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Management of the National Drug Administration Through the Use of Biosimilar Medicines. Expenditures, Numbers of Reimbursed Packages and Shares of Biosimilar Products in the Infliximab Market a Year Prior to and a Year after the Introduction of the National Drug Policy 2018–2022

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Abstract

Purpose: Savings resulting from the use of biosimilar medicines (biosimilars) are important to the management of national drug administration. In September 2018, the Council of Ministers adopted the National Drug Policy (NDP) for 2018–2022. One of the priorities of the document set forth by the Ministry of Health was to increase the proportional use of biosimilars. The purpose of this article is to assess the changes and the dynamics in infliximab (Remicade®) expenditures and the share of biosimilars within the infliximab market before and after the announcement of the NDP.

Design/methodology/approach: The analysis is based on the example of infliximab, a biological medicine widely used in dermatology, gastroenterology and rheumatology.

The analysis period encompasses data for one year before the document was adopted, i.e. the period from September 2017 until August 2018 (year I) as well as one year after the document came into

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force, i.e. the period from September 2018 until August 2019 (year II). Comparative analyses were based on the statistical data of monthly expenditures and the number of packages reimbursed by the National Health Fund (NHF). Fixed base and chain dynamics indices were used in the analysis.

Findings: An increase in the expenditure and the number of packages sold in year II was observed for biosimilars.

Research limitations/implications: It should be stressed, however, that the article pertains to a single example – the infliximab market, and that numerous other important factors may affect the sales of biosimilars.

Originality/value: The analysis may be used to help evaluate the Ministry of Health's work on biosimilars.

Keywords: infliximab, biosimilar medicines, healthcare system, reimbursement, Ministry of Health.

JEL: H51, H75, I15, I18

Zarządzanie gospodarką lekową państwa poprzez wykorzystanie leków biopodobnych. Wydatki, liczba zrefundowanych opakowań i udziały leków biopodobnych w rynku infliksimabu, rok przed i rok po wejściu w życie Polityki Lekowej Państwa 2018–2022

Streszczenie

Cel: oszczędności wynikające ze stosowania leków biopodobnych (biosymilarów) są istotnym zagadnieniem w zarządzaniu gospodarką lekową państwa. We wrześniu 2018 roku Rada Ministrów przyjęła dokument Polityka Lekowa Państwa (PLP) 2018–2022. W dokumencie przedstawionym przez Ministerstwo Zdrowia jednym z priorytetów jest zwiększenie użycia leków biopodobnych. Celem artykułu jest ocena zmian (i ich dynamiki) w wydatkach na infliksimab i udziałach biosymilarów w rynku infliksimabu przed i po ogłoszeniu PLP.

Metodologia: w analizie wykorzystano przykład leku biologicznego infliksimab (lek oryginalny Remicade), szeroko stosowanego w dermatologii, gastrologii i reumatologii. Okres wybrany do analizy to rok przed wejściem w życie dokumentu Polityka Lekowa Państwa (rok I), czyli wrzesień 2017 – sierpień 2018 r. oraz rok po (rok II), czyli wrzesień 2018 – sierpień 2019 roku. Podstawą analizy porównawczej były dane statystyczne dotyczące miesięcznych wydatków oraz liczby opakowań zrefundowanych przez Narodowy Fundusz Zdrowia (NFZ). Pierwsze leki biopodobne do infliksimabu były refundowane już od początku 2014 roku. W związku z powyższym rynek infliksimabu jest silnie zdominowany przez biosymilary. W analizie wykorzystano jednopodstawowe i łańcuchowe indeksy dynamiki.

Wyniki: wykazano, że liczba sprzedanych opakowań i wydatki na lek oryginalny były niższe w roku II, po wprowadzeniu PLP. Dla leków biopodobnych zauważono odwrotne zjawisko – wzrost wydatków i liczby sprzedanych opakowań biosymilarów w roku II.

Ograniczenia/implikacje badawcze: należy jednak podkreślić, że artykuł dotyczy tylko jednego przykładu – rynek infliksimabu i że na sprzedaż leków biopodobnych może wpływać wiele innych ważnych czynników.

Oryginalność/wartość: analiza może być wsparciem i asumptem do podsumowania działań Ministerstwa Zdrowia oraz planowania dalszych działań z zakresie implementacji biosymilarów.

Słowa kluczowe: infliksimab, lek biopodobny, system ochrony zdrowia, refundacja, Ministerstwo Zdrowia.

1. Introduction

1.1. Infliximab

Currently, five medicinal products containing the active substance infliximab are included in the reimbursement list in Poland. These include one original medicine – Remicade – and 4 biosimilars: Flixabi, Inflectra, Remsima and Zessly. According to the registered indications, infliximab may be used in the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, Crohn's disease and ulcerative colitis. Available packages contain 100 mg of infliximab per vial (European Medicines Agency, 2019).

