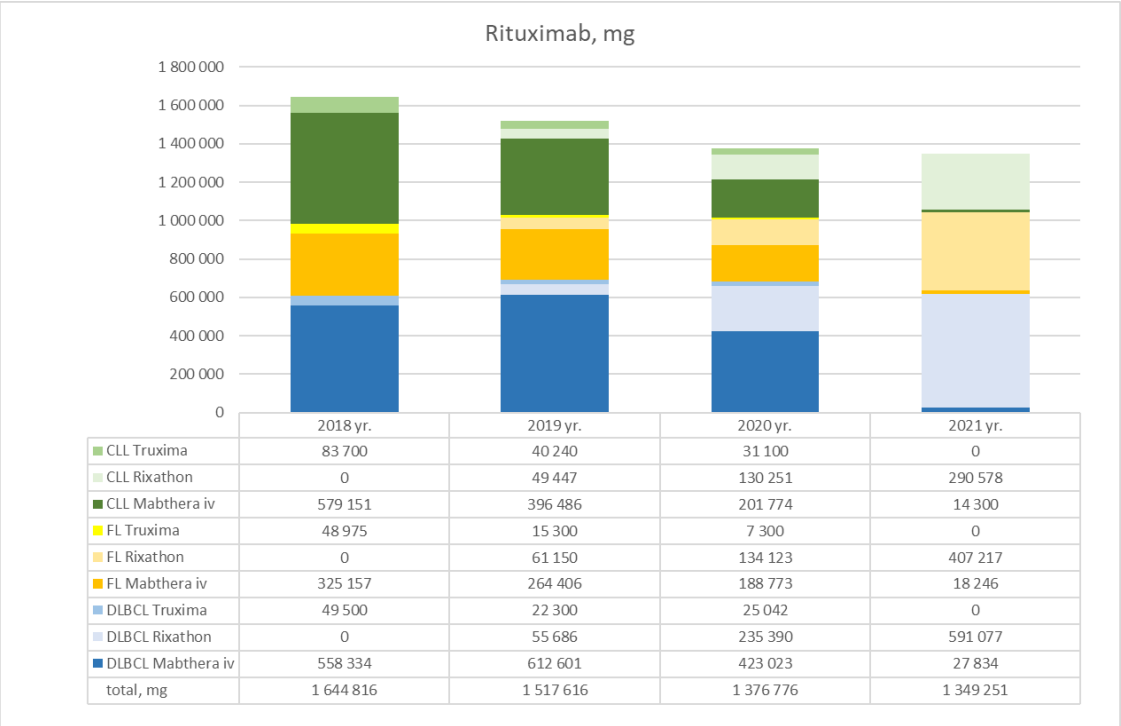
The presence of other therapeutic alternatives used for treatment of the same diseases also affects the market share. The market placement of new therapeutic alternatives determines the smaller number of patients who would benefit from the therapy applied so far in the case of a relatively constant patient population, such as the considered oncohematological diseases.

It is logical to track the number of patients who received drug therapy with Rituximab for intravenous administration and accordingly determine the market share of individual MPs.

Based on the available information from the NHIF, an additional analysis was prepared showing the amount mg of Rituximab paid. When interpreting the obtained results, it should be taken into account that the posology of Rituximab for intravenous administration is calculated as mg/m^2 body surface, i.e. an increase or decrease in the administered amount of MP is not necessarily related to a change in the number of patients treated.

Despite the assumptions made, the results of the analysis show a downrate trend in the administered amount of Rituximab on an annual basis – from 1,644,816 mg in 2018 to 1,349,251 mg in 2021 or -18% (fig. 11). A significant decrease in the amount of Rituximab used was observed in CLL – from 662,851 mg in 2018 to 304,878 mg in 2021 (-54%), which can be explained by the launch of new therapeutic alternatives. Accordingly, no such trend was observed in DLBCL, where Rituximab is the standard of care. Paid by the NHIF mg of Rituximab in total used to treat DLBCL in 2018 was 607,834 mg and 618,911 mg in 2021, and the reported change of 2% cannot be considered significant.

