National Medicines Information Centre

VOLUME 27
NUMBER 3
2021

St James's Hospital, Dublin 8
Tel 01 4730589 or 1850 727 727; twitter @NationalNmic; nmic@stjames.ie

QUESTIONS AND ANSWERS ON BIOSIMILARS

- **Biosimilars are biological medicines that are highly similar in all essential aspects to an already approved (reference) biological medicine and have gone through a robust authorisation process to demonstrate therapeutic equivalence**
- **Under the supervision of a physician, biosimilars can be used interchangeably with the reference medicine or with other biosimilars of that reference medicine**
- **All biological medicines must be prescribed by brand name rather than by International Nonproprietary Name (INN) for traceability and to avoid inadvertent substitution**
- **There are an increasing number of patients being prescribed a biosimilar e.g. the best-value biological medicines for adalimumab and etanercept. This trend is likely to continue in the coming years.**

INTRODUCTION

Biological medicines are well established in clinical practice; they were introduced for autoimmune conditions and cancer but now provide therapeutic options for a wide range of conditions.[1,2] **While biological medicines play a vital role in the treatment of many diseases, they are responsible for a significant proportion of the total drug expenditure.[3,4]** In Europe it is estimated that 30% of all drug expenditure is on biological medicines.[4] In Ireland, biological medicines feature in the "Top 10 medicines" of expenditure reports under the Community Drug Schemes and in secondary care.[3,5]

In Europe and other jurisdictions, an increasing number of biosimilar medicines (biosimilars) are being developed.[2] **Biosimilars are biological medicines that are highly similar in all essential aspects to an already approved biological medicine (so-called "reference medicine").[2]** Companies can market approved biosimilars once the period of market protection of the reference medicine expires (usually after 10 years).[2] The EU approved the first biosimilar in 2006 (Omnitrope®, a biosimilar of the reference medicine Genotropin®), and up to June 2021 there were >65 biosimilars approved in Europe.[2,6] Healthcare professionals (HCPs) have increasing clinical experience with the use of biosimilars and evidence shows that they can be used as safely and effectively as reference biological medicines.[2,7-13] Over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference biological medicines.[2] **The introduction of biosimilars following patent expiry of the reference biological medicine, offers potential economic benefit to healthcare systems, which may result in increased patient access to medicines.[1-3,14-17]** The biosimilars market will continue to grow in the coming years as more medicines lose patent exclusivity and additional biosimilars are approved.[3] This bulletin updates a previous bulletin on biosimilars (2015).

BIOLOGICAL MEDICINES

What are biological medicines? Biological medicines contain one or more active substances produced by or extracted from a biological source (e.g. living cells or organisms), resulting in a specific therapeutic molecule or group of molecules, usually proteins.[1,2,18] There are many different types of biological medicines (see table 1).

Table 1: Examples of biological medicines[18]

- Recombinant proteins such as insulin, epoetin, and follicle stimulating hormone
- Monoclonal antibodies, which are highly targeted engineered antibodies used to treat a wide variety of conditions, such as rheumatoid arthritis e.g. infliximab
- Blood-derived products e.g. clotting factors and animal-derived products (e.g. heparin)
- Vaccines

The structural properties of a biological medicine are key factors that dictate its pharmacological profile, including biological activity, clinical efficacy, side-effect profile and safety.[1] Complex biologicals (e.g. monoclonal antibodies) are characterised not only by their amino acid sequence, but also by their three-dimensional (3-D) structure, the degree and location of their glycosylation sites, their isoform profiles and the degree of protein aggregation.[1] The active substance in a biological medicine can have an inherent degree of minor variability (microheterogeneity).[2,18] The manufacturing of a biological medicine requires multiple complex steps, each of which may have a profound impact on the final structure of the biological medicine.[1] Due to the inherent variability of the active substance and the manufacturing process, biological medicines exhibit a degree of variation, even between batches of the same product (so called batch-to-batch variability).[2,14,18] Due to this variability, it is not possible to make an exact copy of any biological medicine.[18] **Strict controls are always in place during manufacturing to minimise variability and to ensure that any variability does not affect the safety and efficacy of a biological medicine.[2]**