Infliximab is a chimeric human-murine monoclonal antibody. It belongs to a group of immunosuppressants referred to as tumor necrosis factor alpha (TNFα) inhibitors or "TNF blockers". The active substance mechanism of action is based on the selective binding of TNF alpha and, thus, inhibiting its effects. Since TNFα is involved in the inflammatory processes, its inhibition may reduce the inflammatory reaction in the body (European Medicines Agency, 2019).

As defined by the European Medicines Agency (EMA), "a biosimilar medicine is a medicine highly similar to another biological medicine already marketed in the EU (the so-called 'reference medicine')" (European Medicines Agency, 2017). Other names may include non-innovator proteins, follow-on biologics, similar biopharmaceuticals, subsequent entry biologics, or, most frequently, biosimilars (Kucharz et al., 2017). The assumption is that biosimilars should be the replicates of original biologic drugs just as generic drugs are the replicates of original synthetic drugs (Gámez-Belmonte et al., 2018).

Since "biological medicines contain active substances from a biological source, such as living cells or organisms", preparation thereof is more complex and associated with natural variability (European Medicines Agency, 2017). As a result, it is impossible to accurately reproduce these products, and the registered biosimilars are highly similar yet not identical to original drugs (Janjigian et al., 2018).

Biosimilar medicines are subject to comprehensive studies of biosimilarity, i.e. a considerable similarity as to the structure, biological activity, efficacy, safety and immunogenicity; they are also subject to relevant pharmacovigilance measures. In addition, regulatory authorities and pharmaceutical companies have already had an experience of more than 10 years regarding the use of biosimilars. Thanks to the aforementioned considerations and precautions, biosimilars have an established position in the clinical practice (European Medicines Agency, 2017).

All infliximab-containing medicines are accounted for as part of joint-limit group 1050.3, TNF blockers – Infliximab. The first reimbursed infliximab-

containing product was Remicade. It was included in the reimbursement list under drug programs B.32, B.33, B.35, and B.36 in July 2012 with a reimbursement price of PLN 2,261.77 per package. In November 2013, the drug was also included in the reimbursement list under the B.55 drug program. First biosimilars, Inflectra and Remsima, were included in the reimbursement list in January 2014. Since then the joint limit for group 1050.3 has been defined by the price of Remsima rather than by Remicade. Therefore, the base price fell from PLN 2,240.63 per package (PLN 22.41 per 1 mg) down to PLN 1,508.22 per package (PLN 15.08 per 1 mg). This price remained stable until the end of June 2018. Pursuant to the Ministry of Health notice of 24 June 2015, Remsima was also included in the B.47 drug program. The inclusion of another biosimilar medicine, Flixabi, in January 2018, reduced the funding limit to PLN 1,048.95 per package of 100 mg (PLN 10.48 per 1 mg), starting from July 2018. In January 2019 the base price was defined by the reduced price of Inflectra, i.e. PLN 1,037.61 (PLN 10.38 per 1 mg). The most recent biosimilar for infliximab is Zessly, which has been reimbursed by the National Health Fund (NHF) since March 2019 at the price of PLN 850.50. The Ministry of Health notice of 30th April 2019 declared a further decrease in the joint-limit base price to PLN 986.58 (PLN 9.87 per 1 mg), Flixabi continuing to be the benchmark product. According to the latest notice, in force from 1 November 2019, the joint limit has remained the same. This accounts for a 34.6% total reduction in the infliximab joint limit base price between the first day of reimbursement (July 2012 notice) and today (November 2019 notice). (Ministry of Health, 2019) According to current data from the Department of Drug Administration (DDA) summarizing the average costs per 1 mg of selected medicinal substances, the average price for 1 mg of infliximab dropped by 48% between January 2018 and September 2019 and the current average price is 5.77 PLN per 1 mg of infliximab (Department of Drug Administration, 2019).

1.2. National Drug Policy

The National Drug Policy (NDP) is a document developed pursuant to the World Health Organization's 2016 guidelines for the formulation and implementation of medicines policies. According to its guidelines, the role of NDPs is to set forth medium- and long-term objectives for pharmaceutical market stakeholders and decision-makers and to identify tools required to achieve these objectives (Ministry of Health, 2018b).

The strategic goals of the National Drug Policy as presented in the document include the provision of access to safe and effective medicines, with particular attention paid to their availability at suitable locations and times as well as the continuous improvement of public health by means of optimizing public health expenditures. To achieve these goals, ten specific priority objectives have been formulated including an improvement in

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the efficiency of public expenditures. Hence, the best possible health effects and the enhancement of the safety and stability of the drug supply can be obtained by means of a greater market share of medicines, including biosimilar medicines manufactured in Poland (Ministry of Health, 2018a).

