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First and subsequent market entries of biosimilars – Effect on pricing of original medicinal product and already present biosimilars

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1. Executive Summary

a) Objective of the analysis

In Slovenia, the growing public expenditures on biological medicinal products (BMP) are partly caused by increased utilization which could be balanced by growing number of cheaper biosimilars (BSs).

This policy brief aims to evaluate the effect of market entry of BSs on Slovenian healthcare expenditures, to explore the list price changes of adalimumab-containing original BMP and BSs on Slovenian market compared to other EURIPID markets, and to identify the countries with lowest wholesale list prices and earliest list price drops of original BMP and BSs after market entries of new BSs. The analysis focused on list prices that were reported to EURIPID without considering existing national pricing policies.

We used EURIPID data, EMA data on marketing authorizations and Slovenian price information to support our study. This policy brief aims to demonstrate how EURIPID can be used beyond external reference pricing purposes.

b) Key messages

The number of available BSs does not seem to have a direct impact on the minimum wholesale unit price of the original or biosimilar MPs. The wholesale unit prices of original BMP have a descending trend that has increased after the market entry of BSs. The effects of first and subsequent market entries of BSs on competitor prices depends on the country. A considerable difference in the minimum wholesale unit price of the original BMP and BSs remains.

Slovenia has been successful in decreasing the wholesale unit prices of the original BMP and BSs. Slovenia's original BMP price drops before and after BSs' market entries are in the medium to high range compared to other EURIPID countries and were more profound after 2nd and 3rd BS market entry. With the anticipated increased utilization of BMPs in the coming years, more efforts on price control mechanisms should be considered.

Keywords: Slovenia; EURIPID; biosimilar; original biological medicinal product; adalimumab

2. Introduction

Generic medicinal products (MPs) constitute an important tool for containment of healthcare expenditure.¹ The magnitude of their contribution could best be observed in active ingredients with high volume prescription like statins (C10AA) and proton pump inhibitors (A02BC) in early 2000s. A similar effect has been expected of biosimilars (BSs),² but the last years showed that this effect seems to be less pronounced.

In the last decade, BSs as less costly alternatives to original BMPs have been broadly introduced in Europe. Adalimumab as one of the most widely used BMP is a recombinant human monoclonal antibody used for treatment of juvenile idiopathic arthritis, paediatric plaque psoriasis, paediatric Crohn's disease, paediatric uveitis, adolescent hidradenitis suppurativa, paediatric ulcerative colitis, rheumatoid arthritis, axial spondyloarthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis.³

In Slovenia, the number of dispensed packages of adalimumab increased by 236% from 2010 till 2022 and a 29,5% growth was observed after the market entry of biosimilars in 2018 (Figure 1).^{4,5}

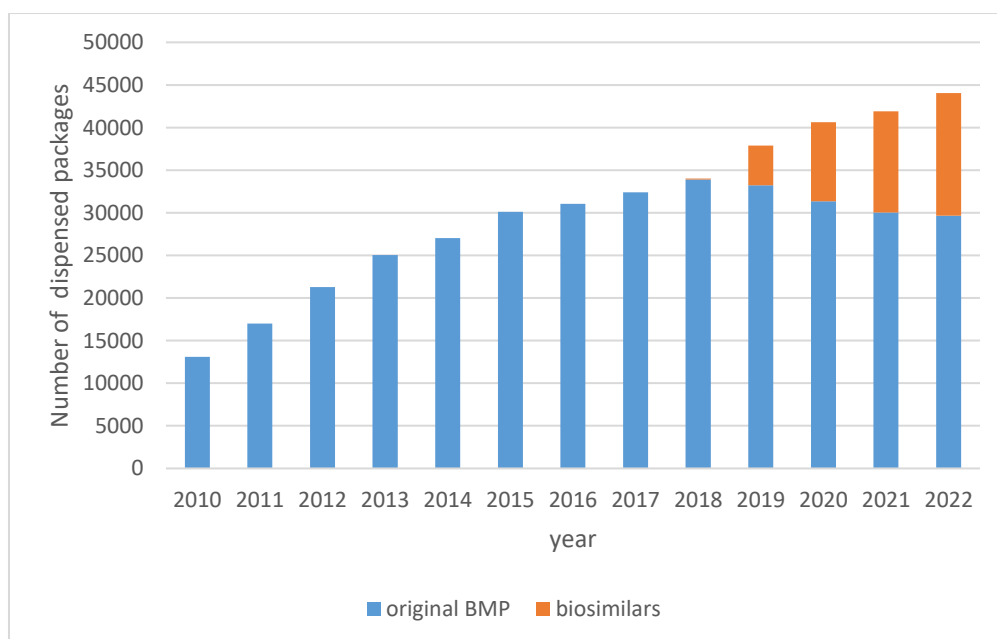


Figure 1: Sales volume of original BMP and BSs with adalimumab in the period 2010-2022 in Slovenia.

