OUTCOMES OF SWITCHING FROM EPOETINS TO THEIR BIOSIMILARS: A SYSTEMATIC REVIEW

FINAL REPORT NOVEMBER 2020

CHIARA GERARDI, ELEONORA ALLOCATI
ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI – IRCCS*

Contacts:
Via Mario Negri 2, Milan, Italy
chiara.gerardi@marionegri.it
eleonora.allocati@marionegri.it

Review question

In people of all ages under active treatment with ESAs (epoetins, darbepoetin) for chronic kidney disease or anaemia due to cancer therapies does switching to their biosimilars (e.g., X575, SB309) [OR a switch from a biosimilar to another of the same biologic medicine] compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

Summary results

We were able to retrieve mainly evidence about switching in adult population affected by chronic kidney diseases. Most of the data derives from observational registry-based studies, though some small RCTs were also retrieved. Overall, these studies suggest that switching is safe and effective. Very few data on immunogenicity were available. Only one study reported on the need for a significantly higher epoetin dose to maintain Hb levels relatively stable after switching haemodialysis patients from originators to biosimilars.
We did not find evidence on switching from a biosimilar to another of the same biologic medicine.

Introduction

The introduction of biological medicines on the market has changed the course of many serious and rare conditions. Over the past few years, the expiry of patents and/or other data protection certificates of biological medicines has fuelled interest in developing biosimilars, i.e. biological agents that are similar to other previously authorized biological medicines. Health systems should benefit from the introduction of biosimilars as they lead to price competition which improves patients' access to safe and effective biological medicines.
Regulatory authorities are responsible for the marketing authorisation of biosimilars. The approach established for generic medicines is not suitable for development, evaluation and licensing of biosimilars, given that biological medicines are relatively large and complex proteins that are produced following different manufacturing processes, which may lead to molecules that are similar but not identical to the originator. The assessment of biosimilarity with respect to the originator slightly differs in the different world regions, but it is basically based on the demonstration of similar analytical, pre-clinical and clinical performance (WHO 2019).

Definition of interchangeability

Interchangeability is the practice of replacing one medicine with another that is expected to achieve the same clinical effect in a given clinical setting. In the case of biosimilars, this could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by:

Switching: the prescriber decides to exchange one medicine with another medicine with the same therapeutic intent.

Substitution (also known as non-medical switching or automatic substitution): the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.

Regulatory authorities usually require no specific studies assessing if alternating or switching from the biosimilar and its originator affect safety and/or efficacy in chronic conditions. In other words, biosimilars are expected to produce the same clinical results as their reference products in any patient, providing that biosimilarity has been demonstrated. The FDA represents a notable exception to this general approach. FDA applications for a biosimilar administered more than once to an individual generally include data from a switching study(ies) demonstrating that the risk in terms of safety or diminished efficacy of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternation or switch (FDA 2019a). The FDA has created a regulatory designation pathway for the scientific evaluation of interchangeability, requiring that the proposed interchangeable product "can be expected to produce the same clinical result as the originator in any given patient; and for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its originator is not greater than the risk of using the originator without such alternation or switch" (FDA 2019b). At the time of this report preparation, no biosimilars have been deemed interchangeable by the FDA.
In Europe, the European Medicines Agency is in charge of the licensing of biosimilars while national authorities are usually responsible for the definition of policies regarding switching and interchangeability with the originator (EMA 2019).

Post-marketing studies comparing switchers to non-switchers have the potential to rule out possible difference in the efficacy, safety and immunogenicity.

Epoetins for chronic renal failure and chemotherapy-induced anaemia

Anaemia is one of the most serious complications of chronic kidney disease and end-stage renal disease and the most common and persistent haematological abnormality in oncology patients. Chronic kidney disease is defined as the presence of kidney damage (usually detected as urinary albumin excretion ≥30 mg/day, or equivalent) or reduced kidney function (defined as estimated glomerular filtration rate [GFR] <60 mL/min/1.73 m2) for three or more months, irrespective of the cause. Normochromic normocytic anaemia is mainly due to erythropoietin deficiency which itself is principally caused by reduced renal erythropoietin production, presumably reflecting the reduction in the number of erythropoietin-producing cells in the kidneys. To a lesser degree, it is caused by the shortened red cell lifespan. Erythropoietin is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow. Renal anaemia can thus be regarded as a hormone deficiency state. The erythropoietin-stimulating agents (ESAs) are critical components in managing anaemia in chronic kidney disease since the 1980s. All those currently available are effective in achieving and maintaining target haemoglobin (Hb) levels.

All epoetins in clinical use have a similar amino acid sequence as endogenous erythropoietin but differ in the glycosylation pattern. Glycosylation influences pharmacokinetics and may affect efficacy and safety including immunogenicity. Biosimilars of epoetin alfa and zeta are available in several countries to treat anaemia due to cancer therapies and chronic kidney failure; in Europe, they were licensed in 2007 (Allocati 2020) while in the US only in 2018 (FDA 2018). Several biosimilars or “similar biologics ”of darbepoetin, the synthetic form of erythropoietin, are licensed in India and Japan (Gabi 2019).

General purpose

The general scope of this report is to summarise the evidence to understand issues and barriers to full interchangeability for wider access to affordable biologic medicines and their biosimilars. This effort includes collecting evidence that reduces uncertainties about the use of biosimilars, evidence of strategies focused on potential mandatory interchangeability at procurement and clinical level, and tackling new approaches to develop, license and monitor biosimilars to improve efficiency of market approval and accelerate access.

This report aims to inform the Expert Committee in charge of issuing recommendations on interchangeability of biosimilar products. Guidance provided by WHO and its Expert Committee will support countries in making evidence-based, timely and informed choices when considering the inclusion of biological and biosimilar medicines on their national lists.

Objective

This report includes a comprehensive review of studies that assessed the outcomes of switching between biologics and their biosimilars and focuses on those treatments considered by the Expert Committee of Essential Medicines List (WHO EML 2019).

Evidence was collected across several diseases and considering both pre-marketing trials and post-marketing drug-utilization data helping to consolidate the practice of switching/substituting from reference to biosimilar medicines.

The review question is the following:

In people of all ages under active treatment with epoetins for chronic renal failure and chemotherapy-induced anaemia does switching to biosimilar [OR a switch from biosimilar X to biosimilar Y of the same epoetin] compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

Methodology

The following sections describes the general methodological approach that will be applied for each dyad class product-indications.

Eligibility criteria

Secondary and tertiary literature

Up-to-date systematic reviews and other types of evidence syntheses (e.g. health technology assessment [HTA] reports, clinical guidelines if developed following a systematic approach) evaluating safety, immunogenicity or efficacy of switching from a biologic medicine to its biosimilars or from different biosimilars of the same biologics. We considered as “up-to-date” those evidence syntheses in which the last date of literature search was conducted after October 2017, e.g. three years from the preparation of this report (October 2020). The reference lists of those evidence syntheses that were considered not up-to-date where anyway checked to identify possible additional studies.