Savings resulting from the use of biosimilars are particularly important in light of the aging population, the increasing life expectancy of patients, the increasing demands of patients and the increasing availability of novel, innovative medical technologies. According to the estimates presented in the NDP, one out of four Poles will be aged 65 years in 2035; in 2050, this age will have been achieved by one in three Poles, with total population of Poles above the age of 65 exceeding 11 million. These statistics are particularly worrying given that approximately 40% of all prescription medicines in the European Union are used in the treatment of this group of senior citizens (Ministry of Health, 2018a). Consequently, one can expect it challenging to ensure a greater supply of effective and safe medicines to meet the public health needs while taking into account a financial capacity of the payer.

In the NDP chapter on the availability of reimbursed medicines, the Ministry of Health has focused on the systematic extension of the catalogue of proven efficacy treatments available within the budget with simultaneous systematic reduction in patients' contribution to reimbursed therapies. Under another objective, the MoH is to support generic substitution by strengthening educational activities, introduction of a voluntary option to prescribe drugs according to their INNs and improvement of IT systems so as to monitor this substitution at the pharmacy level (Ministry of Health, 2018a).

Another strategic objective of the NDP touching the subject of biosimilars is based on the improvement of the pharmaceutical sector innovativeness in Poland. One of presented ideas is based on capacity building for industrial development and manufacture of biologic medicines – both bioequivalent and innovative. The MoH also wants to guarantee the availability of medicines by means of increasing the safety and stability of supply by increasing the market share of medicines, including biosimilar medicines manufactured in Poland (Ministry of Health, 2018a).

The first biosimilars to Remicade, the original medicine containing infliximab, were included in the reimbursement list as of the beginning of 2014. Therefore, the first spectacular change in price and consumption of individual infliximab-containing drugs have already taken place. The market is now well established and stable, its structure being less sensitive to a significant number of factors. This article uses the example of infliximab to reduce the number of potential additional factors while assessing the changes in the biosimilars market resulting from the new National Drug Policy.

2. Methodology and Data

The purpose of this article is to assess the changes (as well as the dynamics thereof) in infliximab expenditures and the shares of biosimilars within the infliximab market before and after the announcement of the NDP. The issue is important due to the limited budget of the country and the savings that could arise from correctly applying the national drug policy. Infliximab and its biosimilars were chosen as an example for the analysis in order to eliminate a possibly largest number of additional factors which could contribute to the changes in the market structure changes, as the market position of infliximab biosimilars is relatively well-established. Subject to the analysis were the sales data covering the period of one year before the adoption of the document (September 2017–August 2018) as well as one year after the adoption of the document (September 2018–August 2019). According to the research hypothesis, market shares and expenditures on biosimilar drugs should increase one year after introduction of the NDP, together with simultaneous reduction in respective figures for the original medicine, i.e. Remicade. Communications of the Department of Drug Administration (DDA) of the National Health Fund (NHF) were used for the calculation of expenditures, numbers of packages, and prices of individual medicinal products. Data collection was stopped as of 5th December 2019. All calculations were made using the Microsoft Excel application. Analyses were carried out in two subperiods: the first subperiod of one year prior to the introduction of the National Drug Policy, i.e. from September 2017 until August 2018, and the second subperiod of one year after the introduction of the NDP, i.e. from September 2018 until August 2019. This division was based on the assumption that 18 September 2018 – a day when the document was accepted by the Council of Ministers – was the day of the policy coming into force. In this article, the first period will be alternately referred to as the year before or year I, while the second period will be alternately referred to as the year after or year II. The expenditures and numbers of packages of individual medicines sold within a particular month were calculated by subtracting data from the previous months (e.g. January–February 2019) from data presented in reports for specific months (e.g. January–March 2019).

The report for the period of January–April 2019 was the first report in which the scope of data published in the NHF DDA communications was changed. Before that date, reports included data on the expenditures on individual packages within the specified accounting period and the number of packages sold. Only the expenditure data were presented in the more recent reports. This means that the full data (expenditures and packages) are available for the period between September 2017 and the end of March 2019. The statistics for the period starting in April 2019 contain only the statements on expenditures, without the numbers of packages sold. Therefore, numbers

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of packages and prices were calculated from the mean price stated in the last three communications containing both types of data, i.e. communications for January 2019, January–February 2019, and January–March 2019. In order to calculate the price of Zessly, which was included in the reimbursement list only in April 2019, the price presented in the MoH notice was taken and reduced by the previously calculated mean percentage difference between the infliximab-containing product prices as stated in the MoH notice and their respective price as reported by the DDA, i.e. by 23%.

Based on the data collected, the dynamics of expenditures and the shares of biosimilar medicines in the infliximab market were measured in the periods before and after the introduction of the NDP. Individual dynamics indices, i.e. the fixed base index and chain index, were used to measure the dynamics of changes in expenditures and shares.