However, a total annual public expenditure for adalimumab decreased by 2% in the period between 2010 and 2022 with a peak annual expenditure seen in 2016. Due to decreasing list price of original BMP in 2017 and 2018, the annual expenditures started to decline despite the rising number of dispensed packages. After the market entry of BSs at the end of 2018, a 40% decrease of annual public expenditure for adalimumab was observed (Figure 2).^{4,5}

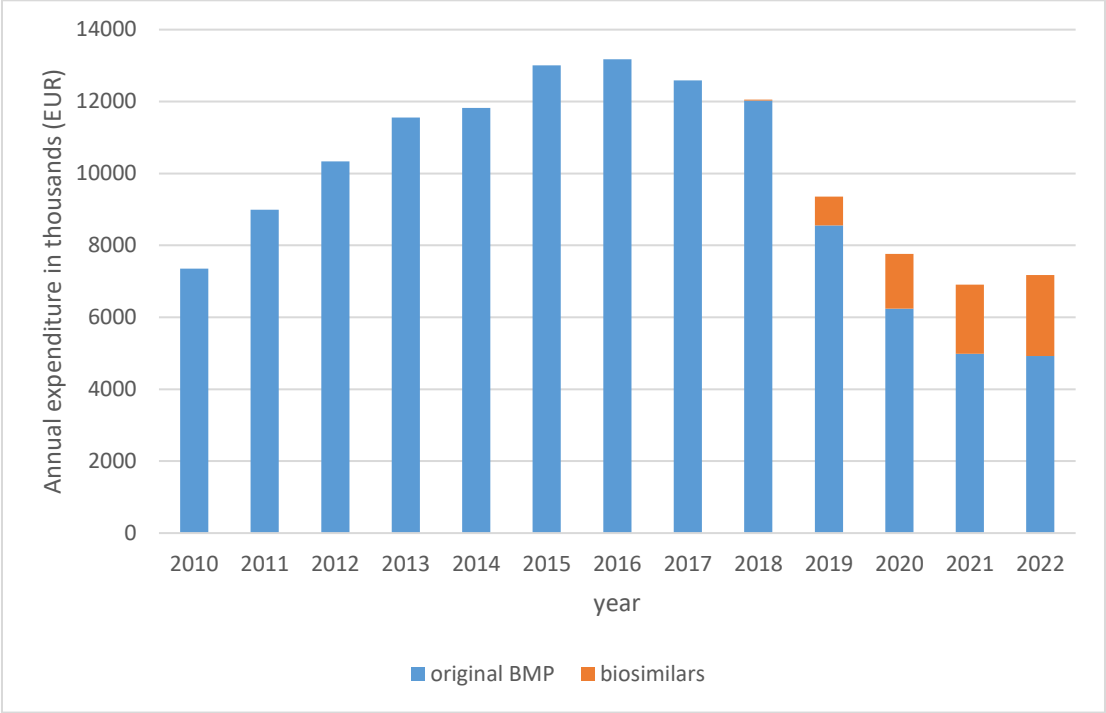


Figure 2: Annual public expenditure on original BMP and BSs with adalimumab in the period 2010-2022 in Slovenia.

The aim of our Quick Check Policy Brief was to evaluate the effect of market entry of BSs on the healthcare expenditure with the use of the EURIPID database. Based on this database, we planned to explore the price changes of original BMP and BSs with adalimumab on Slovenian market compared to other EURIPID markets, understand the dynamic of price decreases of these BMPs, and to identify the countries with lowest wholesale prices and earliest price drops in original BMP and BSs after market entries of new BSs.

3. Methods/study design

3.1. Data sources

Data source for list prices of relevant BMPs across EU countries: EURIPID database (<https://database.euripid.eu/>).

Data source for authorized BMPs containing adalimumab 40 mg: European Medicines Agency (EMA; <https://www.ema.europa.eu/en/homepage>).

3.2. Search strategy

Using EURIPID, 13 active substances with BS list price availability were identified in Slovenia. Adalimumab 40 mg was selected for analysis as the most representative example due to its long-term market access, therapeutic importance, large sales volume, application in out-patient setting, long-term usage as well as high number of available BSs.

A search in the EMA's medicines for human use for "adalimumab" returned one original BMP (Humira) and 16 BSs. Out of 16 BSs, 10 had a valid marketing authorization on October 17th, 2023 (Amgevita, Amsparity, Hefiya, Hukyndra, Hulio, Hyrimoz, Idacio, Imraldi, Libmyris, Yuflyma), 5 marketing authorisations were withdrawn (for Cyltezo, Halimatoz, Kromeza, Solymbic and Trudexa), and 1 application was withdrawn (for Fyzoclad).

For the data retrieval in the EURIPID database, the **Graphs "Price Evolution"** tool was used with the search criteria listed in Table 1.

Table 1: Search criteria used in the Graphs Price Evolution tool.