Figure 11 Reported amount of Rituximab for intravenous administration in mg



	2018 yr.	2019 yr.	2020 yr.	2021 yr.
CLL Truxima	83 700	40 240	31 100	0
CLL Rixathon	0	49 447	130 251	290 578
CLL Mabthera iv	579 151	396 486	201 774	14 300
FL Truxima	48 975	15 300	7 300	0
FL Rixathon	0	61 150	134 123	407 217
FL Mabthera iv	325 157	264 406	188 773	18 246
DLBCL Truxima	49 500	22 300	25 042	0
DLBCL Rixathon	0	55 686	235 390	591 077
DLBCL Mabthera iv	558 334	612 601	423 023	27 834
total, mg	1 644 816	1 517 616	1 376 776	1 349 251

The determined quantities of administered Rituximab were used for the calculation of the average price per mg paid by the NHIF and, therefore, how it relates to the defined reference value in Annex No. 2 of the PDL (Table 1).

Table 1 Estimated average price per mg Rituximab for intravenous administration, paid for by the NHIF

	2018 yr.	**2019 yr.**	**2020 yr.**	**2021 yr.**
Reported mg Rituximab for intravenous use	1,644,816	1,517,616	1,376,776	1,349,251
Reported expenses of the NHIF, BGN	5,708,913	4,440,665	3,399,301	2,442,944
Paid value BGN/mg	3.47085	2.92608	2.46903	1.81059

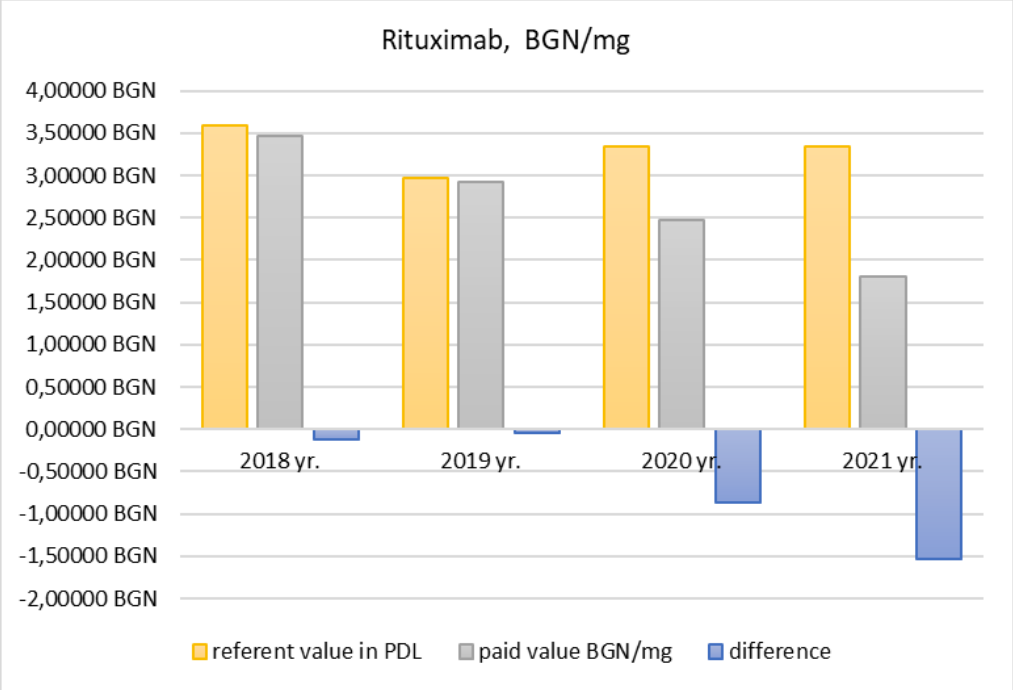
The performed analysis shows a tendency to decrease the real value per mg paid by the NHIF for the period 2018-2021 by -48% (from BGN 3.47085/mg in 2018 to BGN 1.81059/mg in 2021) (table 1). This is partly due to the change of the reference value in Annex No. 2 of the PDL, which is the maximum value that can be paid by the NHIF, given the inclusion of a new biosimilar MP, as well as the implementation of the EPR.

