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School of
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Literature Review of International Biosimilar Medicines: Update December 2016 – March 2017

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Introduction

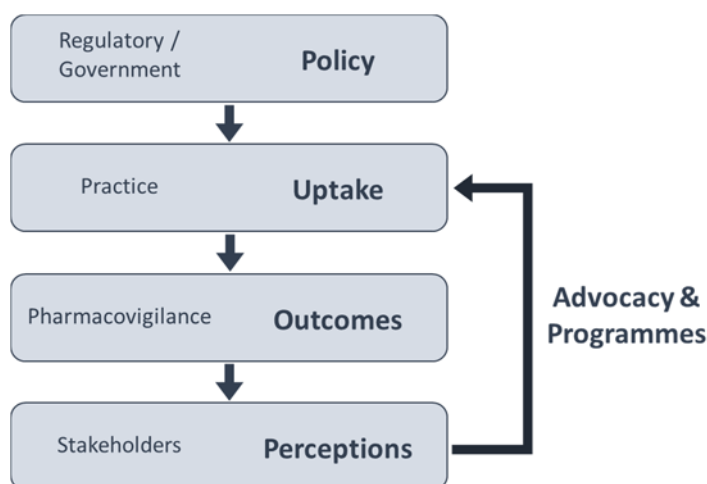
This report provides an update to the comprehensive literature search previously conducted that examined all international and Australian clinical, academic and policy journals and media articles or sources in relation to biosimilar medicines for the purpose of providing evidence which may inform policy development and the communication activities of the Australian Government's Biosimilar Awareness Initiative (the Initiative).

The broad objectives are to provide a review of the literature pertaining to:

- current international policies on biosimilar medicines;
- status of biosimilar use and substitution internationally;
- any current programmes aimed at increasing the uptake or confidence in biosimilars (and an evaluation of their success);
- biosimilar uptake and substitution; and
- impact of biosimilars (if any) on adverse events and health outcomes.

The five stated broad objectives for the review relate to four stages that influence biosimilar use; that is, the national and international regulatory environment that is the foundational determinant of biosimilar availability and associated switching and substitution (Policy); the subsequent uptake of biosimilars by prescribers, pharmacists and patients (Uptake); outcomes resulting from the use of biosimilars outside of the clinical development pathway (Outcomes); and finally the stakeholder perceptions that influence uptake, including the factors that modify these perceptions such as advocacy and associated programmes (Perceptions).

Figure 1: Stages influencing biosimilar uptake and use



In the context of this review it is critical to appreciate that the fundamental central factor to each of these areas is the potential uncertainty that exists in evidence regarding substitution, switching and extrapolation of indication, which is unique to the consideration of biosimilar medicines. This potential uncertainty originates from the highly complex nature of these medicines and the clinical development pathway of biosimilar medicines that extends from initial laboratory-based characterisation (protein structure, pharmacokinetics, etc.) through to the design and conduct of phase III clinical trials to provide evidence of similarity in clinical safety and efficacy in specific patient populations. The considerations involved in each

of these steps are significantly different to those associated with traditional small molecule drugs with which governments, regulators, prescribers, pharmacists and patients are well accustomed. In reflection of this, the following central themes have been identified:

1. Determining Access and Subsidisation: Regulatory, Government and Healthcare Provider Considerations of Biosimilar Medicines
2. Biosimilar Medicine Uptake: Current Practice of Prescribers, Pharmacists and Patients
3. Adverse Events and Health Outcomes of Biosimilar Medicines (Pharmacovigilance): Impact of Substitution, Switching and Extrapolation of Indication
4. Evaluating and Improving Stakeholder Biosimilar Awareness, Confidence, Attitudes and Acceptance of Biosimilar Medicine

Overview of the Published Biosimilar Literature

This report includes literature published 01 December 2016 to 27 March 2017.

Analysis of these manuscripts identifies the following broad types of contributions:

- Education pieces and literature reviews
- Commentaries and individual opinion pieces
- Preclinical characterisation of potential biosimilar medicines
- Technical/methodological development
- Clinical trials of potential biosimilar medicines
- Investigator-initiated studies and case series

Consistent with the observations of the prior review, within the time period encompassed by this update there has continued to be a significant number of papers published that were of an educational or review nature. As discussed previously, these manuscripts have not specifically sought to extend or expand the knowledge base in this area but instead restate what is already known or identified as uncertainties in order to inform the reader of these issues. Some manuscripts provide a broad, relatively superficial, overview of biosimilar medicines. Other manuscripts provide an in-depth review of specific biosimilar medicines reporting only on previously published data but not contributing new information such as the results of a meta-analysis. In the context of this review, these papers do not contribute meaningfully to the specific aims of the initiative; however, they play an important role in propagating the general understanding within the broader scientific and medical communities. A list of manuscripts of this nature published during the period encompassed by this update is provided in Appendix 1.

Within this quarter there have been a significant number of manuscripts published that focus upon fundamental and technological issues relating to the production and characterisation of biological agents. Of particular note are a number of manuscripts that describe the physicochemical characterisation of a number of potential biosimilars. The regulatory processes required for the registration of biosimilar medicines demand rigorous and extensive characterisation of physicochemical (e.g. amino acid sequence, glycosylation pattern) and pharmacological properties (e.g. target binding) of potential biosimilar medicines and comparison of these properties with the reference product. The results of this extensive characterisation and comparison process provides the critical foundation upon which potential biosimilar medicines can then be subjected to further clinical evaluation and as such manuscripts reporting these

findings are of great importance to the development and evaluation of biosimilars. However, these manuscripts are highly detailed and technical in nature; the specific content of which is outside of the scope of the communication aims of the Initiative. Therefore, these manuscripts will not be discussed in greater detail in this review. A list of manuscripts of this nature published during the period encompassed by this update is provided in Appendix 2.

Given the general nature of the publications on biosimilars, it is not possible to differentiate articles of an educational nature or those pertaining specifically to biosimilar development from those that specifically seek to contribute new knowledge to the topic, and as such are pertinent to this review, through the use of specific search terms or exclusion criteria. Therefore, filtering of publications relevant to this review through hand-searching was necessary.

THEME 1: Determining Access and Subsidisation: Regulatory, Government and Healthcare Provider Considerations of Biosimilar Medicines

In the development and regulatory evaluation process of potential biosimilar medicines, compounds that demonstrate appropriate results in the extensive physicochemical and pharmacological characterisation are then subjected to clinical evaluation in phase I studies to compare their pharmacokinetic (PK) characteristics with those of the reference product. As these studies are specifically designed to assess pharmacokinetic endpoints these studies are typically conducted in healthy volunteers but may be conducted in patients depending upon a range of factors such as the potential risks associated with the use of the agent.

During the current update period four phase I pharmacokinetic studies comparing a potential biosimilar medicine with a reference product were reported. In addition, there was a single study of biosimilar insulin glargine that investigated more appropriate pharmacodynamics, rather than pharmacokinetic, endpoints consistent with the nature of the biological actions of insulin. In each of the trials reported, the potential biosimilar met the pre-specified acceptance criteria for the relevant pharmacokinetic/pharmacodynamic parameter endpoints. In some instances, phase I studies with pharmacokinetic endpoints may provide preliminary insight into the pharmacodynamics (PD) or clinical effects of the potential biosimilar medicine, although these studies are not powered for these endpoints. A summary of the results of these studies are presented in the table below (Table 1).

Table 1: Summary of phase I pharmacokinetic studies of potential biosimilar medicines

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Adalimumab						
ABP501 (Amgen)	US and EU Humira 40mg	Randomised, single-blind, single-dose, three-arm, parallel-group study (1:1:1)	Healthy volunteers (n=203)	90% CIs for the geometrical mean test-to-reference ratios for area under the serum concentration time curve (AUC) from time 0 extrapolated to infinity (AUC_{inf}), AUC from time 0 to the last quantifiable concentration (AUC_{last}) and maximum concentration (C_{max}) were within the pre-specified equivalence criteria of 0.80 and 1.25.	No subjects were positive for anti-Drug antibodies (ADA) at baseline. Over the course of the study 36 (54%), 38 (55%) and 45 (67%) participants in the ABP501, Humira (US) and Humira (EU) arms respectively developed binding ADAs. Neutralising ADAs were detected in 12 (18%), 15 (22%) and 14 (21%) subjects in the ABP501, Humira (US) and Humira (EU) arms respectively.	[1]
FKB327 (Fujifilm Kyowa Kirin Biologics)	US and EU Humira 40mg	Randomized, double-blind, parallel-group study (1:1:1)	Healthy volunteers (n=180)	<p>90% CIs for the ratios of area under concentration–time curve up to last nonzero value (AUC_{0-t}), area under concentration–time curve extrapolated to infinity (AUC_{0-inf}), and peak serum concentration (C_{max}) geometric means were in the acceptance range for bioequivalence of 0.80–1.25</p> <p>For the secondary PK parameter endpoints, AUC_{0-360h} was equivalent in all three treatment comparisons; $t\frac{1}{2}$ 90%CI for the FKB327:US-Humira comparison extended below the pre-specified lower limit of 0.8 (0.78) whilst the two other comparisons were within the limit.</p>	Approximately 5% of subjects had detectable ADA at baseline. At last sampling, 69.5%, 73.3% and 70.0% of FKB327, Humira (EU) and Humira (US) participants respectively were positive for ADAs.	[2]

