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Recent changes on the biopharmaceutical market after the introduction of biosimilar G-CSF products

ABSTRACT

The biologic medicine market is the fastest growing segment of the global pharmaceutical market. However, the high price of biologic medicines is a challenge for the constrained budget of healthcare systems. The introduction of biosimilars — copies of therapeutic biologics — has ensured a high degree of competition on the market and consequently has expanded patient access to advanced therapies and has evolved the overall patient treatment costs. One of the first medicines that was approved in Europe *based on* the abbreviated registration process was a biosimilar version of filgrastim. In this review we investigate the impact of biosimilar G-CSF products on the market. The influence of the competition on the price change and the cost of therapy were analysed. Our findings reveal that the impact of biosimilars on the healthcare system is multi-factored and therefore difficult to predict. A competitive environment induces the price reduction even for second-generation products. However, at the same time, no correlation between the biosimilar market share and the discount was noticed. It seems that the observed changes reflect the mix of economic conditions including the situation on the national market before introduction of biosimilars, local adoption of treatment practices influenced by the pricing system, and the payer's decision on drug reimbursement.

Key words: filgrastim, biosimilar medicine, G-CSF, oncology, G-CSF market

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Introduction

Annual global spending on biologic medicines is expected to account for more than \$200 billion in 2016 [1]. This segment of the pharmaceutical market is continuously growing as many companies perceive their future in biologics. In 2014, five from ten top-selling pharmaceuticals were biologics [2]. The high price of biologic medicines is a challenge for the constrained budget of healthcare systems, though. The average daily cost of a biologic is about 20 times higher than a small-molecule drug [3]. The introduction of biosimilars has ensured a high degree of competition on the market and consequently has expanded patient access to advanced therapies and has evolved the overall patient treatment costs.

One of the first medicines that gained EMA approval *based on* the abbreviated registration process was a biosimilar version of filgrastim. Filgrastim is a recombinant granulocyte colony-stimulating factor (G-CSF) that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream [4]. The drug is widely used to treat severe chronic neutropaenia (SCN), to prevent and accelerate the recovery from neutropaenia in patients with HIV or after chemotherapy, and to mobilise peripheral blood progenitor cells (PBPC).

For many years, the competition on the G-CSF market was very limited. Only two products, Neupogen® (INN filgrastim) and Neulasta® (INN PEG-filgrastim) — the long-acting analog, launched by one company — Amgen, captured almost the entire global market.

The main competitor, lenograstim (recombinant G-CSF produced in mammalian cells), did not play the significant role, reaching 5% of the market share in 2007 [5]. The situation changed noticeably in 2008, when biosimilar versions of filgrastim were launched in Europe, capturing about 80% of the market in 2014. The average price of the drug declined, in both the biosimilar/reference group (−19%) and in the whole product class (−28%), including the long-acting filgrastim analogs and lenograstim. Simultaneously, a drug uptake increase of about 100% was noticed [6]. However, these changes varied across European countries indicating that crucial factors driving biosimilar market performance played out differently across the national markets.

The purpose of this review was to assess the impact of the biosimilar G-CSF products on the market. Furthermore, the influence of the competition on the price changes and cost of the therapy was investigated. Parameters such as a change in average price, the biosimilar market share, and the uptake development were analysed. Our findings reveal that the impact of biosimilars on patient care and the healthcare system is multi-factored and therefore difficult to predict. A competitive environment induced price reduction even for the second-generation products. At the same time, no correlation between the biosimilar market share and the discount was noticed. It seems that the observed changes reflect the mix of economic conditions, including the situation on the national market before the introduction of biosimilars, local adoption of treatment practices influenced by the pricing system, and the payer's decision on drug reimbursement.

G-CSF market before introduction of biosimilars

In the early 1990s two recombinant G-CSF products appeared on the biopharmaceutical market. The first one, Neupogen® (INN: filgrastim), was launched by Amgen on the American and European market [7]. The second one, INN: lenograstim, appeared on the Asian market branded as Neutrogin® (Chagai Pharmaceuticals) and three years later on the European market as Granocyte (Chugai-Rhone-Poulenc) [8, 9]. Even though the structures of both products differ as a consequence of the production processes, lenograstim and filgrastim have been characterised as having the same mechanism of action and similar clinical characteristics [10].