Route of Administration	All
INN & strength	adalimumab 40 mg
Status	All
Product name (added search field)	Individual BMP name
Price type	wholesale unit price
Graph type	Line chart
Axys Y	start from 0
Show calculated prices	Yes
Resolution	90 days
Min or max price	Minimum
Currency exchange	non-fixed
Country	All but Albania, Israel, Switzerland and United Kingdom
Date 1	01-07-2010
Date 2	30-11-2023
Exported on	22-12-2023

The data was gathered for the period from July 1st, 2010 (first data availability in the EURIPID database) till November 30th 2023. Due to long time-period analysed (13 years), non-fixed currency exchange rate was selected as changes in these rates could influence the prices at the time of analysis. There is no single price type that would be available for all countries in the EURIPID database. For the analysis, wholesale unit price was selected as it was available for the largest number of countries (21 countries, of which it is calculated for 3 countries automatically in the database – BE, EE, LT), just as is the case with gross retail price, but includes less additional costs to the manufacturer’s unit price and was therefore deemed to better represent the developments on the manufacturer level and exclude any potential changes in pharmacy mark-ups and/or margins. The wholesale unit prices are not available for Czech Republic, France, Italy, Portugal, and Spain, that were subsequently excluded from the analysis.

Search was performed for each BMP individually (‘Product name’ search field was modified in each search). Price data was available for the original BMP Humira and 9 BSs (Amgevita, Halimatoz, Hefiya, Hukyndra, Hulio, Hyrimoz, Idacio, Imraldi, Yuflyma). The data was not available for 2 authorised BSs (Amsparity, Libmyris).

3.3. Tool of collecting, modelling, and analysing searched data

The individual search results were exported as numeric data in Microsoft Excel® and downloaded as a picture in .png format. The individual exports were merged in Microsoft Access® and re-exported as a Microsoft Excel® document, where subsequent calculations and visualization were conducted.

Number of records identified using the search strategy described above: 3,052. Of these, 685 records that reported the price value of 0 were discarded. Of the remaining 2,367 records, additional one was discarded as deemed a mistake (price of Humira in Iceland on June 5th, 2015, in the amount of 0.42 EUR).

3.4. Method of analysis

Following search criteria described in Table 1, 10 datasets (Humira, Amgevita, Halimatoz, Hefiya, Hukyndra, Hulio, Hyrimoz, Idacio, Imraldi, Yuflyma) have been exported from the EURIPID database and merged into a new Microsoft Excel® file.

To analyse minimum wholesale unit prices of original BMP, the lowest and the highest minimum wholesale prices were identified at each timepoint and average minimum wholesale prices were calculated based on original BMP price data. To analyse minimum wholesale unit prices of BSs, the lowest and the highest minimum wholesale prices were identified at each timepoint regardless of the trade name of BS. The average minimum wholesale price took into account all prices of all BSs at each timepoint. There was no data available on prices of BSs in RO and LT, therefore these two countries were excluded from the analysis.

Analysing the impact of BSs' market entries to the prices of original BMP and BSs, the price decrease of original BMP before BSs market entry was calculated between the first reported price and the price reported 2 timepoints before 1st BS market entry. The price decrease of original BMP after BSs market entry was calculated between 1 timepoint before 1st BS market entry and the last reported price. Price decrease of original BMP after 1st BS market entry was calculated from the difference between price 1

timepoint before market entry and 2 timepoints after market entry and captured a period of up to one year. Similarly, price decrease of 1st BS after 2nd and 3rd BS market entry was calculated from the difference between lowest BS's price 1 timepoint before market entry and 2 timepoints after market entry and captured a period of approximately one year. Due to the lack of data, the price changes of original BMP and BSs after new BSs market entries were not calculated for NL.

3.5. Limitations

There exists no single price type that would be available for all countries in EURIPID database resulting in omission of 5 EURIPID countries from the analysis. Additionally, list prices are not representative of actual prices due to increased usage of managed entry agreements (MEAs) and lower prices being achieved through tendering processes. In the EURIPID database, only the information on the existence of MEA is accessible, with further data available only on reciprocity principles. Similarly, the data on sales volumes are not available throughout the whole observed period and for all relevant countries. Minimum wholesale unit prices were used as surrogate data for the analysis of potential savings and budget impact of price changes. No national pricing policies were considered (eg. obligatory price reductions of original BMP after BS's market entry).

4. Results

a) Overview of available biosimilars

The price of original BMP was first published in EURIPID database in September 2010. In most countries, the prices of original BMP were published till 2013, with a few exceptions in 2018 and 2019 (LT, EE). While original BMP with adalimumab 40 mg has a price available in all countries, BSs have a reported price in 19 out of 21 countries. The number of BSs ranges from 2 to 9 with LT and RO without any reported data on BSs' prices. First BSs obtained prices in the second half of 2018 (HU, IE, DK, SI, BE, BG, NL, HR) and by the end of 2019 biosimilars had reported prices in all countries but CY, NO, RO and LT (Table 2).

Table 2: Overview of EURIPID database first price data extraction point of original BMP and BSs with adalimumab 40 mg in European countries.