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
LBA (LG Chem, Ltd. formerly LG Life Sciences, Ltd., Seoul, Korea)	Humira	Randomized, double-blind, single-dose, two-arm, parallel-group (1:1)	Healthy male volunteers (n=116)	90% CIs for the test to reference ratios for drug for the maximum serum concentration (C_{max}), area under the serum concentration-time curve (AUC) from time zero to the last observed time point (AUC_{last}), and AUC extrapolated to infinity (AUC_{inf}) were close to 1 with values of 1.01 (0.92–1.11), 0.98 (0.86–1.11), and 0.96 (0.83–1.10) respectively and within the specified acceptance criteria of 80-125%.	No participants were positive for ADAs at baseline. At day 65, ADAs were detected in 24 (44%) participants in the LBA group and 25 (46%) participants in the Humira group. All ADA positive participants had neutralizing ADAs.	[3]
Insulin Glargine						
LY2963016 (Eli Lilly)	Lantus	Randomized, double-blind, single-dose, two-period, crossover, 42-hour euglycaemic clamp study	Patients with Type 1 Diabetes (n=20)	<p>A variable intravenous infusion of insulin lispro or glucose was initiated to obtain a target blood glucose level of 5.6 mmol/L (100 mg/dL).</p> <p>The survival curves for LY IGlar and Lantus were similar over the 42-hour clamp interval (log-rank test of equality $p = .859$, Cox proportional hazards ratio [LY IGlar/Lantus] was 1.063 ($p = .8777$). The 90% CIs for the [LY IGlar/Lantus] ratios of total glucose infusion during the clamp (G_{tot}) and the maximum glucose infusion rate (R_{max}) overlapped 1, 0.46-1.30 and 0.52-1.61 respectively.</p>		[4]

Potential biosimilar medicines that demonstrate appropriate pharmacokinetic parameters in phase I studies are then subject to phase III clinical trials to evaluate efficacy and safety outcomes in comparison with the reference product. Within the update period there was a single report describing the clinical outcomes obtained in phase III clinical trials of a potential biosimilar medicine.

- ❖ Papp et al, 2017: Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study[5]

This phase III 52-week, double-blind randomized study sought to compare the efficacy and safety of ABP 501 with adalimumab (Humira®) in patients with moderate to severe psoriasis (n=350). This manuscript reports the outcomes to week 20. Participants were required to have moderate to severe psoriasis (Psoriasis Area and Severity Index [PASI] score of 12 or more) which had been stable for at least 6 months and involved at least 10% of body surface area, be candidates for phototherapy or systemic therapy and have had an inadequate response to or were unable to tolerate or receive at least 1 conventional systemic therapy. Patients who had previously received adalimumab or a biosimilar of adalimumab, or two or more biologics for psoriasis were excluded. ABP 501 and adalimumab were administered with an initial loading dose of 80 mg subcutaneously followed by 40 mg subcutaneously every other week for 16 weeks. At week 16, participants achieving at least a 50% improvement in PASI score from baseline (PASI 50) were eligible to continue in the study at which point those initially receiving the reference product (Humira®) were re-randomized (1:1) to either continue reference product (Humira®) or switch to ABP 501 for the remainder of the 52 weeks. Patients who initially received the potential biosimilar (ABP 501) continued to receive that product for the entire study duration. The primary efficacy end point was the percent improvement in PASI score from baseline to week 16 with the pre-specified margin demonstrating clinical similarity of 95%CI: -15 to 15. At week 16, the percent PASI improvement from baseline was 80.9 in the ABP 501 group compared to 83.1 for the reference product (Humira®) group -2.18 (95% CI: -7.39-3.02) which was within the pre-specified margin demonstrating clinical similarity. There were no differences of 5% or more for any treatment emergent adverse events. During the initial 16-weeks, 55.2% (96 of 174) of patients in the ABP 501 and 63.6% (110 of 173) of patients in the reference product group (Humira®) developed binding anti-drug antibodies (ADAs) and 9.8% (17 of 174) and 13.9% (24 of 173) developed neutralizing ADAs respectively. The authors conclude that *“this randomized, double-blind study demonstrated clinical similarity of ABP 501 to adalimumab in percent PASI improvement at week 16”*.

Once biosimilarity of the new product against the reference has been established through phase I and III trials, it is the national and international regulatory environment that is the foundational determinant of use. Within this quarterly update period, two publications were identified that related to this topic. Of these, one paper examined the economic impact of the introduction of a biosimilar within a local region; while this paper does not specifically relate to policy, the cost of treatment is a strong determinant informing policy relating to biosimilar access and use.

- ❖ Vogler et al, 2017: How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries[6]

This paper examined the pharmaceutical pricing and reimbursement policies across Europe with respect to their ability to ensure affordable access to medicines. Whilst the paper does not specifically examine biosimilars, a section describing policies on biosimilar medicines is included. The authors note that *“though*

European countries seem to be advanced with regard to biosimilar medicines compared to the rest of the world, overall governments in European countries appear to be still struggling to develop the best policy option mix for achieving most benefit from biosimilar medicines.” Nonetheless, Norway’s combination of several policies relating to pricing, uptake enhancement and education are claimed by the authors to be a “best-practice example”. The authors note that the “policy of tendering through a public procurement agency for medicines used in public hospitals, and closely works with the clinicians to educate and encourage them to prescribe the tendered, lower-priced medicines”, that the “price reductions that Norway has achieved in tenders are impressive (e.g. discounts of up to 80% between originator and biosimilar medicines)” and “that this is used to ensure that in total more patients can be treated”.

- ❖ Beck et al, 2017: Biosimilar infliximab for the management of rheumatoid arthritis in France: What are the expected savings?[7]

This study examined the potential cost savings associated with the use of biosimilar infliximab to treat rheumatoid arthritis patients, using real-life adult patient data from the Alsace region of France collected in 2012, and taking into account changes in biologic drug cost over the 2012 – 2015 period. The authors examined the economic impact of six biosimilar implementation scenarios, involving not only the use of infliximab but also other antiTNFa agents, compared with a scenario in which no biosimilar infliximab was available. These scenarios included:

- Biosimilar scenario 1: this scenario relates only to the use of infliximab and does not alter the use of other antiTNFa agents. In this scenario, all patients currently receiving originator infliximab are switched to the biosimilar and all patients newly commencing infliximab receive the biosimilar.
- Biosimilar scenario 2a: this scenario focusses on the management of biologic naïve patients only. Patients currently receiving a biologic continue to receive that therapy, including patients who are receiving originator infliximab who would continue to receive the originator product. For biologic naïve patients, two separate scenarios are considered. In scenario 2a, the availability of biosimilar infliximab does not influence which antiTNFa agent is chosen for a patient, but for patients commencing infliximab, treatment is with the biosimilar. In scenario 2b, biosimilar infliximab is the treatment of choice such that patients who would have received an alternative antiTNFa agent would now be commenced on biosimilar infliximab in preference.
- Biosimilar Scenario 3: this scenario examines the impact of varying rates of switching from originator infliximab to biosimilar infliximab; this included scenarios whereby 30% (Scenario 3a), 50% (Scenario 3b) and 80% (Scenario 3c) of patients were switched to biosimilar infliximab.

The cost calculations were based on 1075 adult patients with rheumatoid arthritis who were treated with a biologic medication in 2012 within the Alsace region (10.9% originator infliximab, 26.4% adalimumab, 28.8% etanercept) and included medical costs associated with treatment (i.e. staffing and administration costs associated with in-hospital intravenous administration or at-home subcutaneous administration of the biologic medicines). The predicted annual savings of complete replacement of originator infliximab with its biosimilar (Scenario 1) were €13.6 million across France equating to an additional 1141 patients who could be treated if cost savings were reinvested. Proportional savings were seen with various rates of switching examined under Scenarios 3a-3c (30% €4.1 million, 50% €6.8 million, 80% €10.9 million). The introduction of biosimilar infliximab in treatment-naïve patients only, was associated with an estimated national annual cost saving of €1.4 million and €4.0 million for Scenarios 2a and 2b, respectively.