Fixed base index accounts for the change in the examined variables within the test period as compared to the baseline period and is calculated using the following formula:

$$i_j = \frac{y_i}{y_0}$$

where:
$i = 0, 1, 2, 3, \ldots, n-1, n$
y_i – the level of the phenomenon during the test period
y_0 – the level of the phenomenon during the baseline period

Chain index accounts for the change in the examined variables within the study period as compared to the previous period and is calculated using the following formula:

$$i_l = \frac{y_i}{y_{i-1}}$$

where:
$i = 0, 1, 2, 3, \ldots, n-1, n$
y_i – the level of the phenomenon during the test period
y_0 – the level of the phenomenon during the previous period
(Sobczyk, 2007)

3. Results

3.1. Expenditures

Figure 1 is drawn up based on reimbursement expenditures as reported by the NHF. The figure compares the percentage shares of Remicade expenditures – the original product in the infliximab market – with the total percentage shares of expenditures on all infliximab-containing biosimilars.

It is immediately apparent that biosimilars containing infliximab are widely used and Remicade accounts for only a small part of total expenditure. The percentage share of Remicade was negligible at the beginning of the first year, rose gradually until the transition period as adopted in this study, i.e. August 2018/September 2019, and then started falling gradually at the beginning of year II to reach 0.1% in August 2019. This is evident in the extreme values as the minimum share of the original medicine, i.e. 0.1%, along with the maximum share of the biosimilars, was recorded twice: in October 2017 and August 2019. The maximum share of Remicade, i.e. 5.5%, and the lowest share of biosimilars, i.e. 94.5%, was observed in September 2018, i.e. in the first month of year II. The average shares of the original drug in the year before ad the year after amounted to 2.79% and 2.38%, respectively. For biosimilars, the respective shares were 97.21% and 97.63%. Detailed data are presented in Figure 1.

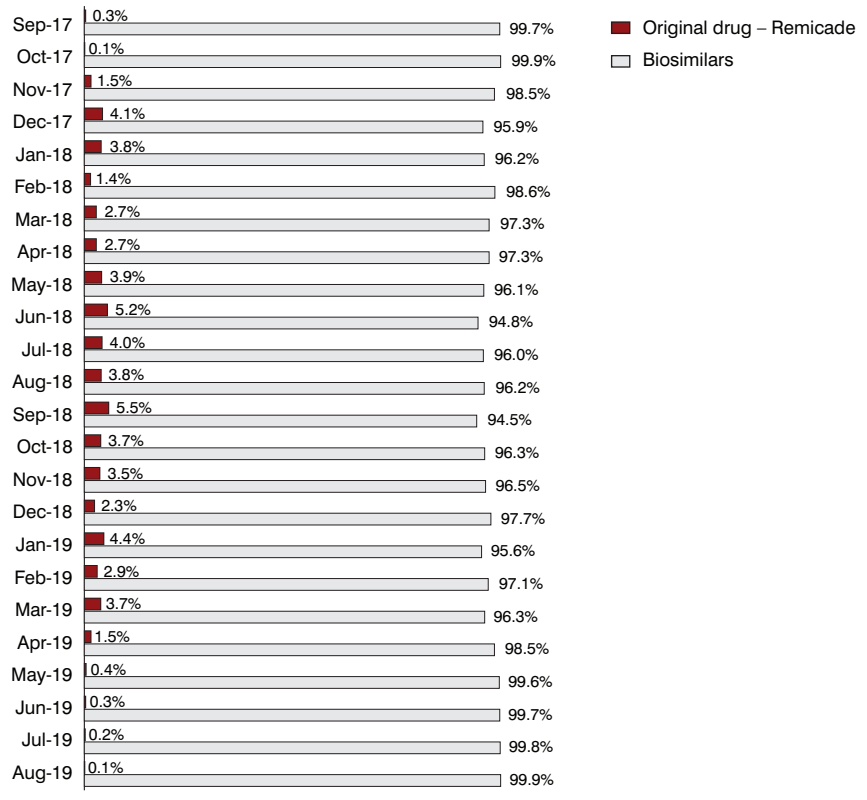

Fig. 1. Percentage shares of monthly expenditures on the original medicine (Remicade) within the infliximab market versus monthly expenditures on all infliximab biosimilars one year before and one year after the adoption of the NDP. Source: Own work.