Unlike filgrastim, which is manufactured in *E. coli* and is not glycosylated, lenograstim is produced in mammalian cells (CHO) and exhibits a glycosylation pattern similar to that in native G-CSF [11]. Is this difference crucial for the drug's efficiency and safety? Several *in*

vitro studies have shown that filgrastim has a lower affinity to the cell receptor G-CSFR than lenograstim and can alter the signal path, which leads to increased production of leucocytes with a disrupted morphology and mobility [11–14]. On the other hand, cumulative data from patients and healthy volunteers received in comparative clinical trials did not reveal significant differences in terms of such clinical parameters as the number of CD34+ cells, and demonstrated no clear reasons to prefer lenograstim over filgrastim in their approved indications [15–19].

The competitive G-CSF products appeared on the market at a similar time and were believed to be equally safe and effective. However, it was filgrastim that dominated the market. The global sale of Neupogen® was growing continuously and reached 1.3 billion dollars in 1999 [20]. There were several reasons for that. First of all, the marketing strategy. Filgrastim was distributed on the biggest world markets by two joint ventures: Krin-Amgen (America, Asia) and Amgen-La Roche (Europe). This business model allowed targeting of the marketing campaign precisely. Chugai Pharmaceutical, a producer of the competitive product, cooperated with numerous companies to distribute lenograstim in different regions. It could have distracted the marketing actions and caused lower sales. Secondly, Amgen could compete on the price as the DNA-derived technology based on *E. coli* cells is much cheaper than the lenograstim production based on mammalian cells [21]. It is a likely reason why glycosylated G-CSF was more expensive than filgrastim [22]. Moreover, several pharmacoeconomic analyses have shown that the price might be a crucial parameter in evaluating the G-CSF treatment strategy [23, 24]. Thirdly, and probably most importantly, lenograstim was not introduced on the American market, which has the largest share of biopharmaceutics sales [2].

The success of Neupogen and its domination on the market did not stop Amgen from further development. A long-acting filgrastim analog, PEG-filgrastim (Neulasta®), was approved in 2002 by the FDA and in 2005 by the EMA. Numerous pharmacoeconomic evaluations showed that PEG-filgrastim was more cost-effective than the therapy based on filgrastim, even when very low prices of filgrastim and high prices of PEG-filgrastim were assumed [25–28]. Therefore, Neulasta® became a new sales leader. In 2007, its sales accounted for 51% of the G-CSF market worldwide, which was worth of 5.6 billion dollars. The second position with a share of sales of 1.3 billion dollars (24%) was taken by Neupogen®. About 18% of the market belonged to products with filgrastim marketed under other brand names. At the same time, lenograstim sales accounted for only about 5% of the G-CSF market [5].

Table 1. A list of biosimilar G-CSF products with EMA approval

Brand name	Developed by	Marketing Authorisation Holder	Authorisation data
Tevagrastim®		Teva Genetics GmbH	
Ratiograstim®	BioGeneriX (Ratiopharm GmbH) and SICOR Biotech (Teva GmbH)	Ratiopharm GmbH	15.09.2008
		From 2010: Teva	
Biograstim®		AbZ-Pharma GmbH	
		From 2010: Teva	
Filgrastim Hexal®	Sandoz GmbH	Hexal AG	6.02.2009
Zarzio®		Sandoz GmbH	
Nivestim®	Pliva Croatia and Hospira Zagreb d.o.o.	Hospira UK Ltd.	8.06.2010
Grastofil®	Intas Biopharmaceuticals Ltd. and	Apotex Europe B.V.	18.10.2013
Accofil®	Apotex Nederland B.V.	Accord Healthcare Ltd	18.10.2014

Biosimilar filgrastim — regulatory aspects and development costs

From 2008 to 2015 the EMA approved eight biosimilar G-CSF products (INN: filgrastim) based on four independent dossiers (Table 1). For all of them Neupogen® was the reference product. To date, no biosimilar lenograstim has been introduced. In the US, the first competitor for Neupogen® appeared in 2012 when Teva gained FDA approval for Granix® (INN: tbo-filgrastim) according to the procedure for new biologics [29]. The first biosimilar G-CSF product, Zarzio® (INN: filgrastim-sndz), was approved by the FDA in 2015. The drug was introduced on the American market by Sandoz, one of the leading generic companies [30].