THEME 2: Biosimilar Medicine Uptake: Current Practice of Prescribers, Pharmacists and Patients

During the current review update period three manuscripts were published that attempted to address the theme of biosimilar uptake. Two publications described epoetin biosimilar uptake in Italian cohorts and one publication described biosimilar infliximab uptake in the UK for the management of inflammatory bowel disease.

Erythropoietin

- ❖ Trotta et al, 2017: Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: A population-based cohort study in Italy[8]

A large observational, record-linkage study undertaken in Italy (Lazio) to investigate the tolerability, effectiveness and factor affecting the uptake of epoetin biosimilars in oncology and chronic kidney disease (CKD) was reported. The authors claimed this study to be “*the largest sample of patients from the real-world practice covering the principle indications of ESAs*”. ESA naïve patients who received either an ESA reference product (Epoetin-alpha [Eprex®], epoetin-beta [Neorecormon®], epoetin-theta [Eporatio®], darbopoetin-alpha [Aranesp®] and methoxypolyethyleneglycol epoetin-beta [Mircera®]) or a biosimilar ESA product (Epoetin-alpha [Abseamed®, Binocrit®] and epoetin-zeta [Retacrit®]) between January 2012 and December 2014 in the Lazio region were included in the study. A total of 8161 CKD patients (male = 4374 [53.6%]) and 5309 oncology patients (male = 2452 [46.2%]) were identified during this period. For both clinical settings epoetin biosimilars were compared separately with epoetin reference (Eprex®) and a composite of the ‘other’ reference products (Neorecormon®, Eporatio®, Aranesp®, Mirera®). The biosimilar rate of uptake across the Lazio region of Italy was found to be 1.9% (154 out of 8161) in the CKD setting and 8.5% (453 out of 5309) in the oncology setting. Pooled analysis of the CKD and oncology patients determined that pre-selected variables related to patient characteristics (namely baseline haemoglobin [Hb], co-morbidity, previous hospitalisation and ESA regimen) did not affect the likelihood of a patient receiving a biosimilar ESA. However, analysis of the CKD population identified that CKD patients without previous hospitalisations were three times more likely to receive a biosimilar than those with previous history of hospitalisation (OR = 3.12 [95% CI = 1.69–5.75]). This pattern was observed in comparison with both the CKD epoetin and other originator subgroups. Comorbidity also influenced the decision to prescribe biosimilar ESAs in the CKD setting. The presence of severe conditions such as heart failure (OR = 1.82 [95% CI = 1.22–2.71]) and heart disease (OR = 2.21 [95% CI = 1.49–3.28]) reduced the likelihood of receiving a biosimilar product. The clinical outcomes regarding the management of anaemia in the patients described in this study are presented under Theme 3.

- ❖ Perrone et al, 2016: Pharmacoutilization of epoetins in naive patients with hematological malignancies in an unselected italian population under clinical practice setting: A comparative analysis between originator and biosimilars[9]

An observational, retrospective cohort analysis of epoetin utilisation in haematology patients that was conducted across three Italian, nationally representative, local health authority databases. All epoetin naïve patients within the studied health authorities who received at least one dispensing of epoetin-alpha biosimilar (Binocrit® or Abseamed®) or epoetin-zeta biosimilar (Retacrit®) or their corresponding reference biologic (Eprex®) to treat chemotherapy induced anaemia (CIA) were eligible. Between January 2010 and April 2012, 69 patients were identified and stratified by diagnosis; lymphoid leukemia (15%), myeloid

leukemia (7%), Hodgkin's disease (6%), multiple myeloma (30%), non-Hodgkin's (42%). Of the 69 enrolled patients, 48 (70%) received reference product and 21 (30%) received a biosimilar epoetin product. The authors compared the observed level of biosimilar epoetin uptake in this study (2010-2012) with the 2014 Italian national report on medicine usage which showed that 55.9% of newly treated epoetin-alpha users were prescribed biosimilar epoetin, demonstrating a 54.6% year-on-year increase in usage across Italy. The patients that were prescribed biosimilar epoetin (mean = 71.8 ± 11.8 [1SD]) were found to be significantly older (Pearson's Chi squared test, 95%CI; $p = 0.0130$) when compared with reference cohort (mean = 62.5 ± 14.7 [1SD]), however the authors did not offer any explanation of this finding except to note that there was *"no significant differences between the originator and biosimilar group with regards to clinical characteristics"* other than their age at baseline. No difference was reported in gender between the reference and the biosimilar groups. The average weekly dose of epoetin supplied was higher for the reference cohort than for the biosimilar group, with mean doses of $32,344 \pm 28,756$ (1SD) IU/week and $30,976 \pm 20,362$ (1SD) IU/week respectively, for the reference and biologic groups. The mean cost to the national health service per patient, attributable to the consumption of epoetins used in the study period, was $\text{€}667.98 \pm 573.93$ (1SD) and $\text{€}340.85 \pm 235.73$ (1SD), for the originator and biosimilar cohorts respectively. However, this observed difference was not reported to be statistically significant (Pearson's Chi squared test, 95%CI; $p=0.065$). No differences were observed in %Hb increase between the reference and biosimilar group during the study (+13.7% and +13.0% respectively) or the rates of blood transfusion required in the following two months (Pearson's Chi squared test, 95%CI; $p = 0.910$).

Infliximab

- ❖ Razanskaite et al, 2017: Biosimilar Infliximab in Inflammatory Bowel Disease: Outcomes of a Managed Switching Programme[10]

This broad ranging manuscript reports on the establishment of a managed switching programme for biosimilar infliximab in patients with inflammatory bowel disease (IBD) and the outcomes that were associated with the program. Only the design of the programme will be discussed in this section of the update. The managed switching programme described in this manuscript represents a gain share agreement between the University Hospital Southampton (UHS) NHS Foundation Trust and the local clinical commissioning groups (CCGs). Under the managed switching programme all infliximab-treated IBD patients under the care of the adult IBD service were offered the opportunity to be switched to CT-P13 (Inflectra®, Hospira, UK) at the same dose and with the same frequency as originator infliximab. The programme was designed with the input of key stakeholders, including the gastroenterologists, pharmacists, the IBD nursing team, and an IBD patient panel (an open forum, usually attended by 8–10 patients, who meet with the IBD clinical team every 6–8 weeks). The influence of the IBS patient panel is further explored in Theme 4 of this update. Under the agreement reached to establish the managed switching programme, additional IBD support was to be provided through the funding of an IBD specialist nurse, a clerical post to support the service (0.5 full-time equivalent [FTE]), a pharmacist (0.2 FTE) and a dietitian (0.2 FTE); this investment as was estimated to amount to approximately 12% of the projected gross savings resulting from the switch. In describing the genesis of this agreement, the authors state that *"They were also clear that, as patients were taking the risk of switching [however small], specific investment in the IBD service caring for them was important, specifically dietitian resources and specialist nurses"*. The managed switching programme commenced in April 2015 and the outcomes associated with its implementation are described under Theme 3.

Commentary

This manuscript represents the first report of a programme of this nature that directly seeks to link economic savings associated with switching to biosimilars to additional investment in service provision.

THEME 3: Adverse Events and Health Outcomes of Biosimilar Medicines (Pharmacovigilance): Impact of Substitution, Switching and Extrapolation of Indication

Within the period encompassed by this update, there have been 20 publications that specifically examine this theme including erythropoietin, human growth hormone, filgrastim and infliximab.

Erythropoietin

- ❖ Broccoli et al, 2017: Efficacy and safety of biosimilar epoetin alpha in patients with chronic lymphoid neoplasms and chemotherapy-induced anaemia: An observational, retrospective, monocentric analysis[11]

This retrospective, observational, monocentric study evaluated patient response to biosimilar epoetin-alpha (Binocrit®) for the management of CIA in Hodgkin and non-Hodgkin lymphoma. 65 patients (median age = 69 years [57% male], range [21-90]) from a clinic in Bologna, Italy were treated subcutaneously with 40,000 IU per week for at least 4 weeks. 50 of the studied patients received first-line therapy, whereas 15 were receiving second or higher line salvage therapy. Treatment was initiated at first occurrence of a Hb level below 10 g/dL. A clinically successful treatment was defined by an increase in Hb of 1 g/dL after 4 weeks or achieving a level greater than 11 g/dL. The mean Hb level at initiation of biosimilar epoetin-alpha treatment was 9.3 (range: 8.4 – 10.4) g/dL. 42 of the treated patients (64.6%) achieved an increase in Hb level of greater than 1 g/dL within 4 weeks, with only two patients (one first line and one salvage) failing to achieve a target Hb level (non-responder) within 8 weeks. Treatment with biosimilar epoetin-alpha was well tolerated with no AEs reported related directly to this agent during the study. No episodes of pure red cell aplasia were reported in the non-responders. The authors concluded that *“biosimilar epoetin-alpha permitted transfusion independence, even in patients who were severely anaemic at the beginning of the first chemotherapy course, and allowed the administration of the most adequate dose of cytoreductive drugs.”*

