Biosimilars in Community Pharmacy Practice

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Dedicated to my family and friends.

Because they always understood.

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Abstract

Biopharmaceutical manufacturers have been prompted by high costs and patent expiration of biologicals to explore development of biosimilars. The lower costs of biosimilars makes them a promising avenue for increased cost-effective healthcare systems and patient accessibility.

The aims were to identify the perceptions, knowledge, and concerns that patients have with regards to biosimilars, and to identify whether a pharmacist intervention can help improve patient perceptions and understanding of biosimilars. The objectives were: i) To assess patients' perceptions, knowledge, and concerns of biosimilars and clarify information needs using validated educational infographics and a questionnaire, and ii) To assess how pharmacist interventions affect patient perceptions, knowledge, and confidence with biosimilar use.

A questionnaire and educational material in the form of infographics were developed in Maltese and English and validated through a panel (2 doctors, 2 pharmacists, 2 patients). The three infographics i) explained what generic medications are, ii) provided an overview on biological medications and biosimilars and similarities between them, and iii) detailed the regulatory criteria that biosimilars must satisfy to be placed onto the market. Research was conducted in ten community pharmacies around Malta which were geographically selected to include the north, centre, and south regions. The pharmacies were selected out of 27 pharmacies managed by a pharmacy group, where the researcher practices at one of these pharmacies. Seventy patients, six to eight patients from each pharmacy, took part in the study. Patients were provided with the validated questionnaire to identify perceptions and concerns on biosimilars, and were all subjected to an educational pharmacist intervention with the aid of infographics.

Fifty-three out of 70 patients lacked biosimilar awareness. Pre-pharmacist intervention, 9 patients believed biosimilars were as effective as the originator biological. Post-intervention this increased to 53 patients. The pharmacist intervention significantly improved perceptions (p= 0.025). Twenty-two patients were apprehensive that they were receiving a biosimilar pre-intervention, whereas post-intervention, 7 patients remained apprehensive. When apprehension pre-pharmacist educational intervention was correlated with patients' confidence with biosimilar use post-intervention, statistical significance was observed (p=0.008). While 38 patients had no concerns post-intervention, of those with concerns (n=32), the primary issue was the potential occurrence of side-effects (n=19), and 42 patients sought the need for further education regarding this. The consultant was referred to the most when patients required information about biosimilars (n=65), followed by the family doctor (n=40) and the pharmacist (n=33). Fifty-nine patients found the infographic information to be a novel educational medium. Out of the 70 interviewed patients, the number of patients that strongly agreed or agreed that i) there is not enough biosimilar education was 63, ii) the pharmacist intervention helped improve their understanding of biosimilars was 66, and iii) a pharmacist intervention prior to initiating a biosimilar would have been beneficial was 49.

Development of validated and easily understood educational material in the form of infographics proved beneficial in closing knowledge gaps and improving patient confidence and acceptance of biosimilars. Educational initiatives targeting patients are a way forward to facilitate biosimilar uptake and enable the pharmacist contribution to evolve the concept whereby the patient moves from a compliant mode to adherence and further more to concordance.

Keywords: biologicals, biosimilars, community pharmacy, education, infographics

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List of Abbreviations

BAP	Biosimilar Action Plan
BPCIA	Biologics Price Competition and Innovation Act
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
POYC	Pharmacy of Your Choice

Chapter 1

Introduction

1.1 The Revolutionisation of Biological Medicinal Products

The introduction of biological medicinal products onto the market has transformed the way chronic diseases are managed. These medicinal products are used worldwide for the treatment and management of several conditions including inflammatory bowel diseases, psoriasis, rheumatoid arthritis, several types of cancers, chronic kidney disease, ankylosing spondylitis, amongst other conditions (Okoro, 2021). Even though biological medicinal products have revolutionised treatment, their accessibility has been inconsistent, and as a result, their benefits have not been available to all patients. The rollout of biosimilars onto the market has been able to enhance the accessibility and affordability of biological treatment to patients by introducing market competition and mitigating financial burdens associated with biological medicinal products (Mestre-Ferrandiz et al, 2024). Manufacturers have been prompted by the high costs of these biological medicinal products, as well as the expiration of some patents, to look into the development and manufacture of biosimilars (Rathore & Bhargava, 2020; Okoro, 2021; Mestre-Ferrandiz et al, 2024). Biosimilars are biological medicinal products which are highly analogous to the originator biological in that they have demonstrated no clinically significant differences in structural and clinical trial comparison in terms of safety, quality, and efficacy in comparability studies to the originator biological (Alnaqbi et al, 2023; Moorkens et al, 2023; Bressler et al, 2024). Since during the development phase, biosimilars can to some extent rely on the data obtained previously from the originator biological, which then allows for adaptation of their development at lower development costs, they can then be placed on the market at a lower price than the originator biological (Barbier et al, 2020). A study by Gleeson et al (2017) concluded that if biosimilars in Australia had been

listed on the Pharmaceutical Benefits Scheme in 2015-2016, at least 367 million Australian dollars would have been saved. The United States health systems could save around 54 billion dollars over a period of 10 years, from 2017 to 2026, with the use of biosimilars (Mulcahy et al, 2017). In the United Kingdom, the budget for health systems increased by 42.5% from 2017 to 2023. This increase in allowance is attributed to the large proportion of medicines dispensed which includes biosimilars (Rosembert et al, 2024). In the European Union, as of 2022, it has been estimated that through the introduction of biosimilars, savings have reached over 30 billion euro (Troein et al, 2022).

1.2 Defining Biosimilars

Up until May 2024, there is still no standardisation between regulatory agencies when it comes to one definition for the term biosimilars. There is significant resemblance when definitions are compared. The U.S. Food and Drug Administration (FDA)[1] states that: "A biosimilar is a biologic that is highly similar to and has no clinically meaningful differences in terms of safety, purity, and potency (safety and effectiveness) from an existing FDA-approved biologic, called a reference product."

The European Medicines Agency (EMA)[2] states that: "A biosimilar is a biological medicine highly similar to another biological medicine already approved in the EU (called

[1] U.S. Food & Drug Administration (FDA). Review and Approval [Online]. Maryland: FDA; 2022 (cited 2024 May 21). Available from URL: https://www.fda.gov/drugs/biosimilars/review-and-approval

[2] European Medicines Agency (EMA). Biosimilar medicines: Overview [Online]. London: EMA; (cited 2024 May 21). Available from URL: https://www.ema.europa.eu/en/human-regulatory-overview/biosimilar-medicines-overview

'reference medicine') in terms of structure, biological activity and efficacy, safety and immunogenicity profile (the intrinsic ability of proteins and other biological medicines to cause an immune response)."

Even though there are slight differences in how these two regulatory agencies define biosimilars, it is agreed that (Agbogbo et al, 2019): Biosimilars are not generic medications but they are molecules of biologic origin, highly analogous the originator biological. Biosimilars need to show no clinically significant difference in terms of quality, safety and efficacy when compared to the originator biological.

1.3 Biosimilars in the European Union and the United States

The introduction of biosimilars onto the market has increased access to patients to biological treatment (Barbier et al, 2020). The first biosimilar that was granted authorisation in the European Union by the EMA was Omnitrope®, having somatropin as the active ingredient back in 2006 (Jacobs et al, 2017; López-Siguero et al, 2017; Arnet et al, 2021; Fox et al, 2024). More biosimilars are being approved, and until May 2024, eighty-three biosimilars have been centrally authorised in the European Union by the EMA.[3]

The uptake of biosimilars in the United States has been slower when compared to European countries. The first biosimilar to be approved in the United States, Zarxio® (filgrastim-sndz),

[3] European Medicines Agency (EMA). Biosimilar medicines: Overview [Online]. London: EMA; (cited 2024 May 30). Available from URL: https://www.ema.europa.eu/en/search?f%5B0%5D=ema_med_status%3A100108&f%5B1%5D=ema_medicine_bundle%3Aema_medicine&f%5B2%5D=ema_medicine_type_fields%3Afield_ema_biosimilar&f%5B3%5D=ema_search_categories%3A83&landing_from=73303

was approved in March of 2015, nine years later than the first biosimilar approved in the European Union (Mack, 2015; Fox et al, 2024). Until May 2024, fifty-three biosimilars have been authorised in the United States by the FDA.[4]

A study by Jung et al (2020) reviewed the approval of sixteen biosimilars, and noted that ten of these biosimilars were approved at a median duration of eighteen months earlier by the EMA than the FDA. This study also noted that in five of these biosimilar approval processes, the same clinical trials were submitted to both the FDA and EMA, however, the EMA still approved four of them first before the FDA had even approved its first one (Jung et al, 2020). Since the approval of the first biosimilar in Europe back in 2006, the European Union has approved more biosimilars when compared to the United States over the past fifteen years (Kvien et al, 2022). This is possibly because the United States faces more challenges due to several patent exclusivity periods which serve as protection to the originator biological (Gherghescu & Delgado-Charro, 2021). Moreover, the FDA has more rigorous considerations that it makes during the assessment and approval process prior to approving biosimilars when compared to the EMA (Franco & Banacu, 2020) as is supported by the study of Jung et al (2020). The authors reported that along with the application for approval, ten particular biosimilars, had to submit thirty-six clinical trials to the EMA which involved a median of 153 participants, compared to the forty-four submitted to the FDA which involved a median of 352 participants. This leads to the implication that the FDA needs a more rigorous demonstration of efficacy for the biosimilar prior to its approval. However, despite the greater number and the fast approvals in the European Union, the FDA has had a faster approval rate when

[4] U.S. Food & Drug Administration (FDA). Biosimilar product information [Online]. Maryland: FDA; 2024 (cited 2024 May 30). Available from URL: https://www.fda.gov/drugs/biosimilars/biosimilar-product-information

compared to the EMA's initial approval rate. Throughout the first four years of biosimilar approvals in the European Union, that is between 2006 and 2009, the EMA had approved thirteen biosimilars. This compared to the first four years of biosimilar approvals in the United States, that is between 2015 and 2018, the FDA approved sixteen biosimilars. This faster approval rate could be attributed to the FDA having already a basis of the approval pathway laid by the EMA. Another reason could be that the EMA was more cautious since these were the first guidelines provided with respect to biosimilar approval processes (Gherghescu & Delgado-Charro, 2021).

Incentive programs have been introduced by individual member states, health authorities, and payers to increase the uptake of biosimilars in the European Union (Kvien et al, 2022). In the United Kingdom, rheumatologists were instructed to prescribe the least expensive treatment option first. In Belgium and Germany, quota systems are set up to incentivise medical physicians to prescribe biosimilars to at least 40% of their patients. In Norway, financial incentives have been given to health systems through a tender system, to switch to biosimilars. This has led to 80% market shares for filgrastim and epoetin biosimilars, and higher shares for tumor necrosis factor inhibitors (Dörner et al, 2016; Kvien et al, 2022). In Italy, tenders for biological medicinal products have resulted in lower prices and increased savings for payers as a result of competition. Most Italian regions have implemented tools aimed at increasing biosimilar uptake. In Campania region, in 2009, a legislature came out on the use of biosimilars, pushing biosimilars as the first treatment choice in new patients. Veneto region published guidelines in 2010 on the use and purchase of biosimilars. The regions of Basilicata, Calabria, Puglia, and Sicilia put legislations in place on the preference of biosimilars in treatment naïve patients back in 2014, when this option is economically sustainable. The Tuscan region deployed three measures: formal top-down, bottom-up and

mixed measures (Guidotti et al, 2020). This contrasts with the situation the United States. In 2018, 126 billion dollars were spent on biologics, of which, only around 2% were on biosimilars (Kvien et al, 2022).

1.4 Difference Between Generic Medicines and Biological Medicinal Products

Biosimilars are a relatively new concept which has been gaining more interest over time. Misconceptions are still common and biosimilars are sometimes erroneously associated with generic medications. To understand that the two are not the same thing, one needs to apprehend the real definition of what a biosimilar medication is (Agbogbo et al, 2019). Since generic medications are small chemical molecules, identical copies of the active ingredient can be developed. Contrarily, biological medicinal products are large complex biological molecules, produced from living cells, of which identical copies cannot be produced, however highly similar copies can be developed through complex and expensive manufacturing processes, leading to innate and inevitable biological variability (Blandizzi et al, 2018; Sayah et al, 2023). Generic medications are chemically stable compounds, contrarily to biosimilars, which are more sensitive to environmental changes (Sayah et al, 2023). Therefore, even though biosimilars are highly similar to the originator biological, they are not exact copies and should not be regarded as generic replacements for the originator biological (Mascarenhas-Melo et al, 2024).

1.5 Regulatory Aspects of Biosimilars

From a regulatory aspect, importance is given to the fact that since completely identical copies of a biosimilar to the originator biological can never be reached, different immunogenic activity is possible. This could lead to the risk of increased production of anti-drug antibodies (Sayah et al, 2023; Song et al, 2023). To combat this issue, guidelines issued by regulatory authorities emphasise the need for evaluation of immunogenicity and involves immunological analysis, pharmacokinetic and pharmacodynamic analysis and clinical efficacy and safety data of biosimilars (Kurki et al, 2021). Regulatory authorities have identified the need for the development of specific biosimilar approval pathways to demonstrate similarity of the biosimilar to its respective originator biological, with respect to physico-chemical properties, safety and efficacy, and pharmacological aspects by conducting a comparability exercise. The greater the level of similarity with respect to structure and *in vitro* biological and pharmacological properties between the originator biological and the biosimilar, the fewer clinical evidence is required to demonstrate clinical similarity. Highly strict post-marketing surveillance programs are then imposed by regulatory authorities to obtain long-term evidence on safety and efficacy of the approved biosimilars with the aim of validating the initial patterns of efficacy and safety obtained prior to approval, and to reduce and appropriately manage any unexpected safety issues which could possibly come up post-marketing. If at any point throughout the comparability study, the comparison fails, the tested biological medicinal product is no longer fitted as a biosimilar. Only those that show substantial similarity can be approved as a biosimilar and placed on the market for clinical use (Blandizzi et al, 2018; Webster et al, 2021). The first approval pathway was implemented back

in 2005 by the EMA (Franco & Banacu, 2021; Ratih et al, 2021), with the Biologics Price Competition and Innovation Act (BPCIA) of 2009 following suit in the United States. The BPCIA was signed into law in 2010 (Timmis, 2015; Franco & Banacu, 2021; Williams, 2022).

There is a global agreement that approval pathways for biosimilars are rooted in the principle of establishing similarity between the originator biological and the biosimilar. This highlights a worldwide consensus in biosimilar regulations, emphasising the need to demonstrate bio similarity between these medicinal products (Kabir et al, 2019; Gherghescu & Delgado-Charro, 2021). For a biosimilar to be approved, it needs to demonstrate similarity to the originator biological medicinal product in terms of purity, potency, and chemical and biological activity. Since biological medicinal products are made up of living cells, some minor differences between the biological medicinal product and the biosimilar are allowed (Cordeiro et al, 2024). It is noticeable that there are certain differences in the approval processes in the United States and Europe because of the different policies and procedures that the EMA and the BPCIA set down (Franco & Banacu, 2021).

Biosimilars have a different development and approval pathway than the originator biological. It takes approximately twelve years for the development of an originator biological. The process involves robust research and discovery followed by a lengthy developmental phase to develop an adequate molecule. Analytical pre-clinical studies are conducted to specify the biological's composition and to identify safety and toxicity associated with the drug. Clinical trials range from phase I, which include clinical pharmacology studies to demonstrate the pharmacokinetics and pharmacodynamics of the biological including determination of safety and dosage, followed by phase II and phase III which involve the demonstration of efficacy through therapeutic benefits and safety without excessive toxicity issues. This rigorous

process affects costs, which explains the initial high prices of originator biologicals (Isaacs et al, 2017; Agbogbo et al, 2019; Mascarenhas-Melo et al, 2024). Since biosimilars are highly similar copies of an originator biological, which attributes and therapeutic benefits are already known, the initial discovery phase and phase II, involving the determination of the initial efficacy, are omitted from the process, allowing for a shortened regulatory approval pathway of eight years or even less, and reducing their development costs at 10-20% less than the originator biological (Blackstone & Joseph, 2013; Declerck et al, 2017; Mascarenhas-Melo et al, 2024). The development of biosimilars focuses more on analytical evaluation, biological functionality studies, and the confirmation of clinical equivalence to the originator biological (Joshi et al, 2023). The biosimilar process needs to include at least two clinical studies that demonstrate comparative pharmacokinetics and another that demonstrates clinical equivalence (Agbogbo et al, 2019; Mascarenhas-Melo et al, 2024).

1.5.1 Regulatory Framework for Market Authorisation in the European Union

In the European Union, new medicines that are undergoing the approval process, need to be initially assessed by the Committee for Medicinal Products for Human Use[5] (CHMP) prior to central approval by the EMA (Franco & Banacu, 2020; Cordeiro et al, 2024).

Manufacturers of biosimilars in the European Union need to demonstrate that the biosimilar is highly similar to the originator biological, which would have already been granted a marketing authorisation, despite natural variability which is common in biological medicines,

[5] European Medicines Agency (EMA). Authorisation of medicines [Online]. London: EMA; (cited 2024 May 24). Available from URL: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines#centralised-authorisation-procedure-10942

and that there are no clinically significant differences between the biosimilar and the originator biological with respect to safety, quality and efficacy through a number of comparability studies.[6] Comparability within the EMA is based on three steps: comparative quality studies, including biological and pharmacological characterisation and physicochemical properties, non-clinical comparability studies, and clinical comparability studies (Khraishi et al, 2016; Iqbal & Sadaf, 2022). An application for a marketing authorisation for the biosimilar, that follows the structure of the Common Technical Document, needs to be submitted after the protection period of the originator biological has expired (Iqbal & Sadaf, 2022). Results of the necessary and suitable pre-clinical tests and clinical trials need to be supplied and the type and quantity of data that needs to be submitted must comply with the relevant criteria and related detailed guidelines set up by the CHMP.[7] The comparability studies need to be robust head-to-head comparisons between the biosimilar and the originator biological, and need to demonstrate the products levels of quality, safety, and efficacy (Rathore & Bhargava, 2020). The evaluation of biosimilars should be conducted using a case-by-case approach and the amount of data needed will depend on the specific characteristic of each medicinal product.[8]

[6] European Medicines Agency (EMA). Guideline on similar biological medicinal products [Online]. London: EMA; 2014 (cited 2024 May 26). Available from URL: https://www.ema.europa.eu/en/similar-biological-medicinal-products-scientific-guideline

[7] European Medicines Agency (EMA). Multidisciplinary: biosimilar [Online]. London: EMA; (cited 2024 May 26). Available from URL: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/multidisciplinary-guidelines/multidisciplinary-biosimilar

[8] European Medicines Agency (EMA). European Medicines Agency procedural advice for users of the centralised procedure for similar biological medicinal products applications [Online]. London: EMA; 2019 (cited 2024 May 26). Available from URL: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-procedural-advice-users-centralised-procedure-similar-biological-medicinal-product-applications-track-changes_en.pdf

The EMA provides guidelines for biosimilar developers to use as guidance, to be able to prepare the marketing authorisation application. Figure 1.1 summarizes the three comprehensive guidelines[7] available which are applicable to all biosimilar applications:

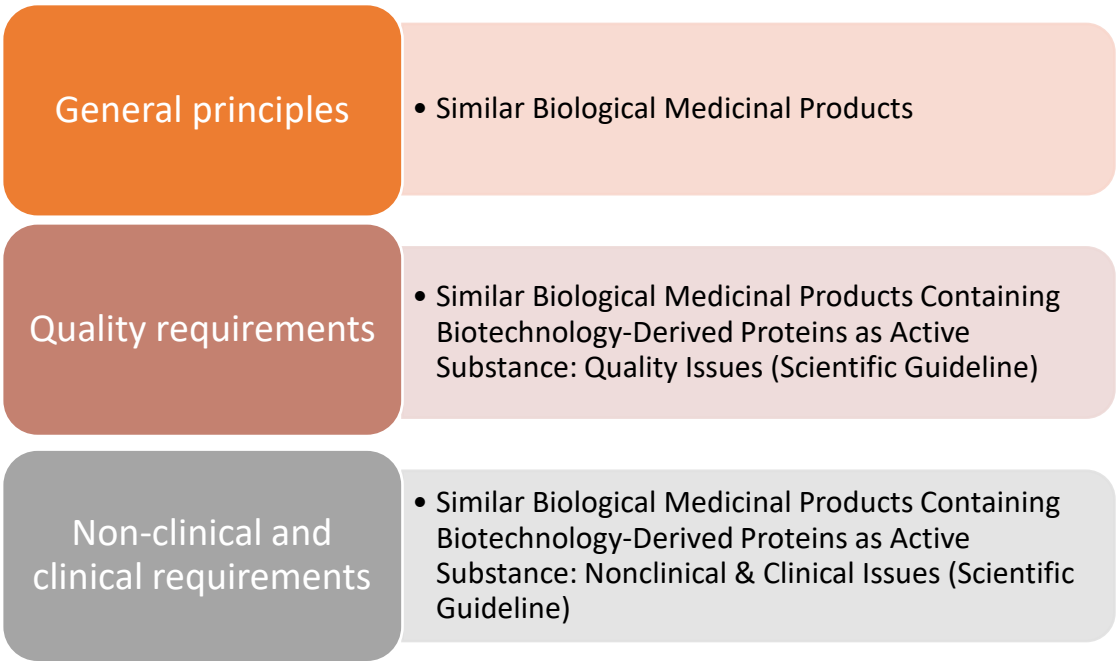


Figure 1.1: Guidelines set by the EMA for the preparation of a marketing authorisation application adapted from European Medicines Agency (EMA). Multidisciplinary: biosimilar [Online]. London: EMA; (cited 2024 May 26). Available from URL: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/multidisciplinary-guidelines/multidisciplinary-biosimilar

[7] European Medicines Agency (EMA). Multidisciplinary: biosimilar [Online]. London: EMA; (cited 2024 May 26). Available from URL: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/multidisciplinary-guidelines/multidisciplinary-biosimilar

The EMA also provides product-specific guidelines which are based on biological classification. The eight available product-specific biosimilar guidelines[7] are: i) “Biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor”, ii) “Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins”, iii) “Non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues”, iv) “Similar biological medicinal products containing interferon beta”, v) “Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues”, vi) “Similar biological medicinal products containing recombinant erythropoietins”, vii) “Similar biological medicinal products containing recombinant follicle-stimulating hormone”, viii) “Similar medicinal products containing somatropin”. However, the EMA has stated that there is no longer the intention of issuing more product-specific guidelines. Instead, tailored case-by-case advice will be opted for. This thought for a change in policy was influenced by the FDA, since detailed product-specific guidelines might misdirect biosimilar development (Niazi, 2022).

