Biosimilars approved for psoriasis treatment in Europe

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ABSTRACT

In recent decades, biologics have emerged as pivotal components in the therapeutic armamentarium, revolutionizing the management of various diseases, including chronic inflammatory skin disorder, the psoriasis. Biosimilars, biological formulations designed to closely mimic but not replicate existing reference biologic drugs, have heralded a seismic shift in healthcare delivery, promising equitable access to innovative therapies while fostering competition in the pharmaceutical market. The advent of biosimilars has democratized access to effective treatments, alleviating the financial burden on healthcare systems and patients alike, particularly pertinent for conditions like psoriasis, notorious for their exorbitant treatment costs. However, despite their widespread adoption and significant promise, significant challenges remain, requiring ongoing research to comprehensively examine their clinical efficacy, safety profiles, and long-term outcomes. This review aims to present all the biosimilars approved so far in Europe. Biosimilars represent a transformative force in modern healthcare, but their optimal integration requires careful monitoring, robust pharmacovigilance mechanisms, and ongoing research initiatives to ensure patient safety, build trust among healthcare providers, and maximize treatment efficacy for individuals struggling with psoriasis and other chronic diseases.

Key words: biological products; biosimilar pharmaceuticals; psoriasis.

APSTRAKT

Poslednjih decenija, biološke terapije su se pojavile kao ključne komponente u terapijskom armamentarijumu, donoseći revolucionarne napretke u upravljanju različitim bolestim, uključujući hronični inflamatorni poremećaj kože, psorijazu. Biosimilari dizajnirani da blisko oponašaju, ali ne i replikiraju referentne biološke lekove, najavili su seizmičku promenu u pružanju zdravstvene zaštite, obećavajući jednak pristup inovativnim terapijama, uz podsticanje konkurencije na farmaceutskom tržištu. Pojava biosimilara je demokratizovala pristup efikasnim tretmanima, ublažavajući finansijski teret, kako za zdravstvene sisteme tako i za pacijente, posebno za stanja kao što je psorijaza, ozooglasišta po prevlekim tragovima lečenja. Međutim, uprkos njihovom širokom usvajanju i značajnim obećanjima, i dalje postoje značajni izazovi, kojima se sada odobrene biosimilare u Evropi, poznate gradiente u dosejanosti i efikasnosti, bezbednosni profil i dugoročni rezultati. Ogled pregleda ima cilj da prikaže sve do sada odobrene biosimilare u Evropi, kao i u Srbiji, posebno osvrtom na etičke principe primene biosimilara. Biosimilari predstavljaju transformativnu silu u savremenom zdravstvenom obrazovanju, ali njihova optimalna integracija zahteva pažljiv nadzor, robne mehanizme farmakovigilance i stalna istraživačka inicijative kako bi se osigurala bezbednost pacijenata, stvorilo poverenje među pružaocima zdravstvenih usluga i maksimizirala efikasnost lečenja kod pojedinaca, koji se bore sa psorijazom i drugim hroničnim bolestim.

Ključne reči: biološki proizvodi; biosimilar; psorijaza.
INTRODUCTION

The emergence of biological drugs and their use in the treatment of psoriasis has led to revolutionary treatment outcomes but also to a financial burden on both health systems and the patient himself. However, as biological drugs have lost their exclusivity, biosimilars have started to play a significant role in the market. Biosimilars are biological medicines with a high degree of similarity in terms of quality, efficacy and safety to an already approved reference medicine.1

The biosimilar approval process begins with drug development, continues to the preclinical phase, and moves on to clinical testing. Approval of biosimilars requires fewer clinical trials, thus reducing development costs. The requirements that are set in the development of this drug include comparative analyses that should answer whether the pharmacodynamic, pharmacokinetic, efficacy and immunogenicity of the product are similar to the reference biological drugs. The design used in the studies is the principle of equivalence, which should show that the differences between the groups of patients treated they are not clinically significant.2

The regulatory body in charge of marketing authorization for biosimilars in Europe is the European Medicines Agency (EMA), whose counterpart in the U.S. is the Food and Drug Administration (FDA). There are currently 17 biosimilars approved by the EMA for the treatment of psoriasis. Such a small number of biosimilars is explained by the fact that companies face intellectual property challenges when creating biosimilars, as well as the fact that patent protection for many biological drugs expired only a few years ago.3

The goal of the introduction of biosimilars is actually to enhance the availability of effective and safe treatments, and evidence from clinical practice demonstrates that biosimilars are effective and secure for all approved indications as well as reference biological medicines. The data also indicate that switching from reference drugs to biosimilars gives good therapeutic outcomes, as well as in the case of vice versa. However, it is emphasized that the interchange should be carried out with a comprehensive consideration of both the patient’s condition and the characteristics of the drug.4

This research aimed to systematically present biosimilar medicines approved by the EMA that are used in the treatment of psoriasis.