Primary literature

Switching studies may apply different designs, including transition, single-switch cross over, multiple-switch studies (Figure 1).

Transition design: patients switch only from one biologic to another (e.g., from originator to biosimilar).

Single-switch cross over: patients starting on the originator are switched to biosimilar and those starting on biosimilar are switched to originator.

Multiple-switch studies: patients undergo a series of switches alternating originator and biosimilar.

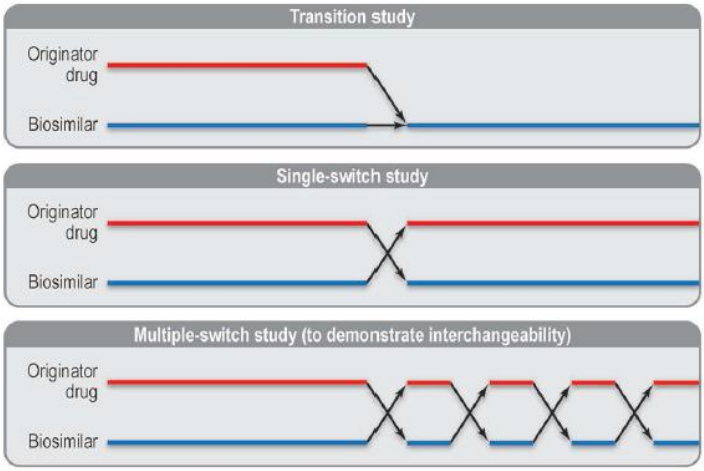

Figure 1: study design for exploring switch between originator biological drugs and biosimilars. Source: Faccin et al 2016.

For the purpose of this review, we applied a hierarchal approach to inclusion of primary studies, focusing on the most robust designs, i.e., randomised design with appropriate control arms, whenever available.

We included randomised controlled trials (RCTs) and prospective controlled cohort studies not included in the previously mentioned secondary and tertiary literature. Retrospective cohort studies, uncontrolled and controlled transition studies, cross over studies are considered eligible only if no evidence from prospective controlled studies are available.

Search strategies

To retrieve the evidence, we searched MedLine, EMBASE, and The Cochrane Library applying the search strategies reported in Appendix 1. The reference lists of the eligible reviews (included and excluded at the full text screening stage) have been checked. To retrieve information on ongoing or unpublished studies, we searched the main trial registries and the International Clinical Trials Registry Platform.

Study selection

Two reviewers independently screened titles and abstracts of the retrieved records to exclude any clearly irrelevant records. The full publications of possibly eligible records were retrieved and checked by two reviewers to confirm eligibility. Any discrepancies were resolved by discussion.

Data extraction and synthesis

The key feature of each review or study were summarised in a tabular format by one reviewer and checked by a second one. The effect of switching on the three clinical areas of drug efficacy, safety, and immunogenicity was noted for each published study. We planned to extract numeric information on the results and perform meta-analysis, using OR with 95% confidence intervals (95% CIs). However, the data we retrieved could not be pooled in meaningful meta-analysis. Thus, we reported a narrative description of the included studies and their results.

Risk of bias assessment

We assessed the risk of bias of included evidence synthesis reports by using the AMSTAR-2 tool (Shea 2017 and AMSTAR-2 2017) and that of primary studies by using the criteria of The Cochrane Collaboration: Risk of bias tool for RCT (Higgins 2011) and ROBINS-I for cohort studies (Sterne 2016). Two review authors independently assessed the risk of bias of each study and resolved disagreements by discussion to reach consensus.
We did not evaluate the certainty of evidence (inconsistency, indirectness, imprecision and publication bias) as defined by the GRADE methodology (GRADE 2019) as planned, given that we considered evidence from narrative reviews including a few RCTs.

Study selection

The systematic searches launched on December 5th, 2019 and updated on October 2nd, 2020 reported in Appendix 1 resulted in 124 records, after duplicates were discarded. As shown in Figure 4, after applying the eligibility criteria 12 records were selected for the full text reading. We included two broad reviews that did not focus only on epoetins but reported summaries of studies on single or multiple switching from reference biological medicines to biosimilars (Barbier 2020, Cohen 2018). We also included one RCT (Thadhani 2018) not included in the reviews.

One study initially considered eligible was excluded as it evaluated only the frequency of switching among ESAs without reporting data on efficacy or safety of these switches (D'Amore 2016). The reference lists of excluded studies were checked to identify studies not retrieved by our literature searches.