The main cost burden of biologics development rests on the clinical studies — the most expensive and risky stage. The EMA guidelines on similar medicinal products containing recombinant granulocyte-colony stimulating factor (CHMP/31329/05) provide two models for conducting clinical trials. The first one assumes the performance of comparative phases I and III studies. Phase I should test the pharmacokinetic and pharmacodynamic parameters of the biosimilar and a reference product in a single dose crossover study. The aim of phase III is to prove the safety of the drug and demonstrate its clinical comparability in a chemotherapy-induced neutropaenia study. The alternative model is possible under certain conditions and after consulting with EMA experts. It involves the extension of phase I to demonstrate the clinical comparability and reduction of the phase III role, which is treated as supportive. Questions remain if this approach is in accordance with the philosophy of biosimilar guidelines in the safety aspects and why the CHMP treats sponsors in an unequal way.

Two submissions of the biosimilar filgrastim approved by the EMA were based on comparative phase III studies: Teva/Ratiopharm's filgrastim and Pliva/Hospira's filgrastim. Teva/Ratiopharm performed

the widest set of exercises, which significantly exceeded the requirements, even in non-clinical aspects. In total, the sponsor conducted two comparative phase I studies that involved 200 healthy volunteers, and three comparative phase III studies encompassing 350 breast cancer patients, 240 lung cancer patients, and 92 non-Hodgkin lymphoma patients [31]. The reason for such extended studies was the sponsor's business strategy. The same data was later used by Teva to support the FDA submission for tbo-filgrastim [32]. Pliva/Hospira's filgrastim submission was supported by two comparative phase I studies that comprised 100 healthy volunteers, and one comparative phase III study involving 279 breast cancer patients [33]. Sandoz and Intas Biotech./Apotex were allowed to design an alternative model of clinical trial. Both sponsors conducted four comparative phase I studies that encompassed, respectively, 146 and 235 healthy volunteers, and one non-comparative phase III study that involved, respectively, 170 and 120 breast cancer patients [34, 35]. At this point, it is obvious that the expenses for developing the biosimilar filgrastims varied considerably. The average cost per patient is highest for phase III [36, 37], and this allows us to assume that the alternative models of clinical trials were more cost-effective for the sponsors.

Submission of the first and at this moment the only biosimilar filgrastim approved by the FDA, Zarzio® (filgrastim-sndz), was partially based on the same exercises that had supported the product of Sandoz in the European approval procedure. Analytical bridging tests comparing Zarzio®, UE-approved Neupogen®, and the US-licensed Neupogen® provided relevant information for acceptance of preclinical and clinical studies conducted with the UE-marketed reference product. However, Sandoz had to perform an additional, comparative phase III study with 218 breast cancer patients to prove biosimilarity in the efficiency and safety aspects between Zarzio® and the US-licensed Neupogen® [38]. Filgrastim-sndz received the license for all indications