- ❖ Losem et al, 2017: Biosimilar retacrit (epoetin zeta) in the treatment of chemotherapy-induced symptomatic anemia in hematology and oncology in Germany (ORHEO) - Non-interventional study[12]

An exploratory sub-analysis of the ORHEO observational study, described in detail in previous biosimilar literature review reports, was conducted to compare the tolerability and effectiveness of the epoetin-zeta biosimilar Retacrit® in the management of CIA in patients with solid tumours, lymphomas or multiple myeloma. Participants were evaluated at enrolment, 3 months and 6 months. Treatment responders were defined by a rise in Hb of 1 g/dL after epoetin treatment or achieving a level greater than 10 g/dL at 6 months. Among the 290 patients enrolled (male = 88 [30.4%]; mean age of 66.2 years [range 29 – 89]), 30 had been diagnosed with myeloma/lymphoma and 260 had a solid tumour. Solid tumours were localised to; breast (n= 95), ovaries (n=32), lungs (n=27), colon or rectum (n= 22), cervix (n=15), urological (n=12), liver (n=6) and head or neck (n=5). Overall 84.8% of patients being treated with epoetin-zeta were reported to be responders with the mean Hb level increasing from 9.6 g/dL at enrolment to 11.2 g/dL at follow up,

with minimal difference observed across the stratified groups. The median hematocrit increased by 5.3% (from 29.9 to 35.2%) during the study; again, little difference was reported across the sub-groups. The authors reported that the efficacy and safety results related closely to previous research and was similar for all the sub-groups analysed and that *“Overall, epoetin-zeta was effective and well tolerated in patients with different types of solid and haematological malignancies”*.

- ❖ Rosti et al, 2017: Management of anaemia in oncohaematological patients treated with biosimilar epoetin alfa: Results of an Italian observational, retrospective study[13]

This manuscript reports on the Sandoz sponsored ANEMONE study, a longitudinal, retrospective, observational study of patient response to biosimilar epoetin-alpha (Binocrit®) in CIA in solid tumours, Hodgkin and non-Hodgkin lymphoma, or multiple myeloma in 23 nationwide Italian oncology or haematological centres. Between June 2013 and March 2014, 215 patients (median age = 70 years [47.4% male], range [22-89]) were enrolled across the study centres. 95 patients presented with primary solid tumour, while 120 had lymphoma or myeloma and were followed for 12 weeks post initial Binocrit® dose. Treatment was initiated at first occurrence of a Hb level below 10 g/dL. A clinically successful treatment was defined by an increase in Hb of 1 g/dL after 4 or an increase in Hb of 2 g/dL after 12 weeks. The median Hb level at initiation of biosimilar EPO- α treatment was 9.6 (IQR: 8.9 – 10.1) g/dL. Of the 205 treated patients who had Hb results at week 4, 101 (49.3%) had achieved an increase in Hb level of greater than 1 g/dL within 4 weeks, whereas 72.6% achieved this target within 12 weeks. 51.6% achieved an increase in Hb level of greater than 2 g/dL within 12 weeks, the response rates were similar for both solid tumour and haematology patients. Among patients with available Hb levels at all of the time points in the study, a statistically significant increase (ANOVA; $p < 0.0001$) in Hb levels was reported for both solid tumour and haematology patients being treated with Binocrit®. Treatment with biosimilar epoetin-alpha was well tolerated with 13.5% of treated patients experiencing AEs during the observation period. ADA formation was not evaluated, however no cases of pure red cell aplasia were detected. The authors stated that the observed results are largely consistent with the literature on epoetin use and that the results of this study *“confirm the effectiveness and safety of biosimilar epoetin-alpha (Binocrit®) in the treatment of anaemia in cancer patients undergoing chemotherapy in routine practice”* and that their results are *“reassuring about the use of Binocrit® in this setting”*.

- ❖ Trotta et al, 2017: Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: A population-based cohort study in Italy[8]

This manuscript reports a large observational, record-linkage study in the Lazio region of Italy and has also been discussed under Theme 2 of this review update. The authors claimed this study to be *“the first study comparing the effectiveness and safety of ESA biosimilars with all the originators in incident ESA users”*. A total of 8161 CKD patients (male = 4374 [53.6%]) and 5309 oncology patients (male = 2452 [46.2%]) were identified during this period. For both clinical settings epoetin biosimilars were compared separately with epoetin reference (Eprex®) and the other reference products (Neorecormon®, Eporatio®, Aranesp®, Mirera®). In the CKD setting, no significant differences in risk estimates were observed between patients treated with biosimilar or reference product using a composite outcome of all-cause mortality, blood transfusion, major adverse cardiovascular event (MACE) and blood dyscrasia. There was no significant difference between biosimilar and originator epoetin (HR = 1.02; 95% CI = 0.78–1.33). A similar outcome

was determined in the oncology cohort, although a marginally protective effect was observed for biosimilars when compared with epoetin originator (HR = 0.82 [95% CI = 0.70–0.97]). However, a sensitivity analysis was performed and determined that a higher proportion of deaths in the oncological epoetin originator group were attributed to tumours which may have resulted in a confounding effect. The authors concluded that the study suggests *“a comparable risk/benefit profile of epoetin biosimilars with all the ESA originators in real-life practice”*.

- ❖ Alifieris et al, 2017: A retrospective open-label uncontrolled study of Epoetin zeta on the treatment of chemotherapy-induced anemia in solid tumors[14]

A retrospective, open label, non-controlled, phase IV study at one medical site, to investigate the tolerability and effectiveness of the epoetin-zeta biosimilar in the management of CIA in patients with solid tumours was reported. Initial subcutaneous dose was fixed as 40,000IU/week and responders were defined by a rise in Hb of 1 g/dL within four weeks, patients who did not meet this target were given a further 4 week cycle at a dose of 300IU/kg three times per week. Once targets were achieved then a 25-50% dose reduction protocol was initiated. The duration of the study was 12 weeks. A total of 1287 patients (male = 807 [62.7%]; mean age of 67.9 years [range 33 – 78]) were enrolled between January 2010 and March 2015, of which 893 (69.4%) completed 12 weeks of treatment. Solid tumours were stratified by diagnosis to; non-small cell lung cancer (n= 438), colorectal (n=374), breast (n=308), other e.g. pancreatic tumours made up less than 5% of the total cohort. 1016 (79%) of patients being treated with epoetin-zeta responded (Hb increase greater than 1 g/dL) within 4 weeks, this number increased to 1120 (87%) by week 8. All of the intention-to-treat group were included in the safety analysis; 575 severe AEs were reported with a possible causal relationship reported for 14 of these SAEs over the 12 weeks of treatment. The authors noted that the rate of thromboembolic events observed in the current study was higher than that observed in the ORHEO cohort, however they attributed this to the population in this study which consisted of 30% stage III and 44% stage IV disease. The authors concluded that the risk of AE is comparable with the historical data for the reference product and demonstrates epoetin-zeta to be effective and safe.

- ❖ Castelli et al, 2017: Biosimilar epoetin alfa increases haemoglobin levels and brings cognitive and socio-relational benefits to elderly transfusion-dependent multiple myeloma patients: results from a pilot study[15]

An observational pilot study investigating the relationship between the management of anaemia and cognitive function deficit using epoetin-alpha biosimilar (Binocrit®) treatment in patients with multiple myeloma was reported. Erythroid response and transfusion rates were considered primary endpoints, with changes in Mini-Mental State Evaluation (MMSE) and QOL as measured by the Functional Assessment of Cancer Therapy Anemia (FACT-An) scale were considered secondary outcomes. Initial subcutaneous dose was fixed as 4,000 IU/week and responders were defined by a rise in Hb of 1 g/dL within four weeks, patients who did not meet this target were given a further 4 week cycle at a dose of 300IU/kg three times per week. Once targets were achieved then a 25-50% dose reduction protocol was initiated. The duration of the study was 12 weeks. A total of 31 multiple myeloma patients (male = 15 [48.4%]; mean age of 75 years [range 65 – 84]) were enrolled between December 2013 and December 2015. 15 (48.3%) patients being treated with biosimilar epoetin-alpha responded (Hb increase greater than 1 g/dL) within 4 weeks, this number increased to 22 (71%) by week 12. The authors reported positive relationships between Hb

levels and patient QOL and cognitive ability. Incremental increases in Hb level were associated with incremental increases in FACT-An difference scores and MMSE difference scores. Successful multiple myeloma treatment was not found to correlate with increases in FACT-An and MMSE. The authors concluded that this preliminary study suggests that biosimilar epoetin-alpha treatment safety, efficacy and cost-saving properties correlates positively with improvements in patients' mental status and global quality of life.