Additionally, the decrease is also the result of the tender procedures conducted by the CPB and subsequently at the hospital level. So the real price per mg Rituximab is significantly below the reference value level in Annex No. 2 of the PDL. From -3.4% in 2018 (paid value

BGN 3.47085/mg compared to the reference value of PDL 3.59144 BGN/mg) the difference reaches -45.8% in 2021 (paid value 1, 81059 BGN/ mg compared to the reference value of PDL 3.33788 BGN/mg) (Fig. 12).

In practice, this, together with the applied criterion for ranking the conducted tender procedures - the lowest price offered, predetermines the market share of the winning MP. It can be seen that in the 4th year after placing on the market, the biosimilars have almost completely displaced the reference MP in all three diseases considered (Fig. 11).

Figure 12 Ratio of the reference price in Appendix No. 2 of the PDS and the calculated value BGN/ mg paid by the NHIF



It should be assessed to what extent lowering the cost of drug therapy through the implementation of several consecutive public procurements under the order of the PPA leads to the sustainability of the drug supply system.

The conduct of a framework negotiation by the CPB, and especially the criterion for concluding framework agreements, limits the subsequent participation of all suppliers in the following tender procedures organized by the medical establishments. This, in the case of a signed framework agreement, with only one supplier and in case of inability to meet the country's needs from the specific MP leads to a direct limitation of patients' access to therapy.

The subsequent mandatory holding of tender procedures for the supply of medicines from publicly owned hospitals and, above all, the conditions for conducting and ranking the participants based on the criterion of the lowest offered price, determines the possibility of re-

establishing a monopoly position, although on the market more than one MP with the same INN is available. The requirement, introduced in 2021, that for all paid by the NHIF medicines applied in hospital care, the NHIF should pay the lowest value of all agreed values within the framework agreements concluded by the Minister of Health in his capacity as the CPB, and the value at which the MP was supplied to the hospital establishments, regardless of whether they are contractors under the PPA further contributes to the creation of a monopolistic situation

Although this avoids the previously observed large differences in the prices of drugs purchased by individual medical establishments, in practice, different conditions for placing on the market are created for medicines included in Annex No. 2 of the PDL and paid by the NHIF for hospital treatment and medicines included in Annex No. 1 of the PDL and paid by the NHIF for home treatment. In addition, the possibilities for medical specialists to choose a therapeutic alternative, as exists for MPs, included in Annex No. 1 of the PDL is limited. This creates the possibility of limiting patients' access to therapy, especially in the lack of a medicinal alternative for treatment, which in some cases may lead to unmet medical need and the associated higher health and social costs in the long term.

6. Assessment of the impact of regulatory requirements on market access for biosimilars

As already commented, the accessibility to the market of a given drug therapy should be considered comprehensively as ensuring physical availability from MP at an affordable, fair price, meeting the capabilities of the national health system and the needs of the population. From this point of view, a SWOT analysis was prepared, to assess to what extent the regulatory requirements guarantee access to the market of a given drug therapy and at what price, based on the results of the analyzes carried out (Table 2). The identified weaknesses and threats define the issues to be addressed and to find a way for optimization so as to achieve a balance between all market participants – patients, health authorities and payers, medical professionals, manufacturers and marketing authorization holders of medicinal products.

For the most part, the conclusions drawn are valid not only for Bulgaria, but also for reference countries with similar regulations.

Table 2 SWOT analysis of regulatory requirements regulating the market placement of biosimilars

Strengths	Weaknesses
✓ the use of EPR, as well as internal price referencing, is a relatively simple and easy-to-apply method for controlling the prices of MPs paid with public funds; ✓ inclusion of MPs in PDL without assessment of clinical and pharmaco-economic indicators hastens the process; ✓ short term for inclusion in the NHIF list; ✓ rapid efficient reimbursement for MPs for home treatment;	✓ EPR-based pricing leads to mechanical price pass-through without a real assessment of the impact of drug market volume; ✓ setting the lowest price does not always means saving in the healthcare system on long-term; ✓ the application of consecutive tender procedures for hospital LPs leads to a delay in effective reimbursement; ✓ limiting the possibilities of prescribing by medical specialists not for medical indications of MP for hospital use;
Opportunities	**Threats**
✓ reduction of public expenditure on drug therapy; ✓ release of funds for innovative therapies; ✓ achieving a balance between the needs and capabilities of the various stakeholders;	✓ strict price regulation can lead to refusal or delayed launch of new-to-market medicines in countries with low prices; ✓ withdrawal of MPs from the market; ✓ limitation of the supplied drugs in the medical establishments, may lead to the impossibility of providing the required quantities of medicines, due to shortage or temporary unavailability and, accordingly, to the interruption of the treatment;

