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ORIGINAL RESEARCH ARTICLE

Long-Term Real-World Post-approval Safety Data of Multiple Biosimilars from One Marketing-Authorization Holder After More than 18 Years Since Their First Biosimilar Launch

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Abstract

Background Biosimilars are additional treatment options that are approved based on robust analytical and clinical comparisons with their reference biologic. At the time of initial approval, the full safety profile of a biosimilar is inferred from the reference biologic. Nonetheless, there are still lingering concerns related to the long-term safety of biosimilars. Therefore, we reviewed the post-approval pharmacovigilance data for eight marketed biosimilars from one Marketing Authorization Holder (MAH) to summarize their safety experience in a real-world setting for up to 18 years since their first biosimilar launch.

Methods Post-approval cumulative patient exposure and safety experience for eight Sandoz biosimilars [adalimumab (Hyrimoz®), epoetin alfa (Binocrit®), etanercept (Erelzi®), filgrastim (Zarzio®), infliximab (Zessly®), pegfilgrastim (Ziextenzo®), rituximab (Rixathon®), and somatropin (Omnitrope®)] was summarized based on the available pharmacovigilance data from Periodic Safety Update Reports (PSURs) and the corresponding health authority-authored PSUR assessment reports, where available, as of 31 January 2023. Exposure to all biosimilars was calculated in patient treatment days (PTD) except for rituximab, which was expressed in number of patient doses (PD).

Results The combined post-approval cumulative exposure to seven out of the eight marketed Sandoz biosimilars was more than 1.3 billion PTD and for rituximab more than 1.8 million PD. Overall, a critical analysis of the cumulative safety data of all eight Sandoz biosimilar PSURs concluded that the overall benefit–risk profile of each remains favorable and is consistent with the respective reference biologics.

Conclusions This is one of the largest reviews of post-approval biosimilar pharmacovigilance data to date by one MAH. The real-world experience of all eight marketed Sandoz biosimilars for up to 18 years demonstrates that Sandoz biosimilars can be used as safely as their respective reference biologics. Therefore, patients and healthcare providers can be confident in the clinical benefit and safety of Sandoz biosimilars. It is reasonable to believe that similar conclusions about safety may be reached for other biosimilars developed and approved to the high standards as are already in place by major health authorities such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). The long-term safety of biosimilars demonstrated here provides strong support for the concept of biosimilarity.

1 Introduction

Biological medicines are well established in clinical practice for the treatment of many serious and chronic conditions [1]. As healthcare expenditure for biological therapies has increased in recent years, biosimilar medicines have been introduced to provide increased access to these therapies and to support the long-term sustainability of healthcare systems [2]. A biosimilar is a biological medicine that has been approved according to the same standards of pharmaceutical product quality as its reference biologic [an already approved biological medicine that shares the same international nonproprietary name (INN)], for which the patent

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Key Points

Biosimilars are approved according to the same standards of pharmaceutical product quality as their reference biologics and can provide treatment alternatives that improve access and may reduce costs of safe and effective biological medicines.

This publication summarizes the cumulative 1.3 billion patient days of post-approval exposure of eight approved biosimilars from one Marketing Authorization Holder based on available pharmacovigilance data from Periodic Safety Update Reports.

In one of the largest reviews of post-approval biosimilar pharmacovigilance data to date, this data review demonstrates that these eight biosimilars can be used as safely as their respective reference biologics.

Given the high standards for biosimilars that are already in place by major health authorities such as the EMA and FDA, it is reasonable to believe that similar conclusions about safety may be reached for other biosimilars approved in those regions.

and/or data protection periods have expired [1]. The basis of biosimilarity is that a biosimilar must have an identical amino acid sequence along with structural and functional similarity to the reference biologic. Biosimilars are approved based on robust comparisons with their reference biologic. They are shown to provide equivalent efficacy and comparable safety and immunogenicity [3]. The data set supporting biosimilarity provides the "totality of evidence" that enables a health authority (HA) to grant market authorization [1, 4–6]. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) state that biosimilars provide the same clinical effect as the reference biologic and may therefore be substituted for the reference biologic (or other approved biosimilars to the reference biologic) for either new or existing patients, subject to local requirements [1, 7–9].

Biosimilars offer advantages to patients and healthcare systems. Having more treatment alternatives available improves access to safe and effective biological medicines and reduces costs, allowing for reallocation of resources to other areas [1, 10–13]. Increased utilization of biosimilars can help ameliorate the increasing financial pressures on healthcare systems.

Sandoz obtained approval of human growth hormone somatropin in Australia in 2004 and as the first biosimilar in the European Union (EU) in 2006. Since then, Sandoz has obtained approval for an additional seven biosimilars, for a total of eight marketed biosimilars: adalimumab (Hyrimoz®/Hefiya®), epoetin alfa (Binocrit®, also marketed as Abseamed®, Epoetin alpha HEXAL®, and Novicrit®), etanercept (Erelzi®), filgrastim (Zarzio®, also marketed as Zarxio® and Filgrastim HEXAL®), infliximab (Zessly®, also marketed as IFIXI®, IXIFI®, IXIFI2®, and Xilfya®), pegfilgrastim (Ziextenzo®), rituximab (Rixathon®, also marketed as Riximyo® and Arasamila®) and somatropin (Omnitrope®, also marketed as Nomazc® and SCITROPIN A®). This review summarizes the post-approval safety experience of these eight biosimilars based on available pharmacovigilance data from Periodic Safety Update Reports [PSURs, more recently referred to as periodic benefit–risk evaluation reports (PBRERs) in many jurisdictions] and available HA authored assessment reports. Sandoz has obtained biosimilar approvals in more than 90 countries, many of which follow International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines [14].