Can biological medicines cause an immune response? All biological medicines have the potential to induce an immune response (i.e. immunogenicity), however they usually cause no or only a minor immune response (e.g. transient appearance of antibodies).[2] Immunogenicity may result in adverse reactions ranging from mild injection-site reactions to more rare, serious and life-threatening reactions.[2] In addition, immunogenicity could potentially result in antibodies against the biological medicine which could neutralise the medicine's activity and reduce its efficacy.[2]

How do biological medicines compare to chemically-based medicines? Biological medicines differ from chemically-based medicines (also known as small molecule medicines) in a number of ways (see table 2). In general, biological medicines tend to be more targeted in their therapeutic activity than chemically-derived molecules.[1,18]

Table 2: Differences between biological medicines and chemically-based medicines[1]

	Biological	Chemically-based (small molecule)
Examples	Insulin, denosumab, adalimumab	Paracetamol, aspirin, propranolol
Properties		
Size	Large	Small
Structure	Complex	Simple
Degradation	Complex mechanisms	Precise and known
Variability	Heterogeneous product	Single, defined structure; no variability
Manufacturing	Unique living cell bank (unlikely to achieve identical copy)	Predictable chemical reaction (identical copy can be made)
Characterisation	Difficult to fully characterise	Easy to fully characterise
Stability	More sensitive	Less sensitive
Immunogenicity	Higher potential	Lower potential

BIOSIMILARS

What is a biosimilar? A biosimilar is a medicine that is highly similar to a reference biological medicine (which already has a marketing authorisation [MA]) in terms of its quality, safety and efficacy.[18] **There are minor differences between a biosimilar and the reference biological medicine, however there are strict controls to ensure that any differences do not affect the biosimilar's efficacy or safety.[2]** The biosimilar must contain the same protein (i.e. amino acid sequence) and the same 3-D structure as the reference biological medicine, as well as having the same posology and usually the same route of administration; there may be differences in the form, formulation, excipients, presentation (e.g. powder to be reconstituted versus solution ready for injection) and administration device.[2,18] **Biosimilars must be manufactured to the same quality standards as the reference biological medicine.[18]**

How do biosimilars compare to generic medicines? While biosimilars have the same primary structure (i.e. identical amino acid sequence) and have a high degree of similarity in molecular and biological terms to the reference medicine, it is not possible to produce an exact copy of a reference biological medicine.[2,18] Biosimilars are more challenging and expensive to develop than generic medicines,[14] and have a defined and comprehensive regulatory approval process.[2] Therefore generic medicines are only possible for chemically-based medicines, while biosimilars are possible for biological medicines.

How do biosimilars get a marketing authorisation? As for all medicines, biosimilars must obtain a MA before they can be marketed in the EU.[18] Biosimilars are approved according to the same strict standards of quality, safety and efficacy that apply to any other biological medicine.[2] **The regulatory evaluation of biosimilarity relies on comprehensive comparability studies with the reference biological medicine. These studies are designed to investigate if there are any clinically meaningful differences between the biosimilar and the reference biological medicine, and to ensure that there are no significant differences in the benefit/risk profile.[18]** The assessment is a tiered approach based on 3 steps: 1) quality comparability (physiochemical and biological), 2) non-clinical comparability (*in vitro* and more rarely *in vivo* studies) and 3) clinical comparability (pharmacokinetics, pharmacodynamics, safety [including immunogenicity] and efficacy).[2,18,19] Further details on the approval process are available on the Health Products Regulatory Authority (HPRA) [www.hpra.ie] and European Medicines Agency (EMA) [www.ema.europa.eu] websites.
The key principle on which a biosimilar is approved for use is that any differences between it and the reference biological medicine have been shown not to affect its safety or efficacy in a clinically significant way.[18]

Do biosimilars have the same indications as the reference biological medicine? Clinical trials are required to support each indication of an approved reference biological medicine, however this may not be the case for biosimilars.[2,18,19] Once biosimilarity has been shown for a biosimilar for one indication by comparability to the reference medicine, safety and efficacy data may be extrapolated to other indications for which the reference medicine is approved. This is on a case-by-case basis.[2,18] It is important to review the Summary of Product Characteristics (SmPC) of a biosimilar to confirm the approved indications, as a **biosimilar may not have the same authorisation for all the indications as the approved reference medicine.[18]** Biosimilars are clearly identified as such in section 5.1 of their SmPC.