CONCLUSIONS AND RECOMMENDATIONS

1. Conclusions

The formulated main conclusions are based on the studies and analyzes carried out. In view of the set research tasks and sub-tasks, they can be divided into the following main groups:

- conclusions arising from the analysis of the legislative framework of the market placement in Bulgaria and in the reference countries;

- conclusions related to the review of the biosimilars market in the EU and in Bulgaria;

- conclusions arising from the analysis of real data from the NHIF on the drug therapy costs of oncohematological diseases, after the launch of biosimilars;

- conclusions coming from the assessment of the impact of regulatory requirements on market access for biosimilars.

1) The review of the regulatory requirements regarding pricing and reimbursement in Bulgaria showed a well-established and regulated process that ensures:

✓ Timely market placement of biosimilars through a shortened procedure for inclusion in the PDL (30 days) in the presence of a valid marketing authorization and when the medicines with the same INN, pharmaceutical form and concentration on the active substance, already are included in the respective annex of the PDL, as well as through the possibility of effective reimbursement immediately after inclusion in the PDL (updating the NHIF list twice a month).

✓ Reducing the drug therapy cost through the implementation of all administrative mechanisms guaranteeing a reduction in the prices of prescription medicines and applied in most of the reference countries such as:

- use of external price referencing (applicable in 6/10 countries – Slovenia, Spain, Latvia, Romania, Greece, Slovakia);

- use of average reference basket (applicable in 2/10 countries – Latvia, Romania);

- reference to the lowest manufacturer's price (applicable in 2/10 countries – Romania, Slovenia);

- existence of a normatively determined ratio between the producer price of the biosimilar and the reference MP (applicable in 8/10 countries – Belgium, France, Italy, Lithuania, Romania, Slovakia, Slovenia, Spain);

- periodic verification of manufacturer's price after initial registration (applicable in 6/10 countries – Slovenia, Spain, Latvia, Romania, Greece, Slovakia) and

- use of internal price referencing (applicable in 6/10 countries – Belgium, Latvia, Lithuania , Slovakia, Spain, Greece).

✓ The use of a larger number of reference countries together with the requirement for the lowest manufacturer's price and the application of internal price referencing potentially leads to the possibility of lower prices and hence greater savings in public funds.

Most often, the price change in Bulgaria is due to a price change in Greece and Slovakia. These are the countries that have the largest reference basket and in EPR refer to the average of the 3 lowest manufacturer's prices.

2) The review of the market of biosimilars in the EU and in Bulgaria showed that the marketing authorization is strictly regulated and unified for the territory of the EU process, and patient access to therapy is directly related to the processes of pricing, reimbursement, supply, prescription and dispensing of drugs:

✓ Biosimilars approved for use under a centralized procedure in the EU belong to 10 pharmacotherapeutic groups. The most authorized products are in the group of antineoplastic agents (19 MPs belonging to 3 INNs). Only 52% of the authorized biosimilars from this group have been placed on the market in Bulgaria.

✓ The time from the marketing authorization to the inclusion in the PDL varies widely, and the initiation of the relevant procedures depends entirely on the MAH.

The average time from the marketing authorization to the inclusion in the PDL in Bulgaria varies from 2.6 to 27.9 months for individual biosimilars with different INNs.

This applies not only to the Bulgarian market. Thus price of the first biosimilar Rituximab – Truxima was registered between 4.6 and 12.6 months after the marketing authorization, and in some markets of the reference countries for Bulgaria there is still no such (registered price was established in 5/10 reference countries). For the second biosimilar Rituximab – Rixathon, despite being authorized for use only 4 months later, this time reaches 29.5 months, but a price was established in all reference countries.

✓ The price of biosimilars in the reference countries has an impact on the Bulgarian market, both through the EPR principle and through internal price referencing.