Once the marketing authorisation application has been received by the EMA, the validation process can start, during which the applicant is expected to answer within a few days in case of any issues that might be raised during this process. An assessment report from the CHMP Rapporteur and Co- Rapporteur is sent to the CHMP members and EMA. The EMA then puts forward the assessment report to the applicant, stating clearly that the documents convey only preliminary conclusions. It is emphasised that these reports, referred to as Day 80 Assessment Reports, do not impose any binding decisions on the CHMP, but are only for

[7] European Medicines Agency (EMA). Multidisciplinary: biosimilar [Online]. London: EMA; (cited 2024 May 26). Available from URL: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/multidisciplinary-guidelines/multidisciplinary-biosimilar

informational purposes, providing the applicant with insights into the initial assessments without committing the CHMP to a definitive stance at this stage. Once the validation process is completed, the EMA initiates the usual procedure on the monthly date that is specified on the EMA website. If the biosimilar is of an originator biological that is centrally authorised, following successful validation, the procedure starts the same month. However, for applications of biosimilars whose reference originator biologic is authorised through National, Mutual Recognition Procedure, or decentralised procedure, then the EMA will request confirmation of authorisation and any necessary information regarding full composition of the reference originator biological to the concerned member state. This information needs to be received within a month and once everything is received by the EMA, the evaluation process starts. If any member of the CHMP does not receive any requested parts of the dossier from the applicant within a month from starting the procedure, the EMA halts the process until the issue is resolved. The EMA ensures that the CHMP provides its opinion within 210 days, excluding any clock stops which might occur during the procedure.[8]

Following market authorisation, biosimilar safety is monitored in the same manner as other medicinal products.[2] As part of the market authorisation application, a risk management plan to describe the safety profile of the biosimilar, the proposed pharmacovigilance plan and measures for risk minimisation need to be included. Once a biosimilar is placed onto the market in the European Union, post-authorisation, post-marketing safety monitoring is

[2] European Medicines Agency (EMA). Biosimilar medicines: Overview [Online]. London: EMA; (cited 2024 May 21). Available from URL: https://www.ema.europa.eu/en/human-regulatory-overview/biosimilar-medicines-overview

[8] European Medicines Agency (EMA). European Medicines Agency procedural advice for users of the centralised procedure for similar biological medicinal products applications [Online]. London: EMA; 2019 (cited 2024 May 26). Available from URL: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-procedural-advice-users-centralised-procedure-similar-biological-medicinal-product-applications-track-changes_en.pdf

necessary and needs to investigate immunogenicity and adverse effects (Daller, 2016; Aakash Deep & Manita, 2019). Regular safety reports should be sent by biosimilar companies to competent authorities (Leung et al, 2016).

1.5.2 Regulatory Framework for Market Authorisation in the United States

In the United States, the FDA is responsible for carrying out assessments, authorisations and approvals of drugs which require market approval.[9] The FDA provides guidelines which take a risk-based, case-by-case, and a totality-of-evidence approach (Daller, 2016; Gherghescu & Delgado-Charro, 2021; Goli & Butreddy, 2022). Before 2012, there were no set of guidelines for the approval of biosimilars in the United States. As a response to allow for more harmonisation and clarifications, both for pharmaceutical industries, as well as to clarify the principles used to analyse the applications, three draft guidelines were issued in early 2012 (Calvo & Zuñiga, 2012; Ventola, 2013; Niazi, 2023). These were: i) "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", ii) "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product" and iii) "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009". These guidelines include important principles that need to be considered during biosimilar development and manufacture, including: robustness in the manufacturing process, structure similarity, understanding of the mechanism of action,

[9] U.S. Food & Drug Administration (FDA). The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective [Online]. Maryland: FDA; 2017 (cited 2024 May 26). Available from URL: https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective

appropriate pharmacodynamic assays, comparative pharmacokinetic data, immunogenicity data, and clinical data available for the originator biological (Wang & Chow, 2012; Daller, 2016; Cordeiro et al, 2024).

The fifteenth and latest draft guideline[10] up until May 2024 was issued on September 2023. The guidelines issued by the FDA, to the contrary of the EMA guidelines, seem to lack a well-established illustration of the approval pathway for product-specific biosimilars. The FDA seems to focus more on a case-by-case approach when it comes to biosimilar approval (Daller, 2016). Data that needs to be provided in the marketing authorisation application includes analytical studies which contain comparative analytical data, animal studies which provide pharmacological and toxicological data, and clinical studies.[1]

In 2018, the FDA issued the 'Biosimilar Action Plan' (BAP), which includes information on the actions taken or to be taken by the FDA to increase biosimilar development and uptake. Key aspects that are included in the BAP are: ways of increasing efficiency of biosimilar development and approval processes, clarity on scientific and regulatory aspects; development of appropriate educational material to improve biosimilar understanding in patients, physicians, and payers; and supporting market competition.[11] However, it does not include methods for improving pharmacovigilance (Cordeiro et al, 2024). With respect to pharmacovigilance, the FDA have adopted a naming convention for approved biological

[1] U.S. Food & Drug Administration (FDA). Review and Approval [Online]. Maryland: FDA; 2022 (cited 2024 May 21). Available from URL: https://www.fda.gov/drugs/biosimilars/review-and-approval

[10] U.S. Food & Drug Administration (FDA). Biosimilars Guidances [Online]. Maryland: FDA; 2024 (cited 2024 May 26). Available from URL: https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/biosimilars-guidances

[11] U.S. Food & Drug Administration (FDA). Biosimilars Action Plan [Online]. Maryland: FDA; 2024 (cited 2024 May 26). Available from URL: https://www.fda.gov/drugs/biosimilars/biosimilars-action-plan#:~:text=Biosimilars%20Action%20Plan%3A%20Goals%20and,the%20biosimilar%20product%20development%20community.

medicinal products, including biosimilars, to be able to distinguish between products and improve pharmacovigilance through accurate identification of the medicinal products when reporting adverse effects (Grampp & Felix, 2015; Stevenson & Green, 2016). The FDA recommends that non-proprietary names for both originator biologicals and biosimilars should have a unique four-letter suffix. This approach not only reduces prescribing errors but it also reduces the risk of unintentional substitution of biosimilars which are not interchangeable according to the FDA at pharmacy level. It also facilitates pharmacovigilance, since the precise identification of a biological medicinal product is crucial in this regard. Associating adverse drug reaction reports with the wrong medicinal product could lead to delayed recognition of risks that are specific to that medicinal product and reduce targeted regulatory action. This naming convention also allows for the accurate identification of biological medicinal products by both healthcare providers and patients. Hence physicians and pharmacists are encouraged to implement the use of the unique product identifier that feeds into pharmacovigilance (Jordan & Christl, 2020; Peters & Hennessey, 2020; Saunders et al, 2020).

1.6 Interchangeability of Biosimilars in the European Union

Switching to biosimilars could mean a reduction in the cost of therapy, leading to substantial annual savings, and a potential increase in accessibility (Mulcahy et al, 2018; Vogler et al, 2021). However, biosimilar uptake has been rather slow (Chen et al, 2020; Dean et al, 2021; Duggan et al, 2021; Lam et al, 2021; Cross et al, 2022). In 2022, the EMA together with the Heads of Medicines Agencies, issued a joint statement with the aim of harmonising the

European Union approach on biosimilar interchangeability. They confirmed that biosimilar medicines that are approved in the European Union are interchangeable with the originator biological or with an equivalent biosimilar. This approach provides a clearer picture to healthcare professionals and increases access to biological medicinal products to patients. However, decisions on how to implement this interchangeability through switching by the prescriber or the allowance of substitution at a pharmacy level are in the hands of the individual member states.[12]

1.7 Current Situation in Malta

In Malta, most patients receive their biological treatment, for chronic conditions, for free, through the Pharmacy of Your Choice (POYC) scheme. Medications are procured by the Central Procurement and Supplies Unit. They are then sent over to the POYC unit who are responsible for supplying the participating pharmacies with the medications (Magno, 2021). An Outpatient's Formulary List, listing all medications which are available for free through the POYC scheme is available. It contains the active ingredient of the medications available, dosage forms and strengths, Schedule V prescriber criteria, whether the medication falls under specific protocols or if a pink card is needed and if so the pink card prescriber criteria, and the conditions of the schedule V entitlement that the medication falls under (Ayran,2021). Biological medications available through POYC are listed on the government formulary list.

[12] European Medicines Agency (EMA). Biosimilar medicines can be interchanged [Online]. London: EMA; 2022 (cited 2024 May 26). Available from URL: https://www.ema.europa.eu/en/news/biosimilar-medicines-can-be-interchanged

Since interchangeability is not regulated by the EMA and is left in the hands of individual member states, not many countries have established a stance on interchangeability, switching, and automatic substitution (Lasala et al, 2023). In Malta, there is not much information or legislative requirements available on biosimilar interchangeability. Procurement of medicinal products follows an open tendering system consistent with procurement regulations. Decisions regarding procurement of biological medicinal products are reached through collaborative efforts with the clinical department in the Health Department based on a case-by-case basis. Epoetin, human growth hormone and filgrastim fall under the open tendering system, therefore the originator biologicals and the biosimilars are considered as being interchangeable, potentially allowing automatic substitution at pharmacy level. Although these biological medicinal products have open specifications, potentially leading to multiple switches between different brands or different biosimilars, tenders are usually awarded for at least twenty-four months, reducing the occurrence of frequent switching (Sciberras, 2020). An internal Ministry for Health guidance was set up to issue policies surrounding switching (Quiroz, 2023). Therefore, medicines are automatically substituted when a new brand is available. The switch between brands is usually communicated with healthcare professionals through a circular. For more complex monoclonal antibodies, a different approach is taken and switching policies are issued as for example the case of infliximab, etanercept, and adalimumab. Therefore, in Malta the mandatory switching of biologicals is taken at policy level by the government, and switching is done on a national level depending on the tender awarded at that particular point in time. In patients on first generation biosimilars, switching is done automatically. For monoclonal antibodies, patients are referred to their consultant for a physician-led switch over. Patients are also given a 'Patient Information Letter Regarding Biological and Biosimilar Medicines'

when they collect the biosimilar for the first time. If treatment fails, the patient is treated with the next level drug (Sciberras, 2020; Quiroz, 2023).

1.8 Barriers to Biosimilar Uptake

Negative perceptions of patients could lead to the reduced uptake of biosimilars and a risk of the occurrence of nocebo effects (Funaki et al, 2023). For the effective introduction of biosimilars, patient acceptance is key (Kovitwanichkanont et al, 2020). Two studies have shown that patient concerns with respect to the quality, safety, and efficacy of biosimilars compared to the originator biological are posing a challenge for patient acceptance of these medicinal products (Teeple et al, 2019; Varma et al, 2022). The nocebo effect, which is when treatment failure occurs due to patients' negative expectations when initiating or changing treatment, is a barrier to biosimilar uptake and it might result in treatment discontinuation. Patient education could be one way to reduce any misconceptions regarding biosimilar treatment, especially when switched from an originator biological to a biosimilar. This is important since in some countries, non-medical switching forms part of policies and strategies designed to increase the use of biosimilars (Fleischmann et al, 2020). Employing a multi-disciplinary collaborative approach to patient education, involving physicians, pharmacists and nurses could be a way of reducing nocebo effects (D'Amico et al, 2021). Communication between healthcare providers and patients should be fully transparent and delivered in an aligned and unified way to make sure patients are receiving the same information from all healthcare providers (Fleischmann et al, 2020). Patients often feel that there is still inadequate education on biosimilars, leading to concerns about biosimilars' clinical effects and regulatory

pathway, and potentially negatively impacting their perceptions (Rosembert et al, 2024). Knowledge gaps amongst patients, coupled up with misinformation and misconceptions are a lead factor of the nocebo effect and an increase in patient concerns. These barriers can be mitigated by increasing the involvement of healthcare providers, including pharmacists, in educating and reassuring patients proactively on the benefits of biosimilar use by for example introducing educational programmes for patients (Cross et al, 2022). Pharmacists hold a key position in educating patients and promoting biosimilar acceptance through the provision of correct information (Chahine et al, 2023). A study by Aladul et al (2017), showed that better communication, reassurance, and more involvement with decision making in their own treatment plan by their healthcare providers would enhance patient acceptance of biosimilars. Considering the complexity of biological medicinal products, pharmacist expertise in informing patients, and supporting physicians, is an important asset.

1.9 Rationale for the Study and Research Questions

Patients are key stakeholders in aiding the increase of biosimilar uptake. However, patient concerns could affect perceptions, leading to reduced adherence and adoption of these medicinal products. Studies are necessary to assess patients' perceptions and concerns. Results could then be used to come up with strategies to overcome barriers associated with reduction in biosimilar uptake (Young et al, 2022). The lack of comprehensive understanding and confidence of patients in biosimilars (Kristensen et al, 2018; Macaluso et al, 2020) is the main driver of this study. Lack of knowledge could potentially be due to limited education of patients on the topic. Potential success of biosimilar uptake could be improved through the

involvement of healthcare providers. As front-line healthcare professionals, pharmacists play an essential role in providing patients with the necessary information on biosimilars. The importance of educating patients for increasing biosimilar uptake is sometimes overlooked (Oskouei & Kusmierczyk, 2021). The development of educational material, incorporated with a pharmacist intervention could be a promising approach. The rationale of this study is to identify the perceptions and concerns of patients on biosimilars in Malta and emphasise the importance of the role of the pharmacist.

The research questions are: i) What are the perceptions of patients towards biosimilars and does it affect their approach towards treatment?, and ii) Could an intervention by the pharmacist improve understanding and perception of patients with respect to biosimilars?

1.10 Aims and Objectives

The aims are to identify the perceptions, knowledge, and concerns that patients have with regards to biosimilars, and to identify whether a pharmacist intervention can help improve patient perceptions and understanding of biosimilars.

The objectives are to:

1. Assess patients' perceptions, knowledge, and concerns of biosimilars and clarify information needs using validated educational infographics and a questionnaire
2. Assess how pharmacist interventions affect patient perceptions, knowledge, and confidence with biosimilar use

Chapter 2

Methodology

2.1 Study design

The research study consisted of the development of a questionnaire and educational infographics to assess patients' perceptions, knowledge, concerns and experiences with biosimilar use. A literature search was conducted to identify previous studies on the topic and get an idea of questions to include and how to structure the questionnaire. The studies by Peyrin-Biroulet et al, 2017; Khoo et al, 2022; Vandenplas et al, 2022, were used as a basis for the design of the questionnaire.

The online website Canva®[13], which is an online graphic design tool, was used to design the educational infographics by creating a personal account. Templates, graphics, and pictures used were available for free through the website. The information in the educational infographics was adapted from a guide called 'Introduction to Biosimilar Medicines' developed by the Research Advocacy Network.[14]

[13] canva.com [Internet]. Sydney: Canva; c2024 [cited 2024 May 26]. Available from URL:https://www.canva.com/

[14] researchadvocacy.org [Internet]. Texas: Research Advocacy Network; c2021 [cited 2024 May 26]. Available from URL: https://researchadvocacy.org/

Figure 2.1 summarizes the study design:

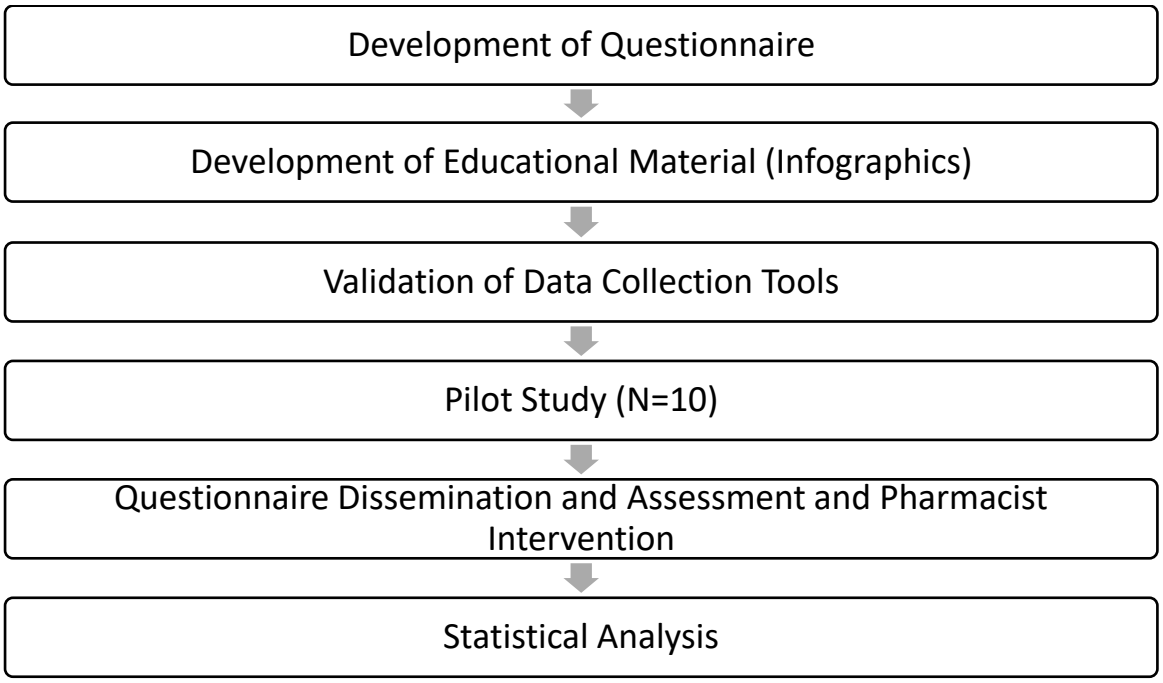


Figure 2.1: Summary of study design

Approval from the University of Malta Faculty of Medicine and Surgery Research Ethics Committee (Appendix 1) was granted to be able to support the study methodology (Ref No: MED-2023-00214).

2.2 Questionnaire Development

A questionnaire to gather information on patients' perceptions, knowledge, and concerns on biosimilars (Appendix 2) was developed and validated. An English version was developed first, which was then translated into a Maltese version, and back-translated, to ensure overall

quality and accuracy, and identify any differences between the original and the translated version. The questionnaire consisted of demographic questions, questions to identify patients' thoughts, perceptions, and concerns on biosimilars prior and post-pharmacist intervention, and a set of questions to analyse the impact of the educational material on the patients' thoughts and perceptions on biosimilars post-pharmacist intervention. For ease of data handling and analysis, a likert scale was used when possible.

Face and content validation of the questionnaire was carried out by a panel consisting of two patients, two doctors and two community pharmacists. They were asked to evaluate the relevance of content, presentation and clarity, and comprehensibility. Comments and feedback for further improvement were taken into consideration and incorporated accordingly into the questionnaire.

2.3 Infographics Development

Three infographics (Appendix 3) were designed and developed as part of the pharmacist educational intervention. The infographics were designed in English and then translated to Maltese and validated by the same previously mentioned panel.

Infographic I explained what generic medications are. This infographic was developed with the aim of making it easier for patients to understand the main differences between generic medications and biosimilars and then analyse and compare patient thoughts and perceptions of generic medications with those of biosimilars.

Infographic II included an overview on biological medications and biosimilars. It provided an overview of what biological medications are and their uses. It also provided an overview of what biosimilars are and how they compare to their counterpart originator biological.

Infographic III contained information on the regulatory criteria that biosimilars need to satisfy for them to be granted a marketing authorisation to be placed onto the market. It also highlighted how biosimilars are a promising avenue for increased cost-effective healthcare systems and patient accessibility.

2.4 Data Collection

The research was conducted in ten community pharmacies around Malta which were selected out of 27 pharmacies managed by a pharmacy group, where the researcher practices at one of these pharmacies. These were geographically chosen to include pharmacies within the north, centre, and south regions via convenience sampling.

A pilot study, involving ten patients on biosimilars, one patient from each of the ten selected pharmacies, was conducted to test the reliability of the developed tools. Further changes to the tools were done accordingly. Any information obtained during the pilot study was only used to improve the data collection tools and were not included with the final results.

Seventy patients, six to eight patients from each pharmacy, all taking biosimilars, took part in the study. Inclusion criteria included patients aged 18 years and over who were taking biosimilar treatment through the Pharmacy of Your Choice (POYC) scheme. The biosimilars considered for this study were Amgevita® (adalimumab), Erelzi® (etancercept), Inhixa®

(enoxaparin), and Binocrit® (erythropoietin alpha) since these were the biosimilars available through POYC during the time of the study. The option for others was included in case other biosimilars were procured during the time of the study.

The patients were introduced to the study and were provided with an information sheet about the study and a consent form which they signed voluntarily if they showed interest in participating in the study. Upon giving consent, patients met up with the researcher where they were required to answer the questionnaire to identify perceptions, knowledge, and concerns on biosimilars. The pharmacist provided educational support to all participants through the use of the infographics. Each intervention took around 20 minutes.