Human Growth Hormone

- ❖ Ferone et al, 2017: Long-term safety and efficacy of Omnitrope® in adults with growth hormone deficiency: Italian interim analysis of the PATRO Adults study [16]

This manuscript reports the results from an interim analysis of an Italian sub-group (n=67) enrolled into the international PATRO-adults post marketing surveillance study of the somatropin biosimilar Omnitrope® to treat human growth hormone deficiency (GHD). Of this sub-group, 15 (22.4%) patients had discontinued treatment for reasons including; wish to discontinue injections (n = 2), adverse effects (n = 1), referral to another endocrinologist (n = 1), non-compliance (n = 1) loss to follow-up (n = 2) reason unknown (n = 8). A similar discontinuation rate (21.9%) was observed across the international PATRO cohort. A total of 89 adverse events (AE) had been reported in 37 (55.2%) of the Italian patients. In comparison AEs were reported in 473 (49.6%) of the international cohort. The most common AEs reported in both the Italian sub-group and the wider international group were arthralgia, asthenia and insomnia. HGH has mitogenic properties and a concern that recombinant hGH therapy could increase the risk malignancy has been previously expressed. The authors reported that there is currently no evidence from the Italian subgroup that Omnitrope® therapy increases the risk of malignancy; one case was reported however it was not thought to be drug related. As such the authors concluded that the findings were consistent with the international PATRO Adults study (September 2015) and that Omnitrope® is well tolerated in Italian adults with GHD in routine clinical practice.

- ❖ Lughetti et al, 2016: Long-term safety and efficacy of Omnitrope, a somatropin biosimilar, in children requiring growth hormone treatment: Italian interim analysis of the PATRO Children study [17]

This manuscript reports the results from an interim analysis of an Italian sub-group enrolled into the international PATRO-children post marketing surveillance study of Omnitrope® to treat childhood hGH disease. Up to August 2015, 186 patients (57.5% male, mean age 10.2 years) had received Omnitrope® for hGH disease (n=156, 84%), Turner Syndrome (n=3, 1.6%), chronic renal insufficiency (n=1, 0.5%), Prader-Willi Syndrome (n=7, 3.8%) and children born small for gestational age (n=12, 6.5%). Of this Italian sub-group, 89.8% were naïve to hormone therapy and Omnitrope® was their first therapy. A total of 142 adverse events (AE) had been reported in 66 (35.6%) of the Italian children. The most common AEs reported in both the Italian sub-group were headache, pyrexia, arthralgia and abdominal pain. To date no confirmed cases of type 1 or type 2 diabetes or malignancy had been reported in the Italian child cohort. As such the authors concluded that the findings were consistent with the international PATRO-children study (January 2016) and that Omnitrope® is well tolerated in Italian children in a range of paediatric indications in routine clinical practice.

Commentary

The 'Patients treated with Omnitrope®' (PATRO)-Adults and PATRO-Children studies are international, multicentre, open-label, longitudinal, non-interventional post-marketing surveillance studies initiated in 2007 as part of the agreed Risk Management Plan between the EMA and Sandoz for the use of the somatropin analogue Omnitrope® to treat growth hormone deficiencies (GHD). The objective of PATRO was to monitor the long-term safety and efficacy of Omnitrope®. In total 954 adult patients across eight countries (Czech Republic, France, Germany, Italy, Spain, Sweden, The Netherlands, and UK) were enrolled into the PATRO-adults study. In total 4675 children across fourteen countries (Austria, Canada, Czech Republic, France, Germany, Italy, Poland, Romania, Slovenia, Spain, Sweden, Taiwan, The Netherlands, and UK) were enrolled into the PATRO-children study. The findings from the PATRO studies have been widely reported at conferences and that data includes the Italian cohorts presented in this review.

Filgrastim

- ❖ Yoshimura et al, 2017: Evaluation of a biosimilar granulocyte colony-stimulating factor (filgrastim XM02) for peripheral blood stem cell mobilization and transplantation: A single center experience in Japan[18]

This manuscript reports on the experience of a single centre in Japan with the use of biosimilar filgrastim (XM02) for the mobilisation of peripheral blood stem cell (PBSC) in patients with malignant lymphoma and multiple myeloma. A total of 12 patients received biosimilar filgrastim between July 2014 and October 2015 were compared with a retrospective group of 34 patients that received originator between December 2006 and July 2013. There were no significant differences between those who received biosimilar filgrastim as compare with originator with regards to outcomes such as the numbers of CD34⁺ cells in harvested and the time to engraftment after transplantation. There were no significant differences in the frequency of side effects such as bone pain and fever.

- ❖ Nicol et al, 2017: Biosimilars of filgrastim in autologous stem cell transplantation: certain differences for myeloma patients only[19]

In this letter, the authors report on a study that aimed to evaluate efficiency and safety of biosimilar filgrastim (Zarzio or Ratiograstim) as compared with a historical group that received originator (Neupogen). The authors report that no differences were identified in the lymphoma patients but that within multiple myeloma patients originator filgrastim was associated ($p = 0.04$) with a shorter duration of neutropenia (mean = 5.8 days) as compared with Zarzio (mean = 6.7 days) and Ratiograstim (mean = 7 days). This observation contrasts with the median duration of hospitalization which was shorter in the Zarzio group than for the originator group (15.2 v 16 days, $p = 0.06$). Whilst the authors state that on the basis of these findings "*Neupogen seems to be the most efficient for reducing cytopenia in patients with myeloma*" and that "*we can therefore assume that they do not have the same intrinsic quality*". However, it must be noted that whilst "*the procedure was identical through the years*" the authors also acknowledge that "*patients receiving Zarzio were also older, perhaps because the age limit for performing ASCT at our institution has increased through the years*" reflecting the limitations with the use of a comparison with a historical originator group.

Commentary

The outcomes reported in this letter are uncertain. There is an inconsistency between outcomes such as duration of neutropenia and duration of hospitalisation. As a result of the use of historical comparisons it is likely that these results are confounded due to changes in local practice that have occurred over this time frame.

- ❖ Maul et al, 2017: Efficacious and save use of biosimilar filgrastim for hematopoietic progenitor cell chemo-mobilization with vinorelbine in multiple myeloma patients[20]

This study compared the efficacy of vinorelbine combined with either biosimilar filgrastim or originator filgrastim for the chemo-mobilization of CD34⁺ hematopoietic progenitor cells (HPC) in 105 patients with multiple myeloma. HPC collection was successful in 93% (n=57) of patients of the originator group as compared with 100% (n=44) of patients in the biosimilar group (P = 0.14) and there was no difference in the duration of neutrophil engraftment after autologous transplantation between the two groups (P = 0.17). No differences in side effects were observed.

- ❖ Harada et al, 2016: Comparison of transplant outcomes and economic costs between biosimilar and originator filgrastim in allogeneic hematopoietic stem cell transplantation[21]

This study investigated a range of transplant outcomes (hematological recovery, overall survival, disease-free survival, transplantation-related mortality, cumulative incidence of relapse, and acute and chronic graft-versus host disease) following bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (PBSCT) in patients receiving biosimilar filgrastim (n=49) versus a historical group that received originator filgrastim (n=49). There were no significant differences in transplant outcomes between those receiving biosimilar or originator filgrastim. Biosimilar filgrastim significantly reduced drug cost but there was no significant difference in total hospitalisation costs.

Anti-Tumor Necrosis Factor-alpha Agents: Adalimumab, Infliximab and Etanercept

- ❖ Komaki et al, 2017: Efficacy, safety and pharmacokinetics of biosimilars of anti-tumor necrosis factor-alpha agents in rheumatic diseases; A systematic review and meta-analysis[22]

Komaki *et al.* report findings of a systematic review and meta-analysis of biosimilar anti-tumor necrosis factor-alpha agents (adalimumab, infliximab and etanercept) in rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Randomized controlled trials evaluating the efficacy and safety of biosimilar agents and their reference products in patients with RA and AS were eligible for inclusion. The primary outcomes of interest were the risk ratios (RR) of clinical response (American College of Rheumatology 20% and 70% response [ACR20, 70] for RA, Assessment of SpondyloArthritis international Society 20% response [ASAS20] for AS) and adverse events between patients treated with biosimilars and their reference product. Response was assessed at 12-16 weeks, 24-30 weeks and 48-54 weeks. A total of nine randomised controlled trials were identified involving a total of 3291 patients. Included within these nine studies are three infliximab biosimilars (BOW015, CTP-13 and SB2), two adalimumab biosimilar (Exemptia, SB5) and two etanercept biosimilars (HD203 and SB4). At some timepoints, in some indications, only a single study

was identified (eg. etanercept in RA at 48-54 weeks only includes results from HD203). Overall, the meta-analysis indicated there were no significant differences in clinical response and adverse outcomes in patients receiving a biosimilar as compared with the reference product. For example, the pooled RRs of ACR20 for RA with biosimilar adalimumab compared to the reference product agent at 12-16 weeks and 24-30 weeks were 0.98 ($P = 0.86$, 95% CI = 0.82-1.18) and 1.01 ($P = 0.91$, 95% CI = 0.90-1.12), respectively. Similarly, for infliximab the pooled RRs for RA at 12-16 weeks was 1.04 ($P = 0.33$, 95% CI = 0.96-1.13), at 24-30 weeks was 1.02 ($P = 0.70$, 95% CI = 0.91-1.15) and at 48-54 weeks was 1.12 ($P = 0.087$, 95% CI = 0.98-1.29).