There was an immediate reduction in the value of drug therapy paid by the NHIF for medicines with 100% reimbursement after the inclusion of biosimilars in the PDL, by reducing the calculated reference value in the PDL under internal price referencing.

In the considered case, the inclusion of the first biosimilar MP with INN Rituximab leads to a reduction of the reference value in Annex No. 2 of the PDS by -26.4% (from BGN 4.88000/mg to BGN 3.59144/ mg), and on the second – with an additional -6% (up to BGN 3.36922/mg).

✓ The application of periodic referencing to the manufacturer's price in the reference countries according to the time of price registration in the presence of more than one MP with the same INN leads to more frequent changes in the reference value in PDL than the statutory period of 24 months and to a possible change on sales prices on all MAH.

For the period 2017 - 2020, the reference value listed in Annex No. 2 of the PDL of medicicnes with INN Rituximab for intravenous administration has been changed 5 times.

In some cases, such an administratively imposed change may be unacceptable and lead to the withdrawal of the product from the market.

3) The evaluation of the impact of the market placement of biosimilars on the NHIF expenditures showed a reduction in the drug therapy costs for MPs with INN Rituximab in oncohematological diseases:

✓ The observed reduction in the drug therapy costs with MPs with INN Rituximab in oncohematological diseases by -42.5% (from BGN 10,261,538 in 2016 to BGN 5,895,494 in 2021) is determined on the one hand by the administrative reduction of the registered price and, accordingly, the determined reference value in Annex No. 2 of the PDL, and on the other hand, from the conduct of public procurement for the supply of MP according to the PPA.

A decrease in the real value per mg paid by the NHIF for the period 2018-2021 compared to the determined reference value in Annex No. 2 of the PDL was found, from -3.4% in 2018 (paid value BGN 3.47085/mg compared to a reference value of BGN 3.59144/mg) the difference reaches -45.8% in 2021 (paid value BGN 1.81059/mg compared to a reference value of BGN 3.33788/mg).

✓ Use essentially of one MP with INN Rituximab for intravenous administration after conducting public procurement for the supply of MPs according to the order of the PPA in two stages (first by the CPB and then by the publicly owned hospitals). This is mainly determined by the applied criteria for ranking the participants and also the requirement that the NHIF pays the lowest value of all the agreed values in the framework agreements concluded by the Minister of Health in his capacity as the CPB, and the value at which the MP is supplied to the hospital establishments, regardless of whether they are contractors under the PPA.

In 2021, 96% of applied mg Rituximab for intravenous administration are from only one biosimilar MP (1,288,871 mg of a total of 1,349,251 mg).

Thus, due to administrative requirements, in practice, the possibility of prescribing therapeutically equivalent medicines by healthcare professionals is limited, not for medical reasons.

Such a limitation does not exist for MPs included in Annex No. 1 of the PDL and paid by the NHIF for home treatment.

✓ Optimizing the drug therapy cost of a given disease through the marketing of biosimilars is directly dependent on the availability of other medicinal alternatives for treatment, which also determine the observed tendency to decrease the use of Rituximab and its biosimilars.

In DBECL, in which the standard of care is immunotherapy with Rituximab, the launch of biosimilars reduces the drug therapy costs by -37% for the period 2018 - 2021 (from BGN 6,239,391 to BGN 3,900,953). The relative share of the drug therapy costs with Rituximab compared to the total drug therapy costs of 74% on average is maintained for the period 2018 - 2021, accordingly the reported amount mg of Rituximab for intravenous administration for the same period is maintained (607,834 mg in 2018 and 618,911 mg in 2021).

In the case of FL, despite the inclusion of a new therapeutic alternative in Annex No. 2 of the PDL, for the same period the drug therapy costs have increased by only +1% (from BGN 3,970,001 in 2018 to BGN 4,011,803 in 2021).

In CLL, where the most therapeutic alternatives are available, the corresponding costs have increased 3.5 times (from BGN 7,809,656 in 2018 to BGN 25,096,427 in 2021), and this increase cannot be compensated by the lower value of drug therapy with Rituximab. The availability of more therapeutic alternatives determines a reduction in used the amount mg of Rituximab for intravenous administration by -54% (from 662,851 mg in 2018 to 304,878 mg in 2021), and the relative share of Rituximab drug therapy costs to total drug therapy costs for the period 2018–2021, respectively decreases by -26% and reaches 3.5 % in 2021.