2.5 Data Handling and Statistical Analysis

All data collected was inputted into a Microsoft Excel® spreadsheet and analysed. Statistical analysis was carried out on IBM SPSS® version 29.0.2.0.[15] Comparative analysis was carried out to study the correlation of several factors with one another. The chi-square test was used to investigate the association between categorical variables. Demographic information was compared, using the chi-square test, to a number of factors. The chi-square test was also used to investigate the impact that the educational infographics had on the perception of patients on biosimilars. The null hypothesis stated that there is no statistical difference in patient's perception post-pharmacist intervention following the use of the infographics. This hypothesis was accepted if the p-value was greater than 0.05. The alternative hypothesis stated that there

[15] IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp

is a statistical difference in patient's perception post-pharmacist intervention following the use of the infographics. This hypothesis was accepted if the p-value was less than 0.05. Another chi-square test was used to investigate patients' apprehension of biosimilar use pre-pharmacist educational intervention with their confidence in biosimilar use post-pharmacist educational intervention. In this instance, the null hypothesis stated that there is no statistical difference between the patients' apprehension with biosimilar use pre-pharmacist intervention and their confidence with biosimilar use post-pharmacist intervention. This hypothesis was accepted if the p-value was greater than 0.05. The alternative hypothesis stated that there is a statistical difference between the patients' apprehension with biosimilar use pre-pharmacist intervention and their confidence with biosimilar use post-pharmacist intervention. This hypothesis was accepted if the p-value was less than 0.05.

The Wilcoxon signed-rank test was used to compare patients' perception of generic medications and their perception of biosimilars. This non-parametric test was chosen as it can be used to determine statistical significance across two sets of information coming from the same group of participants, assuming no specific distribution. The null hypothesis was that there is no difference between the paired observations and was accepted if the p-value was greater than 0.05. The alternative hypothesis was that there was a difference between the paired observations and was accepted if the p-value was less than 0.05.

2.6 Dissemination of Study Findings

Study findings were disseminated as follows (Appendix 4):

Abstract accepted and presented as a poster at the 82nd FIP World Congress of Pharmacy and Pharmaceutical Sciences, Cape Town, South Africa.

Abstract accepted and presented as a poster at the ESCP 2024 52nd Symposium, Krakow, Poland.

Chapter 3

Results

3.1 National Health System Data

This study focused on patients taking biosimilars through the Pharmacy of Your Choice (POYC) scheme. Medications available through POYC are listed on the outpatient's government formulary list.[16] Appendix 5 is a list adapted from this formulary, showing all biological medications that are available for patients through POYC up until April 2024. Some of the biological medications available through POYC are procured, by the Central Procurement and Supplies Unit, as the biosimilar. The biosimilars being procured during the time of the study were four: etanercept, adalimumab, epoetin alpha, and enoxaparin. Table 3.1 shows the frequency of patients in Malta that were taking the biosimilar during the study period.

Table 3.1: Number of patients on biosimilars available through POYC

Biosimilar	Number of patients
Adalimumab	510
Epoetin alpha	466
Enoxaparin	443
Etanercept	415

3.2 Validation of Data Collection Tools

Throughout the validation process, some changes to the questionnaire were made following suggestions by the panel. Specifically, the order in which the questions were asked was changed slightly to make it easier to follow through. Some new questions were added to the

[16] Health.gov.mt [Internet]. Malta: Government of Malta; c2021 [cited 2024 May 26]. Available from URL: https://healthservices.gov.mt/en/pharmaceutical/Pages/formulary/formulary.aspx

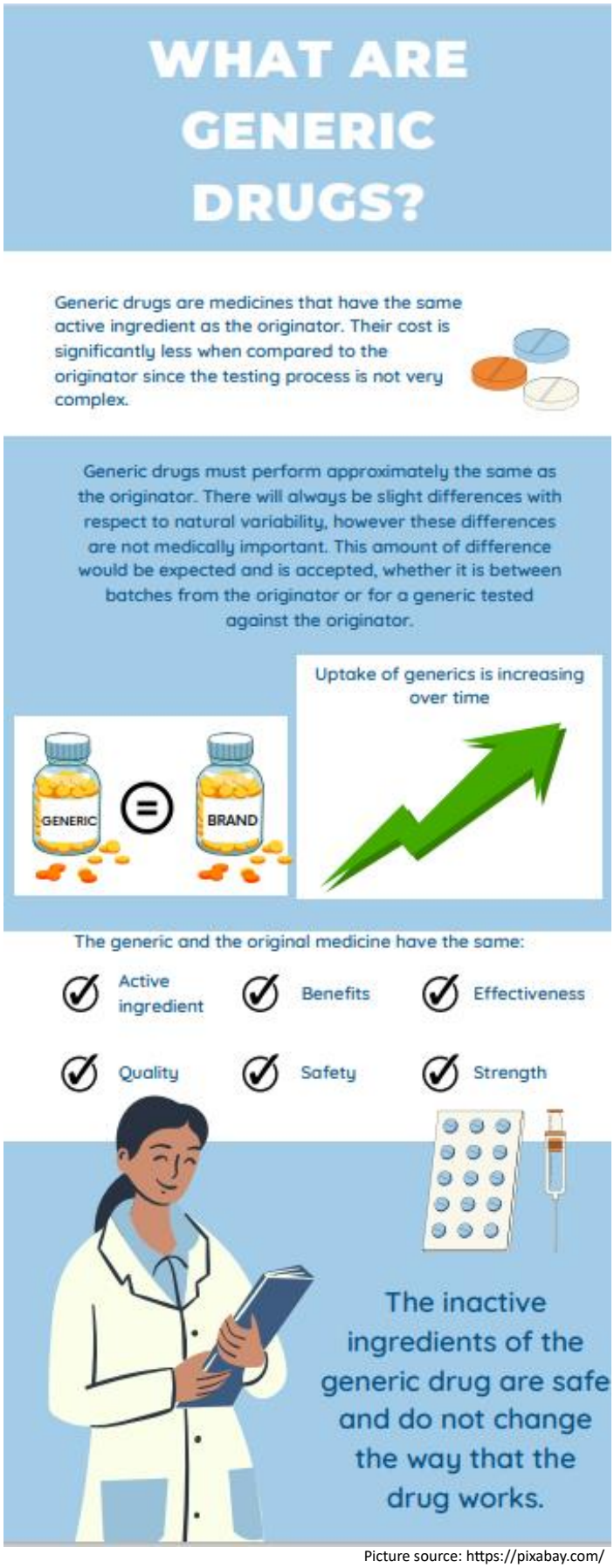
questionnaire to support the results further with the aim of providing useful information that could be used to have improved results.

A question to identify whether the patients were always on the same brand of medication was added to provide an insight of preference in cases where patients were on different brands of biological medications and identify patient attitudes towards biosimilar adoption. A question to identify the level of apprehension with biosimilar use that patients had pre- and post-pharmacist intervention and the reasons for apprehension was also added. Questions evaluating patient concerns with the use of biosimilars were added to provide an insight into the barriers to biosimilar adoption and in turn allow for enhancing and tailoring patient education accordingly to improve patient-centred care.

No changes were made to the educational infographics as the panel agreed that they were concise but still contained all the relevant information that is required to support the pharmacist educational intervention.

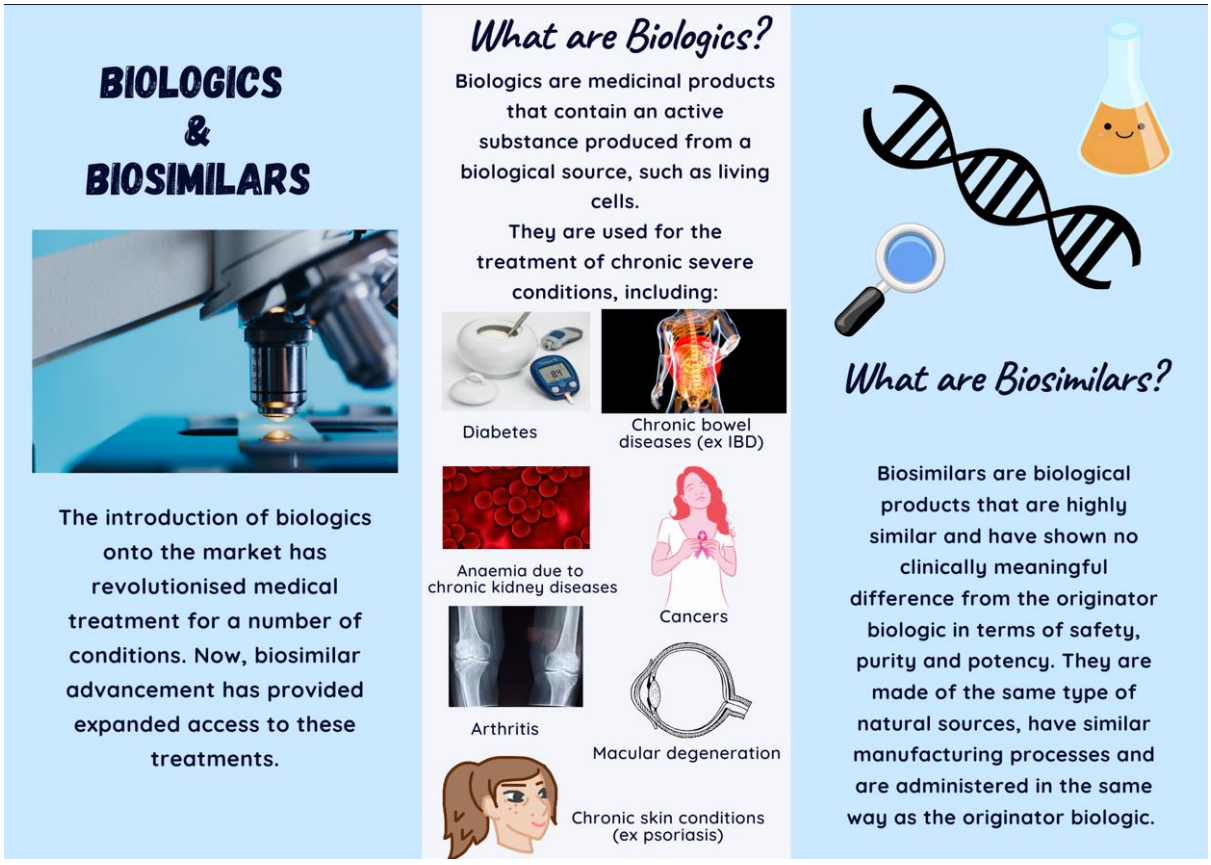
3.3 Educational Infographics

The developed and validated educational infographics were used to support the pharmacist intervention. Their use aided in educating patients on generic medications and how they are different from biosimilars (Figure 3.1), biological medications and biosimilars overview (Figure 3.2), and regulatory criteria required by biosimilars for them to be placed onto the market (Figure 3.3). Maltese versions of the educational infographics were also developed.



Picture source: https://pixabay.com/

Figure 3.1: Infographic I - Generic medications



Picture source: https://pixabay.com/

Figure 3.2: Infographic II - Biological medications and biosimilars overview

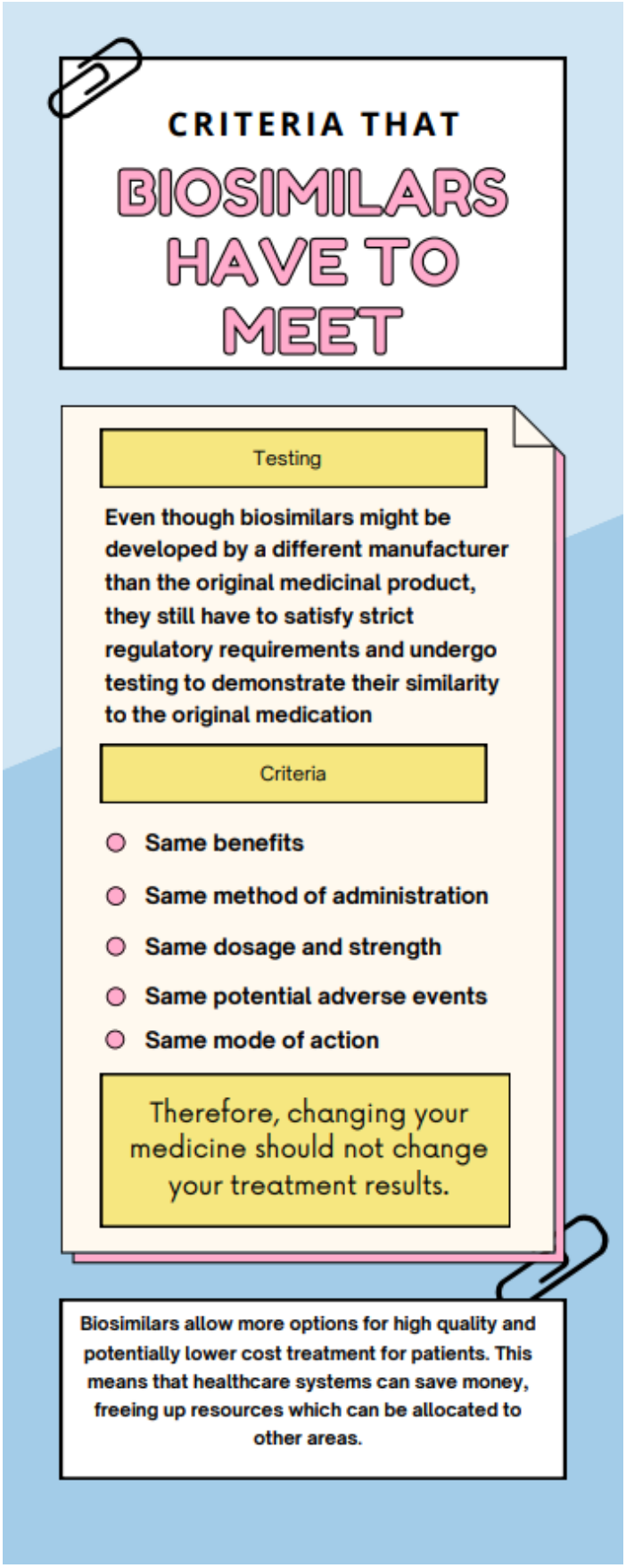


Figure 3.3: Infographic III - Regulatory criteria for biosimilars

3.4 Study Population

The total study population consisted of 70 patients on biosimilar medication dispensed through POYC. No patients withdrew from the study. The patients that participated in this study were either on Amgevita® (Adalimumab), Erelzi® (Etanercept), Inhixa® (Enoxaparin) or Binocrit® (Epoetin Alpha).

3.5 Demographic Data

Seventy patients were recruited (30 male, 40 female; estimated mean age 57.66, range age 56-75 years). Thirty-nine patients were 56 years and over, with 27 patients having a secondary level of education. During the study period, adalimumab was the most dispensed biosimilar (n=31) as seen in Figure 3.4.

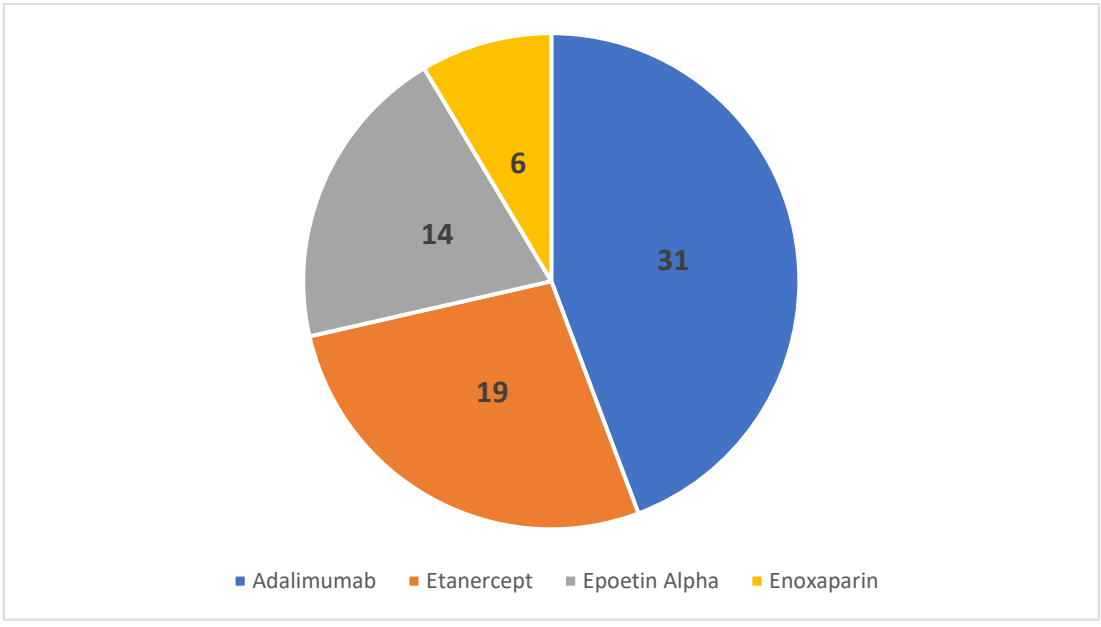


Figure 3.4: Dispensed biosimilar medication frequency of study population (N=70)

Rheumatoid arthritis was the most common indication for which patients were receiving a biosimilar (n=23) (Figure 3.5). Twenty-six patients had been on biosimilar treatment for 1-3 years (Figure 3.6).

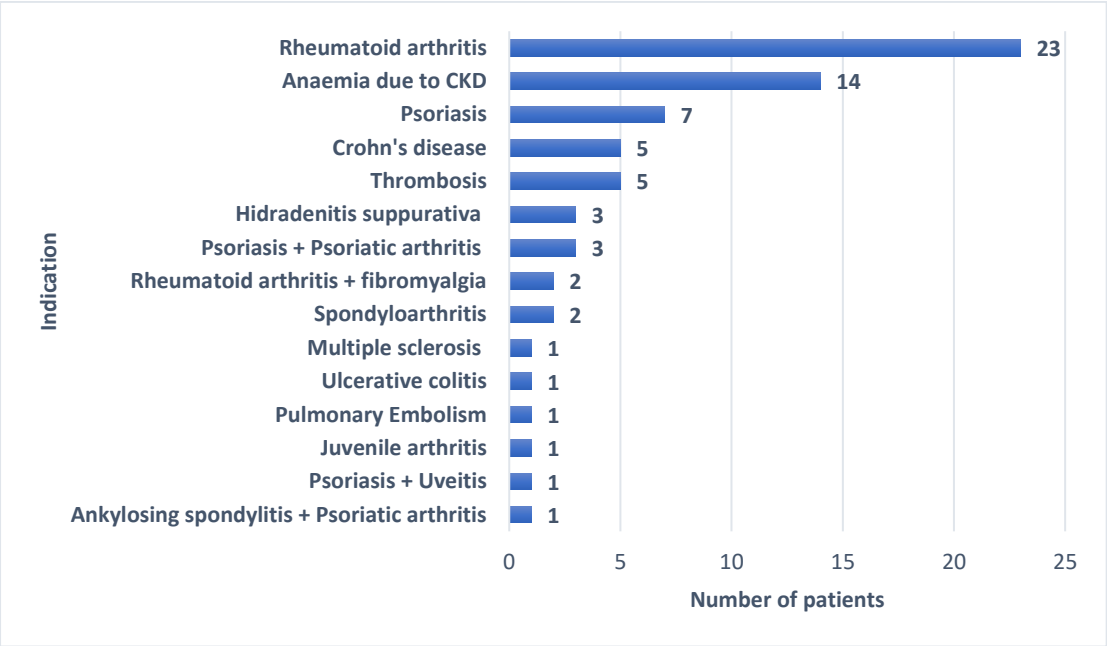


Figure 3.5: Biological medication indication (N=70)

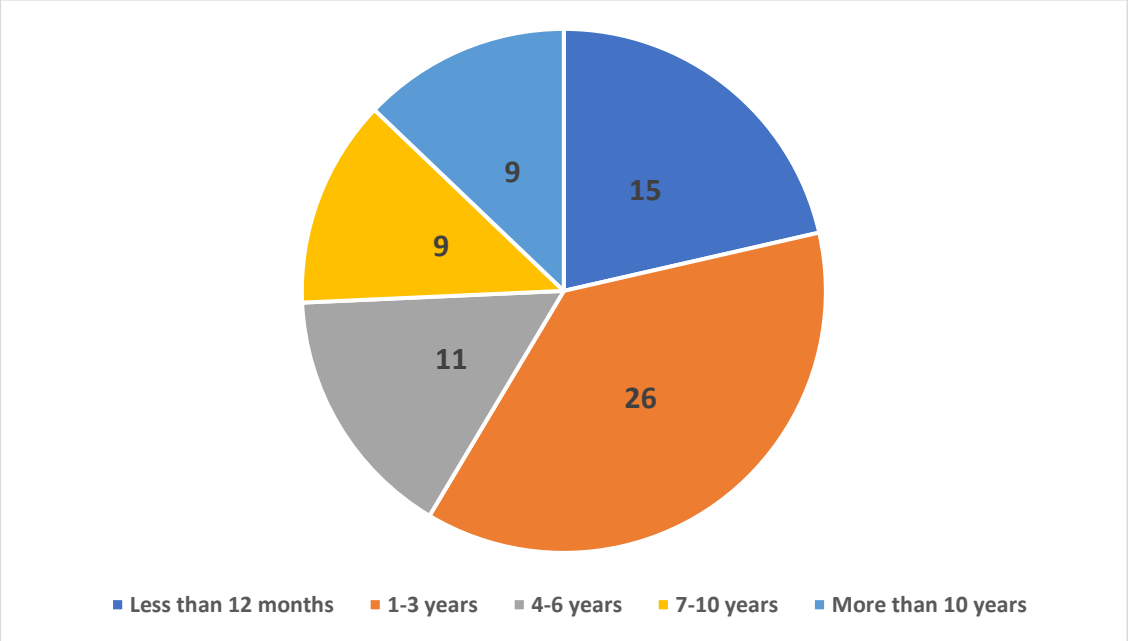


Figure 3.6: Duration of treatment with a biological medication (N=70)

3.6 Identifying the Impact of the Pharmacist Intervention

The impact of the pharmacist intervention, with the use of the developed and validated educational infographics was assessed.