Five studies included compared the rates of anti-drug antibody formation between the biosimilars and their reference products at 14 weeks, 24-30 weeks and 54 weeks. With regards to infliximab, there was no difference in the risk of ADA formation with biosimilars compared to the reference product at 14 weeks (CT-P13 only, RR= 1.00, $P = 1.00$, 95% CI= 0.57-1.76), 24-30 weeks (CT-P13 and SB2, RR=1.22, $P=0.15$, 95% CI=0.93-1.60), and 54 weeks (CT-P13 only, RR=1.05, $P= 0.66$, 95% CI= 0.86-1.28). Rate of ADA formation with biosimilar of etanercept compared to the reference agent at 24-30 weeks was significantly lower at 0.05 ($P=0.81$, 95% CI=0.01-0.21) however this represents the result from a single study of SB2 that has been previously reported.

Commentary

In previous update periods, and this update period, there have been a number of systematic reviews conducted on biosimilars but until now none have attempted to undertake a meta-analysis. Whilst meta-analyses are of clear importance in the hierarchy of evidence, the appropriateness of conducting this meta-analysis is to be questioned. In this study, the authors pooled the individual biosimilars to obtain an analysis of 'biosimilar' outcome versus originator. However, this pooling does not reflect the underlying property of biosimilar medicines that the final product is a result of the entirety of the process used to manufacture that product and that this process is manufacturer specific. It is for this very reason that the regulatory evaluation process of biosimilar medicines is based upon the totality of the evidence, spanning physicochemical characterisation (see Appendix 2 for manuscripts of this nature) through to clinical efficacy and safety in phase I and III clinical trials, for each and every potential biosimilar medicine individually. It is the totality of evidence demonstrating comparability between any individual potential biosimilar and the reference product that provides the basis for regulatory approval. On this basis, the insight that can be gained from combining multiple biosimilars, produced by different manufacturers, in a pooled 'biosimilars' group in a meta-analysis of this nature is somewhat limited, particularly given the limited number of products available and the impact that this has upon the data that is available at particular time points. Ultimately, and unsurprisingly, the findings of this meta-analysis are consistent with the individual study results that indicate that there are no differences that have been detected in the efficacy or safety of any of the biosimilar anti-tumour necrosis factor-alpha agents that have been reported to date.

Infliximab

- ❖ Komaki et al, 2017: Systematic review with meta-analysis: The efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-alpha agent (infliximab), in inflammatory bowel diseases [23]

Komaki *et al.* conducted a systematic review and meta-analysis of biosimilar anti-tumor necrosis factor-alpha agents in inflammatory bowel disease. Randomised controlled studies (RCT) or observational studies evaluating the efficacy and safety of biosimilar in patients with ulcerative colitis (UC) and Crohn's disease (CD) published prior to 1 May 2016 were eligible for inclusion. The primary outcomes of interest were the rates of clinical response, clinical remission and adverse events. The authors note that *"The outcomes of our study included clinical response and remission, but their definitions in each study were not unified"*. A total of 11 eligible observational studies involving a total of 829 patients were included. All studies utilised the biosimilar infliximab CT-P13. No RCTs were identified. The pooled rates of clinical response among Crohn's disease (CD) and ulcerative colitis (UC) at 8–14 weeks were 0.79 (95% CI = 0.65–0.88) and 0.74 (95% CI = 0.65–0.82), respectively, and at 24–30 weeks were 0.77 (95% CI = 0.63–0.86) and 0.77 (95% CI = 0.67–0.85) respectively. With regards to adverse effects, the pooled rates for overall adverse events in UC was 0.22 (95% CI = 0.04–0.63) and 0.10 (95% CI = 0.02–0.31) in CD patients. The authors conclude that the systematic review and meta-analysis indicates that *"CT-P13, a biosimilar of infliximab, was effective and safe among IBD patients"* which is consistent with the findings of the individual observational studies.

Commentary

The studies included in this analysis have previously been reported in these reviews. As identified by the authors, this meta-analysis is subject to a number of limitations. The findings of this meta-analysis are consistent with the conclusions of the individual observational reports.

- ❖ Kolar et al, 2016: Biosimilar infliximab in anti-TNF-naïve IBD patients - 1-year clinical follow-up[24]

In this manuscript, Kolar *et al.* report their experience with the use of biosimilar infliximab (CT-P13) in infliximab naïve patients with inflammatory bowel disease (CD=107, UC=33) between January 2015 and May 2016 in Prague. The mean disease duration in these patients was 6.2 ± 6.5 years. Concomitant immunosuppression was prescribed in 63 (58.9%) patients with CD and 9 (27.3%) with UC. Systemic corticosteroids were prescribed to 31 (29.0%) CD patients and 17 (51.5%) UC patients. Topical corticosteroids were prescribed to 18 (16.8%) CD patients and 2 (6.1%) UC patients. Response to biosimilar infliximab was assessed retrospectively based on clinical, endoscopic and biologic markers at weeks 14 and 54. In patients with UC, endoscopic response, measured by change in Mayo score from baseline, was assessed at week 14. Adverse events were assessed at each visit. A complete response was observed in 33 (30.8%) CD and 10 (30.3%) UC patients. Partial response occurred in 67 (62.6%) CD and 17 (51.5%) UC patients, and no response occurred in 7 (6.5%) CD and 6 (18.2%) UC patients. Of the 100 patients who reached week 54 or who terminated the therapy early, 35 (46.7%) CD and nine (36.0%) UC patients had a complete response. A partial response was achieved in 30 (40.0%) CD and 6 (24.0%) UC patients, and no response in 10 (13.3%) CD patients and 10 (40.0%) UC patients. Two CD patients ended treatment due to infusion reaction and five for other adverse events. Three patients with CD stopped anti-TNF after undergoing surgery. Anti-drug antibodies occurred in 26 (18.6%) patients. These were transient in 13 (50%)

patients. The authors state that *“The frequency and type of adverse events were similar to those observed during the treatment with original IFX (infliximab)”* and conclude that *“According to our results and reports currently available, there is no negative or harmful signal about biosimilar IFX in anti-TNF- α naïve patients and its efficiency and safety seems to be comparable to the original preparation”*.

- ❖ Kolar et al, 2017: Infliximab Biosimilar (RemsimaTM) in Therapy of Inflammatory Bowel Diseases Patients: Experience from One Tertiary Inflammatory Bowel Diseases Centre[25]

In a second manuscript, Kolar *et al.* describe their experience with the use of biosimilar infliximab (CT-P13) in patients with inflammatory bowel disease who were either infliximab naïve or who were switched from originator infliximab between the period of January 2015 and January 2016.

The infliximab naïve group included 119 patients (CD=90, UC=29) with a mean disease duration of 6.2 ± 6.3 years. Concomitant immunosuppression was prescribed to 59 (49.6%) patients, 39 (32.8%) patients were receiving systemic corticosteroids and 19 (16.0%) topical corticosteroids. Of the 97 patients who reached week 46 or terminated therapy early, 35 (48.6%) CD and 10 (40%) UC patients had a complete response. Partial response occurred in 27 (37.5%) CD and 6 (24.0%) UC patients, and no response was observed in 10 (13.9%) CD and 9 (36.0%) UC patients. In UC patients, mean Mayo score decreased from 2.74 at baseline to 1.64 at week 46 ($p = 0.0004$). At week 46, CRP decreased significantly compared with baseline (12.4 ± 19.2 vs. 5.6 ± 7.1 mg/L; $p < 0.0001$). Fecal calprotectin decreased significantly between baseline and the time of last evaluation (583 ± 382 vs. 413 ± 369 $\mu\text{g/g}$; $p = 0.0231$). At week 46, the proportion of patients receiving systemic corticosteroids decreased to 4.9% from 32.8% at baseline and the proportion receiving topical corticosteroids decreased to 0% from 16.0% at baseline. Concomitant immunosuppression remained stable.