How are biosimilars monitored following marketing authorisation? Similar to all biological medicines, the clinical safety of biosimilars must be monitored closely on an ongoing basis following approval, including

continuous benefit-risk assessment.[18] Any specific safety monitoring imposed on the reference medicine will also apply to the biosimilar.[18] **All new medicines, including biosimilars, are subject to additional monitoring following approval which includes the display of the black inverted triangle symbol (▼) in the SmPC and the package leaflet.**[18] HCPs are asked to report any suspected adverse reactions associated with all medicines (including biosimilars) that are subject to these additional monitoring requirements.[18]

What is meant by the terms interchangeability, switching and substitution?

Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect, such as replacing a reference medicine with a biosimilar (or vice versa) or replacing one biosimilar with another.[2,18] It is demonstrated during the approval process that there are no clinically meaningful differences between the biosimilar and the reference medicine, therefore **biosimilars can be used interchangeably with the reference medicine or with other biosimilars of that reference medicine under the supervision of a physician.**[18]

Switching refers to the replacement of a biological reference medicine with an appropriate biosimilar by the **prescriber.**[3,14] Switching to biosimilars has already become routine clinical practice in some European countries (e.g. Denmark, UK) and in some hospitals in Ireland;[3,14,17,19] there have been no new safety signals or reports of loss of efficacy from these "real world" switches.[3,7,13,17-19]

Automatic substitution is when a medicine is substituted for another by a pharmacist without the input of the prescriber.[3,14,18] **The Health Act 2013 specifically precludes biological medicines from inclusion in a list of interchangeable medicines, therefore automatic substitution of biological medicines is not permitted under Irish legislation.**[4,20]

What evidence is there to support a switch to biosimilars? While clinical studies on switching between reference products and biosimilars are not required for regulatory approval, there is nonetheless a large body of evidence (including "real world" data) based on evaluation of the impact of switching (on efficacy and safety [including immunogenicity]) from reference medicines to biosimilars for many biologicals including erythropoietin, human growth hormone, filgrastim, etanercept, adalimumab, infliximab and rituximab.[8,9,11-13,17,21-24] **The overall data from patients who have been switched from reference medicines to corresponding biosimilars shows that there is no clinically significant difference in efficacy and safety (including immunogenicity).**[7-13,23] Experts conclude that biosimilars licensed in the EU can be switched with their reference biological medicine, however as with all biological medicines, continued pharmacovigilance is important to monitor for safety events.[8,11,21]

USE OF BIOSIMILARS IN CLINICAL PRACTICE

The use of biosimilars is supported by many professional organisations.[14,19,25-27] **The use of a biosimilar must be assessed for each patient by the prescriber** and be in accordance with the approved indications in the SmPC.[3,14,19] **All biological medicines, including biosimilars, should be clearly identifiable by brand name and batch number.**[2,14,18,19] This is to ensure that the medicines are traceable should any product-specific safety concerns arise. It also ensures that the substitution with other biologicals (including biosimilars) does not inadvertently occur when the medicine is being dispensed.[2,14,18,19] It is important that the patient (or carer) is aware of the brand of the biological medicine being prescribed to avoid accidental substitution and is educated on the use of a new device (if applicable), with a focus on any different administration or storage requirements.[3]