Despite the many published data demonstrating the efficacy and safety of biosimilars, there are still lingering concerns of some healthcare professionals (HCPs), patients, and policy experts about the long-term safety of biosimilars. The best way to allay these concerns is by providing detailed and extensive long-term safety data. The safety data summarized in this publication are one of the largest summaries of real-world post-approval biosimilar safety experience to date.

2 Methods

Post-approval cumulative patient exposure data for the eight marketed Sandoz biosimilars (adalimumab, epoetin alfa, etanercept, filgrastim, infliximab, pegfilgrastim, rituximab, and somatropin) were calculated based on data available in the most recent PSURs (cut-off date 31 January 2023). The cumulative post-approval exposure in each PSUR range from the date of marketing authorization to the data lock point of the most recent PSUR.

Safety experience (cumulative safety data, summary of safety concerns, evaluation of risks, and new information) was summarized based on information contained in the latest HA-approved respective PSURs available as of 31 January 2023, and the available HA PSUR assessment reports [e.g., as issued by the EMA Pharmacovigilance Risk Assessment Committee (PRAC) for EU PSURs]. Relevant new safety information from respective PSURs related to safety signals, risk management plan (RMP) risks, safety label changes, or from registries, was included for each Sandoz biosimilar.

2.1 Estimated Cumulative Post-approval Exposure to Sandoz Biosimilars

Estimated cumulative post-approval exposure for seven out of the eight marketed Sandoz biosimilars is provided as patient treatment days (PTD). This includes adalimumab, epoetin alfa, etanercept, filgrastim, infliximab, pegfilgrastim, and somatropin. Post-approval patient exposure in these PSURs is based on worldwide sales volumes (Sandoz internal database) and defined daily dose (DDD), as defined by the World Health Organization (WHO) [15]. Exposure was calculated using the following formula: patient treatment days (PTD) = [amount sold in mg/(DDD)]. If the amount sold was provided in international units (IU) it was converted to mg. To allow for instances where PSUR reporting is in patient treatment years (PTY) instead of PTD, all values were converted to PTD (PTD = PTY*365).

Cumulative post-approval exposure to Sandoz rituximab cannot be presented in PTD as no DDD is defined by WHO as dosing is mostly intermittent, not daily. Sandoz rituximab exposure is therefore expressed in number of patient doses as available from the worldwide sales volumes (Sandoz internal database). The calculation is based on the maximal dose recommended based on the mg/m^2 body surface area dosing, i.e., 1 g per patient, as follows: rituximab patient exposure (patient doses) = quantity of rituximab sold (g)/maximum recommended dose (g/patient).

2.2 Post-approval Biosimilar Safety Signal Detection and Evaluation

2.2.1 Main Sources of Safety Cases and Safety Case Collection

PSURs contain safety information based on both unsolicited and solicited safety case reporting. Sources of safety cases incorporated into PSURs include patients/consumers, healthcare professionals, patient support programs, managed access programs, social media/internet reports, customer-facing Sandoz associates, commercialization partners, health authorities (HA), clinical trials, noninterventional studies, registries, health economics and outcomes research studies, and literature reports [even if the Marketing Authorization Holder (MAH) is not identified]. All safety cases are collected in a database.

2.2.2 Safety Signal Detection and Management

Continuous monitoring, evaluation, and assessment for relevant safety cases for Sandoz marketed biosimilars are conducted to determine if there is a safety signal based on the analysis of internal Sandoz data and external data.

A pharmacovigilance safety signal comprises new or additional information on a possible causal relationship between a safety case [adverse event (AE)] and a drug. It typically arises from more than one case of a suspected AE [16]. Safety signals include new and previously unrecognized safety concerns, increased severity, increased frequency, newly identified drug interactions, newly identified product use issues (e.g., medication errors, abuse or misuse, or overdose), newly identified risks in special populations (e.g., the elderly or during pregnancy), or technical defects resulting from technical complaints with an AE.

At Sandoz, safety signal detection is carried out by pharmacovigilance experts through both traditional methods and automated signal detection systems. Traditional safety signal detection applies to the typical, nonautomated sources of signals, and includes, but is not limited to, safety cases, abnormal laboratory findings/other tests, class effects, preclinical/clinical study findings, HA requests and/or HA publications, medical literature, and product technical complaints. Automated signal detection is performed using a validated system with statistical signal detection and signal management capability. The system/application supports the detection and quantification of statistics of disproportionate reporting using advanced data mining techniques applied to a variety of spontaneous reporting databases, including the Sandoz global safety database at regular intervals, and the US FDA's Adverse Event Reporting System (AERS) and the WHO Uppsala Monitoring Center (UMC) VigiBase during evaluation of safety signals [17, 18]. The automated signal detection program includes three different methods: disproportionality analysis, designated medical event alerts, and increased frequency analysis. As part of a pilot initiated by EMA that started on 22 February 2018 and was extended until the end of 2024, medicines with the active substances adalimumab, etanercept, filgrastim, infliximab, rituximab, and somatropin are also continuously monitored in the EMA Eudravigilance database by all MAHs, including Sandoz [19, 20].

After detection of safety signals, the Sandoz safety signal management process supports the management of safety signals and risks, captures key information on the safety profile of biosimilars and provides an overview of product safety profiles and their evolution throughout a Sandoz biosimilar's lifecycle. For biosimilars, safety signals based on reference biologic label changes in more than one country are also assessed.