3.6.1 Pre-Pharmacist Educational Intervention

Pre-pharmacist educational intervention, 22 patients were apprehensive about the fact that they were being given the biosimilar and not the originator biological. No statistical significance was observed when apprehension pre-pharmacist intervention was correlated to age ($p=0.652$), gender ($p=0.206$), and level of education ($p=0.075$). Some of the reasons given for their apprehension included that biosimilars are of lower quality and are inferior to the originator biological, the original medicinal product is always better and is more refined, biosimilars have more side effects, and that even though biosimilars must prove that they are highly similar to the originator biological, treatment might still be affected with the use of biosimilars. Fifty-three patients lacked awareness of biosimilars. Only 9 patients believed that biosimilars were as good as the originator biological.

3.6.2 Post-Pharmacist Educational Intervention

Post-pharmacist intervention, only 7 patients remained apprehensive of biosimilar use. Figure 3.7 shows the improvement in patients' apprehension with biosimilar use before and after the pharmacist-led educational intervention.

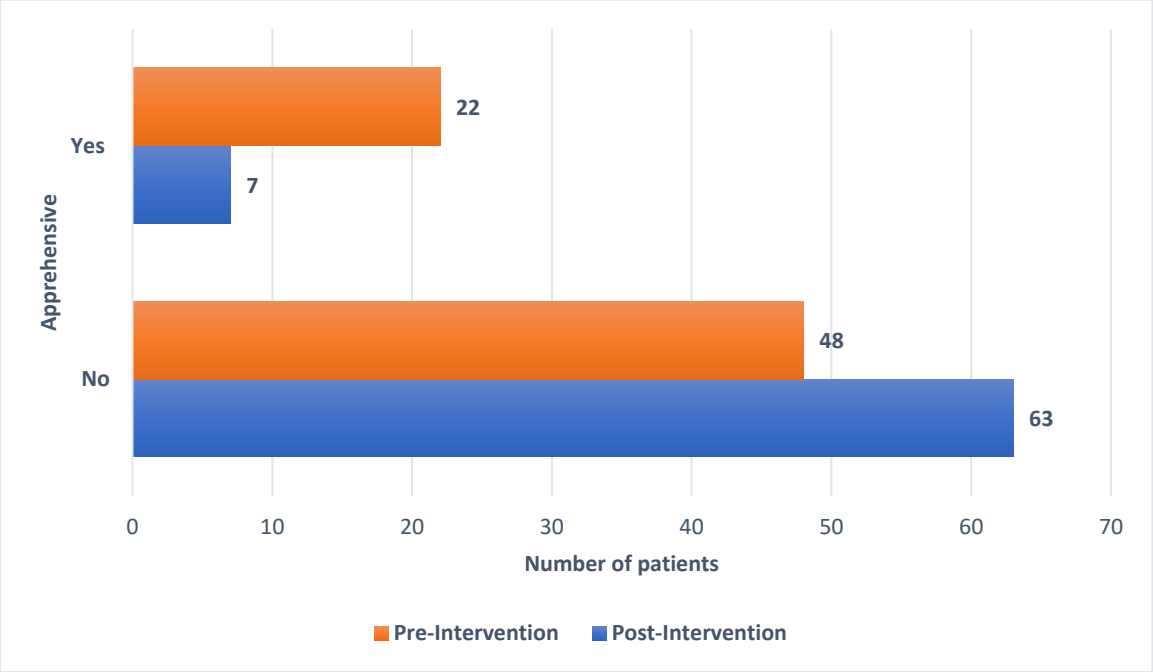


Figure 3.7: Apprehension with biosimilar use pre- and post-pharmacist educational intervention (N=70)

When all 70 patients were given the necessary information using the infographics, numbers improved with respect to awareness of biosimilars and perceptions (Figure 3.8). Following the pharmacist intervention, all 70 patients knew what a biosimilar was. The number of patients who believed that biosimilars were as effective as the originator biological increased from 9 patients to 53 patients.

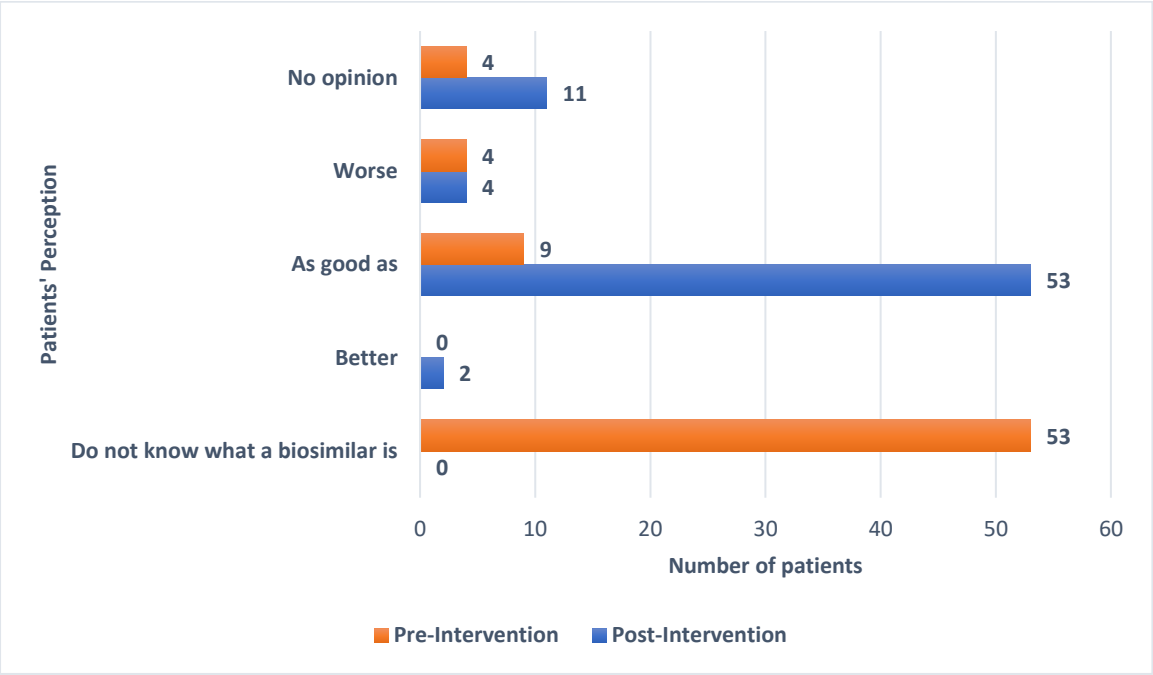


Figure 3.8: Comparing patients' perceptions on biosimilars pre- and post-pharmacist intervention (N=70)

There was a statistically significant difference between patients' perception of biosimilars pre- and post-pharmacist educational intervention (p= 0.025).

Table 3.2: Biosimilar perception of patients pre- and post-pharmacist educational intervention using chi-squared test (N=70)

		Biosimilar perception post-pharmacist intervention				
		Better	As good as	Worse	No opinion	Total
Biosimilar perception pre-pharmacist intervention	As good as	0	9	0	0	9
	Worse	0	0	1	3	4
	No opinion	0	4	0	0	4
	Do not know what a biosimilar is	2	40	3	8	53
Total		2	53	4	11	70

$X^2(9)= 19.032$, p= 0.025

Following the pharmacist educational intervention, 58 out of 70 patients felt confident or very confident that biosimilar use was good for them. There was no statistical significance between patient confidence and age (p=0.598), gender (p=0.236), and level of education (p=0.084).

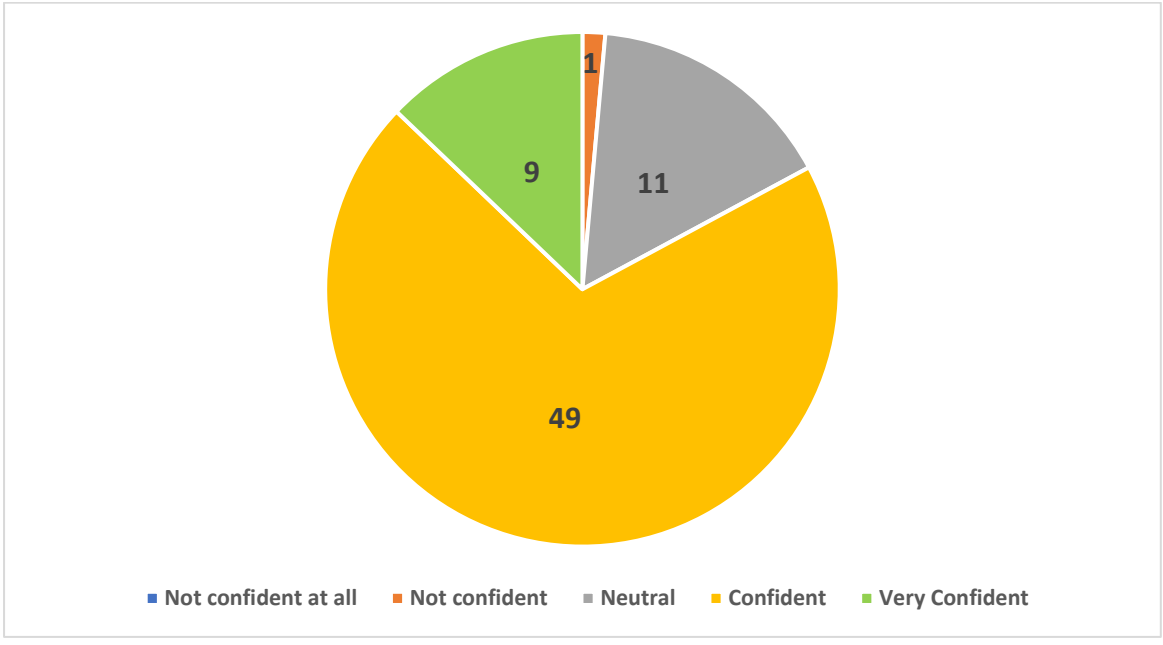


Figure 3.9: Patient confidence with biosimilar use post-pharmacist intervention (N=70)

Statistical significance was observed between patients' apprehension with biosimilar use pre-pharmacist educational intervention and patients' confidence with biosimilar use post-pharmacist intervention (p= 0.008).

Table 3.3: Apprehension pre-pharmacist intervention and confidence post-pharmacist intervention with biosimilar use using chi-squared test (N=70)

		Confidence with biosimilar use post-pharmacist intervention				
		Not confident	Neutral	Confident	Very confident	Total
Apprehensive with biosimilar use pre-pharmacist intervention	Yes	1	7	14	0	22
	No	0	4	35	9	48
Total		1	11	49	9	70

$X^2(3)= 11.787$, p= 0.008

Patients were asked whether the pharmacist intervention had helped them understand what a biosimilar was. Sixty-six patients agreed or strongly agreed with this statement. Forty-nine patients agreed or strongly agreed that if the information was presented to them prior to biosimilar treatment initiation, it would have been more beneficial. Sixty-three patients agreed or strongly agreed that the pharmacist intervention helped them improve their perception on biosimilars.

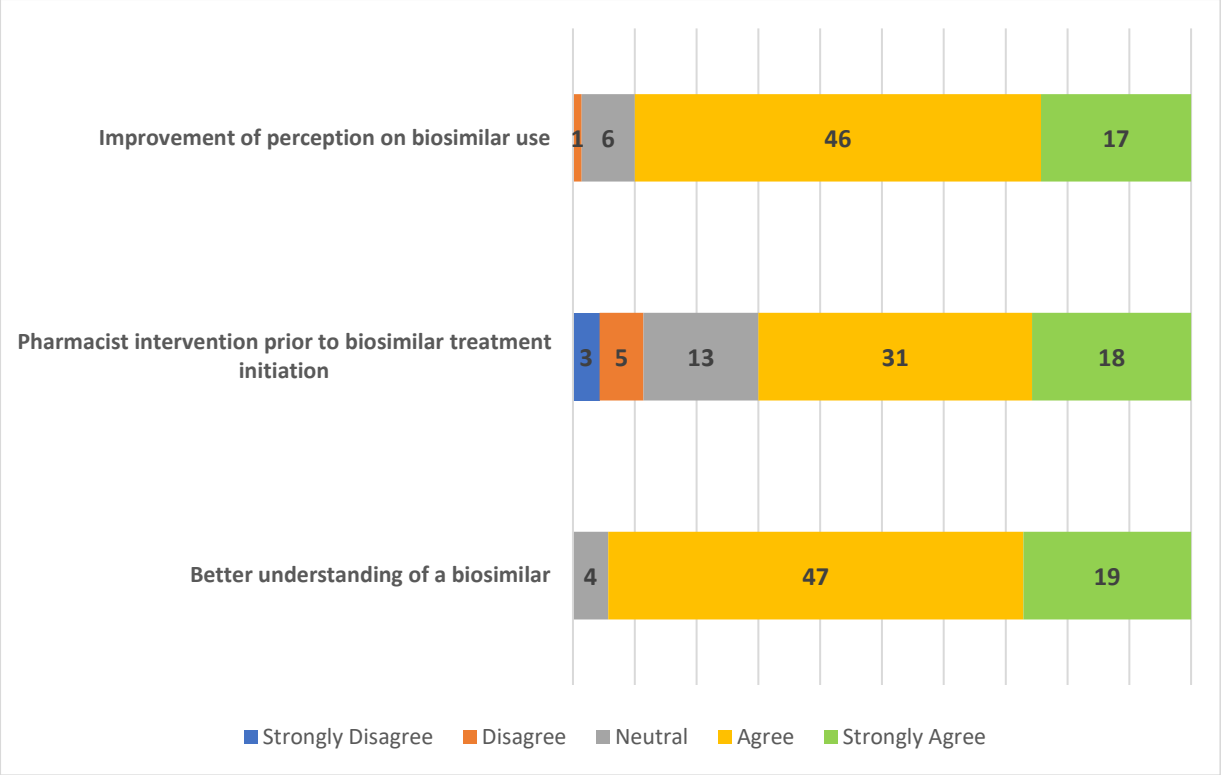


Figure 3.10: Assessment of pharmacist intervention (N=70)

3.7 Assessing Patient Experiences with Biosimilars Compared to the Originator Biological

Sixty-one patients believed that overall, their condition was being well-controlled with the biosimilar medication that they were being dispensed.

Thirty-three patients were not always dispensed the same brand of biological medication. Of these patients, 28 had been previously on the originator biological and were on the biosimilar medication during the time of the study. The remaining 5 patients were previously on a different brand of biosimilar. To compare patients' thoughts on the biosimilar and the originator biological, those patients that had previously been on the originator biological were asked whether they think one of the medication brands was better than the other, or if the

effect was the same for both brands. Eighteen patients perceived both the biosimilar and the originator biological as effective. Nine patients believed that the originator biological was superior to the biosimilar, and 1 patient believed that the biosimilar was more effective than the originator biological.

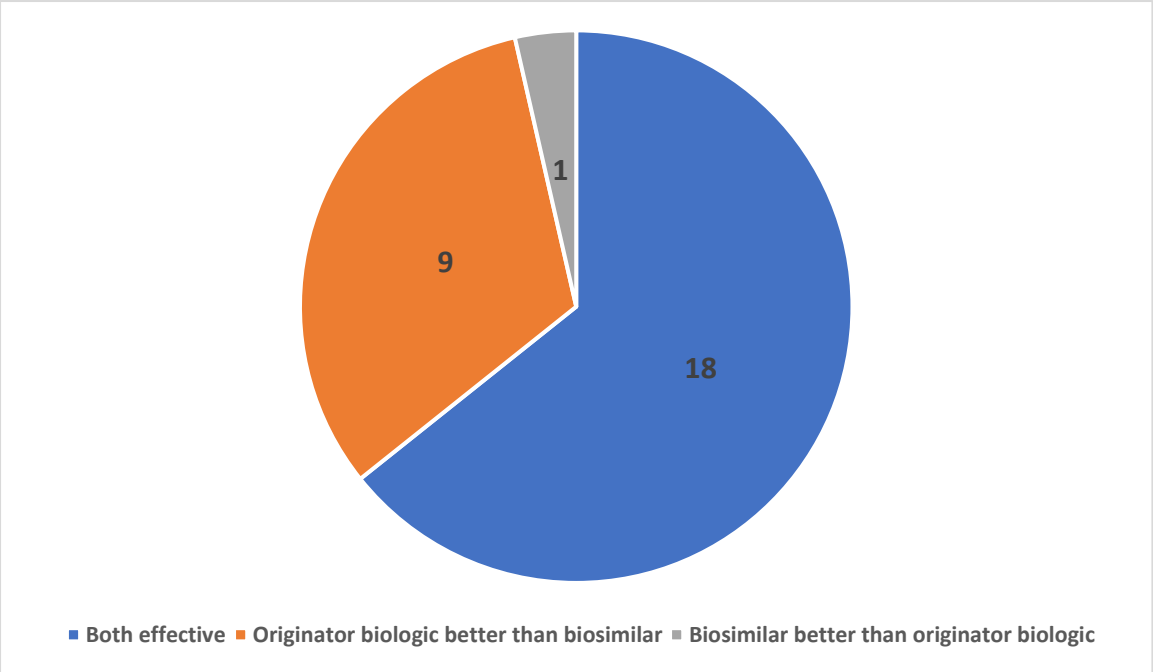


Figure 3.11: Comparing patients' thoughts on biosimilars and originator biological (N=28)

Six out of the 9 patients who perceived the originator biological as being better than the biosimilar were previously on Humira®. Two patients were previously on Enbrel® and 1 on Clexane®.

Reasons given by patients as to why they believed that the originator biological was more effective were that their condition had been better controlled and experienced less flare-ups, the biosimilar caused them more side effects, and administration with the originator biological had been easier and less painful.

The one patient who thought that the biosimilar was better had previously been on Enbrel®, and stated that while on the originator biological, closer to the next dose she would have symptoms, whilst with the biosimilar, the condition was more controlled.

All 70 patients were asked whether they would be willing to pay more money to get the originator biological, even after the pharmacist intervention. Twenty-three patients strongly disagreed with paying more money to get the originator biological. There was no statistical significance observed between willingness to pay for the originator biological and age (p=0.103), gender (p=0.057), and level of education (p=0.563).

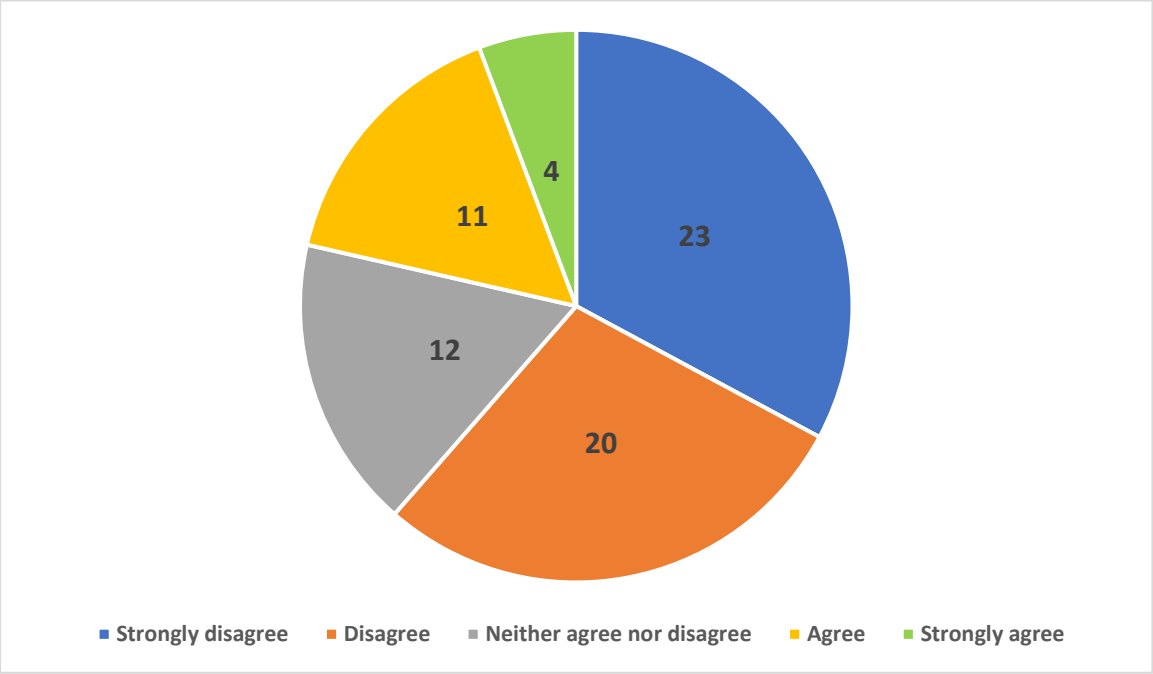


Figure 3.12: Patient willingness to pay more money for the originator biological (N=70)

3.8 Assessing how Patients' Perceptions on Generic Medications are Related to Their Perceptions on Biosimilars

Sixty-five patients used generic medications in their daily lives. When asked on their thoughts of generic medications, 44 patients had good or a very good views of generic medications. Fourteen patients were neutral to generic medications whilst only 7 had a bad view. There was no statistical significance observed when patients' thoughts of generic medications were correlated to age ($p=0.143$), gender ($p=0.636$), and level of education ($p=0.435$).

Those 21 patients with a bad or neutral views of generic medications were asked to give a reason for their response. Eleven patients thought that not all generic medications were as good as the originator, 2 believe that generic medications were of inferior quality, 7 did not have an opinion and 1 believed that if you paid more money, you would get a better-quality product.

Patients were asked about their thoughts of biosimilars. Forty-two patients and 12 patients had good and very good views respectively. There was no statistical significance observed when patients' thoughts of biosimilars was correlated to age ($p=0.665$), gender ($p=0.715$), and level of education ($p=0.692$). Patient views for both generic medications and biosimilars were analysed and compared (Figure 3.13). Patients had positive views for both classes of medications.