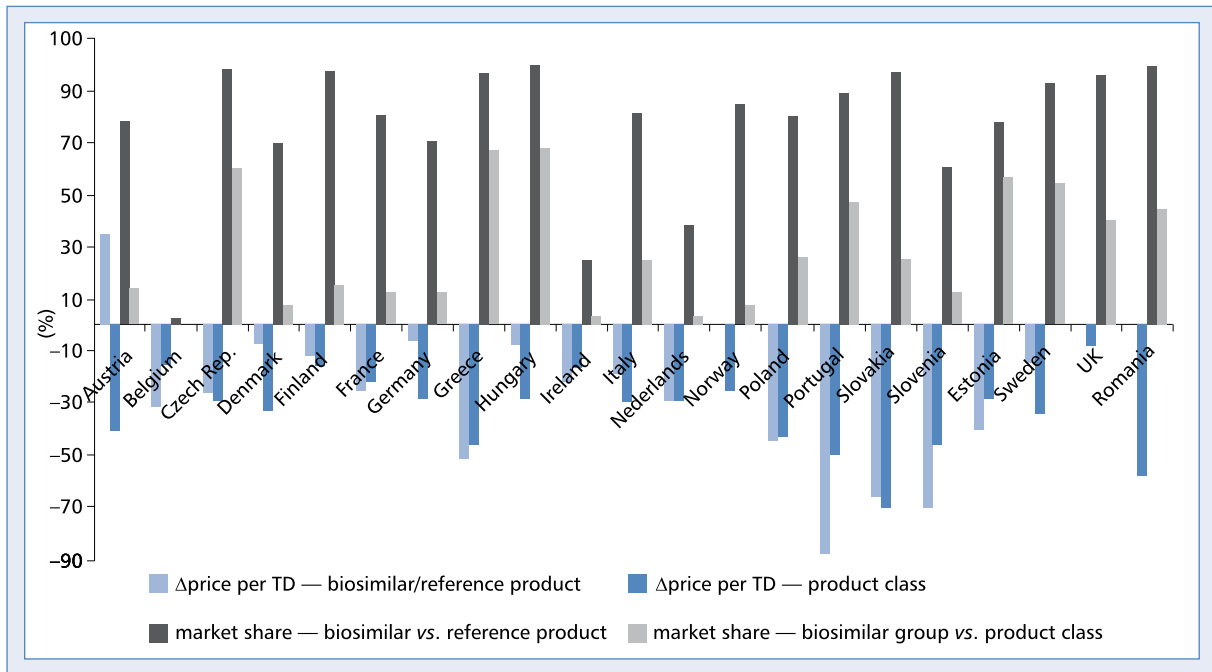


Figure 1. The biosimilar market share (in 2014) and the price reduction (2014/2007) in European countries. Prepared based on [6]. TD — treatment day

for which Neupogen[®] was approved in the US. In contrast, tbo-filgrastim, submission of which was supported by a wider set of preclinical and clinical studies, was approved for only one indication: to reduce chemotherapy-induced neutropaenia in patients with non-myeloid malignancies. Sandoz's development strategy seems to be the most cost-effective. It clearly shows that the development costs of biologics can be significantly limited in the procedure for biosimilars. However, some doubts remain in the safety aspects. In 1998, Neupogen[®] gained FDA approval for an additional indication (not approved in the EU): to reduce chemotherapy-induced neutropenia in patients with acute myeloid leukaemia (AML). Amgen had to prove the safety and efficiency of the product for this indication in a large phase III study with 400 enrolled patients [39]. In 2015, this indication was automatically extrapolated to Zarxio[®] without any additional study on patients with AML.

Competition for long-acting filgrastim (PEG-filgrastim)

The changes on the G-CSF market were not only involved with the introduction of biosimilar versions of filgrastim. In 2013, Teva launched in Europe a competitor for Neulasta[®]. Lipegfilgrastim, branded as Lonquex[®], gained EMA approval as a new biologic medicine [40]. Both competing products were produced by conjugation of a single PEG group to filgrastim. However, the sites and the PEGylation processes were different. Consequently,

the pharmacokinetic and pharmacodynamic profiles varied. Despite that, the comparative clinical trials showed no significant difference in the efficiency and safety of both competitors [41]. These results entailed that Amgen was more willing to compete with the price in Europe. In the US the FDA approval for Lonquex[®] was successfully blocked. However, the US patent protection for long-acting PEG-filgrastim expired in October of 2015 and the position of Neulasta[®] on the American market has been threatened because Amgen faces another rival. In December 2014 Apotex was accepted by the FDA filing an application for the biosimilar version of PEG-filgrastim [42].