	Original BMP	No. of BSs	Biosimilar 1		Biosimilar 2		Biosimilar 3		Biosimilar 4		Biosimilar 5		Biosimilar 6	
	Date ^a		Date ^a	Name ^b	Date ^a	Name ^b	Date ^a	Name ^b	Date ^a	Name ^b	Date ^a	Name ^b	Date ^a	Name ^b
Austria	29.09.2010	7	15.05.2019	Amgevita Hulio Imraldi	13.08.2019	Hyrimoz	11.11.2019	Idacio	29.04.2022	Yuflyma	24.01.2023	Hukyndra		
Finland	29.09.2010	7	14.02.2019	Amgevita Hulio Hyrimoz	09.02.2020	Idacio	03.02.2021	Imraldi	31.10.2021	Yuflyma	28.07.2022	Hukyndra		
Hungary	29.09.2010	6	16.11.2018	Amgevita Hyrimoz	14.02.2019	Hulio	15.05.2019	Idacio	02.08.2021	Yuflyma	21.10.2023	Hukyndra		
Cyprus	28.12.2010	5	09.02.2020	Amgevita Hyrimoz Idacio Imraldi	29.01.2022	Yuflyma								
Ireland	28.12.2010	7	16.11.2018	Amgevita Hulio Imraldi	09.02.2020	Idacio	29.01.2022	Yuflyma	28.07.2022	Hyrimoz	23.07.2023	Hukyndra		
Denmark	28.03.2011	3	16.11.2018	Amgevita Imraldi	14.02.2019	Hyrimoz								
Norway	26.06.2011	2	09.02.2020	Hyrimoz	29.01.2022	Imraldi								
Iceland	24.09.2011	5	15.05.2019	Imraldi	07.08.2020	Amgevita Idacio	24.01.2023	Hyrimoz	24.04.2023	Yuflyma				
Slovenia	23.12.2011	7	16.11.2018	Amgevita	14.02.2019	Hulio Hyrimoz	11.11.2019	Idacio	02.08.2021	Imraldi	29.01.2022	Hukyndra	28.07.2022	Yuflyma
Sweden	23.12.2011	6	14.02.2019	Amgevita Hulio Hyrimoz Imraldi	11.11.2019	Idacio	29.04.2022	Hukyndra						
Latvia	22.03.2012	4	15.05.2019	Hyrimoz	26.10.2022	Hukyndra Idacio	24.01.2023	Yuflyma						
Slovakia	22.03.2012	6	14.02.2019	Hulio Hyrimoz	11.11.2019	Idacio	15.05.2019	Amgevita	02.08.2021	Yuflyma	29.04.2022	Hukyndra		
Greece	20.06.2012	9	14.02.2019	Amgevita Halimatoz Hefiya Hyrimoz	09.05.2020	Hulio Imraldi	07.08.2020	Idacio	29.04.2022	Yuflyma	28.07.2022	Hukyndra		

	Original BMP	No. of BSs	Biosimilar 1		Biosimilar 2		Biosimilar 3		Biosimilar 4		Biosimilar 5		Biosimilar 6	
Belgium	18.09.2012	7	16.11.2018	Amgevita Imraldi	14.02.2019	Hulio Hyrimoz	11.11.2019	Idacio	31.10.2021	Yuflyma	29.04.2022	Hukyndra		
Poland	18.09.2012	5	14.02.2019	Imraldi	15.05.2019	Amgevita Hyrimoz	09.05.2020	Idacio	23.07.2023	Yuflyma				
Bulgaria	17.03.2013	5	16.11.2018	Amgevita	15.05.2019	Hulio Hyrimoz	02.08.2021	Yuflyma	28.07.2022	Hukyndra				
Netherlands	17.03.2013	7	16.11.2018	Imraldi	15.05.2019	Amgevita	04.05.2021	Hulio Hyrimoz Idacio Yuflyma	26.10.2022	Hukyndra				
Romania	12.12.2013	0												
Croatia	26.11.2016	6	18.08.2018	Amgevita	14.02.2019	Hulio Hyrimoz Imraldi	13.08.2019	Idacio	28.07.2022	Hukyndra				
Lithuania	20.05.2018	0												
Estonia	13.08.2019	4	13.08.2019	Amgevita Hyrimoz	09.05.2020	Idacio	29.04.2022	Hukyndra						

^a It refers to the date of first price data extraction point from EURIPID database in the period from 1st July 2010 till 30th Nov 2023 with 90 days intervals.

^b It refers to a trade name of medicinal product.

Abbreviations: BMP – biological medicinal product; BS – biosimilar

b) Analysis of minimum wholesale unit prices of original BMP

The analysis of minimum wholesale unit prices of original BMP (Figure 3) showed that the differences between highest and lowest minimum wholesale unit prices increase with time. The highest minimum wholesale unit prices were observed mostly in DK, LV and EE, whereas the lowest were found in HU, EL, RO, BG and HR. In Slovenia, the highest minimum wholesale unit price was below the average price throughout the observed period. A decreasing trend in the highest, lowest, and average minimum wholesale unit prices was observed.