Seventy-four patients (CD=56, UC=18) were switched to biosimilar IFX after a mean time of 3.0 ± 2.2 years of treatment with the originator. Of these patients, 35 (47.3%) were receiving concomitant immunosuppressants and one patient systemic corticosteroids. At the time of switch 5 (8.9%), patients with CD and 5 (27.8%) patients with UC were receiving an intensified infliximab regimen consisting of an increased dose, shortened interval or a combination of both. At the time of the switch, a majority of patients (52, 72.2%) were in clinical remission, 16 (22.2%) had mild to moderate active disease and 4 (5.6%) had severe disease activity. Disease activity was considered to be stable during the whole 56-week treatment period in the switched cohort of patients (remission at switch v week 56: 72.2 vs. 77.8%; $p = 0.55$; median difference of Harvey-Bradshaw index: 0, median difference of Simple Clinical Colitis Activity Index: 0). There was no significant difference between CRP at the time of the switch versus week 56 (4.3 ± 8.0 vs. 3.3 ± 3.8 mg/L; $p = 0.82$). At week 56, 12 (23.5%) CD and 6 (37.5%) UC patients were receiving an intensified infliximab regimen. Consistent with an increase in the number of patients receiving an intensified regimen, infliximab trough concentrations at week 56 were increased when compared to those at the time of the switch (4.7 ± 4.5 $\mu\text{g/ml}$ v 3.4 ± 3.8 vs.; $p = 0.01$) and the proportion of patients with infliximab trough concentrations greater than 2.8 $\mu\text{g/ml}$ increased to 64.2% from 45.9% ($p = 0.04$). With regards to antidrug antibody formation, there was a nonsignificant decrease after switching from 9.5% to 6.0% ($p = 0.54$).

Consistent with their publication reported above the authors conclude that *“According to our results and reports currently available, there is no negative or harmful signal about biosimilar IFX both in anti-TNF α -naïve and switched patients and its efficacy and safety seems to be comparable to the original preparation.”*

Commentary

Kolar and colleagues have published two closely related manuscripts describing their experience with the use of biosimilar infliximab within this update period; the first reporting on infliximab naïve patients only, the second reporting on both naïve patients and those switching from the originator product. With regards to the results presented for naïve patients, the dates for patient inclusion overlap and as such the second manuscript likely represents a subset of those reported in the first publication but insufficient details regarding the source of patients is provided to confirm this.

- ❖ Arguelles-Arias et al, 2017: Effectiveness and Safety of CT-P13 (Biosimilar Infliximab) in Patients with Inflammatory Bowel Disease in Real Life at 6 Months[26]

This manuscript reports a prospective, observational study conducted in a single centre in Spain in patients with moderate to severe Crohn's disease (CD) or ulcerative colitis (UC) treated with CT-P13. Patients included were naïve or switched from originator infliximab. In naïve CD patients, were considered to be in remission if the Harvey Bradshaw Score was ≤ 4 or to have obtained a clinical response if there was an improvement in the Harvey-Bradshaw score and withdrawal of corticosteroids. In switched patients, remission was considered to be maintained when the patient was still in remission after switching, without needing steroids, surgery or increased dose. In naïve UC patients, remission was according to Partial Mayo Score, compared to the score before starting CT-P13 therapy. In switched UC patients, remission was considered to be maintained when the patient was still in remission after switching, without needing steroids, surgery or increased dose. Of the 80 CD patients, 13 (16.25%) were naïve to antiTNF and 67 (83.75%) were switched from originator infliximab (Remicade) to CT-P13. Of those who switched, 83.5% (56/67) were in remission at the time of the switch and had a median duration of ongoing originator treatment at the start of the study of 297 weeks (range: 158-432). Of the 40 UC patients, nine (22.5%) were naïve to antiTNF and 31 (77.5%) were switched from originator. Of those who switched, 80.6% (25/31) were in remission at the time of the switch with a median duration of ongoing originator treatment at the start of the study of 203 weeks (range: 42-294). In CD patients at 3 months, 87.5% (49/56) of switched CD patients in remission maintained remission and 66.7% of naïve patients attained remission. At 6 months, 83.9% (47/56) of switched CD patients maintained remission and 50% of naïve patients attained remission. In UC patients at 3 months, 92% (23/25) of switched patients maintained remission and 44.4% (4/9) of naïve patients attained remission. At 6 months, 91.3% (21/23) of switched UC patients maintained remission (two stopped treatment due to clinical remission and mucosal healing) and 66.7% (6/9) of naïve patients attained remission. Serious adverse events were reported in 7.5% (9/120) of patients; one skin reaction, one abdominal pain, two headaches and two paresthesias during infusion treatment, one Sweet's Syndrome and two polyarthralgia. The authors conclude that their results have "*demonstrated effectiveness and safety*" of CT-P13 in inflammatory bowel disease "*at 3 and 6 months*".

- ❖ Razanskaite et al, 2017: Biosimilar Infliximab in Inflammatory Bowel Disease: Outcomes of a Managed Switching Programme[10]

In this manuscript, the authors present the outcomes from a managed switching programme of originator infliximab to biosimilar, as described in Theme 2 of this review, in patients with inflammatory bowel disease. A total of 143 patients (CD=118, UC=23s, unclassified=2) were switched from originator infliximab

to CT-P13. The median number of originator infliximab infusions prior to switching was 10 (range: 1–67), with 25.2% receiving infusions more frequently than 8-weekly. Of the 143, 101 [70.7%] were receiving concomitant immunosuppressant therapy, and 9 [6.3%] were receiving corticosteroid therapy at the time of the switch.

At the third dose after the switch to CTP13, IBD-control-8 score improved from 10.4 to 11.2 ($p = 0.041$). The authors postulate that the *“improvement in IBD-Control-8 score after the switch to CT-P13 may have been influenced by the increased monitoring and IBD specialist nursing support included in the switching programme.”* There was no significant change in mean IBD-Control Visual Analogue Score at the third dose of CT-P13 when compared to the pre-switch (72.4 v 72.5 , $p = 0.65$). No clinically significant differences were observed in mean C-reactive protein (CRP), albumin, haemoglobin levels, or platelet and white cell counts. The most commonly reported side effects were joint pains (before the switch, $n = 24$; after switch, $n = 13$), headaches (before switch, $n = 21$; after switch, $n = 16$) and infections (before switch, $n = 17$; after switch, $n = 13$). There was no significant difference in drug persistence between biosimilar and originator infliximab ($p = 0.94$). Drug acquisition costs decreased by £40,000–60,000 per month.

❖ Sung et al, 2017: Characteristics and outcomes of rheumatoid arthritis patients who started biosimilar infliximab[27]

This study was conducted using the BIOlogics Pharmacoepidemiology Study (BIOPSY), biologic DMARDs registry for RA patients of South Korea. A total of 100 RA patients (101.1 person years [PYs]) treated with infliximab were included in this study. Patients were divided into two groups: 45% of patients ($n=45$, 62.8 PYs) were included in the originator infliximab group and 55 patients (54.1 PYs) in the biosimilar infliximab group. The proportion of patients who experienced biologic DMARDs at enrolment (15.6 vs 7.3%, $p = 0.21$) and previous use of non-biologic DMARDs (3.5 ± 1.0 vs. 3.5 ± 1.4 , $p = 0.98$) did not differ between the two groups. At baseline, glucocorticoids were more common in those initiating originator infliximab as compared with those initiating biosimilar infliximab (97.8 vs. 81.8%, $p = 0.02$); however, there was no difference in the mean dose ($p = 0.61$). The prevalence of NSAID users in the originator infliximab group was higher than in the biosimilar infliximab group, although the difference was not statistically significant (95.6 vs. 85.5%, $p = 0.18$). The mean DAS28-ESR at the start of infliximab use was higher in the originator infliximab group than the biosimilar infliximab group (6.4 ± 1.1 vs. 5.8 ± 1.0 in DAS28-ESR, $p = 0.02$).

Discontinuation of infliximab before 6 months was higher in the originator infliximab group than in the biosimilar infliximab group (35.6% (16/45) vs. 23.6% (13/55). After 7.9 ± 1.8 months of treatment there was no difference in DAS28-ESR between those who received biosimilar ($n=64$) and those who received originator ($n=28$), 2.2 ± 1.2 v 2.7 ± 1.3 ($p = 0.06$) respectively. The EULAR response rate was comparable in the two groups ($p = 0.80$). No statistically significant differences between the two groups were observed in any of the remission criteria.

The number of patients who discontinued infliximab for any reason during the observation period was 21 (46.7%) for originator infliximab and 24 (43.6%) for biosimilar infliximab. The reasons for drug discontinuation were not significantly different ($p = 0.92$) with the development of ineffectiveness the most common reason in both groups, followed by adverse events. Among the 45 originator infliximab users, 17 adverse events were reported during the observation period (27.09/100PY), while 39 adverse events were reported among the 55 biosimilar infliximab users. The authors state that *“The occurrence of AEs in*

biosimilar infliximab use was 3.0 times higher than in originator infliximab use, and the occurrence of SAEs with biosimilar infliximab use was 2.5 times higher than with originator infliximab.” but note that “however, they are not conclusive, because the sample size was too small and confounding factors related to safety were not adjusted” and that “this result may be related to a higher AE reporting rate for the new drug”. Overall the authors conclude that “biosimilar infliximab is well-tolerated, safe, and of similar clinical effectiveness to originator infliximab in clinical practice.”