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The expenditures on the original drug and the biosimilars varied within the 2-year study period. However, having considered the scale, differences in monthly expenditures were larger for biosimilars, ranging between PLN 1,598,444 and PLN 4,867,377. For the original medicine, the expenditures varied in the range of PLN 2,550–PLN 183,808. The lowest monthly expenditure in the year before adoption of the NDP was PLN 6,433 as compared to PLN 2,550 in the year after. At the same time, the maximum monthly expenditures amounted to PLN 183,808 and PLN 158,104 in the year before and the year after, respectively. The lowest monthly expenditure on biosimilars in the year before adoption of the NDP was PLN 1,658,732 as compared to PLN 1,598,444 in the year after. The maximum expenditures in years I and II were PLN 4,867,377 and PLN 4,282,378, respectively. The average monthly expenditures on the original medication were PLN 85,685 and PLN 61,761 in years I and II, respectively. For the biosimilars, the respective values were PLN 3,072,555 in the year before and PLN 2,595,412 in the year after. One may notice that in all the aforementioned cases, the extreme monthly expenditures were lower in year II. Outstanding increases in the expenditures, repeated in both study years, were observed in October and April. Table 1 presents the levels and the dynamics of changes in monthly expenditures on the original medicine (Remicade) and monthly expenditures on all infliximab biosimilars (in PLN) in the year before and the year after the adoption of the NDP.

The highest increase in the expenditures on the original medicine relative to September 2017 was recorded in June 2018 (year I), the fixed base index amounting 27.23. The highest decrease of 62% was observed in August 2019 (year II). The highest expenditures on biosimilars were recorded in October 2017 (year I) and were 2.34 times greater than those of September 2017; the lowest expenditures, recorded in June 2019 (year II), were 33% smaller than those of September 2017.

According to the hypothesis adopted for the purposes of this article, the indices for the original medicine were lower in all cases in year II as compared to year I. The most spectacular decrease in the use of Remicade could be seen in fixed base indices for expenditures in year I (Aug 2018/ Sep 2017) – 21.975 and year II – (Aug 2019/Sep 2018) – 0.025.

Data regarding biosimilars revealed that the expenditures on biosimilars were greater in year II in all cases. In three of the four cases described in Table 2 the index was higher in year II. Only in one case, the index was higher in I and amounted to 1.863.

The calculated average tempo of changes over 2 years has shown that the expenditures on the original medicine were reduced by about 4% while that expenditures on the biosimilars remained at the same level.

Period	Original drug – Remicade			Biosimilars		
	Expenditures (PLN)	Fixed base index SEP. 2017 = 100	Chain index (previous year = 100)	Expenditures (PLN)	Fixed base index SEP. 2017 = 100	Chain index (previous year = 100)
Sep-17	6 751	1.00	1.00	2 083 549	1.00	1.00
Oct-17	6 433	0.95	0.95	4 867 377	2.34	2.34
Nov-17	41 126	6.09	6.39	2 678 020	1.29	0.55
Dec-17	80 926	11.99	1.97	1 972 435	0.95	0.74
Jan-18	98 783	14.63	1.22	2 613 393	1.25	1.32
Feb-18	33 087	4.90	0.33	2 387 050	1.15	0.91
Mar-18	44 215	6.55	1.34	1 658 732	0.80	0.69
Apr-18	120 806	17.89	2.73	4 549 475	2.18	2.74
May-18	137 749	20.40	1.14	3 543 471	1.70	0.78
Jun-18	183 808	27.23	1.33	3 514 161	1.69	0.99
Jul-18	126 185	18.69	0.69	3 121 680	1.50	0.89
Aug-18	148 357	21.97	1.18	3 881 317	1.86	1.24
Sep-18	101 542	15.04	0.68	1 846 923	0.89	0.48
Oct-18	158 104	23.42	1.56	4 282 378	2.06	2.32
Nov-18	105 780	15.67	0.67	3 065 800	1.47	0.72
Dec-18	81 366	12.05	0.77	3 574 116	1.72	1.17
Jan-19	79 543	11.78	0.98	1 791 075	0.86	0.50
Feb-19	72 044	10.67	0.91	2 501 254	1.20	1.40
Mar-19	71 492	10.59	0.99	1 929 444	0.93	0.77
Apr-19	51 342	7.60	0.72	3 495 285	1.68	1.81
May-19	6 622	0.98	0.13	1 802 151	0.86	0.52
Jun-19	4 964	0.74	0.75	1 598 444	0.77	0.89
Jul-19	5 780	0.86	1.16	3 014 911	1.45	1.89
Aug-19	2 550	0.38	0.44	2 243 160	1.08	0.74

Tab. 1. The levels and the dynamics of changes in monthly expenditures on the original medicine (Remicade) and monthly expenditures on all infliximab biosimilars (in PLN) in the year before and the year after the adoption of the NDP. Source: Own work.