✓ The conducted analyses of the NHIF costs also determine the factors limiting the practical implementation of both retrospective and prospective analyses of the drug market:

The method of reporting the number of patients who received the relevant drug therapy by the NHIF significantly complicates the determination of the market share of specific medicine alternatives and, accordingly, the measurement of the real impact on the market of entry of biosimilars.

The lack of up-to-date registers of patients with oncohematological diseases and not only, as well as information about the stage of the disease and, respective, the treatment line of individual patients, significantly complicates the preparation of both forecasts for the development of the market and a realistic assessment of the existing drug market and the effect of the entry not only of biosimilars but also of innovative drug therapies.

4) The assessment of the impact of regulatory requirements on market access for biosimilars identified the factors that may have an unfavorable effect on access to therapy, namely:

✓ Limiting patients' access to therapy, especially if no other medicinal alternative exists, which in some cases may lead to unmet medical need and consequently increase health and social costs in the long term, because:

Excessive administrative price regulation without taking into account the volume of the market can determine as economically unjustified the presence of the market by the MAH and, consequently, the withdrawal of products.

On the other hand, maintaining the lowest registered prices is a prerequisite for increased parallel exports and the creation of a shortage on the Bulgarian market.

The inability to meet the country's needs for the specific drug given the existing possibility of creating a monopoly position in medicines for hospital use directly limits patients' access to therapy.

✓ Creation of conditions for unfair competition when, after the inclusion of the biosimilar MP in PDL, there is no real market placement or this launch takes a long time, because:

In the internal price referencing, through the immediate reduction of the maximum value paid by the NHIF, it determines inequality between medicines included in Annex No. 1 and Annex No. 2 of the PDL, despite the positive effect in terms of public funds spent.

In the case of MPs included in Annex No. 1 of the PDL and paid by the NHIF for home treatment, the reduction of the reference value can only be at the expense of the patient, if the MAH does not cover the difference in the co-payment.

For the MPs from Annex No. 2 of the PDL, in practice, this reduction initially affects only the reference product before the biosimilar to be really available in most medical establishments for hospital care, given the obligation to conduct public procurement for supply, which determines a delay in effective reimbursement.

Thus, despite the listed positives of the normative regulation of the prices of biosimilars from the payer`s perspective, it should still be taken into account that the adoption of uttermost decisions does not lead to a sustainable health model in the long term.

2. Recomendations

The proposed recommendations are based on the findings drawn and aim to help maintain the balance by optimizing patient access to the needed drug therapy and ensuring sustainability and stability of the drug supply and health insurance system.

The main recommendations are addressed to the Ministry of Health, the National Council on Prices and Reimbursement of Medicinal Products and the National Health Insurance Fund, which define and implement the basic principles of the drug policy in Bulgaria.

1) Recommendations to the National Council on Prices and Reimbursement of Medicinal Products:

- ✓ Optimizing the use of external price referencing for biosimilars.

In order to achieve the main objectives of using cross-market price comparison, namely monitoring the development of drug prices and the evolution of the pharmaceutical market, as well as their subsequent review, the administration of the prices of biosimilars should be reduced, especially at the presence of 2 or more biosimilars on the market.

This could be achieved by:

- Keeping the basket of reference countries in Bulgaria – the included countries are balanced in terms of those with a high gross domestic product, as well as those with similar economic development, and countries in the region.

- Use of EPR as an additional criterion in the establishment of prices when including the biosimilars in the PDL (applicable in 2/6 reference countries for Bulgaria – Latvia, Spain), by introducing a reference to the average value of the prices in the 10 reference countries.

- Giving precedence to internal price referencing, by maintaining the requirement for a manufacturer's price to be not higher than 80% of the value of the reference MP.

- To unify the date of the periodic submission of the declaration certifying the lowest manufacturer's price compared to the reference countries when preparing and publishing the list of drugs with well-established use in medical practice.