All newly identified signals are subjected to further monitoring and analysis, to confirm or refute a causal association with the biosimilar, or provide a new aspect of a known association, by review of data from additional sources. These additional data sources may include, depending on the nature of the signal and availability of data, preclinical data,

Table 1 Cumulative post-approval exposure to Sandoz biosimilars

Sandoz biosimilar	International birth date/European birth date (year)	Latest PSUR date[a]	Estimated post-approval exposure (patient treatment days)
Adalimumab	26 July 2018/ 26 July 2018	31 December 2022[b]	119,726,205
Epoetin alfa	28 August 2007/ 28 August 2007	31 August 2021	482,786,595
Etanercept	30 August 2016/ 23 June 2017	02 February 2022	33,988,435
Filgrastim	06 February 2009/ 06 February 2009	15 September 2021	50,038,162
Infliximab	18 May 2018/18 May 2018	23 August 2022	344,277,125
Pegfilgrastim	22 November 2018/22 November 2018	31 January 2023	11,239,080
Somatropin	29 Sep 2004/12 April 2006	31 January 2022	323,645,347
Total			1,365,700,949
Sandoz biosimilar	International birth date/European birth date (year)	Latest PSUR date[a]	Estimated post-approval exposure (patient doses)
Rituximab	15 June 2017/15 June 2017	17 November 2022	1,885,105[c]

[a]Latest reporting date for post-approval data from most recently published Periodic Safety Update Report

[b]Based on a defined daily dose of 2.9 mg

[c]Equivalent to 1,885,105 g or 1885 kg of rituximab (based on the maximal dose recommended based on mg/m^2 body surface area dosing i.e., 1 g per patient)

clinical trials, literature reports, HA databases, registries, and class effects. After analysis, the conclusions or recommendations are further presented to an independent, multidisciplinary internal medical safety review board (MSRB) with a dedicated, proactive safety focus. The MSRB either endorses or rejects the conclusions or recommendations. If the conclusion or recommendation that a signal has a causal association to a product is endorsed, then further actions such as product label updates, institution of risk minimization measures, product recall, or product withdrawal from the market may be initiated based on the associated public health risk [21]. If the MSRB refutes a causal association to a product, no further actions are undertaken beyond routine pharmacovigilance (PV) monitoring.

2.3 Periodic Safety Update Reporting and Assessment

Periodic Safety Update Reports (PSURs) are periodic and cumulative reviews of the clinical and post-marketing AEs/ADRs received by the MAH summarizing relevant new safety information that could have an impact on the benefit–risk profile of the medicinal product. As part of ongoing PV and risk management, all MAHs, including Sandoz, are required to submit PSURs to HAs at defined time points after product authorization. PSURs are nonpublic documents compiled by the MAH and provided to HAs. The HAs then assess PSURs to determine if new risks have been identified, if the profile of a known risk has changed, or if the overall risk–benefit balance has changed. The HA then provides an assessment report and their conclusions to the MAH.

3 Results

3.1 Estimated Cumulative Exposure to Sandoz Biosimilars

Combined post-approval cumulative exposure to seven of the eight marketed Sandoz biosimilars (adalimumab, epoetin alfa, etanercept, filgrastim, infliximab, pegfilgrastim, and somatropin) was more than 1.3 billion PTD. Post-approval cumulative exposure to Sandoz rituximab, was more than 1.8 million patient doses (Table 1).

3.2 Safety Experience for Sandoz Biosimilars

An overview of all important identified risks, potential risks, and missing information as listed in the most recent PSURs for Sandoz biosimilars are provided in Tables 2, 3, 4, 5, 6, 7, 8 and 9. Overall, no new or changing safety findings or risks were detected, no new actions were taken due to safety concerns, and there were no changes to the safety information during the last reporting interval that were unique to Sandoz biosimilars. This is consistent with previous PSURs where safety and risk information was aligned with the respective reference biologic. Ongoing pharmacovigilance activities are considered adequate to monitor any potential safety issues or potential risks. The summary of safety concerns for Sandoz biosimilars match the summary of safety concerns of the reference biologic (Tables 2, 3, 4, 5, 6, 7, 8 and 9). A critical analysis of the cumulative safety data and benefit–risk of all Sandoz biosimilar PSURs by Sandoz and the PRAC, where assessment reports were available, concluded that the overall benefit–risk profile of Sandoz biosimilars remains favorable.

Table 2 Overview of risks and missing information for the INN adalimumab as listed in the Sandoz adalimumab PSUR and conclusions/actions from the reporting interval 01 January 2021–31 December 2021. Source: Sandoz adalimumab (Hyrimoz®/Hefiya®) PSUR, 01 January 2021–31 December 2021

Risks/missing information	Conclusion and actions for PSUR reporting interval
Important identified risks	
Serious infections	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Tuberculosis	
Malignancies	
Demyelinating disorders (including MS, GBS, and ON)	
BCG disease following live BCG vaccination in infants with in utero exposure to Sandoz adalimumab	
Important potential risks	
Progressive multifocal leukoencephalopathy	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Reversible posterior leukoencephalopathy syndrome	
Adenocarcinoma of colon in UC patients	
Missing information	
Patients with immune-compromised conditions	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Long-term safety information in the treatment of children aged 6–18 years with CD	
Episodic treatment in PsO, UC, and JIA	
Long-term safety information in the treatment of adults and children with uveitis	
Long-term safety information in the treatment of children aged 6–18 years with UC	Available data supports classification as new missing information; it will be reviewed again in the next PSUR

BCG Bacillus Calmette–Guerin, *CD* Crohn's disease, *GBS* Guillain–Barre syndrome, *INN* international nonproprietary name, *JIA* juvenile idiopathic arthritis, *MS* multiple sclerosis, *ON* optic neuritis, *PsO* psoriasis, *PSUR* Periodic Safety Update Report, *UC* ulcerative colitis

Table 3 Overview of risks and missing information for the INN epoetin alfa as listed in the Sandoz epoetin alfa PSUR and conclusions/actions from the reporting interval 01 September 2018–31 August 2021. Source: Sandoz epoetin alfa (Binocrit®/Abseamed®/Epoetin alpha HEXAL®) PSUR, 01 September 2018–31 August 2021