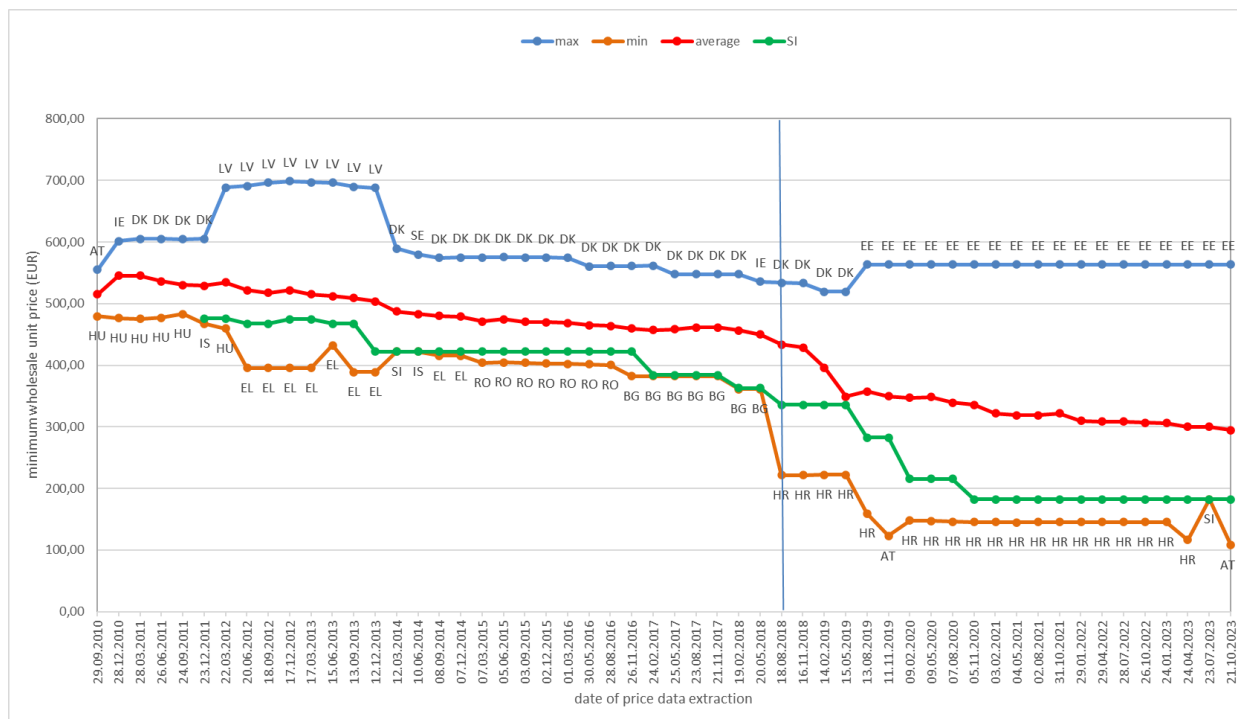


Figure 3: The highest, lowest, and average minimum wholesale unit prices of original BMP in European countries from Sept 29th 2010 till Oct 21st 2023. The vertical blue line marks the market entry date of first biosimilar in EURIPID country.

c) Analysis of minimum wholesale unit prices of BSs

The analysis of minimum wholesale unit prices of BSs (Figure 4) showed that the differences between highest and lowest minimum wholesale unit prices are substantial. Among highest prices, DK was in the lead with the highest minimum wholesale unit price until May 2022, replaced by NO and EE thereafter. Until Nov 2019, the lowest price was found in different countries, followed by a period of lowest prices observed in SE. In Slovenia, the highest minimum wholesale unit price was below the average price in most

of the observed period. A decreasing trend in maximum, minimum and average minimum wholesale unit prices was observed.