METHODS

For this review paper, a systematic search of electronic databases PubMed, NCBI and SCIndex was performed using a series of keywords. The combination of keywords included “psoriasis”, “biosimilar”, “efficacy”, “safety”, and “EMA”. Data was also collected from the official FDA and EMA websites to ensure comprehensiveness and accuracy of information. Additional articles were found through an ad hoc search and review of references in already identified papers. The selection of articles for inclusion was based on their relevance. This search method enabled the collection of relevant data and information necessary for the analysis of the review topic.

RESULTS

Adalimumab (Humira) is a fully human monoclonal antibody approved by the FDA in 2008 for moderate to severe psoriasis treatment. EMA je trenutno odobrila dest biosimilara koji će biti predstavljeni u nastavku. FDA approved biosimilar for adalimumab is Abrilada, Amjevita, Cyltezo, Hadlima, Huilio, Hyrimoz, Idacio, Yuflyma and Yusimry.5,6

ABP 501 (Amgevita) is the first approved biosimilar of Adalimumab for psoriasis treatment in Europe in 2017, while it was approved in the US a year earlier.6,8 It showed its comparability with the reference biological drug in a multicenter study, so the PASI (Psoriasis Area and Severity Index) score decreased by 80.9% after the initial phase of treatment, while with ref-ADA it decreased by 83.1%, which is considered satisfactory.6 Effectiveness and safety were confirmed in patients switching from a biological drug to a biosimilar, and no significant differences were found between originator-naïve patients and those undergoing a non-medical switch.6

PF-06410293 (Amsparity) is a biosimilar of Adalimumab that was approved by the EMA in 2020 and was approved by the FDA a year earlier under the name Abrilada.9,6. Studies show approximately equality of pharmacokinetic and pharmacodynamic properties between PF-06410293 and ref-ADA. In addition to proven efficacy, it was established that switching from Originator to PF-06410293 does not lead to a different therapeutic outcome and that biosimilar is an adequate replacement for Adalimumab.6

GP2017 (Hefiya) is a biosimilar approved in 2018 in the EU and USA. In the USA, GP2017 is produced under the name Hyrimoz, and in the EU, under the name Halimatoz and Hefiya. A study investigating the effects of switching from GP2017 to ref-ADA showed that after 51 weeks, the PASI75 score was achieved in 66.8% for the biosimilar group and 65% for the ref-ADA. In the study, multiple switching was performed, but this did not affect the final effects of the treatment.10

AVT02 (Hukyndra’/Libmyris) is another Adalimumab biosimilar. Clinical similarity assessments study showed that the safety profile is comparable to ref-ADA, as well as that there was an improvement in the clinical picture, i.e. a reduction in the PASI score of 89.2% in patients who were treated with the biosimilar, while the percentage of PASI score reduction in ref-ADA was 86.2%.11 Similar data were obtained in a double-blind, randomized study where, after the initial phase of treatment, the percentage of PASI score reduction in the AVT02...
group was 91.6%, and in the reference drug group 89.6%12.

FKB327 (Hulio®) has a highly similar structure and biological activity to Adalimumab and was approved for use by the EMA in 2018 (GaBi EU). Pharmacodynamic, pharmacokinetic, efficacy and immunogenicity was shown to be comparable to ref-ADA13.

MSB11022 (Idacio®) was approved for use in 2019 by the EMA. A double-blind clinical study comparing the effects of treatment with MSB11022 versus ref-ADA showed high levels of similarity, so after the initial phase of treatment, the PASI75 score in the MSB11022 group was achieved by 89.6% of patients, and in the ref-ADA group by 91.5%. Also, this research showed that no clinically significant differences in immunogenicity and safety exist14.

SB5 (Imraldi®) is a biosimilar of adalimumab used to treat psoriasis in adults and children over four years of age. It was approved by the EMA in 2017, and numerous studies have shown that pharmacokinetic, pharmacodynamic characteristics and immunogenicity are comparable to the original drug15,16.