Price change of G-CSF products

The price decrease was the most expected consequence of the introduction of biosimilars on the market. The evaluation from 2014 showed that the price of filgrastim was very easily affected by the competition. In Europe, from 2007 to 2014, the average price [expressed as price per treatment day (TD)] of a biosimilar/reference product was reduced by 19%. However, most surprising was the 28% reduction of the average price in the whole product class. That includes long-acting filgrastim analogs and lenograstim. On the other hand, no correlation between the biosimilar market share (expressed as treatment day per defined daily dose) and the price reduction was observed [6]. The comparison of these two parameters for each European country is depicted in Figure 1. The highest price reduction (more

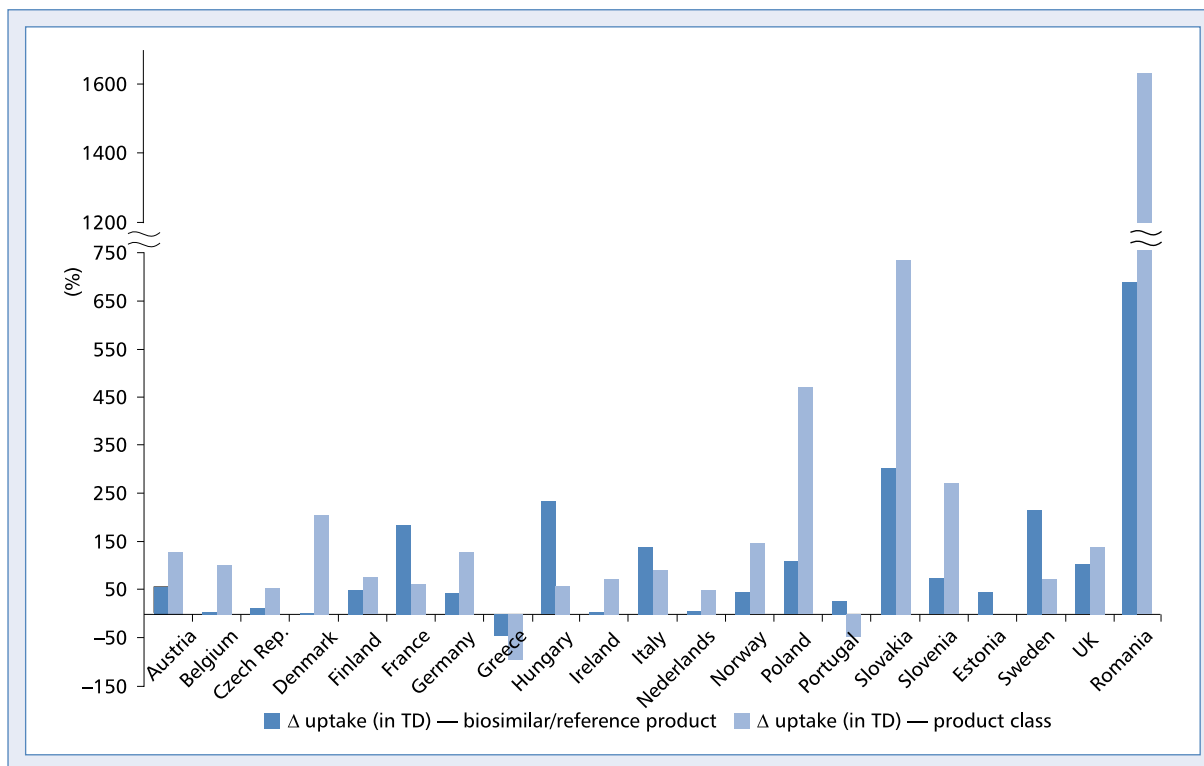


Figure 2. The uptake development in the biosimilar/reference group and in the whole product class (2014/year before biosimilar introduction) in European countries. Prepared based on [6]. TD — treatment day

than 40%) was observed in Portugal, Slovakia, Slovenia, Romania, Greece, and Poland. Moreover, for countries like Sweden, the UK, Norway, Italy, Hungary, Denmark, Germany, and Austria the discount in the whole product class was greater than for the biosimilar/reference group. The presented data clearly show that even the low share of biosimilars on the market had a significant impact on the price change, but the high share did not guarantee a large price decline. Such changes on the national markets were caused by the mix of several factors like the starting price, the refunding and pricing system of each country, and its economic condition.

The first competitor of Neupogen® in the United States, Granix®, was launched on the market in November of 2013. In the following year, it captured approximately 11% of short-acting G-CSF volume [43]. Teva offered its product with a 15% discount [44]. However, tbo-filgrastim, which has limited indication range, did not force Amgen into a price war. Perhaps a biosimilar, Zarixo®, which was launched in 2015, also with a 15% discount, will cause greater price evolution in the US.