Risks/missing information	Conclusion and actions for PSUR reporting interval
Important identified risks	
Pure red cell aplasia	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Hyperkalemia	These risks are well characterized and documented; proposed to stop monitoring in next PSUR and follow routine pharmacovigilance
Hypersensitivity reactions (including anaphylactic reactions)	
Hypertension/hypertensive crisis	
Seizure	
Thromboembolic events	
Severe Cutaneous Adverse Reactions	
Important potential risks	
Disease progression (tumor growth potential)	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Survival impact	
Congestive heart failure	Based on cumulative evidence, no causal relationship was identified; proposed to stop monitoring in next PSUR and follow routine pharmacovigilance
De novo cancer in chronic kidney disease patients	
Misuse	
Missing information	
Safety in children	The totality of evidence does not reveal any new safety signal/potential/identified risk associated with the missing information. Safety in special populations will continue to be monitored as a standard topic; proposed to stop monitoring in the next PSUR and follow routine pharmacovigilance
Safety in lactation	

INN international nonproprietary name, *PSUR* Periodic Safety Update Report

Table 4 Overview of risks and missing information for the INN etanercept as listed in the Sandoz etanercept PSUR and conclusions/actions from the reporting interval 03 February 2021–02 February 2022. Source: Sandoz etanercept (Erelzi®) PSUR, 03 February 2021–02 February 2022

Risks/missing information[a]	Conclusion and actions for PSUR reporting interval
Important identified risks	
Malignancy (including lymphoma and leukemia)	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Serious and opportunistic infections (including tuberculosis, legionella, listeria, parasitic infection)	
Demyelinating disorders	
Aplastic anemia and pancytopenia	
Congestive heart failure in adult subjects	
Lupus-like reactions	As per the PRAC final assessment report for the reference etanercept PSUR (EMEA/H/C/PSUSA/00001295/201902), the list of topics to be evaluated in etanercept PSURs was revised. These risks will therefore not be discussed in the subsequent PSURs
Sarcoidosis and/or granulomas	
Allergic reactions	
Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens–Johnson syndrome)	
Systemic vasculitis (including ANCA-positive vasculitis)	
Macrophage activation syndrome	
Interstitial lung disease (including pulmonary fibrosis and pneumonitis)	
Autoimmune hepatitis	
Liver events in patients with viral hepatitis (including hepatitis B virus reactivation)	
Change in morphology and/or severity of psoriasis in adult and pediatric psoriasis/psoriatic arthritis populations	
Inflammatory bowel disease in patients with JIA	
Important potential risks	
Encephalitis/leukoencephalomyelitis	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Progressive multifocal leukoencephalopathy	
Impaired growth and development in juveniles	
Acute ischemic cardiovascular events in adults	
Autoimmune renal disease	As per the PRAC final assessment report for the reference etanercept PSUR (EMEA/H/C/PSUSA/00001295/201902), the list of topics to be evaluated in etanercept PSURs was revised. These risks will therefore not be discussed in the subsequent PSURs
Pemphigus/pemphigoid	
Amyotrophic lateral sclerosis	
Myasthenia gravis	
Liver failure	
Hepatic cirrhosis and fibrosis	
Severe hypertensive reactions	
Adverse pregnancy outcomes	
Potential for male infertility	
Weight gain	
Potential for medication errors (prefilled pen)	The risk was removed from the Sandoz etanercept RMP to align with the reference product RMP. This topic will now be reviewed under the standard section of medication error

ANCA antineutrophil cytoplasmic antibody, *INN* international nonproprietary name, *JIA* juvenile idiopathic arthritis, *PRAC* Pharmacovigilance Risk Assessment Committee, *PSUR* Periodic Safety Update Report, *RMP* risk management plan

[a]There is no missing information topic

Relevant new safety information from respective PSURs for each Sandoz biosimilar is presented in next sections. Unless otherwise specified, changes to the RMP did not impact the Core Data Sheet (CDS) and associated product labels. The CDS is an internal, nonpublic document prepared by the MAH that summarizes the efficacy and safety information for a given product, and other information including indications, pharmacology, dosing recommendations, and storage details. The CDS serves as the basis for local product information for HCPs and patients once approved by HA. The purpose of a CDS is

Table 5 Overview of all important identified risks and important potential risks as well as missing information for Sandoz filgrastim. Source: Sandoz filgrastim (Zarzio®, Zarxio®, Filgrastim HEXAL®) PSUR, 16 September 2018–15 September 2021

Risks/missing information	Conclusion and actions for PSUR reporting interval
Important identified risks	
Capillary leak syndrome	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Transformation to MDS or leukemia in patients with SCN	
Severe splenomegaly/splenic rupture	These risks are well characterized and documented; proposed to stop monitoring in next PSUR and follow routine pharmacovigilance
Sweet syndrome	
Cutaneous vasculitis	
Allergic reactions	
Osteoporosis in patients with SCN	
Exacerbation of rheumatoid arthritis	
Increased risk of graft versus host disease	
Serious pulmonary adverse events; interstitial pneumonia, ARDS	
Sickle cell crisis in patients with sickle cell disease	
Important potential risks	
Glomerulonephritis	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Hematological malignancies in healthy donors	
VTE in healthy donors	
Cytokine release syndrome	
Extramedullary hematopoiesis	Cumulative review of data does not support a causal relationship; proposed to stop monitoring in next PSUR and follow routine pharmacovigilance
Drug interaction with lithium	
Off-label use	
Immunogenicity (incidence and clinical implications of anti-G-CSF antibodies)	
Missing information	
Use in pregnancy and lactation	Propose to remove this missing information topic on the basis that information is no longer considered "missing" as per GvP module V revision 2. This topic will continue to be presented in future PSURs as a standard topic