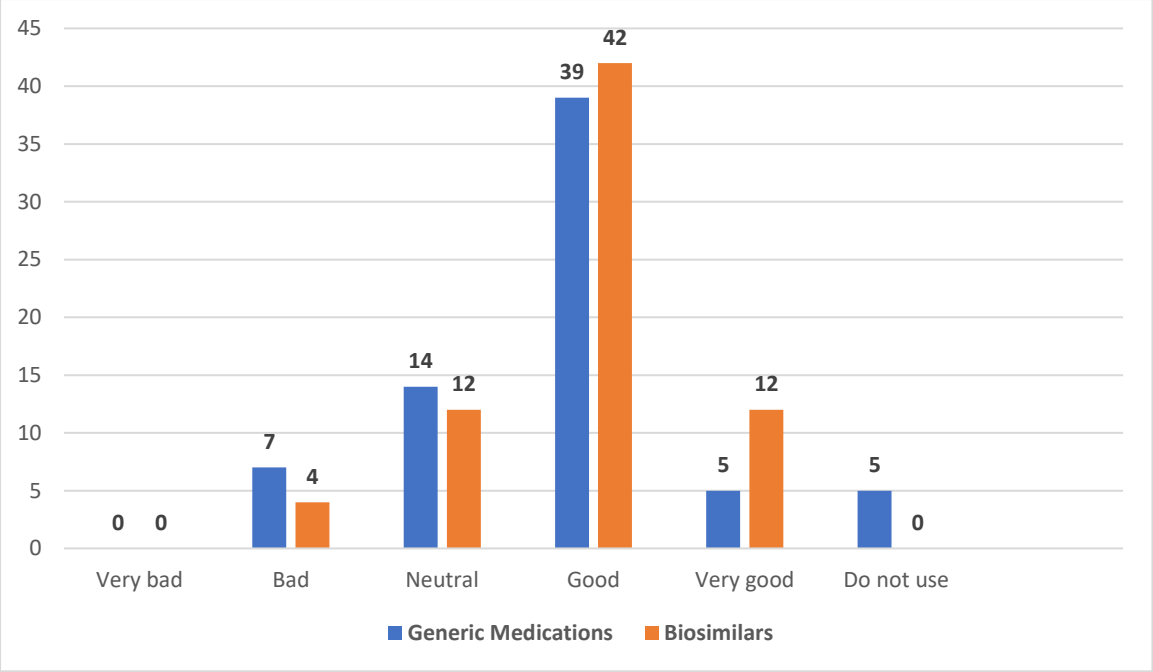


Figure 3.13: Patient views of generic medications and biosimilars (N=70)

Of the 44 patients with a good or very good view of generic medication, 7 were apprehensive of biosimilar use.

There was no statistical significance between patients' thoughts on generic medications and their thoughts on biosimilars (p= 0.544), which could be because patients had similar views for both generic medications and biosimilars.

Table 3.4: Generic medication and biosimilar thoughts using Wilcoxon signed ranks test (N=70)

Ranks

		N	Mean Rank	Sum of Ranks
Biosimilar thoughts - Generic medication thoughts	Negative Ranks	17a	19.47	331.00
	Positive Ranks	21b	19.52	410.00
	Ties	32c		
	Total	70		

Z= -0.607, p= 0.544

3.9 Assessing Patient Education of Biosimilars

Pre-pharmacist educational intervention, 54 out of the 70 participating patients did not know that the medication they were being dispensed at the time of the study was a biosimilar. There was no statistically significant correlation between patients' awareness of taking a biosimilar and their age (p=0.07), gender (p=0.218), and level of education (p=0.155). Fifty-nine patients found the infographics and the information that they contained to be a novel educational medium. There was no statistical significance between familiarity with the information on the infographics and patients' age (p=0.104), gender (p=0.635), and level of education (p=0.108). Patients were asked 6 close-ended yes or no questions to assess their comprehension of the educational infographics. Patients were asked whether biosimilars work in the same way, if they must be manufactured by the same manufacturer, if they must have the same dose, if they are administered in the same way, if they are sold at the same price, and if they have less unwanted effects than the originator biological. Sixty-one patients answered all 6 questions correctly. The question that was the most incorrectly answered pertained to side effects, with 8 patients incorrectly answering that biosimilars always have less unwanted side effects.

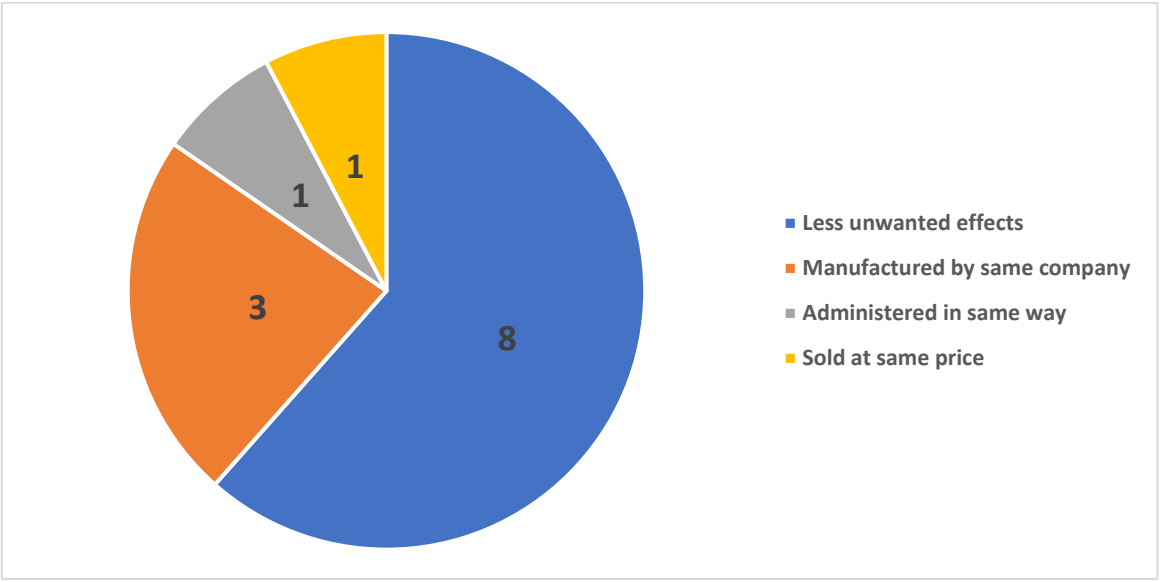


Figure 3.14: Wrongly answered questions post-pharmacist intervention (n=9)

Following pharmacist intervention, patients' perceptions on biosimilars, in comparison to their originator biological counterpart were also assessed. Most of the patients' perceptions were positive, with 43 patients either strongly disagreeing or disagreeing with the statement "I think that biosimilars take longer time to work than the original medicine". Fifty-one patients either strongly disagreed or disagreed with the statement "I think that biosimilars have more unwanted effects than the original medicine". Forty-eight patients either strongly disagreed or disagreed with the statement "I think that biosimilars are of lower quality than the original medicine".

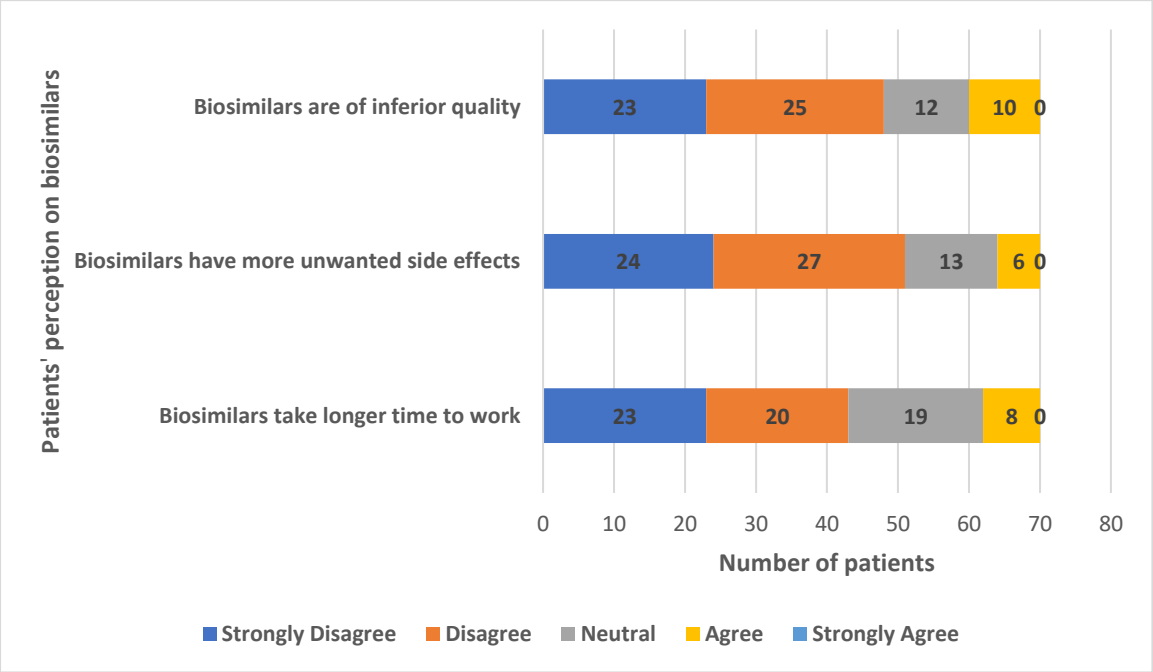


Figure 3.15: Patients' perception on biosimilars compared to originator biological (N=70)

3.10 Assessing Biosimilar Educational Needs

Patient education on biosimilars is important for patients to be knowledgeable on their own medication and treatment, and in turn reduce nocebo effects. Twenty-three patients strongly agree whilst 40 patients agree that there is not enough education on biosimilars.

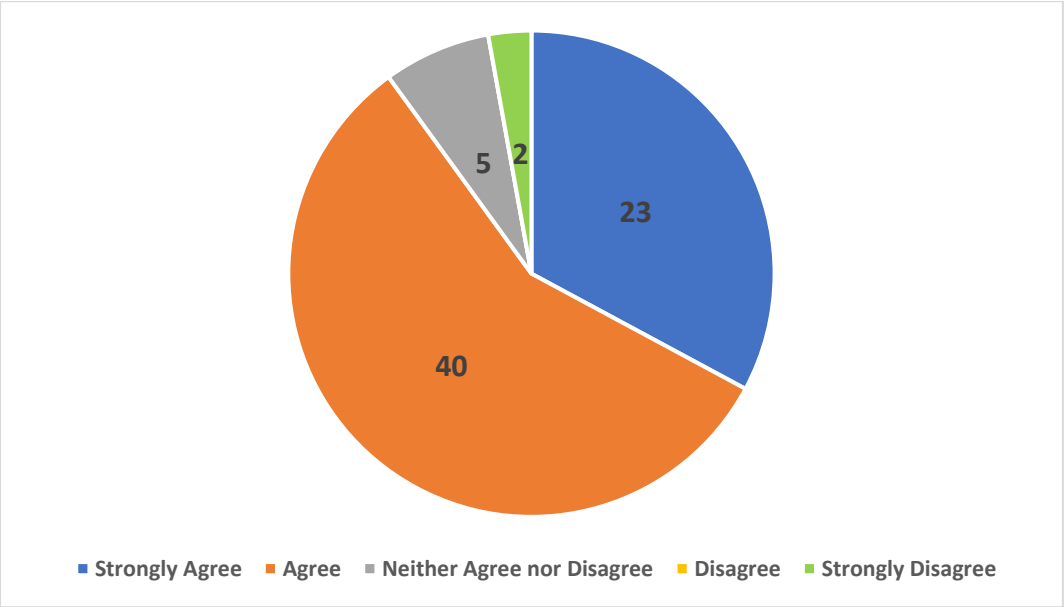


Figure 3.16: Not enough biosimilar education (N=70)

Patients were asked what information interests them and what they would like to know more regarding biosimilars and their use. Forty-two patients, would like to know more about biosimilar side effects. One patient suggested that it would be beneficial if education was also provided to patients' family members, whilst another patient recommended the development of an easily understood booklet on biosimilars which could be disseminated to patients. Nine patients did not require more information.

Table 3.5: Patient information needs (N=70)

Information Needs	Number of Patients
Side effects	42
Quality	27
Effectiveness	26
Clinical development and evidence from clinical trials	23
Process of development	20
Method of administration	9
Comparability studies	2
Long-term effects	2
Source of the active ingredient	1

The consultant was the most referred to source of information when patients required further information on their biosimilar medication, followed by their family doctor and then the pharmacist. Patients were allowed to mention more than 1 source of information. Specifically, 65 patients refer to the consultant, 40 to their family doctor and 33 to the pharmacist. Figure 3.17 summarises the sources of information and the frequency of use by patients.

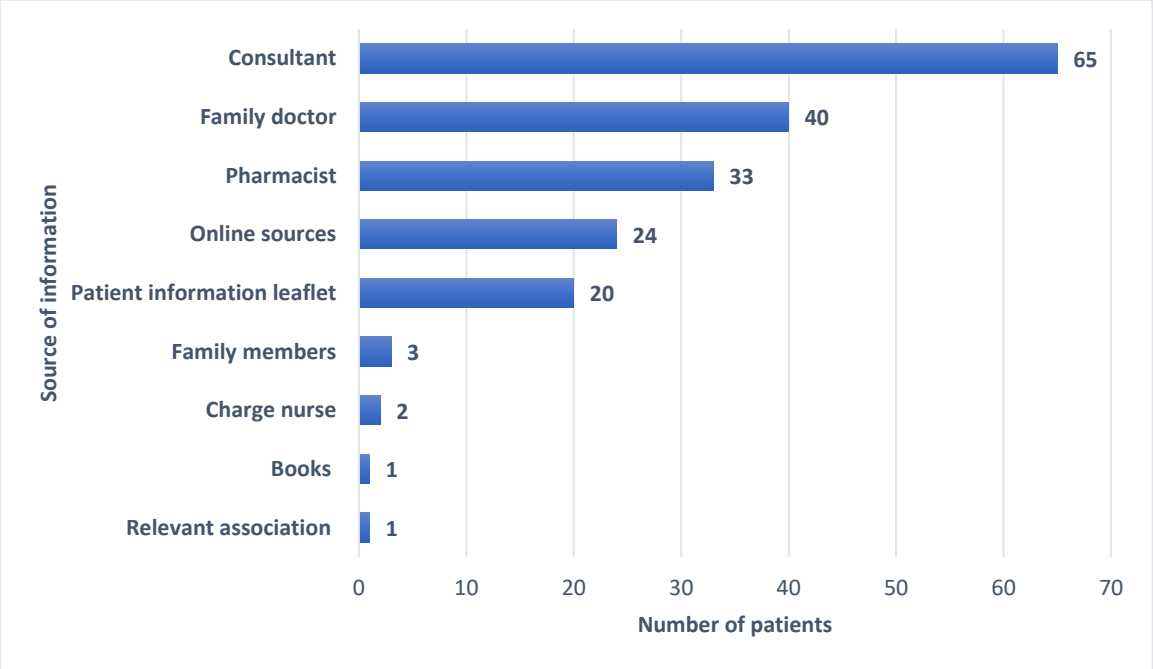


Figure 3.17: Sources of information patients refer to for more information on biosimilar medication (N=70)

The extent to which patients relied on the information provided to them by pertinent sources was analysed and summarized in Figure 3.18. It is evident that most patients (n=62) always rely on the information provided to them by the consultant. Contrarily only 1 patient and 2 patients always rely on the information provided to them from online sources and family members respectively.

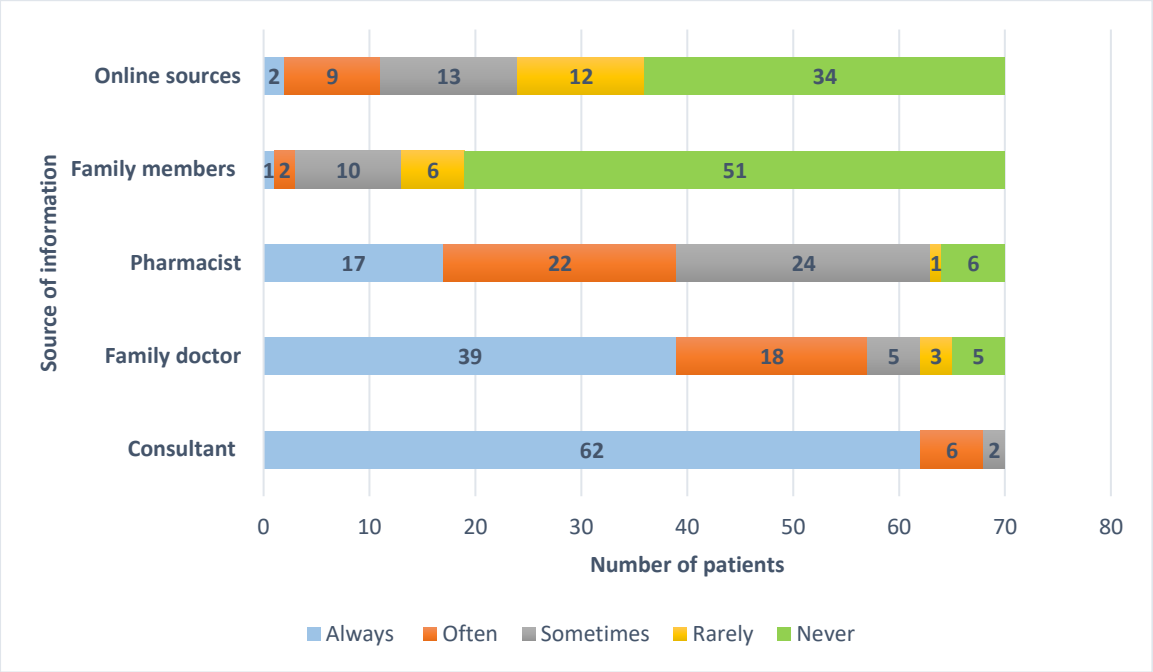


Figure 3.18: Level of reliance of patients on information from pertinent sources of information (N=70)

3.11 Assessing Patient Concerns

Following the pharmacist intervention, any concerns with biosimilar use were analysed. Thirty-eight patients had no concerns following the pharmacist intervention. Of the 32 patients with concerns, 19 patients remained concerned with the possible occurrence of side effects with biosimilars (Figure 3.19). Patients with concerns were allowed to mention more than 1 concern.

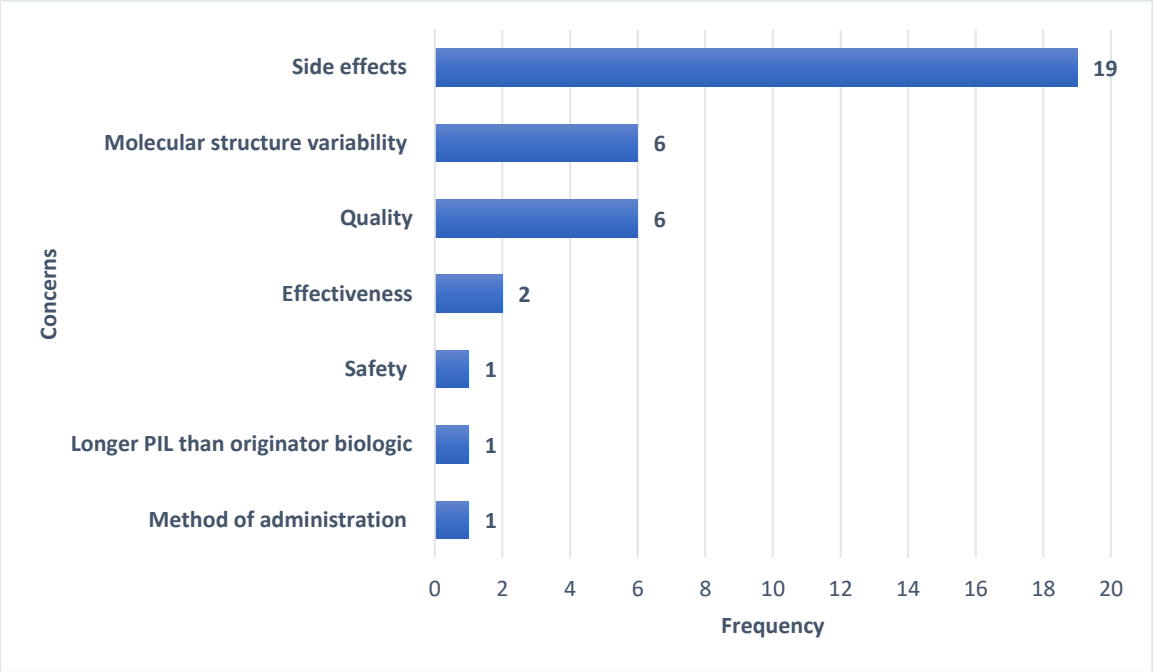


Figure 3.19: Patient concerns with biosimilar use post-pharmacist intervention (n=32)

Chapter 4

Discussion

4.1 Insights into Patient Perceptions, Concerns and Knowledge Gaps Regarding Biosimilars

According to National Health System data, the most prescribed and dispensed biosimilar through Pharmacy of Your Choice (POYC), up until April 2024, was adalimumab. This was reflected in our study population, where most participating patients were on adalimumab. This could be attributed to the fact that adalimumab has a wide range of indications. Rheumatoid arthritis is the most common indication for adalimumab, since rheumatology patients are amongst the largest population that receive tumour necrosis factor inhibitors. In fact, most patients participating in this study were being administered a biosimilar for rheumatoid arthritis. The availability of multiple biosimilar options for adalimumab increases its accessibility, which might cause its preference over others. Moreover, the fact that the originator biological of adalimumab was commercially successful, might have increased its prescribing and dispensing popularity (Bellinvia et al, 2019). Adalimumab also has a high rate of treatment response and disease remission (Wei et al, 2020; Yu et al, 2024) which might influence its appeal in clinical practice.