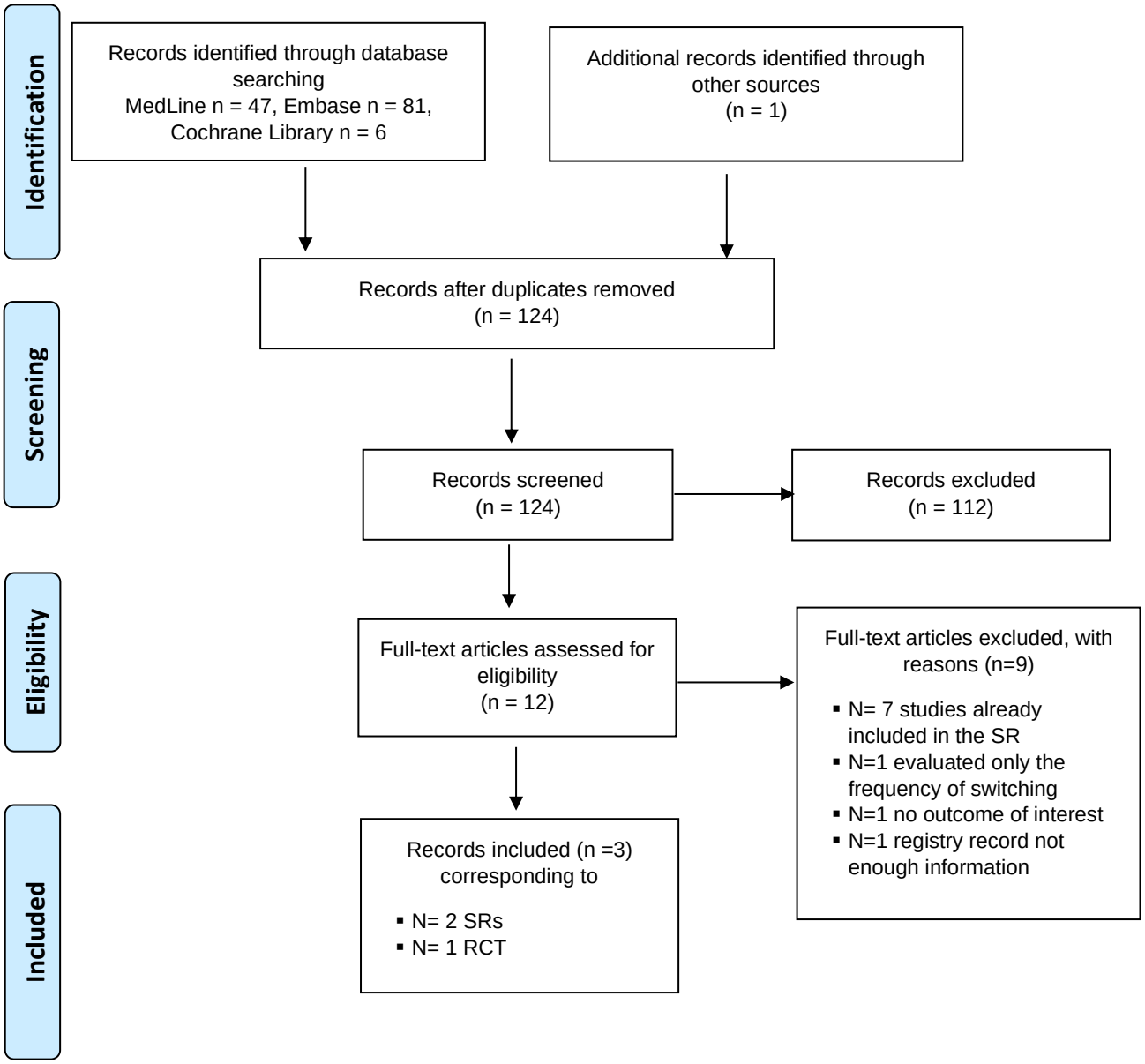

Figure 4: Flow chart (SR: systematic review, RCT: randomised controlled trial)

Included studies

Systematic review (N=2)

The review by Cohen et al (Cohen 2018) reported a summary of studies on single or multiple switching from reference biological medicines to biosimilars from 1993 up to June 2017.

This review was conducted by authors from pharma companies and large research centers. It included studies on monoclonal antibodies and small proteins used to treat a variety of conditions. It did not perform meta-analysis and did not meet any of the critical domains of the AMSTAR 2 checklist (see Appendix 2).

A total of 90 studies were identified involving 14,225 individuals treated with seven molecular entities for 14 disease indications. Thirteen studies assessed switching between the originator and biosimilar epoetins in: chronic kidney disease (seven studies, Harzallah 2015, Wiecek 2010, Haag-Weber 2009, Frei 2009, Turner 2009, Wizemann 2008, Smith 2007), end-stage renal disease (two studies, Lonnemann 2011, Krivoshiev 2010), and haemodialysis (four studies, Minutolo 2016, Ode 2011, Milutinovic 2006, Bren 2002). The review correctly excluded studies that evaluated the switch from erythropoietins to darbepoetin and to pegylated-erythropoietin but included studies that evaluated the switch from one ESA to another, for instance from epoetin alfa to epoetin delta or omega. We considered these studies not relevant for this report. The same applies to switching studies conducted in healthy volunteers included by Cohen and collaborators.

Table 1 reports the main characteristics and results of the nine studies involving epoetin alfa and zeta. The most common efficacy endpoint was a change in Hb levels over time. The safety, efficacy, and immunogenicity profiles of the switching and non-switching arms were similar.

The review by Barbier et al (Barbier 2020) synthesized the switch data for biologicals of every therapeutic class for which a European market authorization has been granted. It included a total of 178 in which switch outcomes from originators to biosimilars were assessed. We reported here only the data on epoetin alpha/zeta. The review did not perform meta-analysis and did not meet any of the critical domains of the AMSTAR 2 checklist (see Appendix 2). The last search date was June 2018. The review identified five RCTs (Wizemann 2008, Haag-Weber 2009, Harzallah 2015, Krivoshiev 2010, Goh 2007) and 15 single arm studies (Baldamus 2008, Turner 2009, Lonneman 2011, Lonneman 2012, Hörl 2012, Lopez 2012, Lopez 2014, Hörbrand 2013, Dellana 2014, Ohta 2014, Picon 2014, Sabbatini 2014, Minutolo 2017, Morosetti 2017, Belleudi 2019).

The studies assessed adult populations treated for anaemia due to renal diseases. Only one single-arm, retrospective, observational study focused on 28 cancer patients who switch from epoetin alfa/darbepoetin to epoetin zeta (Lopez 2014).

Table 2 reports the main characteristics and results of the 20 studies involving epoetin alfa and zeta.

RCT (N=1)

We retrieved one RCT not included in the above-mentioned reviews. This open label, non - inferiority RCT was conducted by a network of haemodialysis centers in the US (Thadhani 2018). Patients with anaemia and chronic kidney disease undergoing maintenance haemodialysis and receiving routine intravenous epoetin alfa (Epogen) were randomised 1:1 to switching to the biosimilar (Retacrit) or continuing the originator for 24 weeks. Of the 432 randomised patients, 418 received the treatment (biosimilar: 212; originator: 206). The proportion of time patients' haemoglobin was within the target range (9–11 g/dL) was similar in the two arms (difference in proportions:–1.4% (95% CI –7.6 to 4.9), and the lower bound of the confidence interval was within the pre-specified non-inferiority margin of –12.5%. The mean change from baseline in the weekly mean ESA dose and safety outcomes were also similar. The authors concluded that switching to the epoetin alfa biosimilar Retacrit was found to be noninferior to continued treatment with epoetin alfa reference product in maintaining haemoglobin levels in patients with anaemia and CKD managed on haemodialysis. The study was judged a moderate risk of bias (Appendix 2); it applied an open label design but the use of algorithm for epoetin-dosing decisions rather than investigator discretion and laboratory-based outcome may have reduced the overall bias.