ARDS acute respiratory distress syndrome, *G-CSF* granulocyte colony stimulating factor, *GvP* good pharmacovigilance practice, *INN* international nonproprietary name, *MDS* myelodysplastic syndrome, *PSUR* Periodic Safety Update Report, *SCN* severe chronic neutropenia, *VTE* venous thromboembolism

Table 6 Overview of risks and missing information for the INN infliximab as listed in the Sandoz infliximab PSUR and conclusions/actions from the reporting interval 24 August 2019–23 August 2022. Source: Sandoz infliximab (Zessly®) PSUR, 24 August 2019–23 August 2022

Risks/missing information[a]	Conclusion and actions for PSUR reporting interval
Important identified risks	
Serious infection/sepsis	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
BCG breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab	
Demyelinating disorders	
Malignancy	
Important potential risks	
Colon carcinoma/dysplasia (in pediatric ulcerative colitis)	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR

BCG Bacillus Calmette-Guérin, *INN* international nonproprietary name, *PSUR* Periodic Safety Update Report

[a]There is no missing information topic

Table 7 Overview of risks and missing information for the INN pegfilgrastim as listed in the Sandoz pegfilgrastim PSUR and conclusions/actions from the reporting interval 01 February 2019–31 January 2022. Source: Sandoz pegfilgrastim (Ziextenzo®) PSUR, 01 February 2019–31 January 2022

Risks/missing information	Conclusion and actions for PSUR reporting interval
Important identified risks	
Capillary leak syndrome	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
ARDS	
Sickle cell crisis in patients with sickle cell disease	
Glomerulonephritis	
Splenomegaly/splenic rupture	These risks are well characterized and documented; proposed to stop monitoring in next PSUR and follow routine pharmacovigilance
Cutaneous vasculitis	
Sweet syndrome (acute febrile neutrophilic dermatosis)	
Hypersensitivity (hypersensitivity, anaphylactic reaction, anaphylactoid reaction)	
Musculoskeletal pain-related symptoms	
Leukocytosis	
Thrombocytopenia	
Important potential risks	
AML/MDS	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Cytokine release syndrome	
Medication errors including overdose	Based on cumulative evidence, no causal relationship was identified; proposed to stop monitoring in next PSUR and follow routine pharmacovigilance
Drug interaction with lithium	
Off-label use	
Immunogenicity (incidence and clinical implications of anti-pegfilgrastim antibodies)	
Extramedullary hematopoiesis	
Missing information	
Risks in children < 18 years of age	Based on cumulative evidence, no causal relationship was identified; proposed to no longer review in next PSUR and follow routine pharmacovigilance
Risks during pregnancy and lactation	

AML acute myeloid leukemia, *ARDS* acute respiratory distress syndrome, *INN* international nonproprietary name, *MDS* myelodysplastic syndrome, *PSUR* Periodic Safety Update Report

to align the labelling (including core safety information) of any product across the globe and provide the "reference safety information" for the assessment of aggregate reports for the product.

3.2.1 Worldwide Marketing Authorization Status and Safety Review of Sandoz Adalimumab

Sandoz is the MAH for a biosimilar adalimumab marketed in 76 countries/regions worldwide. Sandoz adalimumab was first registered in the European Economic Area (EEA) on 26 July 2018 [international birth date (IBD) and European birth date (EBD)] via the EMA centralized procedure. Since first registration in the EEA, six PSURs have been published (see Supplementary Table 1 for all PSUR reporting intervals). The data included here (Table 2) are from the most recent Sandoz adalimumab PSUR, reporting interval 01 January 2021–31 December 2021.

During the reporting interval, Sandoz participated in three European disease-based registries to collect long-term post-approval data on Sandoz adalimumab in a real-world setting: British Association of Dermatologists Biologic Interventions Register (BADBIR), German Registry for Observation of Biologic Therapy in Rheumatoid Arthritis (RABBIT), and UK Inflammatory Bowel Disease Registry (IBDR). No change in the benefit–risk profile of Sandoz adalimumab was identified from these registries during the last PSUR reporting interval.

Before the reporting interval of the last PSUR, the PRAC Rapporteur requested that vitiligo, amicrobial pustulosis of the folds (APF), and human papillomavirus (HPV) infection/cervical dysplasia/cervical cancer be addressed by the

Table 8 Overview of risks and missing information for the INN rituximab as listed in the Sandoz rituximab PSUR and conclusions/actions from the reporting interval 18 November 2020–17 November 2021. Source: Sandoz rituximab (Rixathon®) PSUR, 18 November 2020–17 November 2021

Risks/missing information	Conclusion and actions for PSUR reporting interval
Important identified risks	
Hepatitis B virus reactivation (all indications)	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Hypogammaglobulinemia (nononcology indications)	
Infections (including serious infections; all indications)	
Progressive multifocal leukoencephalopathy (all indications)	
Important potential risks	
Administration route error (NHL/CLL)	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Relapses (for GPA/MPA)	
Malignant events (nononcology indications)	These risks are well characterized and documented; proposed to stop monitoring in next PSUR and follow routine pharmacovigilance
Worsening of preexisting cardiovascular disorders (nononcology indications)	
Missing information	
Long-term use in patients with GPA/MPA	No change to missing information during the reporting interval; it will continue to be reviewed in the next PSUR
Use in pregnancy and lactation (all indications)	Proposed to monitor this population through routine pharmacovigilance activities and present as a standard safety topic in subsequent PSURs

CLL chronic lymphocytic leukemia, *GPA* granulomatosis with polyangiitis, *INN* international nonproprietary name, *MPA* microscopic polyangiitis, *NHL* non-Hodgkin lymphoma, *PSUR* Periodic Safety Update Report

Table 9 Overview of risks and missing information for the INN somatropin as listed in the Sandoz somatropin PSUR and conclusions/actions from the reporting interval 01 April 2020–31 January 2022. Source: Sandoz somatropin (Omnitrope®) PSUR, 01 April 2020–31 January 2022