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Period	Fixed base index	Average tempo of changes	Fixed base index	Average tempo of changes
	Original drug – Remicade		Biosimilars	
By share based on expenditures				
2 years together	0.333	0.953	1.002	1.000
Ist year (Aug.2018/S ep.2017)	12.667	1.260	0.965	0.997
2nd year (Aug.2019/S ep.2018)	0.018	0.695	1.057	1.005
By expenditures				
2 years together	0.378	0.959	1.077	1.003
Ist year (Aug.2018/S ep.2017)	21.975	1.324	1.863	0.715
2nd year (Aug.2019/S ep.2018)	0.025	1.026	1.215	1.018

Tab. 2. Yearly summary – the dynamics of changes in monthly expenditures and market shares for the original medicine (Remicade) and monthly expenditures and market shares for all infliximab biosimilars (in PLN) in the year before and the year after the adoption of the NDP. Source: Own work.

3.2. Number of Packages

The minimum and the maximum shares of the original drug packages in the total sales of infliximab-containing medications amounted to 0.1% and 12.5%, respectively. For biosimilar medicines, the respective range was 87.5–99.9%. The lowest percentages of original medication packages sold were close each other and amounted to 0.13% in year I and 0.10% in year II. Accordingly, the highest percentage sales of biosimilar medicines were similar and amounted to 99.87% in year I and 99.90% in year II. In year I, the highest percentage of Remicade packages sold was 12.5% as compared to 5.1% in year II. In the year before the adoption of the NDP, the lowest the recorded share of biosimilars was 87.5% as compared to 94.9% in year II.

One can notice the very low sales of Remicade at the beginning of year I, an increase in the sales until the turn of August/September 2018, and subsequent gradual decrease to 0.1% (August 2019). It is important to stress that the data from April 2019 to August 2019 are estimations calculated using the method presented in this article.

The analysis of the number of packages of the original drug (Remicade) and all infliximab biosimilars reimbursed monthly by the NHF shows that the monthly sales of the original medication were in the range of 3–187 packages. The lowest monthly sales of Remicade in year I amounted to 6 packages in year I and 3 packages in year II; the respective highest monthly sales amounted to 187 and 164 packages in the year before and the year after. For biosimilars, the extreme values sales amounted to 983 and 5894 packages.

The lowest numbers of packages of reimbursed biosimilar medicines in the year before and the year after were 983 and 1934, respectively. Respectively, the highest values were 5984 in the year before and 4535 in the year after. The average monthly number of Remicade packages sold was 84 in year I and 69 in year II. The average monthly number of the packages of biosimilar drugs was 2827 in year I and 3125 in year II. The monthly average number of biosimilar packages was greater in year II than in year I. With reference to the results from Figure 1, one can notice that the average monthly spending on biosimilars was lower in year II as compared to year I, although the average number of packages purchased was higher than in year I.

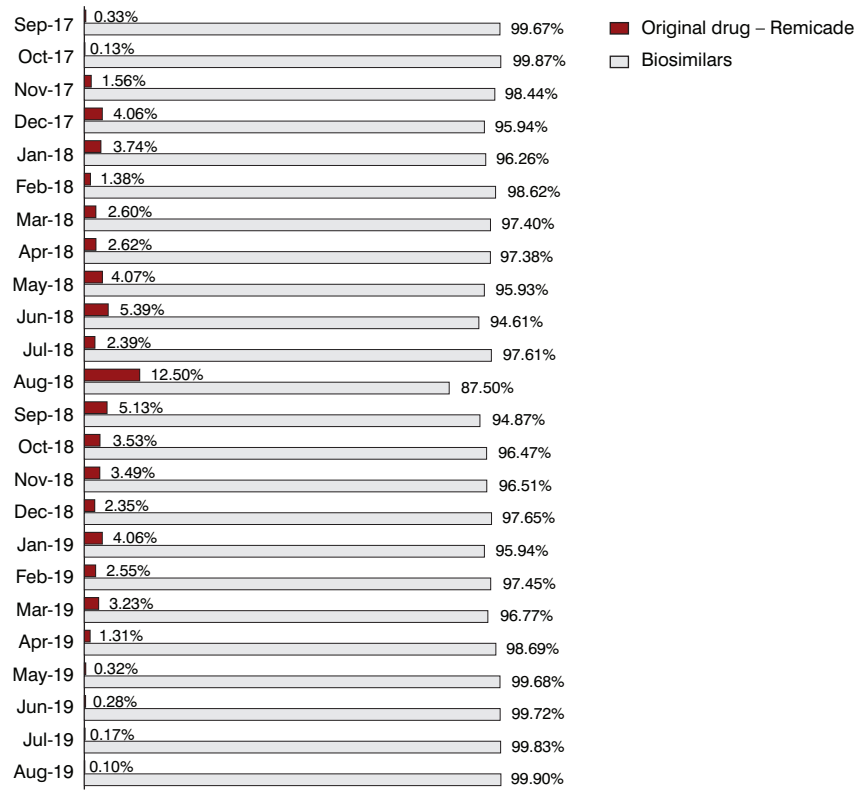

Fig. 2. Monthly sales of the original drug (Remicade) packages vs. monthly sales of all infliximab biosimilars (percentage), one year before and one year after the approval of the NDP. Source: Own work.