CT-P17 (Yuflyma®) is a biosimilar of adalimumab that the EMA approved for psoriasis treatment in 2021, while it was approved by the FDA in 20235,6. This drug's pharmacokinetics safety and immunogenicity proved to be equivalent to the reference originator17.

Etanercept (Enbrel®) is a dimeric soluble fusion protein whose role is to prevent the interaction of TNFα with pro-inflammatory cytokines. Enbrel was approved for psoriasis treatment by the EMA in 1999, while the FDA approved Enbrel five years later18. When it comes to Etanercept biosimilars approved by the EMA, they are Benepalı, Erelezi, and Nepexto, while Erelezi and Eticovo are currently approved in the USA by the FDA19.

SB4 (Benepalı) presents a biosimilar for Etanercept, which was approved by the EMA in January 2016 and the FDA in April 2019 under a different name-Eticovo. In preclinical studies, SB4 showed equivalent results as its originator, with even less unwanted immunogenicity potential20. Comparable pharmacokinetic and pharmacodynamic properties with ref-ETN have been proven, and SB4 represents a favourable option for the treatment of psoriasis21. Also, real-world evidence from an extensive study in Denmark shows that switching from originator to SB4 leads to similar outcomes after three months. The authors also suggest that in the long term, differences between SB4 and ref-ETN outcomes depend more on patient profile and non-specific drug effects than on the type of applied therapies22.

GP2015 (Erelzi®) is also a biosimilar of Etanercept, approved by the EMA in June 2017, while it was approved by the FDA a little earlier in August 2016. It is indicated for the treatment of adults with plaque psoriasis who have not had an adequate therapeutic response to previous systemic therapy, as well as for the treatment of children over six years of age with more severe forms of psoriasis23. Research confirms that there are no differences in the effectiveness of therapy when switching from Etanercept originator to GP2015, as well as that there were no clinically significant differences observed in safety or immunogenicity24.

YLB113 (Nepexto®) is the latest biosimilar of Etanercept, which was approved in the EU in 2020. Indications for use of YLB113 are the same as for GP2015. There are currently no available real-life studies that examine the use of this biosimilar for the treatment of psoriasis, most research is focused on its use in the treatment of Rheumatoid Arthritis. However, those studies showed comparable efficacy and safety profiles with ref-ETN25,26.

Infliximab (Remicade®) is a chimeric IgGκ monoclonal antibody, and the mechanism of action is reflected in the neutralization of the biological activity of TNFα. Remicade received initial marketing approval by EMA in August 1999, just a year after FDA approval. Nowadays, in Europe for use is approved four biosimilars of Infliximab, and four biosimilars have been approved in the US, namely Avsola, Ixifi, Renflexis and Inflectra27,28.

SB2 (Flixabi®) is a biosimilar to infliximab, which has been used since May 2016 for several immune-mediated diseases, including psoriasis. Switching from ref-IFX to SB2 did not show a reduced response to therapy, nor did it cause any side effects not previously reported with ref-IFX29. Additionally, a study focusing on safety and efficacy in Post-Marketing Surveillance demonstrated that the treatment success rate was 94.6% for IFX-naive patients and 82.4% for patients previously receiving Infliximab30. Contrary to this, a case of exacerbation of psoriasis was reported after six years in a patient with Crohn’s disease when switching to SB2. After returning to the original drug, more precisely CT-P13, the lesions significantly receded in a short period31. Those data emphasize the need for more extensive and long-term research for biosimilars to reach their full potential.

CT-P13 (Remsima®, Inflectra®) is a biosimilar of Infliximab, which gained its initial approval for treating psoriasis from the EMA back in September 2013. Consequently, this represents a pioneering instance where the European Union has extended such an endorsement to a biosimilar monoclonal antibody32. A study conducted in Norway across 24 healthcare centers showed that switching from the originator Infliximab to the biosimilar CT-P13 did not result in inferior outcomes. The drugs exhibited a similar profile in terms of efficacy and adverse effects33. This finding is consistent with another study from Brazil34 that followed patients for one year, as well as from Japan35, where CT-P13 proved to be excellent as first-line therapy, even in patients who had failed other biologics.