❖ Jahnsen et al, 2017: Experience with Biosimilar Infliximab (Remsima) in Norway[28]

This manuscript reports on the outcomes associated with biosimilar infliximab in a single centre in Norway in patients with inflammatory bowel disease in the context of induction or switching.

With regards to induction, a prospective observational study was conducted between January 2014 and February 2015, to assess the efficacy, tolerability and safety of biosimilar infliximab (Remsima) in 78 patients with moderate to severe inflammatory bowel disease (CD=46, UC=32) who had failed treatment with steroids and/or immunosuppressants. Concomitant immunosuppressants were prescribed to 30 (65%) CD patients and 8 (25%) UC patients. Corticosteroids were prescribed to 6 (13%) CD patients and 18 (56%) UC patients. No patients were directly switched from originator to biosimilar infliximab but four CD and two UC patients had previously received originator infliximab. At week 14, clinical remission was achieved in 79% (34/43) of CD patients (defined as HBI score ≤ 4) and 56% (18/32) of UC patients (defined as partial Mayo score ≤ 2). Anti-drug antibodies (ADAs) were only evaluated in patients with trough serum levels of 0 mg/l. A total of 8 patients (CD=4, UC=4) had trough levels of 0 mg/l and all had ADAs. None of these 8 patients received concomitant immunosuppressants. The authors state that “*No unexpected immunogenicity or safety findings arose during the current study*”.

The authors also report on the outcomes obtained from an open label observational cohort study of 56 patients with inflammatory bowel disease (CD=37, UC=19) to compare clinical and biochemical parameters before and after switching from originator to biosimilar infliximab. The median duration of the on-going treatment with originator infliximab was 48 months (range: 12- 156) in CD patients and 73 months (19-285) in UC patients. Concomitant immunosuppressants were prescribed to 15 (41%) CD patients and 6 (32%) UC patients. Clinical and biochemical parameters were compared between the 6 prior to the switch and the 6 months after switching. In CD patients, there were no changes in HBI and CRP levels after switching. Fecal calprotectin increased from 216 mg/kg to 585mg/kg over this time period ($p = 0.055$). Trough infliximab concentrations were higher after this switch (6.7mg/L v 78mg/L, $p = 0.026$); attributed by the authors to the use of therapeutic drug monitoring. In UC patients, there were no significant differences were in partial Mayo score, CRP, fecal calprotectin or trough serum levels after switching. The authors state that “*No unexpected adverse events were observed during the study.*”

THEME 4: Evaluating and Improving Stakeholder Biosimilar Awareness, Confidence, Attitudes and Acceptance of Biosimilar Medicines

Four original research articles were published during the review update period addressing the topic of biosimilar perception amongst healthcare professionals.

- ❖ Beck et al, 2017: Knowledge, behaviors and practices of community and hospital pharmacists towards biosimilar medicines: Results of a French web-based survey[29]

This web-based survey, conducted between June and August of 2015, aimed to understand the knowledge, experience and opinions of both community and hospital pharmacists in France toward biosimilar medicines, and to identify the barriers and potential actions to promote their uptake. Of the 74,492 registered pharmacists in France, responses were received from 802 individuals, of whom 616 (76.8%) worked in variety of roles within hospital pharmacy. Of those that responded, 467 (58.2%) had already dispensed at least once, one of the 9 biosimilar drugs available in France at that time, most commonly biosimilar filgrastim or erythropoietin. However, 62.2% of respondents indicated that they had “little knowledge” about biosimilar medicines with most pharmacists (97.4%) having at least one remaining question related to biosimilar medicines including, substitution by a pharmacist of a reference biological medicinal product with its biosimilar equivalent (79.2%), the manufacturing process of biosimilar drugs (54.9%) and naming conventions (49.8%). Pharmacists most commonly reported the main sources of information on biosimilar medicines as self-study and scientific publications (78.9%), followed by pharmaceutical companies (72.7%), fellow pharmacists (53.7%) and health institutions (eg. French National Authority for Health, 37.7%). With regards to the uptake of biosimilar medicines 92% of pharmacists identified potential “*Healthcare cost savings*” as an important consideration whilst 64.8% cited a “*positive impact on patients’ access to innovative drugs*” and 62.9% citing a “*release of resources allowing treating additional patients*”. The “*patients’ wishes to be treated with the reference biological medicinal product*” was stated by 61.8% pharmacists as a barrier to biosimilar uptake.

- ❖ Hemmington et al, 2017: Medical specialists' attitudes to prescribing biosimilars[30]

This online questionnaire explored the understanding and perceptions of specialists within New Zealand with regards to issues such as manufacturing process, extrapolation of indication, switching and explaining to patients. Participants were recruited from their respective New Zealand (NZ) medical specialist society. The time period for the survey is not stated. Of the 327 specialists approached, 110 responses were received. Respondents were mostly aged over 40 and predominantly worked in public practice or a mixture of public and private practice. The majority of participants (76%) reported having a basic understanding of biosimilars with 13% reporting a complete understanding. When asked “*If a biosimilar was funded in NZ in your area of practice, how confident would you be in the efficacy of that biosimilar?*” 70% of respondents were either very or somewhat confident. With regards to manufacturing process, 30% reported being undecided about their confidence in this aspect. When asked how long clinicians felt it would take to explain a biosimilar to a patient, estimates ranged from 1 minute to 30 minutes (mean 10.4 minutes). A significant negative correlation was identified between this estimated duration and the reported likelihood of prescribing a biosimilar ($r = -0.44$, $p = .001$). The authors conclude that “*Most medical specialists indicated that they would prescribe biosimilars for all or some clinical conditions that met relevant criteria*” and their findings “*highlight the need to provide clinicians with guidance on how to explain biosimilars and patient material that effectively explains biosimilars to patients.*”

- ❖ Monk et al, 2017: Barriers to the access of bevacizumab in patients with solid tumors and the potential impact of biosimilars: A physician survey[31]

This survey of oncologists in the US, Europe, Brazil, Mexico and Turkey sought to investigate the use of and barriers to bevacizumab for the treatment of advanced solid tumours including metastatic colorectal cancer, metastatic non-squamous non-small-cell lung cancer, metastatic ovarian cancer, metastatic breast cancer and glioblastoma. Although not the major focus, attitudes towards a biosimilar, if one were available, were also examined. Across all tumour types, oncologists cited efficacy and cost as the most important factors influencing prescribing were a biosimilar available. Of those who would 'probably' or 'definitely' not prescribe a bevacizumab biosimilar, the factors that were cited that would increase their likelihood of prescribing the biosimilar included efficacy and safety data and a larger cost reduction than the 20% upon which the question was premised.

- ❖ Razanskaite et al, 2017: Biosimilar Infliximab in Inflammatory Bowel Disease: Outcomes of a Managed Switching Programme[10]

As discussed in Theme 1 of this update, this manuscript describes the establishment of a managed switching programme for biosimilar infliximab in patients with inflammatory bowel disease (IBD). The IBD patient panel (an open forum, usually attended by 8–10 patients, who meet with the IBD clinical team every 6–8 weeks) was an important stakeholder in the design of the programme. The authors report that the IBD patient panel *"expressed concerns about the gaps in the evidence base around the use of biosimilars in IBD and in particular the concept of switching patients"*, that they acknowledged that infliximab was a high-cost medicine and that *"they were keen to see part of the savings invested in developing the IBD service with a focus on dietitian support and specialist nurses"*. The authors also report that the IBD panel was *"reassured by the increased monitoring patients would experience as part of the managed switching programme and the risk management aspects of the programme"*. In their conclusions, the authors note that in their opinion the *"Key to the acceptance of the switching of their patients to biosimilar infliximab, was the development of an understanding of the science and the regulatory processes behind biosimilars as well as the reassurance of a robust risk management system to minimise any potential risk to patients" and that "using a gain share agreement to ensure that all stakeholders were appropriately incentivised to allow significant service development while delivering significant savings to the health economy"*.

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APPENDIX 1

The following list contains manuscripts that were published during the review period that are of an educational or review nature. These manuscripts did not contribute new information to literature on biosimilar medicines. Some manuscripts provide a broad, relatively superficial, overview of biosimilar medicines. Other manuscripts provide an in-depth review of specific biosimilar medicines, reporting only on previously published data, but not contributing new information such as the results of a meta-analysis.

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APPENDIX 2

The following list contains manuscripts that were published during the review period that are of a technical nature and relate to topics such as the physicochemical and pharmacological characterisation of potential biosimilar medicines.

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