Table 1: Switching studies that evaluated erythropoietins, modified from Cohen 2018

Author, Year	N	Study Design/ Biologic	Efficacy		Safety					Immunogenicity
			Outcome Variables	Results	Incidence of AEs	%TEAE Switch	%TEAE Ref	%TESAE Switch	%TESAE Ref	Outcome
Chronic kidney disease										
Wizemann 2008	313	Double-blinded, crossover, phase III trial/ rHuEPO (epoetin zeta)	● Intra-individual differences in mean Hb levels ● Mean weekly dose/kg of body weight	Epoetin zeta is therapeutically equivalent to epoetin alfa in maintenance of target Hb levels in patients with renal anaemia	● AE profile was similar ● Most commonly reported AEs were infections and infestations (in 26.5% in epoetin zeta and 23.6% in epoetin alfa ● Most AEs (94.8% N=859]) judged to be 'mild' or 'moderate'&majority of events (94.9% [N=860]) judged as 'not related' or 'unlikely to be related' to study drug	Zeta: 0.6%	Alfa: 2.5%	1%	No Info	●3/313 (0.96%) tested positive for NABs. These patients had positive results at baseline ● No patients developed neutralizing anti-erythropoietin antibodies
Haag-Weber 2009	478	Double blinded, randomised, multicenter, parallel-group/ rHuEPO (HX575)	Difference between groups in mean absolute change of Hb levels between baseline & evaluation period (W25 – W28)	● Mean Hb concentrations were stable in both groups ● Mean changes in Hb levels were 0.15±0.09 g/dl in HX575 & 0.06±0.12 g/dl in epoetin-alfa (diff. of 0.08 g/dl)	● Most AEs were mild or moderate in intensity and resolved completely ● Incidence of drug-related AEs was similar for groups treated with HX575 & epoetin-alfa ● Incidence of SAEs was similar	Comparable HX575: 0.21 events per exposure year	Comparable epoetin: 0.11 events per exposure year	Comparable HX575: 1.60 events per exposure year	Comparable epoetin: 1.23 events per exposure year	No antibody formation was detected
Harzallah 2015	53	Phase-III, multicenter, clinical trial/ rHuEPO (epoetin alfa)	Mean blood Hb levels at baseline and after 43 days follow-up	● Epomax & Hemax showed comparable mean Hb. levels ● Epomax was equivalent to Hemax	● The most frequent adverse events were variations in blood pressure and headaches	Comparable (No data presented)	Comparable (No data presented)	None (0%)	None (0%)	No Info
Wiecek 2010	582	Randomised, double-blinded, open label study/ rHuEPO (epoetin zeta)	Mean Hb	● Mean Hb was maintained (10.5-12.5 g/dL) throughout switch ● Epoetin alfa & zeta can be interchanged without any clinically significant alteration in efficacy	● Incidence and nature of treatment-emergent and serious AEs was similar among all 4 groups analysed, and appeared to be unaffected by the switch in study medication	Comparable	Comparable	Comparable	Comparable	None of the patients developed anti-erythropoietin antibodies or PRCA

Author, Year	N	Study Design/ Biologic	Efficacy		Safety					Immunogenicity
			Outcome Variables	Results	Incidence of AEs	%TEAE Switch	%TEAE Ref	%TESAE Switch	%TESAE Ref	Outcome
Turner 2009*	298	Prospective, multi-center observational Study/ rHuEPO (HX575 epoetin-alpha)	● Mean change from baseline in Hb level ● HX575 epoetin-alpha dose	HX575 epoetin-alpha effectively maintains stable Hb level in haemodialysis & with symptomatic renal anaemia with no dose penalty	No Info	No Info	No Info	No Info	No Info	No report of anti-erythropoietin NABs
End-Stage Renal Disease										
Krivoshiev 2010	462	Randomised observer-blinded, multi-center, phase 3/rHuEPO (Epoetin Zeta)	● Mean Hb level ● Mean weekly epoetin dosage per kg body weight during the last 4W of treatment	Epoetin zeta is equivalent to epoetin alfa with respect to its clinical efficacy for maintaining the Hb concentration in anaemic pts with ESRD	● Most common AEs were infections and infestations ● 15.1% of patients on epoetin zeta and 14.8% of patients on epoetin alfa	2.20%	1.30%	1.29%	0.43%	● No patient developed anti-erythropoietin antibodies ● No clinical signs of PRCA
Lonnemann 2011	17	Observational clinical study/ rHuEPO (Epoetin Zeta)	Hb level	● Hb. 11.72±0.64 g/dl vs. 11.62±0.70 g/dl (p=0.64) ● BS epoetin zeta is effective and stable	No side effects attributable to the ESA-therapy have been observed	0%	0%	No Info	No Info	No Info
Hemodialysis										
Ode 2011*	1,695	Single arm, prospective 6-month study/ rHuEPO (HX575 – BS epoetin alfa)	Mean Hb values at baseline and after 6 months	● Mean Hb. values remained stable in patient subgroups with 1, 2, >2 or no switches ● Efficacy was not affected by multiple switches ● Results showed HX575 was safe & effective	● Observed AE profile was in line with expectations for the patient population ● Thrombotic vascular events were reported in 11.9% and incidence of tumour in 1.4% of patients	2.1% of total patients who withdrew	No Info	No Info	No Info	No patient developed anti-epoetin antibodies
Minutolo 2016	149	Retrospective data analysis/ rHuEPO (HX575 or SB309)	● Time-weighted avg Hb. level ● ESA dose	● Post-switch, Hb level were unchanged, but there was progressive significant increase in BS dose (ESA) ● Long-term studies are required	No Info	No Info	No Info	No Info	No Info	No Info

*reported only as abstract.

AE, adverse events; BS, biosimilar; ESA, erythropoietin-stimulating agent; ESRD, end-stage renal disease; Hb, haemoglobin; IV, intravenous; mgmt., management; N, sample size; NAB, neutralizing antibody; NS, non-significant; PRCA, pure red cell aplasia; Ref., reference; rHuEPO, recombinant human erythropoietin; SAE, serious adverse event; SE, standard error; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent severe adverse event; TRT, treatment; W, week.

Table 2: Switching studies that evaluated erythropoietins, modified from Barbier 2020

Study	Switch	Population	Study design	N patients switched	Follow up	Efficacy, safety, immunogenicity outcomes	ADA reporting	Reported conclusion/switch advice
Goh 2007	Originator - GerEPO®	Haemodialysis pts	Randomized, open label, parallel arm, single switch study	87	12 w	Both arms showed a similar decline in Hb. More pts in switch group reported AEs due to subjective symptoms, more pts in switch group were withdrawn due to AE or decrease in Hb (similar Hb decline in both arms).	NR	*Results are convincing with respect to efficacy measured in terms of Hb response, the duration of trial was only 3 m, which is insufficient for safety evaluation.*
Baldamus 2008	Epo alfa – epo zeta	CKD	OLE of double-blind phase III, single arm, single switch study	343	56-108 w	No cases of lack of (or loss of) efficacy. The intensity of AEs was mild/moderate in most (87.5%) cases. Only in 4.7% cases considered as related to the study drug (to well-known undesirable effects of epo). No pts developed neutralizing ADA.	Yes	*Our study shows that intravenous administration of epoetin zeta is safe and effective in maintaining stabilized Hb levels in pts with chronic renal failure.*
Wizemann 2008	Epoetin alfa – epoetin zeta or *vice versa*	CKD, anaemia	Double blind cross-over phase III trial **Multiple switch (2)**: switch at w0, switch at w12	239	12 w	Hb levels were equivalent. Pts underwent minor dose adjustments during treatment crossover. AE profile was similar, no pts developed neutralizing ADA.	Yes	*Epoetin zeta is therapeutically equivalent to epoetin alfa in the maintenance of target Hb levels in pts with renal anaemia. No unexpected AEs were seen.*
Haag-Weber 2009	Originator – HX575	CKD (pts on haemodialysis)	Randomized, controlled, open label, single switch study	314	54 w	Mean changes in Hb levels were 0.15 ± 0.09 g/dl and 0.06 ± 0.12 g/dl in switch and cont. arm respectively. Difference between arms: 0.08 g/dl (95% confidence interval: -0.17; 0.34). No antibody formation detected.	Yes	*No differences in safety, immunogenicity or efficacy profiles following the switch. The long-term safety profile of the BS was comparable to the RP.*
Turner 2009	Any ESA – BS/other ESA	CKD (pts on haemodialysis)	Open label, prospective, multicentre observational study	263	6 m	Slight differences in mean Hb level increase and dose increase. HX575 epoetin alfa was well tolerated and no reports of anti-erythropoietin neutralising antibodies. No safety events related to switching reported.	Yes	*Treatment with HX575 epoetin-alpha effectively maintains stable Hb levels in pts on haemodialysis and symptomatic renal anaemia; no dose penalty, well tolerated.*
Krivoshiev 2010	Epoetin zeta (BS) –	CKD	Randomized, observer blind	230	28 w	Equivalence between epoetin zeta and alfa in terms of clinical	Yes	*Epoetin zeta is equivalent to epoetin alfa in respect of its*