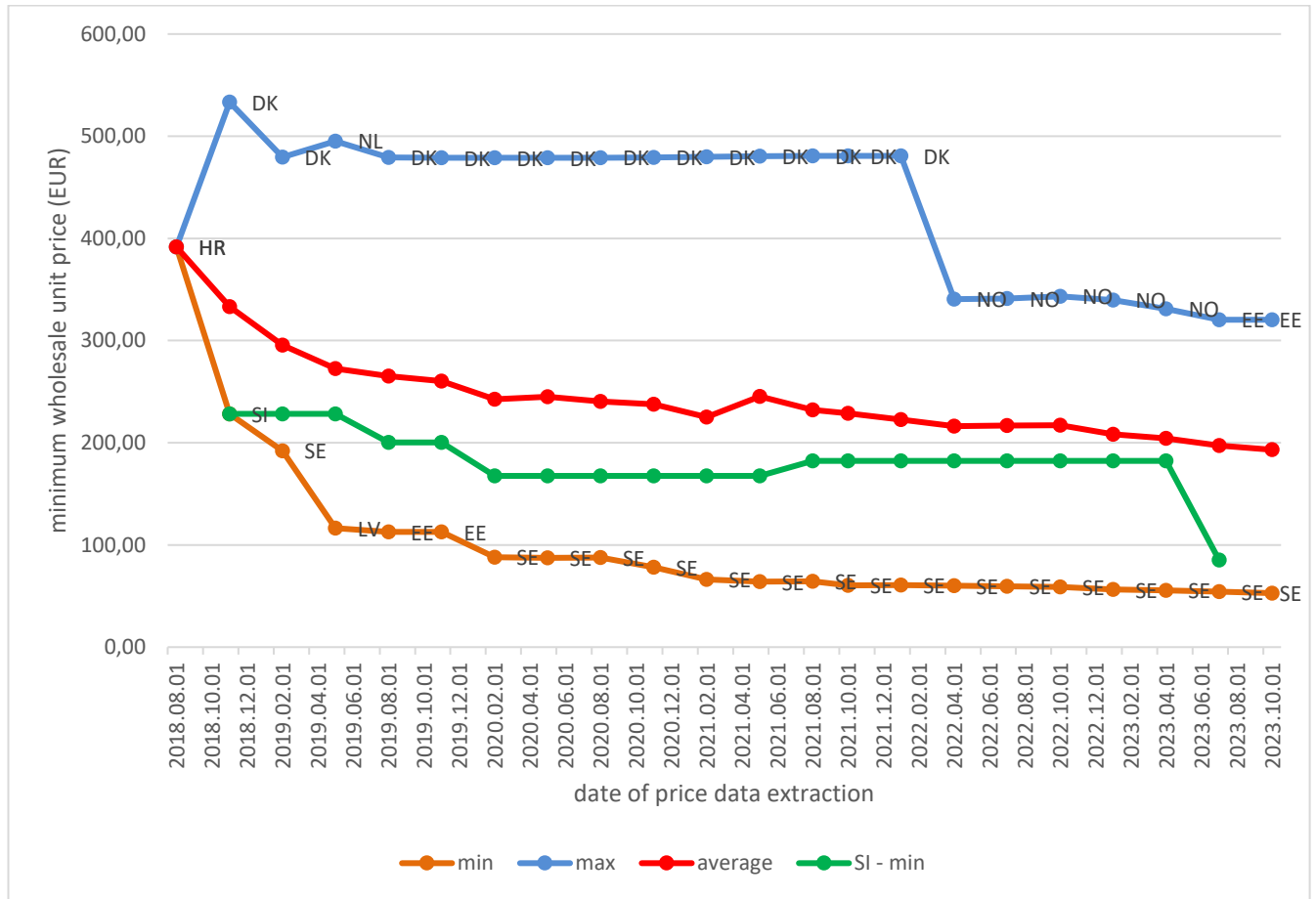


Figure 4: The highest, lowest, and average minimum wholesale unit prices of BSs in European countries and Slovenia from Aug 1st 2018 till Oct 1st 2023.

d) Analysis of original BMP price changes after market entry of BSs

The analysis of price changes of original BMP before and after market entry of first BSs (Figure 5) showed that the prices of original BMP decreased substantially more after the BS market entry than before in most of the countries. Before market entry of BSs, the prices of original BMP decreased for up to 25 % in 17 out of 19 countries except for LV where a more than 40% drop was seen. The prices of original BMP changed less than 3% in PL, NL, HR, and EE. In 14 out of 19 countries, market entry of BS was associated with the decrease of original BMP prices for 25% or more with 4 countries (AT, FI, BE, HR) experiencing a more than 50% price decrease. No original BMP price drop was seen in LV and EE. In Slovenia, a more substantial price

drops of original BMPs were observed after market entry of BSs, although the original BMP price drop was among highest also before BSs' market entries.