PF-06438179/GP1111 (Zessly®) is another biosimilar of in-
fliximab used in the treatment of severe to moderate psoriasis as a systemic agent and in cases where previous therapies have failed. It was approved for use by the EMA in May 2018. The demonstrated pharmacokinetic and pharmacodynamic similarity between PF-06438179/GP1111 and ref-IFX justifies the scientific validity of using PF-06438179/GP1111 in all clinical indications of ref-IFX.36

Ustekinumab (Stelara) is an IL-12/IL-23 inhibitor used in the psoriasis treatment. It is a fully human monoclonal antibody that specifically binds to the p40 subunit of IL-12 and IL-23 and inhibits their binding to receptors, reducing their activity and thus alleviating the inflammatory response. Stelara was approved by the EMA and FDA in 2009, and since then has proven its efficacy and favourable safety profile in numerous studies37,38. In the US, the only biosimilar for ref-UST was registered in October 2023 under the name Wezlanâ, while in the EU, the first biosimilar received its initial approval by EMA in 2024.39

AVT04 (Uspruvo) was authorized by the EMA in January 2024 as a biosimilar of Ustekinumab. It is the newest and currently the only biosimilar of ref-UST approved for psoriasis treatment in the EU. Uspruvo has demonstrated its effectiveness, with the PASI score being reduced by approximately 87% after the initial phase of treatment, similar to the results observed in the Stelara group. Therefore, since the AVT04 has just been approved, more studies are needed to evaluate its safety and efficacy in post-marketing surveillance.

Table 1. Biosimilars approved in Europe

<table>
<thead>
<tr>
<th>Originator</th>
<th>Biosimilar</th>
<th>Manufacturer</th>
<th>Authorized</th>
<th>Conducted studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgevita (Adalimumab)</td>
<td>Amgen</td>
<td>Mar 2017</td>
<td>Papp et al. 2017; Giunta et al. 202140</td>
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<tr>
<td>Amsparity</td>
<td>Pfizer</td>
<td>Feb 2020</td>
<td>Gerzi et al. 202041</td>
<td></td>
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<tr>
<td>Hefiya</td>
<td>Sandoz</td>
<td>Jul 2018</td>
<td>Blauvelt et al. 201842</td>
<td></td>
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<tr>
<td>Hukynda Libmyris</td>
<td>Alvotech-Stada</td>
<td>Nov 2021</td>
<td>Wynne et al. 202243</td>
<td></td>
</tr>
<tr>
<td>Hulio</td>
<td>Mylan-Fujifilm</td>
<td>Sep 2018</td>
<td>Genovese et al. 201944</td>
<td></td>
</tr>
<tr>
<td>Idacio</td>
<td>Fresenius Kabi</td>
<td>Apr 2019</td>
<td>Hercogova et al. 202045</td>
<td></td>
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<tr>
<td>Infranavi</td>
<td>Samsung Bioepis</td>
<td>Aug 2017</td>
<td>Prignano et al. 202146, Barker et al. 202047</td>
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<tr>
<td>Yufyima</td>
<td>Celltrion Healthica</td>
<td>Feb 2021</td>
<td>Hanaoka et al. 202348</td>
<td></td>
</tr>
<tr>
<td>Benepali</td>
<td>Samsung Bioepis</td>
<td>Jan 2016</td>
<td>Cho et al. 201649, Girnborg et al. 201950</td>
<td></td>
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<tr>
<td>Erelzi</td>
<td>Sandoz</td>
<td>Jun 2017</td>
<td>Fasansico et al.20214, Yamanaka et al. 202051, Fassanika et al. 202052</td>
<td></td>
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<tr>
<td>Nexpento</td>
<td>Mylan</td>
<td>May 2020</td>
<td>Yamanaka et al. 202053, Yamanaka et al. 202054</td>
<td></td>
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<tr>
<td>Remicade (Infliximab)</td>
<td>Samsung Bioepis</td>
<td>May 2016</td>
<td>Kim et al. 202355, Paglini et al. 202056</td>
<td></td>
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<tr>
<td>Inflectra Remsima</td>
<td>Hospira Celltrion</td>
<td>Sep 2013</td>
<td>Goll et al. 201957, Kuritzky et al. 201958</td>
<td></td>
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<tr>
<td>Zessly</td>
<td>Sandoz</td>
<td>May 2018</td>
<td>McCellan et al. 201959</td>
<td></td>
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<tr>
<td>Stelara (Ustekinumab)</td>
<td>Stada Artimettel</td>
<td>Jan 2024</td>
<td>Feldman et al. 202360</td>
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</table>

Several biosimilars, all derivatives of adalimumab, initially received approval for clinical use but subsequently faced withdrawal. These include:

- Cyltezo, which received initial approval in November 2017 but had its approval revoked in January 2019.
- Kromeya, initially approved in April 2019, underwent withdrawal of approval in December 2019.
- Solymbic, approved in March 2017, experienced withdrawal of approval in March 2019.