	epoetin alfa RP		phase III, single switch trial			efficacy for maintaining the Hb concentration. Most common AEs were infections and infestations (15.1% of pts on epoetin zeta and 14.8% of pts on epoetin alfa). No pts developed ADA.		*clinical efficacy. The safety profile of both products is similar: no unexpected AEs were observed, no pts developed anti-erythropoietin antibodies.* No switch advice
Lonneman 2011	Various ESA – epoetin zeta	ESRD (pts on haemodialysis)	Observational clinical, single centre, single switch study	18	6 m	Comparing pre and 6 m post switch, no significant changes were observed in Hb and weekly dose of ESA. The frequency of application could be reduced to once a week or less with epoetin zeta in 66% of pts. No significant changes in mean blood pressure, body weight and haemodialysis efficiency. No side effects have been observed.	NR	*The BS is safe in clinical practice and is effective and stable in the weekly dose as well as in the frequency of application.* No switch advice
Hörl 2012	ESA – HX575 (BS epoetin alfa)	CKD	Open-label, multicentre, single switch, safety database	1384	6 m	Mean Hb levels were effectively maintained. The proportion of pts within the Hb target range increased from 57.5% at baseline to 66.8% at study end. Observed AE profile was in line with expectations for the pt population. No pts developed ADA	Yes	No switch advice
Lonneman 2012	ESA – epoetin zeta	CKD, anaemia	Observational clinical, single switch study	33	Up to 30 m	During the first 18 m, mean Hb level was stable between 11 and 12 g/dl. The mean weekly dose of epoetin zeta was 7939 IU/week in m 6 and 7909 IU/week in m 18 (p = not significant). The mean frequency (injections/week) was 1.27 in m 6 and 1.29 in m 18 (not significant).	NR	*Epoetin zeta proved to be safe, well tolerated, and without severe AEs.* No switch advice.
Lopez 2012	Epoetin alfa – epoetin zeta	CKD	Prospective study with survey	NR	NR	No pts noticed the change in treatment of epoetin alfa to epoetin zeta, none has noticed difference or any discomfort. All pts surveyed had a good tolerability.	NR	*The replacement of epoetin alfa with epoetin zeta has been well accepted by pts and epoetin zeta has shown to be well tolerated.*
Hörbrand 2013	Originator ESA – BS or	CKD	Population based database of	507	12 quarters	Doses were not increased when the therapy was switched from	NR	*ESA consumption of pts on chronic haemodialysis is*

	vice versa		accounting information and claims			originator to BS. The prescribed daily dose was comparable for BS and RP epoetin.		*similar for BS and originator ESAs. It was reassuring to note that consumption did not increase in pts who switched from originator to BS.*
Dellana 2014	Epoetin alfa – epoetin zeta	CKD	Multicentre, observational, single centre study	652	Up to 1 y (median exposure 52 w)	Lack of efficacy occurred in 2.4%, 27/39 cases were attributed to infection or inflammation. No reports of pure red cell aplasia, neutralizing antibodies, anaphylactic reactions, or angioedema. Hb was stable over the study.	Yes	No switch advice.
Lopez 2014	ESA – epoetin zeta	Chemo-therapy induced anaemia	Retrospective, observational, single switch study	28	12 m	When comparing the mean Hb concentration before and after switching to epoetin zeta, there were no statistically significant differences in 71% of pts ($p > 0.05$). 46% of pts needed an increase in the dose of epoetin, during treatment with epoetin zeta to maintain the concentration of Hb within the target level.	NR	*Despite the limited number of pts, it has been demonstrated that epoetin zeta was effective in the treatment of anaemia in pts with cancer receiving chemotherapy.* No switch advice.
Ohta 2014	Epoetin beta –epoetin kappa	Haemodialysis pts	Retrospective, single switch study	30	3 m	Good control was maintained upon changing from epoetin beta to epoetin kappa. Moreover, 3 m subsequent to this switch, the degree of instability observed among the pts had decreased.	NR	*Although the situation subsequent to the change from epoetin beta to epoetin kappa requires further investigation, it may be concluded that the results are indicative of the clinical equivalence and the efficacy of epoetin kappa.* No switch advice.
Picon 2014	Epoetin – epoetin BS Bio-Manguinhos & BS epoetin (Alfaepoetina Blausiegel®)	Haemodialysis pts	Randomized, double-blind, non-inferiority, single switch, clinical trial (both arms switch, so no RCT comparing switch and non-switch arm)	74	6 m	No significant differences between arms (epoetin –Bio-Manguinhos switch arm and epoetin to Alfaepoetina Blausiegel® switch arm) in Hb levels. The incidence of AEs was similar between groups. No significant difference in the incidence of SAEs.	NR	*No difference in Hb levels or epoetin alfa doses between groups throughout follow-up. Mean Hb levels remained within the predefined target range throughout the study.* No pre-post switch comparison, or comparison between a switch and non-switch. No switch advice.
Sabbatini 2014	ESA – epoetin zeta	Renal transplant pts	Prospective, single centre, single	10	12 m	In the switch group, mean plasma Hb levels >11 g/dL were	NR	*Epoetin zeta may be a valid alternative to different ESAs in*