Risks/missing information	Conclusion and actions for PSUR reporting interval
Important identified risks	
Impaired glucose tolerance during treatment phase	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Important potential risks	
Occurrence of neoplasms (benign malignant, unspecified): new first neoplasm, recurrence, or progression of a preexisting neoplasm, or second neoplasm (of childhood cancer survivors)	No change to risk profile during the reporting interval; it will continue to be reviewed in the next PSUR
Possibility of clinically relevant interaction with compounds know to be metabolized by cytochrome P450 3A4 (e.g., sex steroids, corticosteroids, anticonvulsants, and cyclosporine)	Based on cumulative evidence, no causal relationship was identified; proposed to stop monitoring in next PSUR and follow routine pharmacovigilance
Missing information	
Immunogenicity (development of anti rhGH antibodies)	There has been no change in the risk profile. The risk is well characterized and documented. Proposed to no longer review in next PSUR and follow routine pharmacovigilance

INN international non-proprietary name, *PSUR* Periodic Safety Update Report, *rhGH* recombinant human growth hormone

MAHs of all adalimumab products (reference biologic and biosimilars) for the next PSUR to discuss whether a potential causal relationship exists between adalimumab and vitiligo or APF and whether events of cervical dysplasia/cervical cancer were reported in the context of HPV infection/reactivation during therapy with adalimumab. An analysis of data received in the PSUR reporting interval did not identify any new relevant safety findings for Sandoz adalimumab for these conditions, and they will continue to be monitored in the subsequent PSUR.

For the adalimumab reference biologic, "weight increased" was added to the label as an "undesirable effect", which in consequence resulted in a change to the Sandoz adalimumab CDS and corresponding labels to align with this change. This is consistent with previous PSURs where safety and risk information related to Sandoz adalimumab

was aligned with the reference biologic label. "Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis" was also added as a missing information topic during the reporting interval to align with an update to the reference biologic RMP.

3.2.2 Worldwide Marketing Authorization Status and Safety Review of Sandoz Epoetin Alfa

Sandoz and the license partner Medice Arzneimittel Putter GmbH and Co. KG are the MAHs for a biosimilar epoetin alfa marketed in 70 countries/regions worldwide. Sandoz epoetin alfa was first registered in the EEA on 28 August 2007 (IBD and EBD). Since first registration, 25 PSURs have been published (Supplementary Table 1). The data included here (Table 3) are from the most recent Sandoz epoetin alfa PSUR, reporting interval 01 September 2018–31 August 2021, and from the corresponding EMA PRAC assessment report, publication date 7 April 2022 (procedure number: EMEA/H/C/PSUSA/00001237/202108).

One signal "bone fractures," detected by Sandoz during clinical and nonclinical literature review, was evaluated. Following a cumulative review of all sources, the signal was assessed as "undetermined/inconclusive" due to insufficient information to confirm or refute the signal. The PRAC rapporteur proposed to keep this signal open for all MAHs and that a thorough cumulative review for this risk be conducted during the next PSUR period.

For the epoetin alfa reference biologic, the RMP was updated to redefine "premature death" and replace it with "survival impact," "tumor growth potential" was renamed as "disease progression," and nine safety concerns ["hyperkalemia," "hypersensitivity reactions (including anaphylactic reactions)," "hypertension/hypertensive crisis," "seizure," "thromboembolic events," "congestive heart failure," "misuse," "safety in lactation," and "safety in children"] were removed. This resulted in a change of the Sandoz epoetin alfa RMP during the reporting interval to align with the reference biologic. This is consistent with previous PSURs where safety and risk information related to Sandoz epoetin alfa was aligned with the reference biologic RMP.

3.2.3 Worldwide Marketing Authorization Status and Safety Review of Sandoz Etanercept

Sandoz is the MAH for a biosimilar etanercept marketed in 59 countries/regions worldwide. Sandoz etanercept was first registered in the USA on 30 August 2016 (IBD) and in the EEA on 23 June 2017 (EBD). Since first registration, six PSURs have been published (Supplementary Table 1). The data included here (Table 4) are from the most recent Sandoz etanercept PSUR, reporting interval 03 February 2021–02 February 2022.

During the reporting interval, Sandoz participated in three European disease-based registries to collect long-term post-approval data on Sandoz etanercept: BADBIR, RABBIT, and the British Society for Rheumatology Biologics Register in Rheumatoid Arthritis (BSRBR). No change in the benefit–risk profile of Sandoz etanercept was identified from these registries during the last reporting interval.

During the last reporting interval, the CDS and associated labels for Sandoz etanercept was amended in line with the changes to the reference biologic EU Summary of Product Characteristics (SmPC) to include headache as a new AE and remove inflammatory bowel disease and uveitis as ADRs specific for the pediatric population.

3.2.4 Worldwide Marketing Authorization Status and Safety Review of Sandoz Filgrastim

Sandoz is the MAH for a biosimilar filgrastim marketed in 83 countries/regions worldwide. Sandoz filgrastim was first registered in the EEA on 06 February 2009 (IBD and EBD). Since first registration, 19 PSURs have been published (Supplementary Table 1). The data included here (Table 5) are from the Sandoz filgrastim PSUR, reporting interval 16 September 2018–15 September 2021.

During the most recent reporting interval, the Sandoz filgrastim RMP was updated, in line with other filgrastim product labels, to include "glomerulonephritis" as a new important potential risk. One signal "Immune Reconstitution Inflammatory Syndrome" was initiated by the PRAC for all MAHs of filgrastim products; however, having assessed the responses submitted by the MAHs, the PRAC agreed that the likelihood of a causal relationship was not sufficiently strong and no further actions were required aside from routine pharmacovigilance activities.