This study demonstrates that there is still lack of knowledge of biosimilars in patients in Malta, and that a pharmacist educational intervention is a possible way forward to improving patients' knowledge and perceptions on biosimilar use. The study findings reveal that the pharmacist intervention had a positive impact on patients' comprehension and perception of biosimilars. A large number of patients expressed strong agreement or agreement that pharmacist-led educational interventions improved their understanding of biosimilars. With the help of the pharmacist intervention, patients also believed that receiving an educational intervention prior to initiating treatment with the biosimilar would have been of an

advantage. This accentuates the pivotal role that pharmacists have within the community, not only in dispensing medications, but also in providing crucial education to patients. The study findings suggest that an early educational intervention could potentially mitigate uncertainties surrounding biosimilars. The statistically significant positive shift in perception, from patients not knowing what biosimilars were, and patients who were apprehensive of biosimilar use prior to the pharmacist intervention, to patients believing that biosimilars were as good as the originator biological and having a high level of confidence with biosimilar use, highlights the influence of pharmacist-led educational interventions on shaping attitudes and perceptions towards biosimilars. Similarly to our findings, the study by Wu et al (2023) concluded that in general, there is still a lack of knowledge on biosimilars. From the analysed studies, 6-51% of participants were familiar with biosimilars, 25-58% believed that they did not have enough information on biosimilars. In this study, 53 out of 70 patients did not know what a biosimilar was prior to the pharmacist intervention and 54 did not know that they were currently taking a biosimilar. Also, 63 patients strongly agreed or agreed that there is not enough education on biosimilars. This is also comparable to the results obtained by Peyrin-Biroulet et al (2019), where it was concluded that unfamiliarity with biosimilars amongst patients on biologicals was common.

While there were some patients associating the lower price of biosimilars with a lower quality product, following the pharmacist educational intervention, more than half of the patients were not willing to pay more money to get the originator biological. The pharmacist intervention could have possibly addressed these misconceptions about biosimilars, clarifying that these medicinal products undergo rigorous testing and proving that they are highly similar to the originator biological in terms of safety, quality and efficacy.

The concept of patient and healthcare professional collaboration in shared decision-making is being advocated within healthcare. This approach, not only helps patients in understanding their disease and become more knowledgeable of it, but it has been associated with enhancement of patient care through improved patient satisfaction and adherence as well as ameliorated clinical outcomes. Therefore, a switch or initiation with a biosimilar medication should be communicated clearly, and the necessary information given to patients (Sheridan et al, 2024). Findings from this study suggest that probably patients were not being communicated that the medication that they were being dispensed was a biosimilar, with 54 out of 70 patients not knowing that the medication they were getting was a biosimilar.

Patients in this study had positive views of biosimilars, despite initial apprehensions, where 54 patients responded that they thought that biosimilars were good or very good. It might be worthy to highlight that despite this positive view towards biosimilars, patient responses could have been biased. Patients might have believed that the biosimilar they were using was good simply because they were feeling well controlled and were not experiencing any side effects. Therefore, it might not necessarily mean that patients understood what they were responding to. Those patients that thought that biosimilars were bad or had neutral views on biosimilars are important to consider because understanding their perspectives enables healthcare providers to identify barriers of acceptance. The positive views of the patients in this study align with the overall positive trend observed in the systematic review conducted by Wu et al (2023). Their study gives an outline of the findings of 43 published studies that assessed patients' perceptions of biosimilars. One of the main findings was, that of the 31 studies that looked at patient acceptance of biosimilars, 22 concluded that participants were satisfied with the use of biosimilars.

Negative perceptions on biosimilars could increase the risk of the nocebo effect, leading to perceived reduction or lack of effectiveness, or the occurrence or increase in the number of side effects. Consequently, this has been related to a decrease in adherence and an increase in treatment discontinuation (Sheridan et al, 2024). A study by Wetwittayakhlang et al (2024) demonstrated comparable clinical efficacy between the originator biological and the biosimilar, with clinical remission and corticosteroid-free clinical remission rates remaining unchanged, and the levels of anti-drug antibodies remaining the same as they were at baseline, following a non-medical switch from the originator biological to the biosimilar for 24 weeks. Despite this, 10% of the participating inflammatory bowel disease patients still reported nocebo effects following the switch, and 20% of these patients discontinued the biosimilar. In this study, prior to the pharmacist educational intervention, 22 patients had been apprehensive of biosimilar use. Following the intervention, during which the concept of what biosimilars are was explained, only 7 patients remained apprehensive of biosimilar use. This reduction in apprehension suggests that providing clear information and education to patients about biosimilars could potentially alleviate concerns and improve their acceptance. Patient confidence in biosimilars, as also demonstrated in this study, could be increased through an explanation of what biosimilars are, their development process, and regulatory criteria. This could in turn increase adherence and improve clinical outcomes. Numbers were statistically significant when comparing patients' apprehension with biosimilar use pre-pharmacist educational intervention and patients' confidence with biosimilar use post-pharmacist intervention, further supporting this idea ($p= 0.008$).

It is also common for patients to mistake generic medications with biosimilars, in thinking that they are the same. Generic medications are sometimes associated with a negative reputation due to misconceptions and lack of information (Jaber et al, 2021; Hatem et al, 2023), which

could then be reflected badly on biosimilars. This study showed parallels between misconceptions for generic medications and biosimilars. From this study it could be concluded that both generic medications and biosimilars are subject to the misconceptions that a lower price is associated with lesser quality, inferiority, and increase in side effects. During this study, the differences between generic medications and biosimilars were explained using the infographics to try mitigate this bad reflection on biosimilars. Pharmacist-led interventions could effectively improve a switch to a biosimilar (Levivien et al, 2022), and healthcare professionals could play an important role in preventing and managing the nocebo effect (Pouillon et al, 2019).

Evaluation of patient concerns prior to the pharmacist intervention was not possible due to a general lack of knowledge and awareness of biosimilars by most patients. However, the pharmacist educational intervention, using infographics, contributed to closing knowledge gaps since there were patients (n=38) having no concerns post-pharmacist intervention, continuously highlights the importance and the positive effect of the pharmacist intervention. Following the intervention, there was still a subset of patients with remaining concerns. Amongst those with concerns, the risk of the occurrence of side effects was the most common (n=19), followed by molecular structure variability (n=6) and quality (n=6). In a study by Peyrin-Biroulet et al (2019), only 22% of patients had no concerns about biosimilars. This number varies from our study where 54% of patients (n=38) had no concerns. This could be attributed to the pharmacist educational intervention in educating patients and improving their knowledge and perception of biosimilars. In the same study by Peyrin-Biroulet et al (2019), of those with concerns, the most common concern was safety and efficacy. Contrarily to our study, safety and efficacy were among the least mentioned concerns. This suggests that within the Maltese setting, patients might have different reflections regarding biosimilars,

with the risk of the occurrence of side effects, molecular structure variability and quality being more salient concerns for patients. Understanding variations in patient concerns is essential for tailoring interventions and educational efforts to be able to address specific needs and concerns of different patient populations. Other studies support the results in both our study and that by Peyrin-Biroulet et al (2019), with some concerns mentioned by patients including side effects, non-similar molecular structure, safety, and efficacy (Frantzen et al, 2019; Gibofsky et al, 2022; Varma et al, 2022; Gibofsky et al, 2023). The systematic review by Wu et al (2023) found that, the most frequently mentioned patient concerns with biosimilar use, which could influence their perceptions negatively, were uncertainties on the clinical effects of biosimilars including safety and efficacy, regulatory approval pathways for biosimilars, and concerns on price and accessibility advantages that biosimilars offer where patients associate low costs with low quality. Even though patients understood that biosimilars could improve access to biological treatment through lower costs of treatment, some still believed that lower prices correlated to lower quality medicinal products. These results are also comparable to this study.

The most observed knowledge gaps related to side effects (n=42), followed by quality (n=27), effectiveness (n=26) and clinical development and evidence from clinical trials (n=23), since most patients believed that they would like to obtain more information on these subjects. This study is in accordance with a study by Vandenplas et al (2022), where most patients required more information on biosimilars' safety and efficacy, clinical development processes, method of administration, and quality, all of which were mentioned in this study.

When requiring more information on biosimilars, healthcare professionals including physicians and pharmacists, medicine agencies, academia and patient associations were

sources of information for the participants in a study by Wu et al (2023). In this study, healthcare professionals were the go-to source of information, with more than half of the patients always or often relying on the information provided to them by the consultant, the family doctor, and the pharmacist. The consultant was the most trustworthy source of information, with no patients mentioning that they never rely on information regarding biosimilars provided to them by the consultant. Only 24 out of the 70 patients refer to online sources when they require information on biosimilars. This could be attributed to the fact that most of the patients that participated in the study corresponded to the older generation. Even though online sources were mentioned by patients as a source of information, the majority of patients never or rarely rely on the information that they obtain from this source. Therefore, even though information online is easily accessible by everyone, patients seem to be aware that not all information found on this source of information is reliable. This further underlines the important role that healthcare providers have in disseminating information to patients. This can only be achieved if healthcare professionals are knowledgeable, well-informed, and updated on the subject.

4.2 Impact of Healthcare Providers Perception on Patients

The introduction of biosimilars onto the market at a lower cost than the originator biological, has been a promising avenue for increased cost-effective healthcare systems and patient accessibility (Halimi et al, 2020; Hariprasad et al, 2022; Mestre-Ferrandiz et al, 2024). Over the past five years, there has been substantial progress when it comes to biosimilar acceptance and understanding amongst healthcare providers. However, knowledge gaps still exist

(Giavatto et al, 2024). The clinical uptake of biosimilars might be affected by the reduced prescribing, dispensing and lack of confidence by healthcare providers (Halimi et al, 2020; Oskouei & Kusmierczyk, 2021), which can be attributed to the lack of knowledge and understanding of biosimilars. The introduction of educational activities and material with the use of evidence supported data could help mitigate these knowledge gaps (Marín-Jiménez et al, 2021; Giavatto et al, 2024). Healthcare providers play an important role in making patients active participants in their own treatment-decision making and can increase biosimilar uptake by supporting patients and educating them on important aspects of biosimilar use. They can advocate the affordability and cost-savings to healthcare systems that biosimilars bring about and present scientific evidence through clinical trial results to patients (Joshi et al, 2023). By adopting a collaborative approach between physicians and pharmacists, one can achieve more effective patient care through increased biosimilar accessibility, acceptability, and affordability (Giavatto et al, 2024). Adequate evidence-based education of healthcare professionals is reflected onto patients, hence understanding pharmacists' and physicians' perceptions and existing knowledge gaps within these professions, and comparing them to those of patients, is essential.

The results of this study emphasise the crucial role of pharmacists in the continuous education on biosimilars. It is important that pharmacists feel confident in this role to be able to effectively educate others. Studies have shown that there are knowledge gaps on biosimilars within community pharmacists and hence more training is required (Arnet et al, 2021; Bugeja, 2022; Okoro et al, 2022; Stevenson et al, 2023). Pharmacists, as the lead medication experts, should be equipped with the latest biosimilar knowledge to ensure maximised use of biosimilars and reduce misconceptions that patients might have (Okoro et al, 2022).

In a systematic review by Sani et al (2022), pharmacists' perceptions and knowledge on biosimilars were assessed. The level of knowledge on biosimilars among the participating pharmacists varied. The studies that were analysed in this systematic review reported a level of knowledge on biosimilars as good, considerable, above average or excellent for 47–86% of the participating pharmacists. This is a relatively wide range which could be attributed to the fact that the studies that were included were conducted in different countries where the introduction of biosimilars occurred at different timeframes. It is also surprising to note that the highest percentage of 86% of pharmacists having adequate knowledge of biosimilars pertained to a study that was conducted on pharmacists in the United States. This is an interesting finding since biosimilars in the United States were only introduced back in 2015, which is much later than when they were introduced in Europe in 2006. This difference in level of knowledge could be because there were differences in the way in which knowledge was defined and assessed between the different studies, making it more difficult to compare. However, this emphasises the need for standardisation in assessing the knowledge levels on biosimilars amongst healthcare professionals through the establishment of common definitions and criteria. Contrarily, three studies reported the pharmacists' knowledge as being poor or minimal. Even though there are some pharmacists that have a satisfactory understanding of biosimilars, there is still inadequate knowledge (Sani et al, 2022). Dealing with knowledge gaps can ensure that pharmacists are well equipped with the appropriate information to educate patients on biosimilars as their availability and infiltration in the market is continuously increasing (Stevenson et al, 2023). Eighteen studies analysed the perceptions of pharmacists on biosimilar use and a lack of confidence with biosimilar use was reported (Sani et al, 2022). In another study, it was found that only 33% of the participating

pharmacists felt moderately comfortable in addressing patients' questions on biosimilars and only 18% were very comfortable (Stevenson et al, 2023).

Disadvantages of biosimilar use was also analysed and included immunogenicity issues, differences in the pharmacokinetics between the originator biological and the biosimilar and the fact that the biosimilar is not completely identical to the originator biological in a study by Sani et al, (2022). Concerns and barriers to biosimilars were also identified and included concerns regarding safety and efficacy, the occurrence of side effects, insufficient safety data on biosimilars, limited availability of resources for obtaining data on biosimilars, a deficit of confidence and knowledge regarding biosimilars amongst the different stakeholders involved, the preference for originator biologicals rather than the biosimilar by the prescribing physician and the patient, and indication extrapolation concerns (Sani et al, 2022). It is worthwhile to note that patients share some common concerns that healthcare providers have regarding biosimilars. This could mean that healthcare professionals concerns might be reflected onto patients. These findings highlight the need for education to pharmacists in these areas, with a particular focus on clinical aspects like immunogenicity, safety and efficacy, and regulatory aspects of biosimilars.

With biosimilars likely being more commonly used within the hospital setting, hospital pharmacists are possibly more knowledgeable and have more experience with biosimilars than community pharmacists (Beck et al, 2017; Oqal et al, 2022). There are no studies in Malta that compare the knowledge of hospital and community pharmacists on biosimilars. However, more education should be provided to community pharmacists as they are the most frequented healthcare providers for patients who collect their biosimilar medications through the POYC scheme.

Pharmacists are in a favourable position to lead education to all stakeholders involved in biosimilars, starting from patients, and continuing with other pharmacist colleagues, physicians, nurses, and others. This will be a way forward towards biosimilar acceptance and improved patient care which will benefit mostly patients, but also the healthcare system (Hobbs & Crawford, 2019). To be able to effectively handle patient concerns, and in certain instances, even physician concerns, pharmacists need to be equipped with the necessary updated and evidence-based information. This could be achieved by the introduction of educational programs so that they are confident enough to pass on this information to both patients and physicians (Giavatto et al, 2024).

Alongside pharmacists, physicians also play a vital role in the delivery of information to patients regarding biosimilars. A study conducted in Malta by Cassar et al in 2016, when biosimilars had just been introduced onto the Maltese market, reviewed and assessed the knowledge and perception of Maltese physicians on biosimilars. Findings showed that physician awareness and familiarity of biosimilars was below that of physicians in other European countries. Of the 942 physicians that participated in the study, 59% were not familiar with biosimilars, whilst only 35% of the participants had a basic understanding of biosimilars. Only 34% of the physicians prescribed biologicals in their practice, while 40% had encountered patients taking biologicals (Cassar et al, 2016). In a follow-on study conducted by Bugeja in 2022, the number of physicians prescribing biologicals as well as those that had encountered patients on biologicals both went up to 49% (Bugeja, 2022). In another local study conducted by Quiroz in 2023, the number of physicians that prescribed biologicals further increased to 50% whilst the those that encountered patients on biologics increased to 70%. Physicians were also questioned on their familiarity with biologicals and biosimilars. Of the participating physicians, 80% felt that they were somewhat familiar, and 25% felt very

familiar with the topic. Half of the participating physicians incorrectly believed that the originator biological and the biosimilar were structurally identical. When asked if therapeutic results would be the same with both the originator biological and biosimilar, 65% of the participating physicians answered correctly. When asked if patients could switch between the originator biological and the biosimilar and expect the same result, 55% of the participating physicians answered correctly (Quiroz, 2023). When comparing the results of these three studies amid each other, it is evident that the prescribing of these agents, and their rate of exposure has been increasing over time in Malta, however there are still some knowledge gaps which need to be addressed to be able to increase the uptake and trust in these agents.

In another study conducted in Spain in 2021, 81% of the participating physicians were quite or very satisfied with the use of biosimilars, and the majority of the participants believed that biosimilar use has a positive impact on healthcare costs. However, it was evident that knowledge gaps existed, mainly regarding biosimilar fundamentals and regulatory aspects, even though the participating physicians perceived these issues as being of a high level of importance (Marín-Jiménez et al, 2021). In a study by Giavatto et al (2024), the knowledge gaps identified amongst physicians were related to safety, efficacy, and the progression of the condition following a switch to a biosimilar, especially amongst patients who had obtained successful remission on the originator biological. The occurrence of these knowledge gaps could be associated with a general lack of knowledge on biologicals (Giavatto et al, 2024). For physicians, common barriers include lack of knowledge, lack of experience with biosimilar use, and lack of confidence with biosimilars. To overcome these barriers, data on safety and efficacy, interchangeability data obtained from both real-word and clinical trials, and guidance and experiences from other experts in the field could be beneficial (Marín-Jiménez et al, 2021).

4.3 Strategies for Patient Education

This study, by analysing patients' perceptions and concerns with biosimilar use, allows for the identification of a plan of action to develop and tailor information and educational material to meet specific patients' needs. There was no statistical significance when demographic data was correlated with questions relating to patients' perceptions, knowledge, and concerns on biosimilars. Lack of statistical significance could be attributed to the sample size. Had the sample size been larger, it is possible that there could have been significance in certain instances. However, this result suggests that regardless of factors such as age, gender, or educational level, there is still a general lack of awareness and knowledge about biosimilars amongst patients, hence education is required across the board. This study also revealed a unanimous sentiment amongst patients, where the majority agreed that there is not enough education on biosimilars and their use. Moreover, there seems to be interest within patients in enhancing their knowledge and wanting to know more about the medication they are taking. One way to bridge knowledge gaps could be through pharmacists providing education to patients. The use of information leaflets can be beneficial in explaining reasons behind initiation, switching or substitution with a biosimilar while at the same time it is important that patients are still allowed preference in treatment choice. Such strategies can be helpful in fostering trust and acceptance amongst patients with biosimilar use (Joshi et al, 2023). The use of educational infographics, coupled up with a pharmacist explanation, as supported by this study, provides an ideal scenario for educating patients on biosimilars and clarifying information needs. Information should be presented to patients in an easy-to-understand way, tailored specifically to each patient and using basic health literacy terms using written

information with graphics or videos providing the relevant information. One should abstain from overshooting information to patients since not every patient could be interested and it might also bring concern on patients as to why so much emphasis is being given (Peyrin-Biroulet et al, 2017). The way in which the information is delivered to patients needs to be understandable to them, concise, using simple words, and providing the most recent data. The pharmacist intervention in this study, conducted as a one-on-one questionnaire, in the form of an interview, allowed it to be a discussion with the patient, where they could ask questions. This allows the patient to be more involved (Vandenplas et al, 2021). Positive communication is also deemed key when conveying information on biosimilars. Studies have shown that when healthcare providers use a positive and confident approach in relaying information on biosimilars, patients are more likely to be willing to take the biosimilar and expect positive results. An example would be emphasising the equalities or similarities between the originator biological and the biosimilar and not the differences (Scherlinger et al, 2019; Gasteiger et al, 2020; Sheridan et al, 2024). The same approach was used in this study, and from the results obtained it proved beneficial, since post-pharmacist intervention, 58 out of 70 patients felt confident or very confident that biosimilar use was good for them.

Another way could be by mapping the information that is available for patients. This would provide an overview of material that is available and that is supported by evidence, making it scientifically correct, and at the same time prevent patients from obtaining misinformation by accessing the wrong data. This idea could be supported further by having the different stakeholders involved with procuring, prescribing, and dispensing, in the creation of an inventory such as in the form of a website (Vandenplas et al, 2021). The only downside to this could be that it would require regular updating to ensure the latest information is being given to patients (Chan et al, 2020).

Different patients have different concerns, hence tailored communication is important by assessing patients' individual needs and then providing the necessary required information (Vandenplas et al, 2021). In this study, the educational infographics focused on what generic medications are, what biologicals and biosimilars are and the similarities between them, and the regulatory criteria for biosimilar placement onto the market. It was evident that using educational material, patient concerns were answered as the number of patients who were apprehensive to biosimilar use decreased. Some patients still had concerns on biosimilars even post-pharmacist intervention, and this indicates the need for personalised education, allowing patients to ask questions and allocating enough time for explanations, as throughout the study, time was limited to approximately 20 minutes per patient.

The use of real-life experiences from other patients who had previously undergone a switch from an originator biological to a biosimilar could prove beneficial in patients who are about to initiate a biosimilar or undergo a switch themselves. This approach emphasises the importance of including patients' personal stories to increase understanding through empathy so that patients are empowered by relatable resources (Rosembert et al, 2024).

The delivery of information needs to be supported by convincing information and delivery. Healthcare providers' positive perceptions and knowledge of biosimilars is crucial for patient acceptance, as observed in a study by Scherlinger et al (2019). One way of increasing education for healthcare professionals would be to include study units within the university curriculum (Li et al, 2017). The integration of biosimilars within a healthcare system usually has the potential of producing cost-savings, which could then be re-invested (Cornes, 2012) in long-term educational programmes for both patients and healthcare providers (Cross et al, 2022).

4.4 Strengths and Limitations

To the knowledge of the researcher, this is the first study in Malta that explores the perceptions, knowledge and concerns of patients taking biosimilars.