Evolution of uptake of G-CSF products

The price reduction seemed to have a significant impact on the increased access to G-CSF products. How-

ever, the uptake development (expressed in treatment days) varied considerably across different European countries (Fig. 2). The most meaningful growth in the whole product class was observed in Romania (1621%), Slovakia (734%), Poland (474%), and Slovenia (272%). It can be assumed that the high price limited the uptake of G-CSF products in these countries. The competitive environment allowed fitting the price and effectively reducing the treatment costs. However, as presented in Figure 3, different uptake development in Romania, Slovakia, Poland, and Slovenia was caused by similar discounts. It seemed that other factors, such as the starting uptake, local adoption of treatment practices, and payer actions, affected the uptake increase. Probably, one of the most influential factors was a cost-sharing system that defined an apparent patient fee. In each country the systems combined several cost-sharing models that divided the overall cost of the medicine between the payer and the patient. For instance, Polish patients paid a lump sum fee or a percentage rate of the full price. In Slovenia, medicines were reimbursed by about 75% of the price by obligatory insurance and the rest was paid by voluntary insurance or by the patient. This could cause disproportion between the uptake development in Poland and Slovenia (Fig. 3).

The second interesting group of countries was Belgium, Czech, Denmark, Ireland, and the Netherlands,

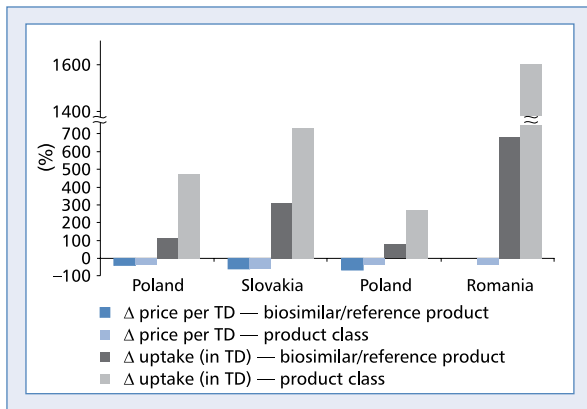


Figure 3. The price change and the uptake development in biosimilar/reference group and in the whole product class (2014/year before biosimilar introduction) in Poland, Slovakia, Slovenia, and Romania. Prepared based on [6]. TD — treatment day

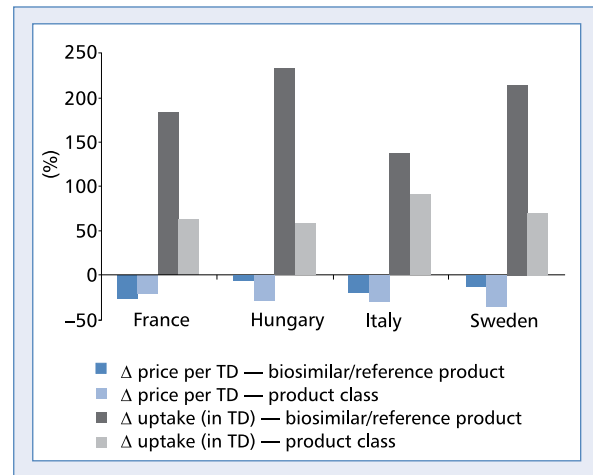


Figure 5. The price change and uptake development in the biosimilar/reference group and in the whole product class (2014/year before biosimilar introduction) in France, Hungary, Italy, and Sweden. Prepared based on [6]. TD — treatment day