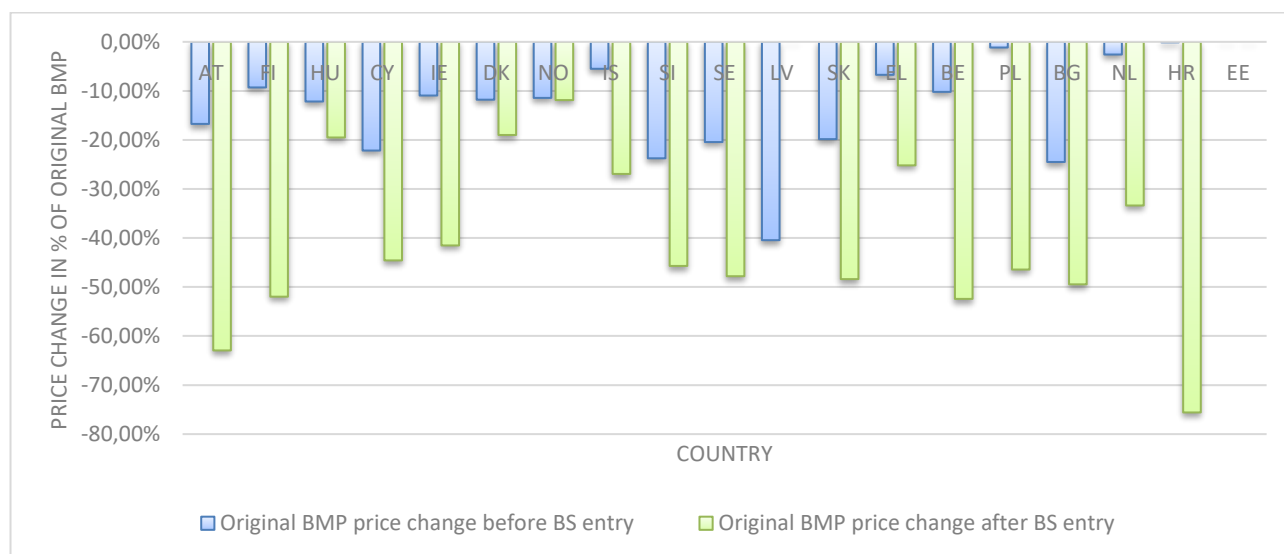


Figure 5: Price change in percentage of original BMP before and after market entry of BSs.

The analysis of price changes of original BMP after market entry of first, second and third group of BSs (Figure 6) showed that the prices of original BMP decreased most after the entry of the first group of BSs. In 5 out of 18 countries (CY, SI, LV, EL, EE), no original BMP price decrease was observed after market entry of 1st group of BS. After 2nd and 3rd BS market entry, a less profound decrease in original BMP prices was observed. A substantial decrease of 10% or more in original BMP prices was seen in 8 out of 18 countries (AT, FI, SI, SK, BE, PL, BG, and HR). Limited (less than 10% price reduction) or no effect on the prices of original BMP was seen in 7 out of 18 countries (HU, CY, DK, NO, LV, EL, EE). In Slovenia, no original BMP price decrease was seen after 1st BS market entry, followed by a substantial price decrease after 2nd and 3rd BS market entry.

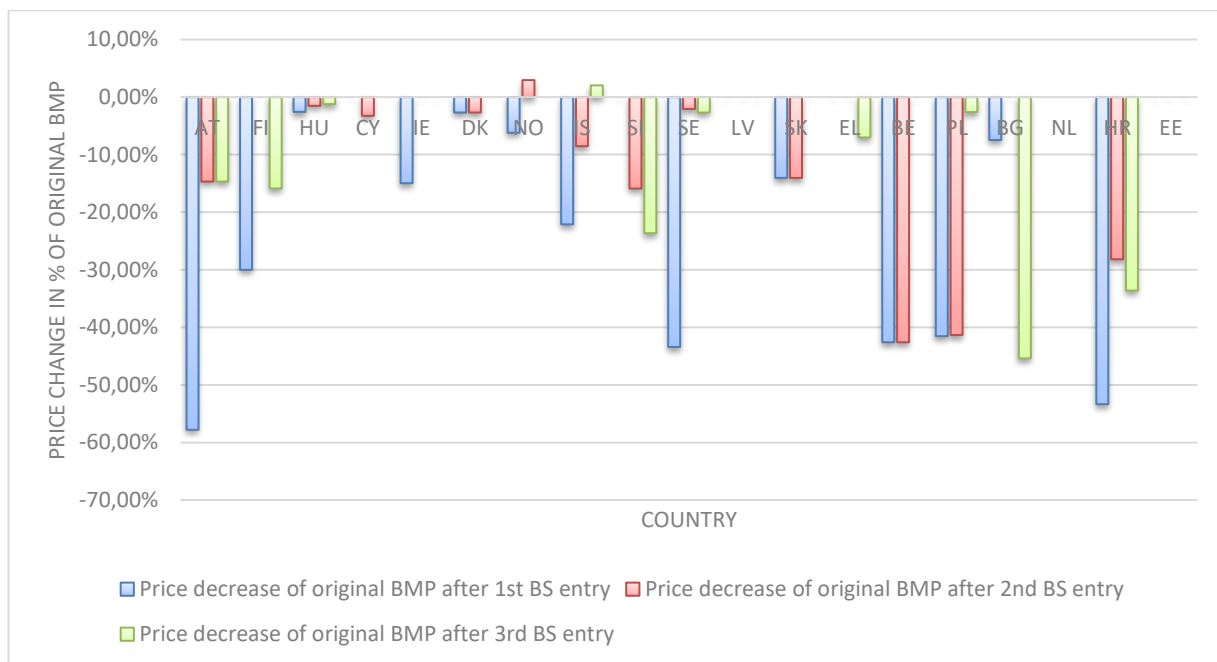


Figure 6: Price changes in percentage of original BMP after market entry of first, second and third group of BSs.

e) Analysis of BS's price changes after market entry of new BSs

The analysis of price changes of BSs after market entry of second and third group of BSs (Figure 7) showed that the prices of first group of BSs decreased after the entry of the second and third group of BSs, but the decrease was below 25% in most of the countries except BE. In 7 out of 18 countries (CY, SI, SE, SK, BE, BG, HR), a more than 10% decrease of price of already marketed BS was observed. However, limited (5% or less price reduction) or no effect on the prices of BSs was seen in 8 out of 18 countries (FI, HU, IE, NO, LV, EL, PL, EE).