The reasons for the withdrawal approvals may vary and could encompass concerns related to efficacy, safety, manufacturing, or regulatory compliance.

DISCUSSION

Biosimilars in Europe have promising potential to improve access and cost-effectiveness of psoriasis treatment, but their integration into health systems does not seem timely. In research of Sciberras and colleagues point out that in Europe of 332 biological drugs, only 17 have biosimilars (55 biosimilars are currently approved because one biologic drug has several biosimilars). They point out that the small number of permits is caused by complex development procedures, but also due to the protection of intellectual property of biological drugs, which enables monopoly status for the originators. They propose to revise the rules of intellectual property through knowledge exchanges, simplification of regulatory frameworks, increased transparency on development costs, as well as a reduced period of intellectual property protection. The authors point out that the weak application of biosimilars is often influenced by untimely approval by the regulatory health authorities of a certain country, unclearly defined protocols on switching to biosimilars, as well as regulatory frameworks that do not emphasize switching to biosimilars. They also point out that at the national level initiatives for the approval of biosimilars have not been expressed, although there is an ample need for biosimilars.41

A study comparing the prices of biosimilars in Europe and the US showed that the prices were higher in the US. However, the authors point out that a smaller number of biosimilars were approved in the US in the period from 2011 to 2020, which can be linked to the later establishment of regulatory framework in the US (2009) compared to Europe (2003)44. For example, in the UK, savings of £38.8 million were achieved in two years with the introduction of biosimilars infliximab and etanercept. Prediction models estimate that using the biosimilar etanercept would save €90 million over five years for the National Health Service in Italy.46 Data from Denmark show that only with the use of adalimumab biosimilars, the fi-
Financial expenses in the three months fell from 28 million Danish kroner to 6.5 million, which represents a saving of 77.45%. In the example of the SB4 biosimilar, the cost of treatment was €5940 per patient per year compared to the expenditure for ref-ETN, which was €73067. For MSB11022 in 16 weeks, the price per subject was €500 compared to €1831, which would be the expenditure for the originator. For the biosimilar ABP501, €968 was allocated for the same time, compared to the price for the originator, which was €19498.

Switching to biosimilars is primarily non-medical switching because this type of switching is most often carried out due to the lowering of treatment costs and greater availability of treatment49. Numerous studies investigating the transition from reference originators to biosimilars have confirmed that these two groups are comparable in terms of efficacy and safety and that they do not lead to significantly different clinical outcomes11,12,16,18. Contrary to this evidence, some studies have shown that switching to biosimilars can lead to a worsening of the condition, and the necessity of conducting studies with larger samples is suggested50. Some authors also point out that the possible presence of a nocebo effect in patients who switched to biosimilars led to worse treatment outcomes49.

When it comes to the perception of patients regarding biosimilars, it is definite that patients are afraid that the biosimilar will not be effective or safe enough, which the authors explain by the fact that patients are not sufficiently informed about biosimilars by doctors51. Thus, in an extensive study conducted in Denmark, patients on biological therapy expressed their reluctance to switch to biosimilars at some point due to fear of exacerbation of symptoms, as well as possible side effects, while patients who were treated with biosimilars from the very beginning of therapy had a slightly more positive attitude about biosimilars. In addition to this, both groups of respondents expressed the view that they are not sufficiently familiar with the mechanisms of action of biosimilars53. Although Denmark is one of the examples of countries where the use of biosimilars is widespread and where continuous efforts have been made to accept and acquaint both medical professionals and patients with biosimilars, there is still mistrust that can be overcome through intensive information programs.

As biosimilars do not need to be tested for all indications for which the reference drug is used to receive approval, there is currently insufficient research dealing with switching from reference biological drugs to biosimilars in psoriasis treatment. More expansive use of biosimilars can significantly affect the economic sustainability of health systems and enable greater access to adequate therapies in low-income countries as well. From the above, it can be concluded that such real-world research is necessary to shed light on as many unknowns as possible and increase the trust of both doctors and patients in biosimilars.
REFERENCES