Table 3 presents the levels and the dynamics of changes in monthly sales of the the original drug (Remicade) packages vs. monthly sales of all infliximab biosimilars (number of packages), one year before and one year after the approval of the NDP.

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Period	Original drug – Remicade			Biosimilars		
	No. of packages	Fixed base index SEP. 2017 = 100	Chain index (previous year = 100)	No. of packages	Fixed base index SEP. 2017 = 100	Chain index (previous year = 100)
Sep-17	6	1.00	1.00	1866	1.00	1.00
Oct-17	6	0.95	0.953	4366	2.34	2.34
Nov-17	38	6.20	6.510	2408	1.29	0.55
Dec-17	75	12.20	1.966	1772	0.95	0.74
Jan-18	92	14.89	1.220	2354	1.26	1.33
Feb-18	30	4.90	0.329	2158	1.16	0.92
Mar-18	40	6.54	1.335	1507	0.81	0.70
Apr-18	112	18.13	2.771	4141	2.22	2.75
May-18	136	22.12	1.219	3204	1.72	0.77
Jun-18	187	30.36	1.373	3274	1.75	1.02
Jul-18	144	23.45	0.772	5894	3.16	1.80
Aug-18	140	22.84	0.974	983	0.53	0.17
Sep-18	105	17.00	0.744	1934	1.04	1.97
Oct-18	164	26.61	1.565	4471	2.40	2.31
Nov-18	119	19.27	0.724	3275	1.76	0.73
Dec-18	96	15.55	0.807	3966	2.13	1.21
Jan-19	94	15.22	0.979	2209	1.18	0.56
Feb-19	85	13.78	0.906	3234	1.73	1.46
Mar-19	83	13.54	0.982	2498	1.34	0.77
Apr-19	60	9.79	0.723	4535	2.43	1.82
May-19	8	1.26	0.129	2383	1.28	0.53
Jun-19	6	0.95	0.750	2107	1.13	0.88
Jul-19	7	1.10	1.164	3957	2.12	1.88
Aug-19	3	0.49	0.441	2931	1.57	0.74

Tab. 3. The dynamics of changes in monthly sales of the original drug (Remicade) vs. monthly sales of all infliximab biosimilars (number of packages), one year before and one year after the approval of the NDP. Source: Own work.

In a manner similar to that observed for expenditures, the highest increase in the sales of the original medicine relative to September 2017 was recorded in June 2018 (year I), the fixed base index amounting 30.36. The highest decrease of 51% was observed in August 2019 (year II). In contrast to the hypothesis adopted for the purposes of this article, the highest sales of biosimilars were recorded in July 2018 (year I) at 3.16 times higher than in September 2017. The lowest number of biosimilar drug packages sold in the 2-year study period was recorded in August 2018 (year I) and was 47% lower than that in September 2017.

According to the hypothesis adopted for the purposes of this article, the indices for the original medicine were lower in all cases in year II as compared to year I. Just as in the case of expenditures, the most spectacular decrease in the use of Remicade could be seen in the fixed base indices for shares in year I (Aug 2018/Sep 2017) – 38,050 and year II – (Aug 2019/Sep 2018) – 0,020.

In all cases, the increase in the number of biosimilar packages was demonstrated for year II and all indices for biosimilar products were higher in year II as compared to year I. In the first year, all indices for biosimilars had values of less than 1, corresponding to decreasing sales.

The calculated average tempo of change over 2 years has shown that the number of packages of the original medicine was reduced by the average of 3% to 5% while the number of packages of biosimilars remained at the same level.

Period	Fixed base index	Average tempo of changes	Fixed base index	Average tempo of changes
	Original drug – Remicade		Biosimilars	
By share based on number of packages				
2 years together	0.310	0.950	1.002	1.000
Ist year (Aug.2018/Sep.2017)	38.050	1.392	0.878	0.988
2nd year (Aug.2019/Sep.2018)	0.020	0.700	1.053	1.005
By number of packages				
2 years together	0.486	0.969	1.570	1.020
Ist year (Aug.2018/Sep.2017)	22.839	1.329	0.527	0.943
2nd year (Aug.2019/Sep.2018)	0.029	0.724	1.516	1.039

Tab. 4. Yearly summary – dynamics of changes in monthly sales and market shares of the original drug (Remicade) vs. monthly sales and market shares of all infliximab biosimilars (number of packages) one year before and one year after the approval of the NDP. Source: Own work.