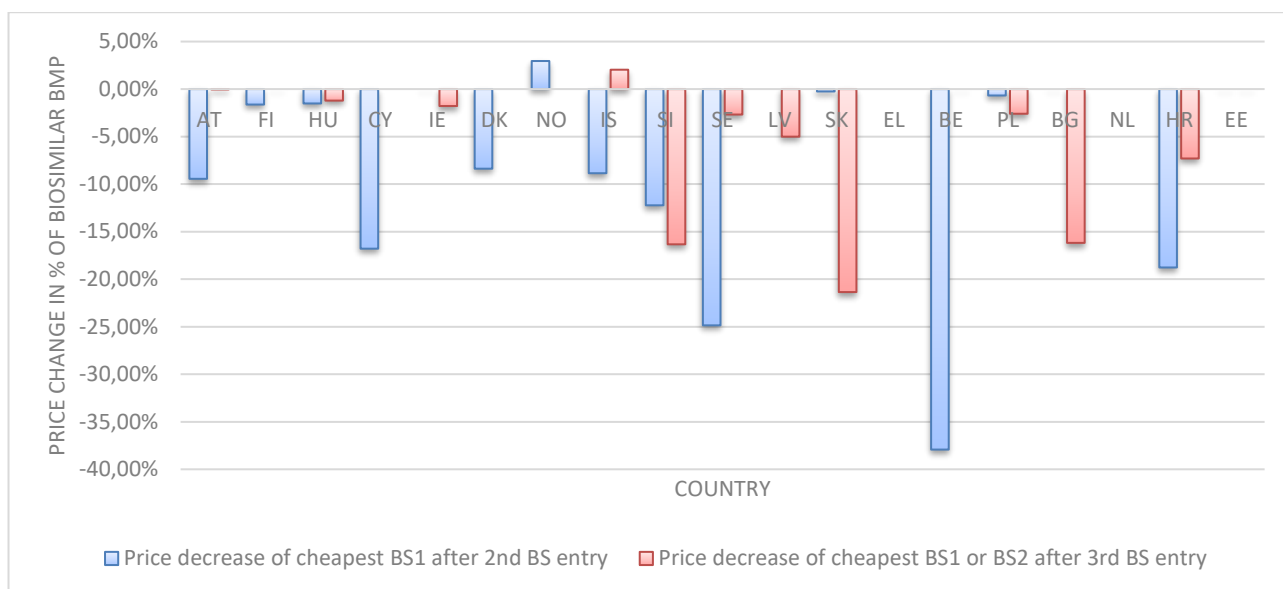


Figure 7: Price changes in percentage of the cheapest BS after market entry of second and third group of BSs.

5. Conclusions

a) General conclusions

There are considerable differences in availability of BSs measured by published list prices among EURIPID countries, ranging from none in LT and RO to as many as 9 in EL in the observed period. Interestingly, this does not seem to have a direct impact on the minimum wholesale unit price of either the original or the biosimilar MPs. The wholesale unit prices of original BMP have already declining trend before patent expiration that has been accelerated by the market entry of BSs. The effects of first and subsequent market entries of BSs on competitor prices is country dependant. A considerable difference in the minimum wholesale unit price of the original BMP and BSs remains.

Slovenia has been successful in decreasing the wholesale unit prices of both the original BMP as well as BSs. An above average number of BSs with adalimumab is available on the Slovenian market. Slovenia's original BMP price drops before and after BSs' market entries are in the medium to high range compared to other EURIPID countries and were more profound after 2nd and 3rd BS market entry. The impact of new BSs' market entries on BSs' prices is observed but limited. In Slovenia, the overall annual expenditures on adalimumab-

containing BMPs have been reduced since BSs market entry at the end of 2018 due to reduction of the price of original BMP and increased utilization of cheaper BSs.

b) Potential further analysis (optional)

As Slovenia has started to share volume information in late 2023, volume data could also be included in an updated analysis to better understand the budget impact of the introduction of BSs.

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7. Disclaimer

The views expressed in this publication are those of the author/s and should not be attributed to EURIPID COLLABORATION and/or its funders.

8. List of abbreviations

AT – Austria

BE – Belgium

BG – Bulgaria

BMP – biological medicinal product

BS - biosimilar

CY – Cyprus

DK – Denmark

EE – Estonia

EL – Greece

FI – Finland

HR – Croatia

HU – Hungary

IE – Ireland

LT – Lithuania

LV – Latvia

MEA – Managed Entry Agreement

MP – medicinal product

NL – Netherlands

PL – Poland

RO - Romania

SE – Sweden

SI - Slovenia

SK – Slovakia

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