- In the case of establishing a lower price in the reference countries, which does not lead to a change of the reference value set in the PDL below the achieved one, during the tender procedures, the lower price found should not be reflected in the register of approved prices of the MPs, under medical prescription, included in the PDL and paid for with public funds.

2) Recommendations to the Ministry of Health:

✓ Optimizing the conditions for conducting e-tenders both at the level of the CPB and at the hospital level, through:

- Establish the ability for negotiation at a level of a therapeutic indication.

- Ability to ensure supplies on a quota basis.

- Enabling to supply medicines for which no framework agreement has been signed, in case of identified shortage or absence of the agreed drugs in order to secure the needs and, therefore, continuity of drug therapy.

3) Recommendations to the National Health Insurance Fund:

✓ Establish the possibility to report the actual number of patients by diseases who passed through the hospitals and received drug therapy accordingly.

✓ Optimizing the collection and subsequent use of data from the drug therapy conducted for outcome-based payment.

4) Recommendations to relevant medical societies:

Preparation and/or updating of national guidelines for the interchangeability of biological medicines in order to guarantee the achievement of optimal results from the conducted drug therapy.

5) Recommendations to patients and patient organizations:

✓ Patients should increase their health awareness about biosimilars and, accordingly, be involved in the decision-making process for the determination and subsequent administration of the necessary treatment, which determines their responsible behavior towards rational medicinal use.

Through the introduction of the proposed recommendations, a reduction in regulation would be achieved and, accordingly, a preponderance of competitive market mechanisms would be achieved, especially in the presence of 2 or more biosimilars on the market. This, in turn, would ensure that a balance is achieved between the needs, opportunities and interests of patients, health authorities and the pharmaceutical industry. Optimizing the use of external price referencing in relation to biosimilars would lead to a reduction in the administrative burden of regulatory authorities and a redirection of resources and efforts in the processes of effective evaluation of innovative drug therapies and the subsequent monitoring of the effect of therapy with the active involvement of patients.

CONTRIBUTIONS

The results obtained from the conducted own research, the conclusions drawn and corresponding recommendations determine the contributions of the present dissertation, which can be summarized from a scientific-theoretical, scientific-methodical and scientific-applied point of view.

1) Scientific-theoretical contributions

From a scientific-theoretical point of view, the following contributions can be mentioned:

- ✓ An analytical framework was developed to thoroughly assess the advantages and disadvantages of the legislative framework regulating the market placement of biosimilars by quantifying the penetration of biosimilars in oncology from the payer perspective, in this case, the NHIF.
- ✓ Analysis of the public drug therapy spending on specific diseases in detail by specifying financial indicators and determining their dependence on the regulatory requirements in Bulgaria in such a volume after the launch of biosimilar monoclonal antibodies for hospital use is being conducted for the first time.
- ✓ Defining the milestones related to the market placement of biosimilars confirmed the importance of rules and mechanisms for pricing and achievement of effective reimbursement.
- ✓ The identified main external and internal factors for Bulgaria, influencing the prices of biosimilars and therefore the drug therapy costs in Bulgaria, showed the need to introduce an individual pricing approach for biosimilars by giving precedence to internal price referencing and market mechanisms, to ensure that medicines remains on the market.
- ✓ The analysis of the public funds spent after the launch of biosimilars found a dependence on drug therapy costs both on the availability of other therapeutic alternatives and on the availability of biosimilars with one INN. This, in turn, defines the existence of strict administrative regulation of the prices of biosimilars, especially for hospital use as unjustified.
- ✓ The determination of the factors (such as excessive administrative regulation of prices, as well as the possibility of creating a monopoly position for medicines for hospital use) that limit patients' access to drug therapy showed a need to reconsider the introduction of the CPB for medicines simultaneously with the implementation of electronic hospital tenders, as well as specifying the conditions and criteria for conducting public procurement for the supply of medicines.

2) Scientific-methodical contributions

As a contribution from a scientific-methodological point of view, the determination of the factors and shortcomings that hinder the execution of a both retrospective and prospective analyzes of the market of publicly funded medicines in the long term can be indicated.

Thus, once again, confirm the urgent need to maintain up-to-date registers of patients not only with oncological diseases, as well as the necessity to collect and use real-world data for the specific drug therapy in order to assess the effective spending of public funds.