Are biosimilars widely used in clinical practice? The biosimilar market in Europe is the largest worldwide and many policy recommendations have been adopted to increase biosimilar uptake and reduce drug expenditure.[5,17] Despite the introduction of policies to increase the use of biosimilars, large differences remain in the price and the uptake of biosimilars between countries and even within a country.[15,16,28] For example, despite increasing biologic utilisation, Denmark has realised considerable cost savings by implementing biosimilar switching policies for infliximab, etanercept and adalimumab, with the majority of patients switched on the basis of a national tender.[7,17,29] There was no associated increase in disease activity or development of antibodies following these switches.[6,7,17] There has been lower uptake of biosimilars in some other EU countries.[5] Reasons for poor uptake include lack of familiarity with biosimilars, therapeutic inertia, concern about patient confusion between different brand names and different looking formulations, perceived lack of efficacy and nocebo effect (negative expectations towards a given treatment).[21]

What about the use of biosimilars in Ireland? In Ireland the majority of biological medicines are prescribed and initiated in the hospital setting (e.g. antineoplastic and immunomodulatory drugs); patients can then access them either from a community pharmacy where they are supplied via the High Tech Arrangement, or they can be supplied and administered to a patient in a hospital setting.[5] Some hospitals in Ireland have biosimilar policies in place that detail the changeover process when switching from a reference biological medicine to a biosimilar (and vice versa).[3,18,19] The utilisation of biosimilars in Ireland was significantly lower compared to other European countries; for example, in 2016 the market share of biosimilars for tumour necrosis factor-alpha (TNF-α) inhibitors was 5% in Ireland compared with 90% in Denmark and 82% in Norway.[30,31] The Health Service Executive (HSE)-Medicines Management Programme (MMP) highlighted the potential for biosimilars to significantly reduce drug expenditure and facilitate greater access to such treatments in the Irish healthcare setting, and introduced the best-value biological medicine (BVB) initiative in 2018.[30,32]

What is a best-value biological medicine? A best-value biological medicine (BVB) is a biosimilar of a biological medicine that has been evaluated and recommended by the MMP. The evaluation process includes consultation with relevant stakeholders and uses set criteria as outlined in table 3.[30] In addition, resources to support the prescribing and utilisation of the BVB medicine are published by the MMP for clinicians, pharmacists, nurses and patients.[29,32-34]

Table 3: Criteria considered by the HSE Medicines Management Programme to identify a best-value biological medicine[30]

Criteria include:	
• Acquisition cost • Therapeutic indications • Formulation considerations • Product range e.g. pack sizes & strengths available • Product stability including storage requirements • Administration devices • Patient factors	• Expenditure in the therapeutic area & potential for cost saving • Clinical guidelines • Robustness of supply to the Irish market • Department of Health National Biosimilar Policy • Utilisation & clinical experience with the biological medicine • Any other relevant factors

Examples of best-value biological medicines used in clinical practice in Ireland The TNF-α inhibitors were the first BVB medicine initiative which commenced in 2019.[5] Biological medicines containing TNF-α inhibitors were the highest expenditure category on the High Tech Arrangement in 2017, representing 10.9% of the total expenditure on medicines by the Primary Care Reimbursement Service (PCRS).[30] The availability of biosimilars for Humira® (adalimumab) and Enbrel® (etanercept) was seen as an opportunity to reduce expenditure for these medicines.[5] The MMP identified four BVB medicines for adalimumab; Amgevita®, Hulio®, Idacio® and Imraldi™, and one BVB medicine for etanercept; Benepali™. A number of measures were implemented to support the uptake of the BVB medicines, including the delivery of information sessions to clinicians in the areas of rheumatology, gastroenterology and dermatology, and the introduction of a gain-share incentive which offered the relevant clinical service €500 for each patient initiated on or switched to a BVB medicine (for investment in patient care).[5,35] Twelve months after introducing the initiative, these BVBs accounted for 50% of the market share, resulting in estimated savings of €22.7 million (facilitating access to new innovative medicines for patients) and €3.6 million (for the specialities to invest back into patient care).[5,36] The HSE recommended in February 2020, that reimbursement of adalimumab and etanercept under the High Tech Arrangement would only be supported for the BVB medicines in adult patients commencing these therapies.[35] It is likely that there will be further BVB initiatives in the future.

What biosimilars are approved in the EU and available in Ireland? There are a large number of biosimilars approved in the EU; examples of biosimilars that are available in Ireland are shown in table 4.