			switch study			maintained during the follow-up, with average epoetin-zeta doses 3.4% higher than the corresponding doses of previous ESA. MCV did not vary in either group. No drug-related side effect reported.		*renal transplant recipients. Either when introduced to substitute a different ESA or in naive pts, the correction of anaemia was performed and Hb levels maintained in the desired range with negligible modification of its doses and with no change in MCV,*
Harzallah 2015	RHu-Epo (Hemax®) – rHu Epo alfa (Epomax®)	Chronic haemodialysis pts	Phase-III, multicentre, single switch, clinical trial	53	43 d	No significant difference in mean Hb levels between arms. No significant difference in doses at the end of the study. 5 pts discontinued after switch (2 due to unrelated abdominal pain, unclear for other 3).	NR	*Epomax® was effective at maintaining the Hb levels at target concentrations and was well tolerated.*
Minutolo 2017	Different ESA (including Eprex®) – epoetin BS	Haemodialysis pts	Retrospective, matched-control, single switch study	163	24 w	In both groups, Hb levels remained substantially stable; however, Hb in the switch group was slightly lower than in controls from w 4 to 20. In the switch group, Hb was kept stable by a progressive increase in dose. In pts treated with ESA originators, anaemia control was stable and ESA therapy remained unchanged.	NR	*Switching from ESA originators to BS is associated with lower Hb levels, despite a significant dosing difference of approximately 40%. In pts switched to BS, the phenomenon of hyporesponsiveness to ESA seems to be more pronounced.*
Morosetti 2017	Different ESAs – epoetin BS	Haemodialysis pts	Observational, single centre, single switch study	87	12 m	No significant changes in Hb, ferritin, and transferrin saturation observed after the switch. No changes in PAV, thrombosis and cardiovascular events	NR	*The switch from different ESAs to BS was safe and effective.*
Trotta 2017 (Belleudi 2019)	Epoetin alfa originator – different epoetin (including epoetin BS)	CKD	Database, single switch	98 pts switched to BS	2 y	No differences between switchers and non-switchers of epoetin alfa RP on risk of blood transfusions and safety outcomes.	NR	*Switching from epoetin alfa RP to other epoetins (whether they are BS or not) in CKD pts appears to be not associated with increased risk of blood transfusions or major AEs.*

*Follow-up after switch, ADA rep.: ADA measurements (or trough levels) reported, +: switching was defined as any transition between different epoetins in a series of two consecutive prescriptions during the study period. DA: anti-drug antibody, ADRs: adverse drug reactions, AE: adverse event, BS: biosimilars, CKD: chronic kidney disease, d: days, ESA: erythropoiesis-stimulating agent, ESRD: end stage renal disease, Hb: haemoglobin, m: months, MCV: mean corpuscular volume, N: number, NR: not reported, OLE: open label extension, pts: patients, RCT: randomized controlled trial, RP: reference product, SAE: serious adverse event, w: weeks, y: year

References:

Allocati 2020 Allocati E, Bertele' V, Gerardi C, Garattini S, Banzi R. Clinical evidence supporting the marketing authorisation of biosimilars in Europe. Eur Journ Clin Pharm. 2020;76(4):557-566

AMSTAR-2 2017 The new and improved AMSTAR. Available at: https://amstar.ca/Amstar-2.php Accessed October 2020.

Baldamus 2015 Baldamus C, Krivoshiev S, Wolf-Pflugmann M, Siebert-Weigel M, Koytchev R, Bronn A. Long-term safety and tolerability of epoetin zeta, administered intravenously, for maintenance treatment of renal anemia. Adv Ther 2008; 25: 1215–1228.

Barbier 2020 Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. Clin Pharmacol Ther. 2020; 108(4):734-755.

Belleudi 2019 Belleudi V, Trotta F, Addis A, et al. Effectiveness and Safety of Switching Originator and Biosimilar Epoetins in Patients with Chronic Kidney Disease in a Large-Scale Italian Cohort Study. Drug Safety 2019;42:1437–1447.

Bren 2002 Bren A, Kandus A, Varl J, Buturovic J, Ponikvar R, Kveder R et al. A comparison between epoetin omega and epoetin alfa in the correction of anemia in hemodialysis patients: a prospective, controlled crossover study. Artif Organs. 2002;26(2):91-7.

Cohen 2018 Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes Drugs 2018;78:463–478.

D'Amore 2016 D'Amore C, Da Cas R, Rossi M, Traversa G. Switching Between Epoetins: A Practice in Support of Biosimilar Use. Bio Drugs 2016;30:27–32.

Dellanna 2014 Dellanna F, Fluck R, Lonnemann G, Wild C, Iwanowitsch A, Audhya P et al. PASCO I: A 1-year long post-registration safety study on biosimilar epoetin zeta across Germany, Spain, Italy, and the United Kingdom. Am J Kidney Dis 2014; 63: A42.

EMA 2019 Biosimilar medicines: Overview. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview Accessed October 2020.

Faccin 2016 Faccin F, Tebbey P, Alexander E, Wang X, Cui L, Albuquerque T. The design of clinical trials to support the switching and alternation of biosimilars. Expert Opin Biol Ther. 2016;16(12):1445-1453.

FDA 2019a FDA US Food and Drug Administration. Therapeutic Biologics Applications (BLA) Biosimilars. Available at: https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars. Accessed October 2020.

FDA 2019b FDA US Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product. Guidance for industry. 2019. https://www.fda.gov/media/124907/download Accessed October 2020.

FDA 2018 FDA US Food and Drug Administration. FDA approves first epoetin alfa biosimilar for the treatment of anemia. https://www.fda.gov/news-events/press-announcements/fda-approves-first-epoetin-alfa-biosimilar-treatment-anemia Accessed October 2020.

Frei 2009 Frei U, Kwan JT, Spinowitz BS, The Epoetin Delta Study G. Anaemia management with subcutaneous epoetin delta in patients with chronic kidney disease (predialysis, haemodialysis, peritoneal dialysis): results of an open-label, 1-year study. BMC Nephrol. 2009;10:5.

Gabi 2019 Biosimilars of darbepoetin alfa http://gabionline.net/Biosimilars/General/Biosimilars-of-darbepoetin-alfa. Accessed October 2020.

GRADE 2019 The GRADE working group. Available at: https://www.gradeworkinggroup.org/ Accessed October 2020.

Goh 2007 Goh BL, Ong LM, Sivanandam S, Lim TO, Morad Z. Randomized trial on the therapeutic equivalence between Eprex and GerEPO in patients on haemodialysis. Nephrology 2007; 12: 431–436.

Haag-Weber 2009 Haag-Weber M, Vetter A, Thyroff-Friesinger U, Group INJ-9 Study G. Therapeutic equivalence, long-term efficacy and safety of HX575 in the treatment of anemia in chronic renal failure patients receiving hemodialysis. Clin Nephrol. 2009;72(5):380-90.