3) Scientific-applied contributions

Scientific-applied contributions are related to:

✓ The presented results - can serve as a starting point for optimizing the pricing principles of biosimilars by borrowing good practices from other European countries, such as the use in EPR of the average value from prices in the 10 reference countries (applicable in 4 countries from EU - Austria, Croatia, Netherlands, Portugal), giving precedence to internal price referencing in presence of more than 1 biosimilar on the market.

✓ The applied analyses - can be used as a model by the health authorities, by being applied accordingly to other diseases not only in oncology, for which there are monoclonal antibodies launched in order to fully assess the evolution trend of the biosimilars` market and their role in terms of access to drug therapy.

SUMMARY

The present work examines an issue that is relevant both at the national and European level, given the continuously increasing healthcare costs due to the observed demographic trends of population aging and increasing morbidity on the one hand, and scientific progress in the medical sciences on the other.

The elaboration of the present work has shown to what extent the expectation of "reducing costs for medication and increasing patient access to treatment" after the launch of biosimilars is valid for Bulgaria. Analyzing costs for specific diseases in detail and determining their dependence on regulatory requirements in Bulgaria in such an extent after the launch of biosimilars monoclonal antibodies for hospital use has not been conducted. The available so far comparative analyzes of the legislation regarding the market placement of biosimilars in different countries of the region do not provide a clear picture and quantitative dimension of the penetration of biosimilars in oncology from the payer point of view, in this case the NHIF.

For this purpose, the main characteristics of biosimilar medicines from their development to their release on the market have been examined and discussed. The subsequent analysis of the legislation identifies the milestones that are key to market access for biosimilars. To the extent that production and market authorization are regulated and controlled at the Community level by the EMA, the focus is on the processes of pricing and effective reimbursement, which prove to be key to the accessibility to the market of biosimilars in the given country.

Once providing opportunities for better health is a top priority for all health policymakers, the development of rules on price regulation and the inclusion of biosimilars in the social and health insurance system should ensure a balance between all market players. The analysis of the regulatory requirements in Bulgaria and the reference countries showed that all administrative mechanisms guaranteeing a reduction in the prices of prescription drugs are applied in Bulgaria, namely: external price referencing and its periodic application, normatively determined ratio between the price of the reference and the biosimilar MP, as well as internal price referencing. In addition to this, public procurement for medicines for hospital use is performed at two stages - at the central level through the CPB and at the level of a medical establishment. As far as all the listed mechanisms have been proven to lead to a significant reduction in the value of drug therapy, which in turn determines the saving of funds and their redirection for other therapies or activities, their unjustified combined application in the long term can disrupt the optimal functioning of the health system as a whole .

The case study discussed with the entry of biosimilar Rituximab in oncohematology, clearly delineates the trends and factors that determine the actual market penetration of biosimilars in three distinct diseases where different numbers of therapeutic alternatives are available. A decrease in the funds paid by the NHIF for drug therapy with MP with INN Rituximab was also observed when biosimilars with INN Rituximab were included in Annex No. 2 of the PDL. It has been found that reductions in the drug therapy cost and savings are achieved in the absence of a therapeutic alternative. Offsetting the increased costs of the introduction of innovative therapies is achieved with a limited number of therapeutic alternatives on the market, which are gradually displacing drugs with well-established use in medical practice. As the cost-effectiveness and, accordingly, the added health benefits of the individual therapeutic alternatives were not evaluated when considering the costs of drug therapy, it is not correct to categorically talk about savings in the long term.

It was also found that, despite the positive impact on drug therapy costs, the possibility of establishing a monopoly position after only one biosimilar MP remains on the market puts patient treatment at risk in the event of a shortage or supply disruption. This would be a problem especially when MP is included not only in main treatment regimens but also in combination with innovative therapies.

The presented results can serve as a starting point for a change in the legislation in a direction not only aimed at the financial resources of the healthcare insurance system, but also to place the individual patient and his needs at the center of the healthcare system by guaranteeing accessibility to the necessary therapy. Ensuring sustainable access to drug therapy is a necessity directly related to ensuring the health well-being of the population.

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