Table 4: Examples of biological medicines for which a biosimilar is currently approved in the EU and available in Ireland[2,37-76]*

Classes of biological medicines and active ingredients	Reference biological medicine	Examples of biosimilars available in Ireland**
Growth factors		
Epoetin	Eprex®	Retacrit®
Filgrastim	Neupogen®	Accofil®, Grastofil®, Nivestim®, Tevagrastim®
Pegfilgrastim	Neulasta®	Pelgraz®, Pelmeg®
Hormones		
Follitropin alfa	Gonal-f®	Bemfola®
Insulin glargine	Lantus®	Abasaglar®
Somatropin	Genotropin®	Omnitrope®
Teriparatide	Forsteo®	Movymia®, Terrosa®
Fusion proteins		
Etanercept	Enbrel®	Benepali™
Proteins		
Adalimumab	Humira®	Imraldi™, Idacio®, Amgevita®, Hulio®
Infliximab	Remicade®	Flixabi®, Inflectra®
Rituximab	MabThera®	Ruxience®, Truxima®
Trastuzumab	Herceptin®	Herzuma®, Trazimera®, Kanjinti®, Ogivri®,
Bevacizumab	Avastin®	Mvasi®, Zirabev®,

* the Summary of Product Characteristics contains full prescribing details; **available under the High Tech Arrangement/ Community Drug Scheme or listed on www.medicines.ie (June 2021)

USEFUL RESOURCES

- Medicines Management Programme - Best-Value Biological Medicines, available on https://www.hse.ie/yourmedicines
- Health Products Regulatory Authority (HPRA) – Guide to Biosimilars for Healthcare Professionals (August 2020), available on www.hpra.ie
- National Cancer Control Programme – NCCP Guidance on the use of Biosimilar Medicines in Cancer Treatment (version 4 May 2021), available on www.hse.ie
- European Medicines Agency - Biosimilars in the EU: Information guide for healthcare professionals (2019), available on www.ema.europa.eu
- Irish Society for Colitis and Crohn's Disease – Biosimilars Patient Information Leaflet available on www.iscc.ie
- HPRA – Biologicals and Biosimilars: What Patients Should Know, available on www.hpra.ie

List of references available on ePublication on www.nmic.ie. Date of publication: June 2021

Final References Biosimilars (5th July 2021)

1. NMIC – Update on biosimilar medicines 2015, Volume 21, Number 5, accessed from www.nmic.ie (on file) on the 4th May 2021
2. European Commission, Biosimilars in the EU: information guide for healthcare professionals (Updated 2019), prepared jointly by the European Medicines Agency and the European Commission, accessed from www.ema.europa.eu on the 4th May 2021 https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf
3. National Steering Committee for Biological Medicines in Acute Hospitals, Guidance for biological medicines in acute hospitals (April 2019), accessed from www.hse.ie on the 4th May 2021
4. IQVIA, White paper – the impact of biosimilar competition in Europe October 2019, accessed from www.ec.europa.eu on the 25th June 2021
5. Duggan B, Smith A, Barry M, Uptake of biosimilars for TNF-α inhibitors adalimumab and etanercept following the best-value biological medicine initiative in Ireland, International Journal of Clinical Pharmacy 2021;http;//doi.org/10.1007/s11096-021-01243-0
6. Wolff-Hotz, Tiitso K, Vleminckx C et al, Evolution of the EU biosimilar framework: past and future, BioDrugs 2019;33(6):621-634
7. Glintborg B, Loft A, Omerovic E, et al, To switch or not to switch: results of a nationwide guidelines of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry, Ann Rheum Dis 2019;78:192-200
8. Cohen HP, Blauvelt A, Rifkin RM et al, Switching reference medicines to biosimilars: a systematic literature of clinical outcomes, Drugs 2018;78:463-78
9. Blair HA, Deeks ED, Infliximab biosimilar (CT-p13; infliximab-dyyb): a review in autoimmune inflammatory diseases, BioDrugs 2016;469-480
10. Editorial, The switch to infliximab biosimilars, Lancet 2017;389:
11. Kurki P, van Aerts L, Wolff-Holz E, et al, Interchangeability of biosimilars: a European perspective, BioDrugs 2017;31:83-91
12. Trotta F, Belleudi V, Fusco D et al, Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: a population-based cohort study in Italy, BMJ Open 2017;7:e011637
13. Glintborg B, Sorensen IJ, Loft A, et al, A nationwide non-medical switch from originator infliximab to biosimiular CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry, Ann Rheum Dis 2017;76:1426-1431
14. NHS, What is a biosimilar medicine? (May 2019) accessed from https://www.england.nhs.uk/wp-content/uploads/2019/05/what-is-a-biosimilar-medicine-guide-v2.pdf on the 4th May 2021
15. Moorkens E, Simoens S, Troein P et al, Different policy measures and practices between Swedish counties influence market dynamics: part 2 – biosimilar and originator etanercept in the outpatient setting, BioDrugs 2019;33:299-306
16. Moorkens E, Vulto A, Huys I, Biosimilars in Belgium: a proposal for a more competitive market, Acta Clinica Belgica 2020; DOI:10.1080/17843286.2020.1761690
17. Jensen TB, Bartels D, Saedder EA et al, The Danish model for the quick and safe implementation of infliximab and etanercept biosimilars, European Journal of Clinical Pharmacology 2020;76:35-40
18. HPRA, Guide to biosimilars for healthcare professionals, (August 2020), accessed from www.hpra.ie on the 4th May 2021