One of the limitations of this study is that only patients taking biosimilars were included. This attributed to another limitation, which is a smaller patient sample size then initially predicted. The initial aim was to include hundred patients in the study; however, seventy patients were recruited in the end. This could be partially attributed to the limited time for data collection, and that each patient-researcher interaction took approximately twenty minutes. Biosimilars, even though their use in Malta is increasing, are still a relatively new concept. The fact that there is a limited number of patients on biosimilars, and not every biological medicinal product has a biosimilar, also affected the sample size. Including patients taking both the originator biological and those taking biosimilars would have allowed for a greater sample size. Moreover, including more pharmacies in the study would have helped in the recruitment of more patients.

4.5 Recommendations for Further Research

This study only included patients already taking biosimilars. It is recommended that future studies would investigate the perceptions, knowledge and concerns of patients who are taking the originator biological on the use of biosimilars.

Future studies being conducted over a longer period of time could overcome the sample size limitation. A further recommendation would be to conduct follow-up meetings with patients on biosimilars to assess further the impact that the pharmacist intervention had on their perception and knowledge in the long-term.

Another recommendation would be to provide a pharmacist intervention, with the aid of infographics, through a one-on-one session between the patient and the pharmacist in a patient sensitive manner to those patients who are going to start taking biosimilars. Their perception on biosimilars could then be analysed and compared to the perception of patients who are already on a biosimilar but had never had a pharmacist intervention. The success rate of this intervention could then be measured to analyse the importance of the pharmacist in educating patients on biosimilars within the community setting.

4.6 Conclusion

Knowledge gaps with respect to awareness about biosimilars and concerns were identified. Following the pharmacist educational intervention, a number of patients did not have any concerns with biosimilar use. Of those with concerns, doubts regarding side-effects, molecular structure variability and effectiveness were the most commonly identified. This underscores the need for personalised communication with patients and ongoing educational interventions since single interventions might not be sufficient.

Communication between patients and their healthcare providers is essential in increasing the accessibility, acceptability, and uptake of biosimilars. Communicating the initiation of a

biosimilar, or a switch from an originator biological to a biosimilar to patients, is not only good practice, but it also encourages patients to actively participate in their own treatment, and may help in the mitigation of the nocebo effect (Stevenson et al, 2023). Patients perceived healthcare professionals, mainly the consultant, family doctor, and the pharmacist, as the most trustworthy and main sources of information. However, it is important that healthcare providers are equipped with evidence-based information on biosimilars and feel confident both in their own understanding of biosimilars and in the information that they are relaying to the patients.

The development of validated and easily understood educational material, in the form of infographics, proved beneficial in closing knowledge gaps, increasing the confidence of patients, and improving perceptions and acceptance of biosimilars. Educational initiatives targeting both healthcare professionals and patients should focus on similarities between the originator biological and biosimilars, their clinical outcomes as well as the regulatory aspect. These initiatives are a way forward to facilitate the uptake of biosimilars and enable the pharmacist contribution to evolve the concept whereby the patient moves from a compliant mode to adherence and further more to concordance.

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Appendices

Appendix 1: Ethics Approval

L-Università ta' Malta

Faculty of Medicine & Surgery

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Ref No: MED-2023-00214

28 August 2023

Ms Francesca Borg
83, 'L-Ajkla',
Triq Karmenu Vassallo,
Siggiewi

With reference to your application submitted to the Faculty Research Ethics Committee in connection with your research entitled:

Biosimilars in Community Pharmacy Practice

The Faculty Research Ethics Committee is granting ethical approval for the above-mentioned application.

Professor Anthony Serracino Inglott
Chair
Faculty Research Ethics Committee

Appendix 2: Questionnaire (English & Maltese)

Data Collection Questionnaire (English)

Patient Study Number:

For internal use

Demographics

1. How old are you?
    - □ 18-35
    - □ 36-55
    - □ 56-75
    - □ 76 or more

2. What is your gender?
    - □ Male
    - □ Female
    - □ Other
    - □ Prefer not to say

3. What is your level of education?
    - □ Primary
    - □ Secondary
    - □ Post-secondary
    - □ Graduate
    - □ Post-graduate

4. What biosimilar medication are you on?
    - □ Amgevita®
    - □ Erelzi®
    - □ Inhixa®
    - □ Binocrit®
    - □ Other:

5. For which condition/s were you prescribed a biosimilar?
    - □ Rheumatoid Arthritis
    - □ Thrombosis
    - □ Psoriasis
    - □ Crohn's disease
    - □ Ulcerative colitis
    - □ Other:

6. How long have you been on biologic treatment?
    - □ Less than 12 months
    - □ 1-3 years
    - □ 4-6 years
    - □ 7-10 years
    - □ More than 10 years

7. Have you always been on the same brand of this medicine?
    - □ Yes
    - □ No

    If yes – proceed to question 9
    If no – proceed to question 8

8. Do you think the other one was better or did you find this one better? Why?

9. Do you feel that your condition is well controlled?
    - □ Yes
    - □ No

Use the 'infographic' regarding generic medicines to explain better.

Afterwards, ask the patient these questions.

10. Generic medicines are medicines that have the same active ingredient as the original medicine.

    Do you use generic medicines, as are the majority of 'POYC' medicines?
    - □ Yes
    - □ No

If yes, ask question 11.

If no, explain what a 'biologic' and 'biosimilar' are and skip to question 13.

11. What are your thoughts on generic medicines?

Very bad	Bad	Neutral	Good	Very good
1	2	3	4	5

If the patient chose 1,2,3 – skip to question 12

If the patient chose 4 or 5 – skip to question 13

12. Why?

13. You think that biosimilars, which is the medication which you are currently taking, are_____ than the original medicine:
    - □ Better
    - □ As good as
    - □ Worse
    - □ No opinion
    - □ I don't know what a biosimilar is

You may have heard the term 'biologic'. 'Biologic' is a product that we call biological, meaning its structure is similar to natural and biological structures. These medicines have been studied and originated by established medicine brands, and have been clinically proven, like other medicines. There are other brands that have made a product very similar to these products, which will have the same expected effects. Since these products are similiar to one another, they are called 'biosimilars'. In your case, you are using a 'biosimilar' product that improves your condition. This product works in the same way as the original medicine.

14. Did you know that your medication is a biosimilar?
    - □ Yes
    - □ No

15. Does it bother you that you are using a biosimilar rather than the original medication?
    - □ Yes
    - □ No

16. Why?

17. What are your thoughts of biosimilars? (like the medication you are using)

Very bad	Bad	Neutral	Good	Very good
1	2	3	4	5

Use the 'infographic' regarding biologics and biosimilars and the 'infographic' regarding the criteria that a 'biosimilar' product must meet to explain better.

18. Did you know this information before?
    - □ Yes
    - □ No

19. Now I am going to ask you some questions about what I just explained to you. Answer the following questions with yes or no.

For biosimilars to be placed on the market, they must meet these criteria:

a. They work in the same way as the original medicines
   □ Yes
   □ No

b. They must be manufactured by the same company
   □ Yes
   □ No

c. They must have the same dose
   □ Yes
   □ No

d. They are administered in the same way, for example orally, or by the same route of injection
   □ Yes
   □ No

e. They are sold at the same price as the originator
   □ Yes
   □ No

f. They always have less unwanted effects
   □ Yes
   □ No

20. Are you willing to pay more money to get the original product, even when you are informed that the products are similar?

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
1	2	3	4	5

21. Do you think there is enough education about biosimilars?

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly Agree
1	2	3	4	5

22. What would you like to know more about the use of biosimilar medicines?

- □ Side effects
- □ Process of development
- □ Clinical development and evidence from clinical trials
- □ Quality
- □ Effectiveness
- □ Method of administration
- □ I don't require information
- □ Other:

23. Who/ what do you refer to when you need more information regarding biosimilar medicines?
    - □ Consultant
    - □ Family doctor
    - □ Pharmacist
    - □ Family
    - □ Online
    - □ Package insert
    - □ Other:

24. How much do you rely on the opinion and information provided to you about biosimilars by:

	Never 1	Rarely 2	Sometimes 3	Often 4	Always 5
Consultant					
Family Doctor					
Pharmacist					
Family					
Online					

Questions regarding perception on biosimilars after the educational pharmacist intervention

25. For each statement, mark which is most suitable for you, where:

1= strongly disagree; 2= disagree; 3= neutral; 4= agree; 5= strongly agree

	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5
This session has helped you understand better what a biosimilar is.					
I think that biosimilars take longer time to work than the original medicine.					
I think that biosimilars have more unwanted effects than the original medicine.					
I think that biosimilars are of lower quality than the original medicine.					
I think that if all this had been explained to me prior to initiating treatment, it would have been better.					
This session has helped you improve the perception that you had regarding biosimilars.					

26. You think that biosimilars are _____ than the original medicine:
    - □ Better
    - □ As good as
    - □ Worse
    - □ No opinion

27. Is there anything that concerns you about the use of biosimilars?
    - □ Safety
    - □ Quality
    - □ Effectiveness
    - □ Side effects
    - □ The fact that their molecular structure might vary a bit from the original even though it is highly similar
    - □ No concerns
    - □ Other:

28. How confident are you that using biosimilars is right for you?

Not confident at all	Not confident	Neutral	Confident	Very confident
1	2	3	4	5

If the answer to question 15 was 'Yes' ask:

29. After this explanation on 'biosimilars', does it still bother you that you are using a biosimilar rather than the original medication?
    - □ Yes
    - □ No

Kwestjonarju tal-Ġbir tad-Data (Malti)

Numru ta' Studju tal-Pazjent:

Għal użu intern

Demografija

1. Kemm għandek żmien?
    - □ 18-35
    - □ 36-55
    - □ 56-75
    - □ 76 jew iktar

2. X'inhu s-sess tiegħek?
    - □ Raġel
    - □ Mara
    - □ Oħrajn
    - □ Nippreferi ma ngħidx

3. X'inhu l-livell ta' edukazzjoni tiegħek?
    - □ Primarja
    - □ Sekondarja
    - □ Post-sekondarja
    - □ Gradwat
    - □ Post-gradwat

4. Liema medicina bijoloġika qed tieħu?
    - □ Amgevita®
    - □ Erelzi®
    - □ Inhixa®
    - □ Binocrit®
    - □ Oħrajn

5. Għal liema mard ġejt preskritt bijoloġiku/bijosimili?
    - □ Rewmatiżmu
    - □ Tromboži
    - □ Psorjaži
    - □ Crohn's
    - □ Kolite ulċerattiva
    - □ Oħrajn:

6. Kemm ilek fuq trattament bijoloġiku?
    - □ Inqas minn 12-il xahar
    - □ 1-3 snin
    - □ 4-6 snin
    - □ 7-10 snin
    - □ Aktar minn 10 snin

7. Minn dejjem kont fuq l-istess ditta ta' din il-mediċina?
    - □ Iva
    - □ Le

Jekk iva – ipproċedi għall-mistoqsija 9

Jekk le – ipproċedi għall-mistoqsija 8

8. Taħseb li l-ieħor kien aħjar jew dan sibtu aħjar? Għaliex?

9. Tħoss li l-kundizzjoni tiegħek hija kkontrollata tajjeb?
    - □ Iva
    - □ Le

Uża l-'infographic' rigward mediċini ġeneriċi biex tispjega aħjar.

Wara, staqsi dawn il-mistoqsijiet lil-pazjent.

10. Mediċini ġeneriċi huma mediċini li għandhom l-istess ingredjent attiv bħall-mediċina oriġinali.

    Inti tuża mediċini ġeneriċi, bħal ma huma l-maġġoranza tal-mediċini tal-'POYC'?

    □ Iva

    □ Le

Jekk iva, staqsi mistoqsija 11.

Jekk le, spjega x'inhu 'biologic' u 'biosimilar' u imxi għall-mistoqsija 13.

11. X'inhuma l-ħsibijiet tiegħek dwar il-mediċini ġeneriċi?

Ħażin ħafna	Ħażin	Newtrali	Tajjeb	Tajjeb ħafna
1	2	3	4	5

Jekk il-pazjent għażel 1,2,3 – ipproċedi għall-mistoqsija 12

Jekk il-pazjent għażel 4 jew 5 - ipproċedi għall-mistoqsija 13

12. Għaliex?

13. Inti taħseb li mediċini 'biosimilar', bħalma hi l-mediċina li qed tieħu inti, huma _____ mill-mediċini oriġinali:

    □ Aħjar
    □ Tajbin daqs
    □ Agħar
    □ M'għandekx opinjoni
    □ Ma tafx x'inhuma 'biosimilars'

Jista' jkun li ġieli smajt bit-terminu 'biologic'. 'Biologic' huwa prodott li nsejħulu bijologiku, jiġifieri l-istruttura tiegħu tixbaħ ħafna lill-strutturi naturali u bijologiċi. Dawn il mediċini ġew studjati u oriġinati minn ditti stabiliti tal-medicini, u pruvati klinikament, bħal mediċini oħra. Hawn ditti oħrajn li għamlu prodott simili ħafna għal dawn il-prodotti, li jkollom mistennija l-istess effetti. Dawn il-prodotti, billi huma simili, jissejħu 'biosimilars'. Fil-kas tiegħek, inti qed tuża prodott 'biosimilar' li jammeljora l-kundizzjoni tiegħek. Dan il-prodott jaħdem bl-istess mod tal-mediċina oriġinali.

14. Inti kont taf li l-mediċina li tieħu int hija 'biosimilar'?
    - □ Iva
    - □ Le

15. Idejqek il-fatt li l-mediċina li tieħu int hija 'biosimilar' u mhux l-oriġinali?
    - □ Iva
    - □ Le

16. Għaliex?

17. X'inhuma l-ħsibijiet tiegħek dwar il-'biosimilars'? (il-mediċina li qed tuża bħalissa)

Ħażin ħafna	Ħażin	Newtrali	Tajjeb	Tajjeb ħafna
1	2	3	4	5

Uża l-'infographic' rigward 'biologics' u 'biosimilars' u l-'infographic' rigward il-kriterji li jrid jissodisfa prodott 'biosimilar' biex tispjega aħjar.

18. Din l-informazzjoni kont tafa qabel?
    - □ Iva
    - □ Le

19. Issa ser nistaqsik xi mistoqsijiet dwar dak li għadni kif spjegajtlek. Wieġeb dawn il-mistoqsijiet li ġejjin b'iva jew le.

    Il-'biosimilars', sabiex jitpoġġew fis-suq, iridu jissodisfaw dawn il-kriterji:

    a. Jaħdmu bl-istess mod bħall-mediċini oriġinali
        - □ Iva
        - □ Le
    b. Ikunu bilfors manifatturati mill-istess ditta
        - □ Iva
        - □ Le
    c. Ikollom l-istess doża
        - □ Iva
        - □ Le
    d. Jiġu amministrati bl-istess mod, eżempju mill-ħalq, jew injezzjoni bl-istess mod
        - □ Iva
        - □ Le
    e. Jinbiegħu bl-istess prezz tal-oriġinatur
        - □ Iva
        - □ Le
    f. Ikollhom dejjem inqas effetti mhux mixtieqa
        - □ Iva
        - □ Le

20. Inti lest/a tħallas iżjed flus biex tieħu l-prodott oriġinali, anke meta inti infurmat li l-prodotti huma simili?

Ma naqbel xejn	Ma naqbilx	La naqbel u lanqas ma naqbilx	Naqbel	Naqbel ħafna
1	2	3	4	5

21. Taħseb li hawn biżżejjed edukazzjoni dwar il-'biosimilars'?

Ma naqbel xejn	Ma naqbilx	La naqbel u lanqas ma naqbilx	Naqbel	Naqbel ħafna
1	2	3	4	5

22. X’tixtieq tkun taf iżjed dwar l-użu tal-mediċini ‘biosimilar’?

- □ Effetti mhux mixtieqa
- □ Il-proċess ta' kif ġew żviluppati
- □ Żvilupp kliniku u evidenza minn provi kliniċi
- □ Kwalità
- □ Effettività
- □ Metodu ta' amministrazzjoni
- □ M'għandix bżonn ta' informazzjoni
- □ Oħrajn:

23. Għal min/ għal xiex tirrefferi meta jkollok bżonn iżjed informazzjoni rigward il-mediċini ‘biosimilar’?

- □ Konsulent
- □ Tabib tal-familja
- □ Spiżjara
- □ Familja
- □ Onlajn
- □ Fuljett tal-mediċina
- □ Oħrajn:

24. Kemm toqgħod fuq l-opinjoni u l-informazzjoni li jipprovdulek dawn dwar il-mediċini ‘biosimilar’:

	Qatt 1	Rari 2	Xi kultant 3	Spiss 4	Dejjem 5
Konsulent					
Tabib tal-familja					
Spiżjar					
Familja					
Onlajn					

Mistoqsijiet rigward il-perċezzjoni dwar 'biosimilars' wara l-intervent edukattiv mill-ispiżjara

25. Għal kull dikjarazzjoni t'hawn taħt, immarka liema l-iktar tgħodd għalik, fejn:

1= ma naqbel xejn; 2= ma naqbilx; 3= newtrali; 4= naqbel; 5= naqbel ħafna

	Ma naqbel xejn 1	Ma naqbilx 2	Newtrali 3	Naqbel 4	Naqbel ħafna 5
Din is-sessjoni għenitni biex issa naf aħjar x'inhu 'biosimilar'.					
Jien naħseb li 'biosimilars' idumu iktar ma jibdew jaħdmu mill-mediċini oriġinali.					
Jien naħseb li 'biosimilars' għandhom iktar effetti mhux mixtieqa mill-mediċini oriġinali.					
Jien naħseb li 'biosimilars' huma ta kwalita' inqas mill-mediċini oriġinali.					
Li kieku dan l-intervent mingħand l-ispiżjara kien mgħoti lili qabel ma bdejt it-trattament, naħseb li kien ikun aħjar.					
Din is-sessjoni għenitni intejjeb il-perċessjoni li kelli dwar il-'biosimilars'.					

26. Inti taħseb li mediċini 'biosimilar' huma _____ mill-mediċini oriġinali:

- □ Aħjar
- □ Tajbin daqs
- □ Agħar
- □ M'għandekx opinjoni

27. Hemm xi ħaġa li tinkwetak mill-użu tal-‘biosimilars’?
    - □ Sigurtà
    - □ Kwalità
    - □ Effettività
    - □ Effetti mhux mixtieqa
    - □ Il-fatt li l-istruttura molekulari jaf tvarja xi ftit mill-oriġinali anka jekk simili ħafna
    - □ Ma jinkwetani xejn
    - □ Oħrajn:

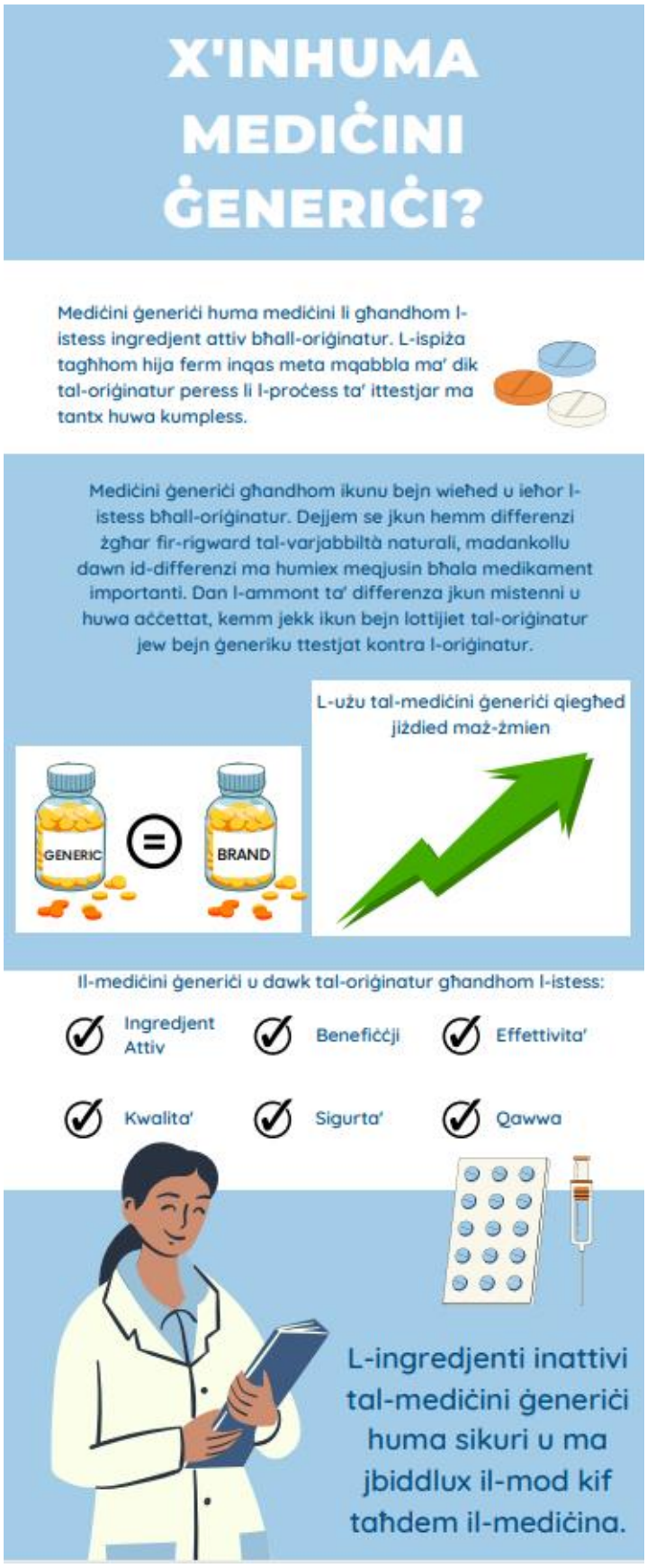
28. Kemm inti kunfidenti li l-użu tal-‘biosimilars’ huwa tajjeb għalik?