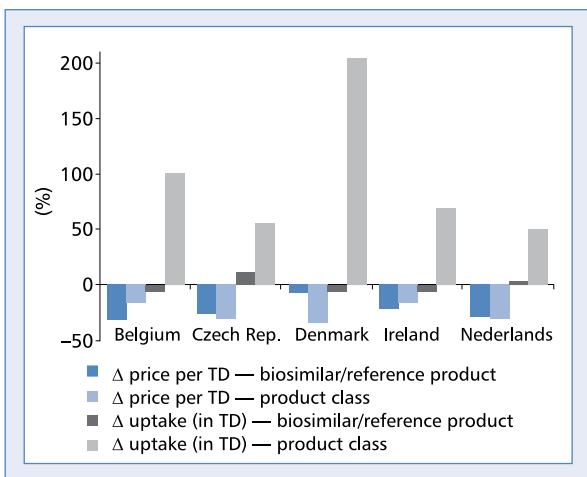


Figure 4. The price change and the uptake development in biosimilar/reference group and in the whole product class (2014/year before biosimilar introduction) in Belgium, the Czech Rep., Denmark, Ireland, and the Netherlands. Prepared based on [6]. TD — treatment day

for which the uptake in the whole product class rose significantly (50–200%), whereas a very low increase or even reduction of the uptake in the biosimilar/reference group was noticed (Fig. 4). These results indicate that under some circumstances competition in the biosimilar/reference group increases access to analog products. On the other hand, in France, Hungary, Italy, and Sweden the uptake development of biosimilar/reference products was significantly higher than in the whole product class (Fig. 5). These surprising findings are difficult to explain because the reimbursement systems of these countries are very different. However, they could

indicate that another factor, for example the habits of a particular physician or the local treatment procedures, affected the observed changes.

In some countries such as Portugal, Greece, and Spain, which struggled with economic crisis, uptake reduction or stagnation in the whole product class was observed. Uptake growth in the biosimilar/reference group was noticed in Portugal (27%) and Spain (47%), although in Greece, the most touched by crisis, the uptake decreased by 48% [6].

Treatment cost savings

The range of indications for G-CSF products has expanded greatly in recent years, e.g. as a support for high-dose chemotherapy or haematopoietic stem cell collection, which is increasingly widely used for transplant procedures especially in haematological malignancies. The price reduction and the following uptake increase meant that the overall cost of G-CSF products in Europe was higher in 2013 compared to 2006 (Fig. 6). The highest growth of spending was noticed in Romania (600%) and Poland (213%), and the lowest in the Czech Republic (3%) and Sweden (6%) [45]. These observations are surprising, but in fact they reflect the difference in the refunding system of each country. Payer decisions are based on the evaluation of the therapeutic strategy, which usually includes the therapeutic efficiency and the financial aspects. High growth of spending in some countries indicates that the refunding decision was focused on the medicine unit costs rather than a broader view that considers the full cost of medicine administration