19. National Cancer Control Programme (NCCP), NCCP Guidance on the use of biosimilar medicines in cancer treatment, Version 4 (May 2021), accessed from www.hse.ie on the 25th June 2021
20. Government of Ireland. Health (Pricing and Supply of Medical Goods) Act 2013. S.I. no 14/2013
21. Editorial: Aronson JK, Goldacre B, Ferner RE, Prescribing biosimilars – slow adaption is costly, British Medical Journal 2018;362:k3141
22. Jergensen KK, Olsen IC, Goll GL et al, Switching from originator to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52 week, randomised, double-blind, non-inferiority trial, Lancet 2017; 389:2304-16
23. Melville AR, Yusof MY, Fitton J et al, Real-world experience of effectiveness of non-medical switch from originator to biosimilar rituximab in rheumatoid arthritis, Rheumatology January 2021 (in press); doi.org/10.1093/rheumatology/keaa834
24. Barbier L, Ebbers HC, Declerck P et al, The efficacy, safety and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review, Clin Pharmacol Ther 2020;108(4):734-755
25. Irish Society for Colitis & Crohn's Disease, National Clinical Programme for Gastroenterology & Hepatology, Biosimilars patient information, accessed from www.hse.ie/yourmedicines on the 31st May 2021
26. National Clinical Programme for Dermatology: A model of care for Ireland, accessed from www.hse.ie on the 31st May 2021
27. National Institute for Health and Care Excellence, Biosimilar medicines, published February 2016 accessed on www.nice.or.uk
28. Ferrario A, Strategies to achieve fairer prices for generic and biosimilar medicines, BMJ 2020;368:l5444
29. Jensen TB, Kim SC, Jimenez-Solem E, et al - Research Letter, Shift from adalimumab originator to biosimilar in Denmark, JAMA Internal Medicine 2020;180(6):902-903
30. HSE-Medicines Management Programme, MMP roadmap for the prescribing of best-value biological (BVB) medicines in the Irish healthcare setting (December 2018, Version 2), accessed from www.hse.ie/yourmedicines on the 31st May 2021
31. HSE-Medicines Management Programme: Biosimilar Medicines in the Irish Healthcare setting, January 2016 accessed from www.hse.ie/yourmedicines on the 31st May 2021
32. HSE-MMP Best-value biological medicines: tumour necrosis factor-alpha inhibitors, Questions and Answers for Healthcare Professionals, accessed from www.hse.ie/yourmedicines on the 31st May 2021
33. HSE-MMP, Patient support services – best-value biological medicines: TNF-α inhibitors, March 2021, accessed from www.hse.ie/yourmedicines on the 31st May 2021
34. HSE-MMP, Best-value biological medicines: MMP support for initiation and switching, accessed from www.hse.ie/yourmedicines on the 31st May 2021
35. HSE-MMP letter to prescribers, Best value biological medicines; adalimumab & etanercept, January 2020, accessed from www.hse.ie/yourmedicines on the 31st May 2021
36. HSE-MMP letter to prescribers, Best value biological medicines; adalimumab and etanercept, January 2021, accessed from www.hse.ie/yourmedicines on the 31st May 2021
37. Personal communication from the HSE MMP (9th June 2021) on file
38. SmPC Retacrit® accessed on www.medicines.ie on the 14th June 2021
39. SmPC Neupogen® accessed on www.medicines.ie on the 14th June 2021
40. SmPC Accofil® accessed on www.hpra.ie on the 14th June 2021
41. SmPC Grastofil® accessed on www.hpra.ie on the 14th June 2021
42. SmPC Nivestim® accessed on www.medicines.ie on the 14th June 2021