3.2.5 Worldwide Marketing Authorization Status and Safety Review of Sandoz Infliximab

Sandoz and Pfizer are the MAHs for a biosimilar infliximab marketed in 59 countries/regions worldwide. Sandoz infliximab was first registered in the EEA on 18 May 2018 (IBD and EBD). Since first registration, two PSURs have been published (Supplementary Table 1). The data included here (Table 6) are from the Sandoz infliximab PSUR, reporting interval 24 August 2019–23 August 2022, which includes data from Sandoz and Pfizer, and from the corresponding EMA PRAC assessment report, publication date 14 April 2023 (procedure number: EMEA/H/C/PSUSA/00010759/202208).

During the reporting interval, Sandoz participated in three European disease-based registries to collect long-term post-approval data on infliximab: BADBIR, RABBIT, and UK-IBDR. No information relevant to the benefit–risk assessment for Sandoz infliximab was identified from these registries during the last PSUR reporting interval.

In a previous PRAC assessment report, all infliximab MAHs were requested to assess "acquired perforating dermatosis" and "antimicrobial pustulosis of the folds;" however, a cumulative analysis of data from all available sources did not reveal any evidence of a causal association. One signal of "Kaposi's sarcoma" was validated for the entire infliximab drug class and closed by the PRAC with a recommendation to update the EU SmPC for all infliximabs.

Updates to the Sandoz CDS and associated labels during the reporting interval to align with the reference biologic label were the addition of Kaposi's sarcoma, cerebrovascular accident, and dyslipidaemia under "undesirable effects". During the reporting interval, a direct HCP communication letter was mandated by the PRAC for all infliximab-containing products in the EU to inform HCPs on the need to postpone the use of live vaccines in infants that were exposed to infliximab during pregnancy or breastfeeding; the SmPCs were updated accordingly.

3.2.6 Worldwide Marketing Authorization Status and Safety Review of Sandoz Pegfilgrastim

Sandoz is the MAH for a biosimilar pegfilgrastim marketed in 51 countries worldwide. Sandoz pegfilgrastim was first registered in the EEA on 22 November 2018 (IBD and EBD). Since first registration, four PSURs have been published (Supplementary Table 1). The data included here (Table 7) are from the most recent Sandoz pegfilgrastim PSUR, reporting interval 01 February 2019–31 January 2022, and from the corresponding EMA PRAC assessment report, publication date 29 September 2022 (procedure number: EMEA/H/C/PSUSA/00002326/202201).

The safety information for all pegfilgrastim products was updated during the most recent reporting interval to include Stevens–Johnson syndrome as an adverse drug reaction and to include warnings on thrombocytopenia, myelodysplastic syndrome, and acute myeloid leukemia. The Sandoz CDS and associated labels were updated accordingly.

3.2.7 Worldwide Marketing Authorization Status and Safety Review of Sandoz Rituximab

Sandoz is the MAH for a biosimilar rituximab marketed in 75 countries/regions worldwide. Sandoz rituximab was first registered in the EEA on 15 June 2017 (IBD and EBD). Since first registration, seven PSURs have been published (Supplementary Table 1). The data included here (Table 8) are from the Sandoz rituximab PSUR, reporting interval 18 November 2020–17 November 2021, and from the corresponding EMA PRAC assessment report, publication date 10 June 2022 (procedure number: EMEA/H/C/PSUSA/00002652/202111).

During the most recent reporting interval, the RMP was updated to align with changes to the reference biologic RMP. The important potential risks "malignant events" and "worsening of preexisting cardiovascular disorders" were removed for nononcology indications and "use in pregnancy and lactation" was removed from the category "missing information." The PRAC also recommended that the SmPC for all rituximab products be amended to add the risk of serious viral infections. The Sandoz CDS and associated labels were updated accordingly.

During the reporting interval, Sandoz participated in the RABBIT and BSRBR registries. No information relevant to the benefit–risk profile of Sandoz rituximab was identified from these registries during the last reporting interval.

3.2.8 Worldwide Marketing Authorization Status and Safety Review of Sandoz Somatropin

Sandoz is the MAH for a biosimilar somatropin marketed in 80 countries/regions worldwide. Sandoz somatropin was first registered in Australia on 29 Sep 2004 (IBD) and in the EEA on 12 April 2006 (EBD). Since first registration, 28 PSURs have been published (Supplementary Table 1). The data included here (Table 9) are from the most recent Sandoz somatropin PSUR, reporting interval 01 April 2020–31 January 2022.

During the most recent reporting interval, the safety information of all somatropin containing products was updated to add a warning on "pancreatitis" and to add the adverse reactions "face edema," "headache," "hypothyroidism," "rash," "pruritus," "urticaria," and "gynecomastia." The Sandoz CDS and associated labels were updated accordingly.

4 Discussion

This review summarizes the cumulative exposure and safety experience of eight biosimilars marketed by Sandoz through a review of PSURs: pharmacovigilance documents that provide a snapshot of the worldwide safety experience of a medicinal product at defined time points post-authorization. Over a combined post-approval exposure of more than 1.8 million doses of Sandoz rituximab and more than 1.3 billion PTD globally for the other seven marketed biosimilars, all Sandoz biosimilars demonstrate an overall favorable benefit–risk profile that is consistent with their

respective reference biologics. As a result, patients and their caregivers can be confident in their safety.

Upon approval of a biosimilar based on the totality of evidence provided with the initial dossier, there is an assumption that its safety profile will be comparable to that of the reference biologic. In 2019, the EMA reviewed the cumulative data with all biosimilars approved in Europe and concluded that "the evidence acquired over 10 years of clinical experience shows that biosimilars approved through EMA can be used as safely and effectively in all their approved indications as other biological medicines [1]."