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4. Discussion

Numerous debates are ongoing on the substitutability of reference drugs with biosimilars due to the substitution-related immunogenicity. Immunogenicity is substance's capability of producing an immune response against itself. This is usually accompanied by the development of specific antibodies against this substance. This mechanism is widely used with vaccines; however, in the case of biological drugs, immunological responses may lead to the development of antibodies directed against the drug itself (Polskie Towarzystwo Onkologii Klinicznej, 2018). Such harmful immunogenicity, albeit not very likely, may result in reduced circulation levels, reduced efficacy, and increased toxicity of the treatment (Trifirò et al., 2018). In view of the concerns regarding original medicines replaced by biosimilars, numerous studies have been carried out to compare such drugs, including Remicade and its biosimilars. The studies have revealed a similar efficacy, tolerance, and safety profiles as well as similar physicochemical and biological properties of these drugs compared to the original product in rheumatoid arthritis (Becciolini et al., 2017), inflammatory bowel disease (Razanskaite et al., 2017), Crohn's disease (Meyer et al., 2019), psoriatic arthritis, ankylosing spondylitis and psoriasis (Al-Salama, 2018; Lamb et al., 2019).

The issue of substitutability is not regulated by EMA and each country adopts its own rules in this respect. It is important that the decision to switch between biological drugs is based on both patient-related and drug-related criteria (Woroń, 2017). Usually, wealthier countries are more cautious when substituting drugs due to the aforementioned potential for immunogenicity while countries with lower incomes may encourage substitution to reduce expenditures (Mezones-Holguin et al., 2019; Trifirò et al., 2018).

Given the significantly growing expenditures on medicines and a disproportionate increase in the state budgets, the states have an option either to restrict the access to the treatment or to reduce the price of medicines (Gronde et al., 2017). According to the National Drug Policy 2018–2022, ensuring the availability of effective and safe medications is one of the main roles of the State (Ministry of Health, 2018a). The development of the market of biosimilar and generic products not only directly reduces costs borne by the payer and the patients on specific medicines, but also indirectly affects the prices of competing medicines including the originals.

The results presented in this article confirm the significant share of biosimilars in the infliximab market. An increased share of biosimilars one year after the introduction of the NDP is also noticeable. However, one should bear in mind that despite the fact that infliximab was chosen as the active substance of interest in this article due to its relatively stable market in an attempt to reduce the impact of other confounding factors, the results presented in the publication may depend on other factors, as well. An

interesting example of the multitude of interdependencies is presented by Sweden which is divided into 21 districts with different health management strategies. A study reported on the shares of infliximab biosimilar in the markets of individual districts ranging from 18 to as much as 96%. This is explained by differences in price reductions between the original and the biosimilar drug, different strategies for promoting the competitiveness of biosimilars, the involvement of key opinion leaders and experts, local guidelines and profit-sharing agreements (Moorkens et al., 2019). In the case of the Polish market and the time period chosen for the purposes of this study, another important factor affecting the infliximab market should be highlighted, namely the inclusion of Flixabi and Zessly in the reimbursement list in January 2018 and March 2019, respectively (Ministry of Health, 2019).

5. Conclusions

Promotion of biosimilars use is one of the objectives of the National Drug Policy 2018-2022. Savings resulting from the use of biosimilars are important for decision-makers due to the limitations to the state budget and the constantly growing expenditures on the health care system. Within the time frame examined in the article, the share of biosimilars in the infliximab market ranged from 87.5% to 99.9%. The results revealed a repeatable pattern where the expenditures, numbers of reimbursed packages and market shares for the original drug were negligible at the beginning of the first year, rose gradually until the transition period as adopted in this study, i.e. August 2018/September 2019, and then started falling gradually at the beginning of year II to reach 0.1% in August 2019. The highest (ca. 30-fold) increase in the expenditures and the numbers of original product packages sold relative to September 2017 was recorded in June 2018 (year I) while the highest decrease of (50–60%) was observed in August 2019 (year II). According to the hypothesis adopted for the purposes of this article, the indices for the original medicine were smaller in all cases in year II as compared to year I. This means that considering the calculated yearly indices, the numbers of packages sold and the expenditures on the original drug were lower in year II, following the introduction of the NDP. The opposite, i.e. an increase in the expenditure and the number of packages sold in year II was observed for biosimilar medicines. The calculated average tempo of change over 2 years has revealed that the expenditures and the numbers of packages of the original medicine were reduced by about 4% on average while the expenditures and the numbers of packages of biosimilars remained at the same level. One might expect that the new National Drug Policy was one of the factors underlying the increase in sales of biosimilars and the less common use of the original medicines. In the case of the time period chosen for the purposes of this

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study, another important factor affecting the infliximab market should be highlighted, namely the inclusion of Flixabi and Zessly in the reimbursement list of January 2018 and March 2019, respectively. Further research on factors affecting the use of biosimilars is needed.

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