Harzallah 2015 Harzallah A, Zouaghi K, Dridi A, et al. Therapeutic efficacy of a biosimilar epoetin alfa in hemodialysis patients. Saudi J Kidney Dis Transpl. 2015;26(1):78-82.

Higgins 2011 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials BMJ 2011;343:d5928.

Hörbrand 2013 Hörbrand F, Bramlage P, Fischaleck J, Hasford J, Brunkhorst R. A population-based study comparing biosimilar versus originator erythropoiesis-stimulating agent consumption in 6,117 patients with renal anaemia. Eur J Clin Pharmacol 2013;69:929–936.

Horl 2012 Hörl WH, Locatelli F, Haag-Weber M, Ode M, Karsten R. Prospective multicenter study of HX575 (biosimilar epoetin-α) in patients with chronic kidney disease applying a target hemoglobin of 10-12 g/dl. Clin Nephrol 2012; 78: 24–32.

Krivoshiev 2010 Krivoshiev S, Wizemann V, Czekalski S, et al. Therapeutic equivalence of epoetin zeta and alfa, administered subcutaneously, for maintenance treatment of renal anemia. Adv Ther. 2010;27(2):105-17. doi:10.1007/s12325-010-0012-y.

Lonnemann 2011 Lonnemann G, Wrenger E. Biosimilar epoetin zeta in nephrology - a single-dialysis center experience. Clin Nephrol. 2011;75(1):59-62. doi:10.2379/CNP75059.

Lonneman 2012 Lonnemann G, Wrenger E. Biosimilar Epoetin Zeta in Nephrology: Effect of Injection Frequency on Weekly Dose. Int J Clin Med 2012; 3: 598–602.

Lopez 2012 López MJ, Antonino G, Vicente I, Mejía L, García P, Sánchez A. Erythropoietic factors in renal chronic disease: Economic management. Int J Clin Pharm 2012; 34: 221–222.

Lopez 2014 Lopez MJ, García del Busto N, Carrascosa O, Mejía L, Antonino G, De La Vega I et al. Biosimilar epoetin zeta in the treatment of chemotherapy-induced anaemia. Eur J Hosp Pharm 2014; 21: A38–A39.

Milutinovic 2006 Milutinovic´ S, Plavljanic E, Trkulja V. Comparison of two epoetin brands in anemic hemodialysis patients: results of two efficacy trials and a single-dose pharmacokinetic study. Fundam Clin Pharmacol. 2006;20(5):493-502.

Minutolo 2016 Minutolo R, Borzumati M, Sposini S, et al. Dosing Penalty of Erythropoiesis-Stimulating Agents After Switching From Originator to Biosimilar Preparations in Stable Hemodialysis Patients. Am J Kidney Dis. 2016;68(1):170-2. doi:10.1053/j.ajkd.2016.01.011.

Minutolo 2017 Minutolo R, Bolasco P, Chiodini P, et al. Effectiveness of Switch to Erythropoiesis-Stimulating Agent (ESA) Biosimilars versus Maintenance of ESA Originators in the Real-Life Setting: Matched-Control Study in Hemodialysis Patients. Clin Drug Investig 2017;37:965–973.

Morosetti 2017 Morosetti M, Dominijanni S, Calzona AB, Zappalà L, Nicolais R, Di Turi R. Switch to biosimilars in hemodialysis patients: Efficacy, safety and cost analysis in a single centre. Ric e Prat 2017; 33: 5–12.

Ode 2011 Ode M, Roth K, Locatelli F, Hörl WH. Switch from a broad range of erythropoiesis stimulating agents to HX575 (Biosimilar Epoetin Alfa): A 6-month prospective multicenter study. ERA-EDTA Congress; June 23-26, 2011; Prague, Czech Republic: European Renal Association and European Dialysis and Transplant Association 2011; 2011. p. 1826.

Ohta 2014 Ohta S, Yasuno N, Inomoto Y, Matsuda K, Nakagawa Y, Sasagawa I et al. Efficacy of once or twice weekly administration of epoetin κ in patients receiving hemodialysis: A retrospective study. Exp Ther Med 2014; 7: 27–30.

Picon 2014 Picon P, Pribbernow S, Prompt C, Schacher S, Antunes V, Mentz B et al. Randomized double-blind clinical trial of a new human epoetin versus a commercially available formula for anemia control in patients on hemodialysis. Clinics 2014; 69: 547–553.

Sabbatini 2014 Sabbatini M, Vitale S, Garofalo G, Torino M, Gallo R, Carrano R et al. Efficacy of Subcutaneous Epoetin-Zeta on Anemia in Renal Transplant Recipients: A Single-Center Experience. Transplant Proc 2014; 46: 2238–2240.

Shea 2017 Shea BJ, Reeves BC, Wells G., et al AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008

Smith 2007 Smith WB, Dowell JA, Pratt RD. Pharmacokinetics and pharmacodynamics of epoetin delta in two studies in healthy volunteers and two studies in patients with chronic kidney disease. Clin Ther. 2007;29(7):1368-80.

Sterne 2016 Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919.

Thadhani 2018 Thadhani R, Guilatco R, Hymes J, Maddux FW, Ahuja A. Switching from Epoetin Alfa (Epogen®) to Epoetin Alfa-Epbx (RetacritTM) Using a Specified Dosing Algorithm: A Randomized, Non-Inferiority Study in Adults on Hemodialysis Am J Nephrol 2018;48:214–224.

Turner 2009 Turner M, Hartmann U, Dellanna F. HX575 Epoetin-Alpha Effectively Maintains Stable Haemoglobin Levels in Patients on Haemodialysis with Symptomatic Anaemia due to Chronic Renal Failure. 9th BANTAO Congress; 18-22 November 2009; Antalya: The Balkan Cities Association of Nephrology, Dialysis, Transplantation and Artificial Organs (BANTAO); 2009. p. 32.

Wiecek 2010 Wiecek A, Ahmed I, Scigalla P, Koytchev R. Switching epoetin alfa and epoetin zeta in patients with renal anemia on dialysis: Posthoc analysis. Adv Ther. 2010;27(12):941-52.

Wizemann 2008 Wizemann V, Rutkowski B, Baldamus C, Scigalla P, Koytchev R, Epoetin Zeta Study G. Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anaemia treatment. Curr Med Res Opin. 2008;24(3):625-37.

WHO 2019 Biologicals: similar biotherapeutic products. Available at: https://www.who.int/biologicals/biotherapeutics/similar_biotherapeutic_products/en/ Accessed October 2020.

WHO EML 2019 WHO Model Lists of Essential Medicines Available at: https://www.who.int/medicines/publications/essentialmedicines/en/ Accessed October 2020.