An independent analysis of the safety of Sandoz filgrastim-sndz was provided by utilizing data from SENTINEL, an independent pharmacovigilance database that is maintained by the US FDA. The FDA used the safety data within SENTINEL for filgrastim-sndz to help evaluate TreeScan™, a safety signal detection software. Filgrastim-sndz has become the filgrastim market leader in the USA by volume, and as a result there is sufficient product usage to be able to detect safety signals that may have arisen. The study sought to determine whether filgrastim-sndz has a different safety signal profile relative to the reference biologic. Results revealed that there were no new clinically relevant safety signals. The results from this analysis corroborate the conclusions reached from the analysis of PSUR data for Sandoz filgrastim [22].

Another recently published safety analysis was conducted using data from EudraVigilance comparing biosimilar monoclonal antibodies used in oncology [three bevacizumabs, five rituximabs (including Sandoz rituximab), and six trastuzumabs] with their respective reference biologics [23]. EudraVigilance is a public spontaneous reporting system that collects data from all EU countries. All biosimilars to a given reference biologic were combined in this analysis, limiting the conclusions to a group of biosimilars versus the reference biologic. The authors concluded that "there were no significant differences in the safety profiles between bevacizumab, trastuzumab, and rituximab biosimilars and their respective originators in Europe," and that their "findings provide reassurance regarding the safety equivalence of biosimilars and support their use as viable alternatives to originator biologics." Given the methodological differences and the products studied, this study cannot be directly compared with the results presented here. However, it is reassuring that an analysis of a different database yielded results consistent with those that we found.

Pre-approval clinical trials are usually limited to highly selective populations. Post-approval safety data are important in providing information on the product from routine use by providing information not anticipated at initial approval or that clinical trials are not powered to detect [24]. The PSUR is one of the main tools used by MAHs to periodically evaluate the benefit–risk profile of a medicinal product post-approval and communicate on the safety of that product to HAs. PSURs provide an update on the worldwide safety experience of a product by collecting and evaluating new or changing safety information from all relevant data sources in the context of cumulative information on the known benefit–risk profile of the product. In addition to identifying new safety signals and determining changes in the benefit–risk profile, they are used to communicate risk to HAs, and can indicate the need for risk management initiatives, as well as track the effectiveness of such initiatives over time [24–27]. The MAH then draws conclusions based on this evaluation to optimize product use, such as updates to the label or risk management plan. PSUR evaluations contribute to a substantial proportion of post-approval, safety-related regulatory actions or label changes [26]. Considerable experience has been gained with biosimilars since their first approval in the EU and the USA and it is now widely accepted that they can be safely and effectively exchanged with their reference biologics [1, 28]. As of September 2023, 93 biosimilars had been approved in the EU and 42 in the USA. At that time none had been withdrawn for safety reasons nor had any biosimilar specific AEs been added to product labels. Based on increased scientific knowledge and cumulative experience with biosimilars to date, recommendations have been made by HAs and other stakeholders for a more streamlined approach in biosimilar clinical development and a reduction in the requirement for clinical data [5, 29–32]. It may also be possible to streamline post-approval reporting requirements based on data provided over time by the MAH.

The strength of this review is that the cumulative information on which the PSURs are based comes from one of the largest global pharmacovigilance databases for biosimilars worldwide. Sandoz is also the MAH with the longest commercial biosimilar experience as evidenced by the lengthy exposure time for many of the products and with biosimilars licensed in up to 90 countries, depending on the molecule. As a result of the extended exposure and diversity of countries in which Sandoz biosimilars are marketed, the pharmacovigilance data reflect a diverse patient population.

A limitation of this review is that the pharmacovigilance assessments rely on the reporting of safety information and therefore it cannot be ruled out that there are cases that have not been reported; however, this is an issue inherent to all safety systems. A second limitation is that exposure to Sandoz biosimilars during the PSUR periods may be different than that of the reference biologics or other biosimilars to that reference biologic. However, this does not impact the results because the effectiveness as well as the safety profile was consistently replicated for the biosimilars

compared with the reference biologic. It should be acknowledged that the eight different Sandoz biosimilars included in this review have been licensed for different periods of time (between 4 and 18 years) and differ in their post-approval exposure (ranging from 11.2 million PTD for pegfilgrastim to 482.8 million PTD for epoetin alfa) and, therefore, the level of post-approval safety data available. In addition, the estimated PTD could be inaccurate since these biosimilars are approved for several indications with varying posology and the WHO-defined standardized DDD [15] was used for calculation.

5 Conclusion

This is one of the largest reviews of post-approval biosimilar pharmacovigilance data to date by one marketing authorization holder derived from all eight Sandoz biosimilar PSURs and available HA assessment reports. The real-world experience of all eight marketed Sandoz biosimilars for up to 18 years demonstrates that Sandoz biosimilars can be used as safely as their respective reference biologics. Therefore, patients and healthcare providers can be confident in the clinical benefit and safety of Sandoz biosimilars. Given the high standards for biosimilars that are already in place by major health authorities such as the EMA and FDA, it is reasonable to believe that similar conclusions about safety may be reached for other biosimilars approved in those regions. The long-term safety of biosimilars demonstrated here provides strong support for the concept of biosimilarity. Given that biosimilars provide the same efficacy and long-term safety as their reference biologics, more extensive utilization of biosimilars can increase patient access and can ameliorate the financial burden on healthcare systems.

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Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material PSURs and PSUR source data, HA assessments of the PSURs and the product CDSs are confidential to Sandoz and are not publicly available.

Code Availability Not applicable

Author Contributions AK and SS developed the concept for the publication. HPC developed the manuscript outline. AK compiled the patient exposure data from the PSURs. HPC, SS and AK drafted portions of the manuscript. PA and SK contributed to the Methods and the Results sections. All authors participated in the review of the manuscript. The final manuscript was approved by all authors who take responsibility for the content.

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