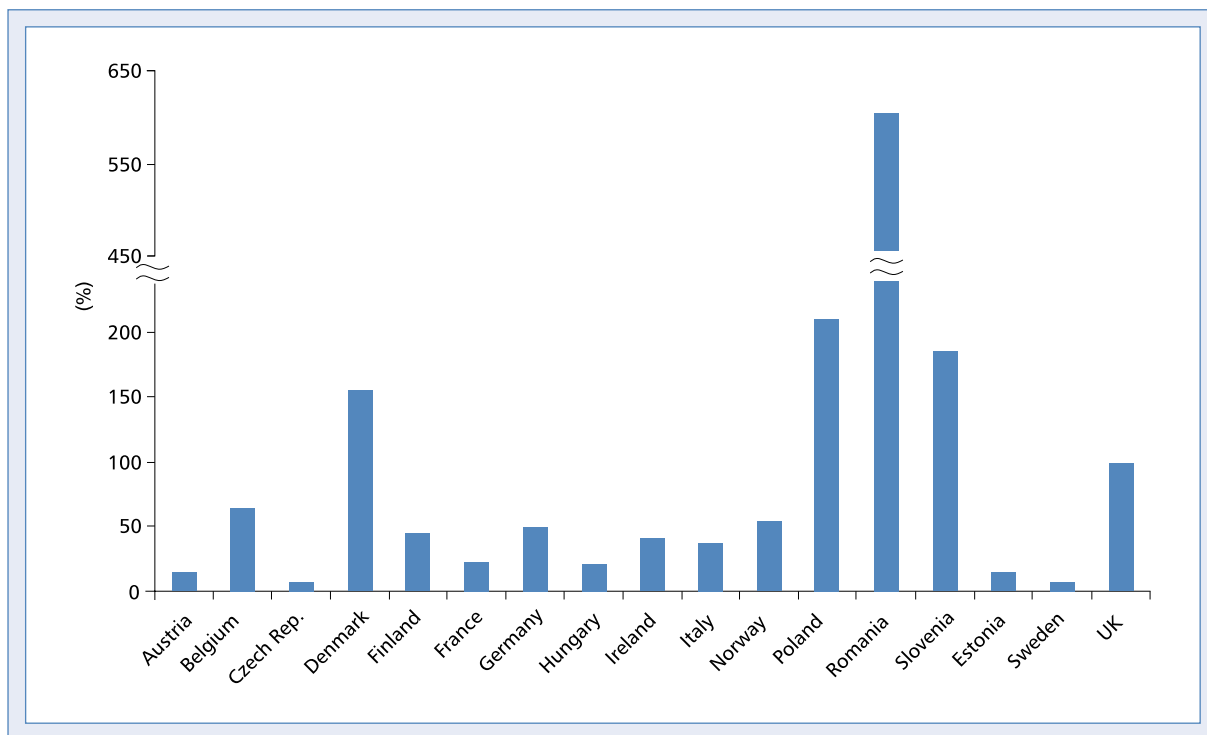


Figure 6. The change of the overall G-CSF products cost (2013/2006) in Europe. Prepared based on [45]

to patients. In the long perspective this approach could be risky. Especially when the prescription rules are insufficiently supervised by health authorities. On the one hand, the expanded range of indications for G-CSF products increases the patients access to the drug. However, on the other hand the high financial burden may overwhelm the payer budget and in turn lead to tightening of the reimbursement policy. The cases of the Czech Republic and Sweden clearly show that the payer making decision system was crucial to achieve balanced and cost-effective healthcare performance.

Summary

One of the first biosimilar medicines that was approved in Europe was filgrastim (*E. coli* recombinant G-CSF). This product has been widely used to treat and prevent chronic and induced neutropaenia. Before introduction of the biosimilars, the global market of G-CSF was captured by two products: short-acting filgrastim (Neupogen®) and long-acting PEG-filgrastim (Neulasta®). The situation changed between 2008 and 2014, when the EMA approved biosimilar versions of the filgrastim product. An abbreviated registration process allowed limitation of the development costs of biosimilars. However, the savings were not equal for all sponsors. The development strategy of Sandoz, which introduced its product in Europe (2008) and in the US

(2015) with an optimised set of exercises, turned out to be the most cost-effective.

The reduction of the development costs allowed price competition and caused the discount not only in the biosimilar/reference group, but also in the whole product class. On the other hand, the comparison of the biosimilar market share and the price reduction revealed that there is no correlation between these two parameters in European countries. Analysed data show that even a low share of biosimilars on the market had a significant impact on the price competition, but a high share did not guarantee a big price reduction.

The price reduction was the factor enhancing the uptake of the G-CSF products. However, the uptake development varied across European countries. The most meaningful growth was observed in Romania, Slovakia, Poland, and Slovenia. In Belgium, the Czech Republic, Denmark, Ireland, and the Netherlands the uptake in the whole product class rose significantly, whereas a very low increase or even reduction of the uptake in the biosimilar/reference group was noticed. On the other hand, in France, Hungary, Italy, and Sweden the uptake development in the biosimilar/reference group was significantly higher than in the whole product class. It seems that such changes in the national markets were caused by the mix of the starting price, the starting uptake, the refunding and pricing system of each country, and its economic condition.

Data analysed in this review showed that biosimilar introduction changed the market in an expected way. The price was reduced and access to the G-CSF products for patients was increased. The competition affected not only the biosimilar/reference group, but also the whole product class. However, these changes were positive also for pharmaceutical companies — the overall spendings on G-CSF products were higher in 2013 compared to 2006. The highest growth of spending was noticed in Romania (600%) and Poland (213%), the lowest in the Czech Republic (3%) and Sweden (6%). These differences indicate that in some countries the refunding decisions were focused on medicine unit costs rather than on the full cost of medicine administration to patients. It clearly shows that the payer making decision system was crucial to achieve balanced and cost-effective healthcare performance.

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