Appendix 1: search strategy erythropoetins (02.10.2020)

PubMed (N= 43)

((((((“Drug Substitution”[Mesh] OR “Switch”[All] OR “switching”[All] OR “switched”[All] OR “switches”[All] OR “substitute”[All] OR “substitutes”[All] OR “substitution”[All] OR “substituted”[All] OR “substituting”[All] OR “interchange”[All] OR “interchanges”[All] OR “interchanged”[All] OR “interchanging”[All] OR “interchangeability”[All] OR “interchangeable”[All] OR “inter-change”[All] OR “inter-changes”[All] OR “inter-changed”[All] OR “inter-changing”[All] OR “inter-changeability”[All] OR “inter-changeable”[All] OR “inter change”[All] OR “inter changes”[All] OR “inter changed”[All] OR “inter changing”[All] OR “inter changeability”[All] OR “inter changeable”[All] OR “switchability”[All])

AND

(“Biosimilar pharmaceuticals"[Mesh] OR "biosimilar"[All] OR "biosimilars"[All] OR “biosimilarity”[All] OR "similar biological medicine"[All] OR "similar biological medicines"[All] OR "similar biological medicinal product"[All] OR "similar biological medicinal products"[All] OR “follow on biologic”[All] OR “follow-on biologic”[All] OR “follow on biologics”[All] OR “follow-on biologics”[All] OR “Subsequent entry biologic”[All] OR “Subsequent-entry biologic”[All] OR “Subsequent entry biologics”[All] OR “Subsequent-entry biologics”[All] OR “follow on biological”[All] OR “follow-on biological”[All] OR “follow on biologicals”[All] OR “follow-on biologicals”[All] OR “Subsequent entry biological”[All] OR “Subsequent-entry biological”[All] OR “Subsequent entry biologicals”[All] OR “Subsequent-entry biologicals”[All])))))

AND

("Erythropoietin/therapeutic use"[MeSH] OR "Erythropoietin/administration and dosage"[Mesh] OR "Erythropoietin"[MAJR] OR epoetin zeta[Supplementary Concept] OR epoetin alfa[Supplementary Concept] OR epoetin theta[Supplementary Concept] OR epoetin beta[Supplementary Concept] OR darbepoetin alfa[Supplementary Concept] OR Erythropoietin[tiab] OR Epoetin[tiab] OR Eprex[tiab] OR recombinant human EPO[tiab] OR r-HuEpo[tiab] OR rHuEpo[tiab] OR erythropoiesis-stimulating agent*[tiab] OR erythropoietin OR epoetin alpha OR epoetin beta OR darbepoetin alpha OR EPO OR methoxy polyethylene glycol epoetin beta OR epoetin zeta OR epoetin theta)

Embase (N=80)

('erythropoietin'/exp OR 'erythropoietin' OR 'recombinant erythropoietin'/exp OR 'recombinant erythropoietin' OR 'epoetin alpha'/exp OR 'epoetin alpha' OR 'epoetin beta'/exp OR 'epoetin beta' OR 'darbepoetin alpha'/exp OR 'darbepoetin alpha' OR 'epo' OR 'methoxy polyethylene glycol epoetin beta'/exp OR 'methoxy polyethylene glycol epoetin beta' OR 'continuous erythropoietin receptor activator'/exp OR 'continuous erythropoietin receptor activator' OR 'epoetin zeta'/exp OR 'epoetin theta'/exp) AND ('drug substitution'/exp OR 'drug substitution' OR 'switch'/exp OR 'switch' OR 'switching'/exp OR 'switching' OR 'interchange' OR 'interchangeability' OR 'switchability') AND ('biosimilar agent'/exp OR 'biosimilar agent' OR 'biosimilar drug'/exp OR 'biosimilar drug' OR 'follow on biological') AND [embase]/lim

Cochrane Library (N=6)

#1 (“Drug Substitution” OR “Switch” OR “switching” OR “switched” OR “switches” OR “substitute” OR “substitutes” OR “substitution” OR “substituted” OR “substituting” OR “interchange” OR “interchanges” OR “interchanged” OR “interchanging” OR “interchangeability” OR “interchangeable” OR “inter-change” OR “inter-changes” OR “inter-changed” OR “inter-changing” OR “inter-changeability” OR “inter-changeable” OR “inter change” OR “inter changes” OR “inter changed” OR “inter changing” OR “inter changeability” OR “inter changeable” OR “switchability”)

#2 MeSH descriptor: [Drug Substitution] explode all trees

#3 #1 OR #2

#4 "Biosimilar pharmaceuticals" OR "biosimilar" OR "biosimilars" OR “biosimilarity” OR "similar biological medicine" OR "similar biological medicines" OR "similar biological medicinal product" OR "similar biological medicinal products" OR “follow on biologic" OR “follow on biologics” OR “Subsequent entry biological” OR “Subsequent-entry biological” OR “Subsequent entry biologicals” OR “Subsequent-entry biologicals"

#5 MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees

#6 #4 OR #5

#7	erythropoietin
#8	"darbepoetin alpha"
#9	'epoetin theta'
#10	'epoetin zeta'
#11	"methoxy polyethylene glycol epoetin beta"
#12	"Epoetin Alfa"
#13	"Erythropoietin"
#14	EPO
#15	"epoetin beta"
#16	r-HuEpo
#17	"continuous erythropoietin receptor activator"
#18	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19	MeSH descriptor: [Epoetin Alfa] explode all trees
#20	MeSH descriptor: [Erythropoietin] explode all trees
#21	#18 or #19 or #20
#22	#3 AND #6 AND #21
#23	"accession number" near pubmed
#24	"accession number" near EMBASE
#25	#23 or #24
#26	#22 NOT #25

Appendix 2: risk of bias assessment of included reviews studies

Systematic reviews assessed with AMSTAR 2

Author (year)	1	2*	3	4*	5	6	7*	8	9*	10	11*	12	13*	14	15*	16
Barbier 2020*	yes	no	yes	yes	no	no	no	yes	no	no	No MA	No MA	no	no	No MA	yes
Cohen 2018	yes	no		part yes	no	no	no	yes	no	no	No MA	No MA	no	no	No MA	yes

MA: meta-analysis, NRSI: non-randomised studies included

AMSTAR Critical domains (Shea 2017):

2. Protocol registered before commencement of the review
4. Adequacy of the literature search
7. Justification for excluding individual studies
9. Risk of bias from individual studies being included in the review
11. Appropriateness of meta-analytical methods
13. Consideration of risk of bias when interpreting the results of the review
15. Assessment of presence and likely impact of publication bias

RCT assessed with Cochrane Risk of Bias tool (Higgins 2011)

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	RoB Overall
Thadhani 2018	low risk - computer-generated	low risk - Interactive response system	unclear risk - open label but ESA dosing standard, several protocol violation but balanced in the two groups	unclear - open label but objective outcome	low risk (FAS: lost to FU 4% vs 2.4%)	low risk - ClinicalTrials.gov NCT02504294	moderate