43. SmPC Tevagrastim® accessed on www.hpra.ie on the 14th June 2021
44. SmPC Neulasta® accessed on www.medicines.ie on the 14th June 2021
45. SmPC Pelgraz® accessed on www.hpra.ie on the 14th June 2021
46. SmPC Pelmeg® accessed on www.medicines.ie on the 14th June 2021
47. SmPC Gonal-f® accessed on www.medicines.ie on the 14th June 2021
48. SmPC Bemfola® accessed on www.medicines.ie on the 14th June 2021
49. SmPC Lantus® accessed on www.medicines.ie on the 14th June 2021
50. SmPC Abasaglar® accessed on www.medicines.ie on the 14th June 2021
51. SmPC Genotropin® accessed on www.medicines.ie on the 14th June 2021
52. SmPC Omnitrope® accessed on www.hpra.ie on the 14th June 2021
53. SmPC Forsteo® accessed on www.medicines.ie on the 14th June 2021
54. SmPC Movymia® accessed on www.hpra.ie on the 14th June 2021
55. SmPC Terrosa® accessed on www.medicines.ie on the 14th June 2021
56. SmPC Enbrel® accessed on www.medicines.ie on the 14th June 2021
57. SmPC Benepali™ accessed on www.medicines.ie on the 14th June 2021
58. SmPC Humira® accessed on www.medicines.ie on the 14th June 2021
59. SmPC Imraldi™ accessed on www.medicines.ie on the 14th June 2021
60. SmPC Idacio® accessed on www.hpra.ie on the 14th June 2021
61. SmPC Amgevita® accessed on www.medicines.ie on the 14th June 2021
62. SmPC Hulio® accessed on www.medicines.ie on the 14th June 2021
63. SmPC Remicade® accessed on www.medicines.ie on the 14th June 2021
64. SmPC for Flixabi® accessed on www.medicines.ie on the 25th June 2021
65. SmPC for Inflectra® accessed on www.medicines.ie on the 25th June 2021
66. SmPC MabThera® accessed on www.medicines.ie on the 14th June 2021
67. SmPC for Ruxience® accessed on www.medicines.ie on the 25th June 2021
68. SmPC for Truxima® accessed on www.medicines.ie on the 25th June 2021
69. SmPC Herceptin® accessed on www.medicines.ie on the 14th June 2021
70. SmPC for Herzuma®, accessed on www.medicines.ie on the 25th June 2021
71. SmPC for Trazimera®, accessed on www.medicines.ie on the 25th June 2021
72. SmPC for Kanjinti®, accessed on www.medicines.ie on the 25th June 2021
73. SmPC for Ogivri® accessed on www.medicines.ie on the 25th June 2021
74. SmPC Avastin® accessed on www.medicines.ie on the 14th June 2021
75. SmPC for Mvasi®, accessed on www.medicines.ie on the 25th June 2021
76. SmPC for Zirabev® accessed on www.medicines.ie on the 25th June 2021