Mhux kunfidenti xejn	Mhux kunfidenti	Newtrali	Kunfidenti	Kunfidenti ħafna
1	2	3	4	5

Jekk it-tweġiba għal mistoqsija 15 kienet ‘Iva’ staqsi:

29. Wara din l-ispjegazzjoni dwar il-‘biosimilars’, għadu jdejqek il-fatt li l-mediċina li tieħu inti hija ‘biosimilar’ u mhux l-oriġinali?
    - □ Iva
    - □ Le

Appendix 3: Educational Infographics I-III (Maltese Version)



Sors tal-istampi: https://pixabay.com/

BIOLOGICS U BIOSIMILARS

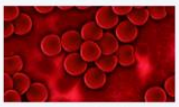
L-introduzzjoni tal-'biologics' fuq is-suq irrevoluzzjonat it-trattament mediku għal numru ta' kundizzjonijiet. Bl-avvanz li sar fil-qasam tal-'biosimilars' żdied l-aċċess għal dawn it-trattamenti.

X'inhuma 'Biologics'?

Il-'biologics' huma prodotti mediċinali li fihom sustanza attiva li tiġi pproduċuta minn sors bijoloġiku, bħal ma huma ċelloli ħajjin.
Dawn il-mediċini jintużaw għat-trattament ta' kundizzjonijiet severi u kroniċi, bħal:

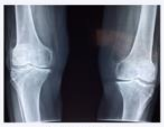
Dijabete

Kundizzjonijiet intestinali kroniċi (ex IBD)



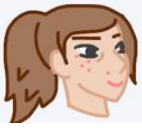
Anemija minħabba mard kroniku tal-kliewi

'Cancers'

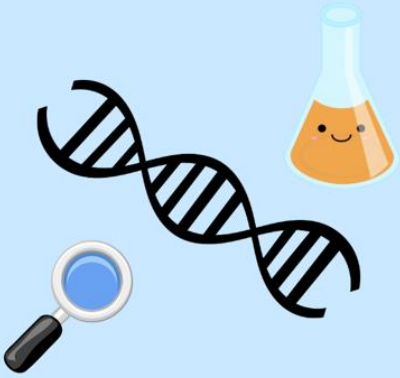


Artrite

Deġenerazzjoni makulari



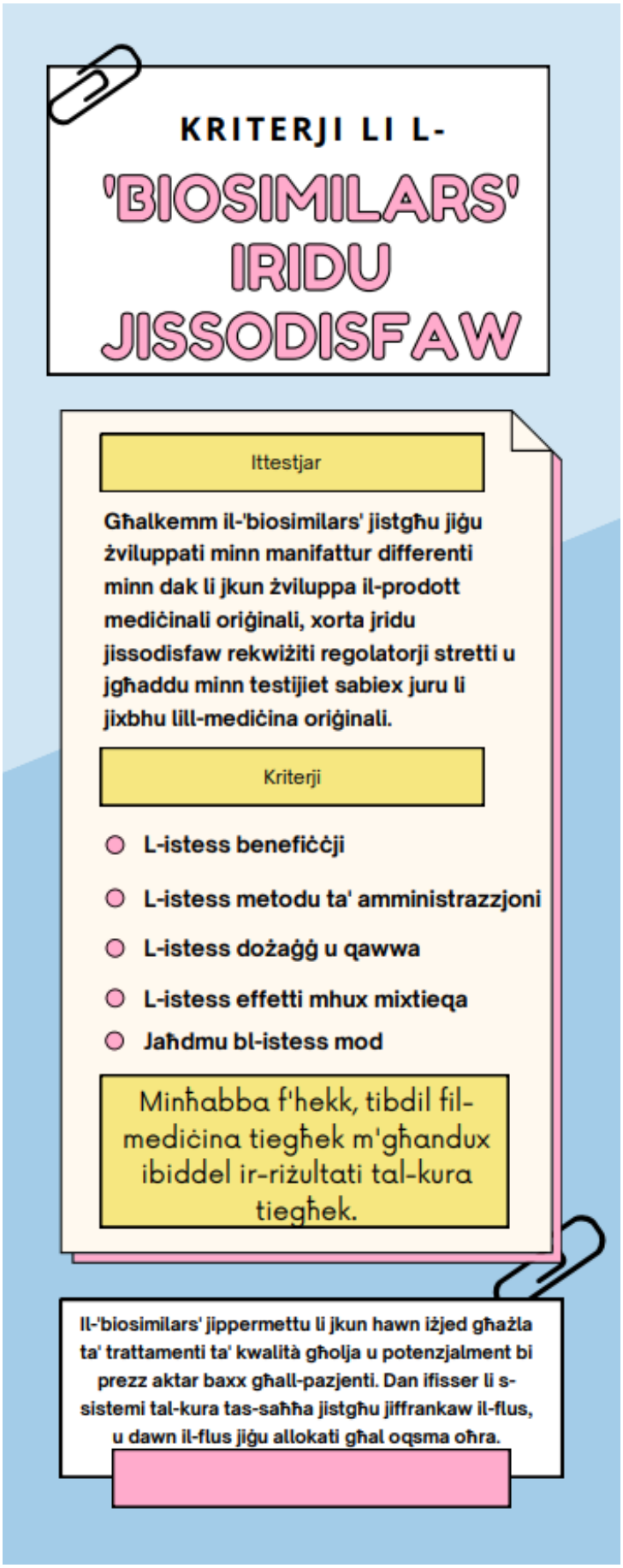
Kundizzjonijiet tal-ġilda kroniċi (ex psorjasi)



X'inhuma 'Biosimilars'?

Il-'biosimilars' huma prodotti bijoloġiċi li huma simili ħafna u li ma wrew l-ebda differenza li hija klinikament sinifikanti mill-mediċina oriġinali ('biologic') mill-aspett ta' sigurtà, purità u qawwa. Huma magħmula mill-istess tip ta' sorsi naturali, għandhom proċessi ta' manifattura simili u huma amministrati bl-istess mod bħall-'biologic' oriġinali.

Sors tal-istampi: https://pixabay.com/


KRITERJI LI L-
'BIOSIMILARS'
IRIDU
JISSODISFAW
Ittestjar
Għalkemm il-'biosimilars' jistgħu jiġu żviluppati minn manifattur differenti minn dak li jkun żviluppa il-prodott mediċinali oriġinali, xorta jridu jissodisfaw rekwiżiti regolatorji stretti u jgħaddu minn testijiet sabiex juru li jixbhu lill-mediċina oriġinali.
Kriterji
L-istess benefiċċji
L-istess metodu ta' amministrazzjoni
L-istess dożaġġ u qawwa
L-istess effetti mhux mixtieqa
Jaħdmu bl-istess mod
Minħabba f'hekk, tibdil fil-mediċina tiegħek m'għandux ibiddel ir-riżultati tal-kura tiegħek.
Il-'biosimilars' jippermettu li jkun hawn iżjed għażla ta' trattamenti ta' kwalità għolja u potenzjalment bi prezz aktar baxx għall-pazjenti. Dan ifisser li s-sistemi tal-kura tas-saħħa jistgħu jiffrankaw il-flus, u dawn il-flus jiġu allokati għal oqsma oħra.

Appendix 4: Dissemination of Study Findings

Poster presented at the 82nd FIP World Congress of Pharmacy and Pharmaceutical Sciences

L-Università ta' Malta | Department of Pharmacy
Faculty of Medicine & Surgery

Pharmacist Intervention in Biosimilar Education within Community Pharmacy Practice

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INTRODUCTION

The lower costs of biosimilars, compared to originator biologicals, makes these biopharmaceuticals a promising avenue for increased cost-effective healthcare systems and patient accessibility.

AIMS

1. To develop a questionnaire and infographics to assess patients' perceptions and concerns of biosimilars and clarify information needs
2. To assess how pharmacist interventions affect perception on biosimilar use

METHOD

- A questionnaire and three infographics were developed in Maltese and English and validated by pharmacists, doctors, and patients.
- Research was conducted in ten community pharmacies across Malta, selected from twenty-seven managed by a pharmacy group where researcher practices, and geographically selected to include north, centre, and south regions.
- Seventy patients on adalimumab, etanercept, epoetin alpha or enoxaparin biosimilars were recruited and provided the questionnaire to identify perceptions, knowledge, concerns and experiences with biosimilars. They were all subjected to an educational pharmacist intervention, taking 20 minutes, using infographics explaining generic medications, biologicals and biosimilars and regulatory criteria (Figure 1).

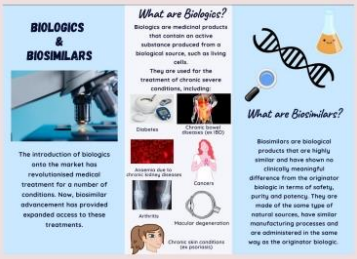

Figure 1: Educational infographic excerpt used to support the pharmacist intervention

RESULTS

- Out of 70 patients, 22 were apprehensive about receiving a biosimilar medication pre-pharmacist intervention. Following the intervention, only 7 remained apprehensive.
- Initially, 53 patients lacked awareness of biosimilars, and only 9 believed biosimilars were as good as the originator (Figure 2). Pharmacist intervention significantly improved perceptions (p=0.025).
- Fifty-nine patients found the infographics to be a novel educational medium. Post-intervention, 38 patients had no concerns. Of those with concerns (n=32), the main issue was potential occurrence of side-effects (n=19) (Figure 3), and 42 patients sought the need for further education regarding this.
- Patients strongly agreed or agreed that there is insufficient biosimilar education (n=63), pharmacist intervention helped improve their biosimilar understanding (n=66), and pharmacist intervention prior to biosimilar initiation would have been beneficial (n=49).

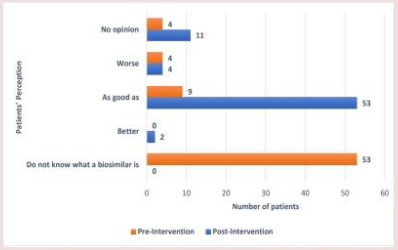

Figure 2: Comparing patients' perceptions on biosimilars pre-and post-pharmacist intervention (N=70)

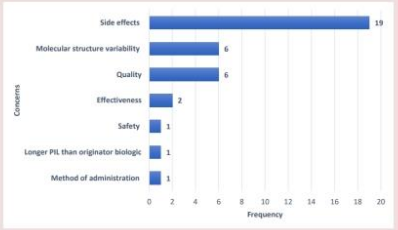

Figure 3: Concerns with biosimilars post-intervention (N=32)

CONCLUSION

A pharmacist intervention, involving use of validated and easily understood infographics, proved beneficial in increasing patient confidence and acceptance of biosimilars and closing knowledge gaps. Educational initiatives aimed at patients are essential for promoting uptake of biosimilars and to enable pharmacist contribution to evolve the concept whereby patients move from compliance, to adherence, to concordance.

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Poster presented at the ESCP 2024 52nd Symposium, Krakow, Poland.

L-Università ta' Malta | Faculty of Medicine & Surgery | Department of Pharmacy

Identifying the Impact of a Pharmacist Intervention using Infographics in Educating Patients on Biosimilars

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INTRODUCTION

Lower costs of biosimilars, compared to originator biologicals, makes these biopharmaceuticals a promising avenue for increased cost-effective healthcare systems and patient accessibility. Knowledge gaps still exist within patients, hindering acceptance and uptake of biosimilars.

AIMS

1. To develop a questionnaire and infographics to assess patients' knowledge and concerns on biosimilars and clarify information needs
2. To assess how a pharmacist intervention affects confidence on biosimilar use

METHOD

Development of questionnaire to determine knowledge and concerns and educational material (infographics) in Maltese and English → Validation of data collection tools through a panel (2 pharmacists, 2 doctors, 2 patients) → Pilot study (N=10) → Questionnaire dissemination and pharmacist-led educational intervention to patients on biosimilars (N=70) from 10 community pharmacies across north, centre, and south Malta. → Assessment of pharmacist intervention and statistical analysis

RESULTS

- Three infographics explained what generics are, provided an overview on biologicals and biosimilars, and explained regulatory criteria for biosimilars (Figure 1).
- Fifty-three out of 70 patients lacked biosimilar awareness, and only 9 believed biosimilars were as good as the originator. Intervention significantly improved perceptions (p=0.025).
- Pre-intervention, 22 patients were apprehensive on receiving a biosimilar. Post-intervention only 7 remained apprehensive. Statistical significance (p=0.008) was observed when apprehension pre-intervention was correlated with patient confidence post-intervention.
- Post-intervention, 38 patients had no concerns. Of those with concerns (n=32), the main issue was potential occurrence of side-effects (n=19) (Figure 2), and 42 patients expressed need for further education regarding this.
- Fifty-nine patients found the infographic information to be a novel educational medium.
- Patients strongly agreed or agreed that there is not enough biosimilar education (n=63), pharmacist intervention helped improve biosimilar understanding (n=66), and pharmacist intervention prior to biosimilar initiation would have been beneficial (n=49).

Figure 1: Educational infographic excerpt used to support the pharmacist intervention

Figure 2: Concerns with biosimilars post-intervention (n=32)

CONCLUSION

Development of validated and easily understood educational material in the form of infographics proved beneficial in closing knowledge gaps and improving patient confidence and acceptance of biosimilars. Educational initiatives targeting patients are a way forward to facilitate biosimilar uptake and enable pharmacist contribution to evolve the concept whereby the patient moves from compliance to adherence to concordance.

Appendix 5: Biological Medications Available Through Pharmacy of Your Choice

ATC Code	Active Ingredient	Dosage Form and Strength	Schedule V Prescriber Criteria	Protocol	Pink Card	Pink Card Prescriber Criteria	Schedule V Entitlement
Drugs affecting the immune response							
L04AB04	Adalimumab	Solution for Injection in Pre-filled Syringes 40mg	Consultant Dermatologists; Consultant Gastroenterologists; Consultant Ophthalmologists; Consultant Paediatricians; Consultant Rheumatologists	MP 307			Hidradenitis Suppurativa; Inflammatory Bowel Disease; Psoriasis; Rheumatoid Arthritis; Spondyloarthritis
Parenteral anticoagulants							
B01AB05	Enoxaparin Sodium	Pre-filled syringe 20mg (2,000 IU); 40mg (4,000 IU); 60mg (6,000 IU); 80mg (8,000 IU); 100mg (10,000 IU)	Consultants	MP 204			Enzyme Disorders; Malignant Diseases; Thromboproph ylaxis in pregnancy
Antifibrinolytic drugs and heamostatics							
B02BD02	Anti-Haemophilic Factor VIII (standby)	Infusion 1000IU	Consultant Haematologists, Consultant Paediatricians, Consultant Infectious Diseases Physician	To dispense from hospitals only			Inherited Bleeding Disorders
B02BD06	Anti-Heamophilic Factor VIII Intermediate	Injection IV 500IU	Consultant Haematologists, Consultant Paediatricians, Consultant Infectious Diseases Physician	To dispense from hospitals only			Inherited Bleeding Disorders
B02BD03	Anti-Haemophilic Factor VIII inhibitor bypassing activity/fraction	Injection IV 500U or 1000U	Consultant Haematologists, Consultant Paediatricians, Consultant Infectious Diseases Physicians	To dispense from hospitals only			Inherited Bleeding Disorders
B02BD04	Anti-Haemophilic Factor IX	Infusion 500IU	Consultant Haematologists, Consultant Paediatricians, Consultant Infectious Diseases Physicians	To dispense from hospitals only			Inherited Bleeding Disorders
B02BD08	Eptacog Alfa (Recombinant Factor VIIa) (stand-by)	Vials	Consultant Anaesthetists, Consultant Haematologists	To dispense from hospitals only			Inherited Bleeding Disorders

B02BB01	Fibrinogen Concentrate	Powder for Solution for Injection 1g	Consultants Haematologists	MP 212 To dispense from Mater Dei Hospital pharmacy only			Inherited Bleeding Disorders
B02BD07	Factor XIII Concentrate	Powder and Solvent for Solution for Injection 250IU	Consultant Haematologists	MP 211 To dispense from hospitals only			Inherited Bleeding Disorders
Allergen Immunotherapy							
R03DX05	Omalizumab	Injections 75mg	Consultant Respiratory Physicians, Consultant Paediatricians	MP 296			Chronic Asthma
R03DX05	Omalizumab	Injections 150mg	Consultant Respiratory Physicians, Consultant Paediatricians, Consultant Dermatologists, Consultant Paediatricians specialised in Allergic Diseases	MP 294			Chronic Asthma, Severe Chronic Urticaria
Mucolytics							
R05CB13	Dornase Alfa	Nebuliser Solution 1000units/mL (2.5mg)	Consultant Paediatricians, Consultant Respiratory Physicians	MP 52			Cystic Fibrosis
Short-acting Insulins							
A10AB05	Insulin Aspart	Cartridge 100IU/mL in 3mL	Consultants Endocrinology & Diabetes	MP 207	Pink Card for Diabetes Mellitus Only	Consultants Endocrinology & Diabetes	Diabetes Mellitus Type 1
A10AB01	Insulin Neutral (Soluble Insulin)	Cartridge 100units/mL in 3mL	Consultants Endocrinology & Diabetes, Consultant Geriatricians, Consultant Paediatricians		Pink Card for Diabetes Mellitus Only	Consultants Endocrinology & Diabetes	Diabetes Mellitus Type 1, Diabetes Mellitus Type 2
A10AB01	Insulin Neutral (Soluble Insulin)	Injection SC 100IU/mL in 10mL	Consultants Endocrinology & Diabetes, Consultant Geriatricians, Consultant Paediatricians		Pink Card for Diabetes Mellitus Only	Consultants Endocrinology & Diabetes	Diabetes Mellitus Type 1, Diabetes Mellitus Type 2, Gestational Diabetes
Intermediate- and long-acting insulins							
A10AD01	Insulin Biphasic Isophane	Cartridges (70%. 30%) 100IU/mL	Consultants Endocrinology & Diabetes,		Pink Card for Diabetes	Consultants Endocrinology & Diabetes	Diabetes Mellitus Type 1, Diabetes Mellitus Type 2

	(Isophane + Neutral)		Consultant Geriatricians, Consultant Paediatricians		Mellitus Only		
A10AD01	Insulin Biphasic Isophane (Isophane + Neutral)	Injection 100IU/mL	Consultants Endocrinology & Diabetes, Consultant Geriatricians, Consultant Paediatricians		Pink Card for Diabetes Mellitus Only	Consultants Endocrinology & Diabetes	Diabetes Mellitus Type 1, Diabetes Mellitus Type 2, Gestational Diabetes
A10AE04	Insulin Glargine	Cartridge 100IU/mL	Consultants Endocrinology & Diabetes	MP 101	Pink Card for Diabetes Mellitus Only	Consultants Endocrinology & Diabetes	Diabetes Mellitus Type 1, Diabetes Mellitus Type 2
A10AC01	Insulin Isophane	Cartridge 100 units/mL in 3mL	Consultants Endocrinology & Diabetes, Consultant Geriatricians, Consultant Paediatricians		Pink Card for Diabetes Mellitus Only	Consultants Endocrinology & Diabetes	Diabetes Mellitus Type 1, Diabetes Mellitus Type 2
A10AC01	Insulin Isophane	Injection 100 IU/mL in 10mL	Consultants Endocrinology & Diabetes, Consultant Geriatricians, Consultant Paediatricians		Pink Card for Diabetes Mellitus Only	Consultants Endocrinology & Diabetes	Diabetes Mellitus Type 1, Diabetes Mellitus Type 2, Gestational Diabetes
Treatment of hypoglycaemia							
H04AA01	Glucagon	Injection 1mg	Consultants Endocrinology & Diabetes, Consultant Geriatricians		Pink Card for Diabetes Mellitus Only	Consultants Endocrinology & Diabetes	Diabetes Mellitus Type 1, Diabetes Mellitus Type 2, Gestational Diabetes
Hypothalamic and anterior pituitary hormones and anti-oestrogens							
G03GA01	Chorionic Gonadotrophin (HCG)	Injection 1000 IU; Injection 5000 IU	Consultants				Hypogonadism, Hypopituitarism
H01AC01	Growth Hormone Recombinant (Somatropin)	Injection	Consultant Paediatricians, Consultants Endocrinology & Diabetes	MP 88			Prader Willi Syndrome, Turner Syndrome, Hypopituitarism
Calcitonin							
H05AA02	Teriparatide	Pre-Filled Pen 20mcg/ 80mcL	Consultant Rheumatologists, Consultants Endocrinology & Diabetes	MP 190			Multiple Sclerosis, Myasthenia Gravis, Inflammatory Bowel Disease, Chronic Liver Disease, Malignant Diseases, Chronic Kidney Disease, Chronic Asthma, Chronic Obstructive Pulmonary Disease, Chronic

							Respiratory Failure, Cystic Fibrosis, Dermatomyositis/ Polymyositis, Lupus Erythematosus, Polyarthritis Nodosa, Polymyalgia Rheumatica, Rheumatoid Arthritis, Spondyloarthritis, Systemic Sclerosis
Other immunomodulating drugs							
L03AB11	Peg-Interferon Alfa 2a	Pre-filled Syringe 180mcg	Consultant Gastroenterologists, Consultant Haematologists, Consultant Infectious Diseases Physicians, Consultant Oncologists	MP 102			Hepatitis B and C, Malignant Diseases
L03AB07	Interferon Beta 1a	Injection 30mcg (6M IU)	Consultant Neurologists				Multiple Sclerosis
L03AB08	Interferon Beta 1b	Injection 9.6M IU	Consultant Neurologists				Multiple Sclerosis
L03AB03	Interferon Gamma	Injection 100mcg	Consultant Paediatricians, Consultant Respiratory Physicians, Consultant Infectious Diseases Physicians	MP 104 To dispense from hospitals only			Primary Immunodeficiency Disorder
Somatostatin analogues							
H01CB02	Octreotide	Injection 200mcg/mL (multidose)	Consultants Endocrinology & Diabetes, Consultant Gastroenterologists, Consultant Oncologists, Consultant Surgeons, Consultant Palliative Care	MP 147 To dispense from hospitals only			Pituitary Adenomas, Malignant Diseases
H01CB02	Octreotide Long Acting (stand-by)	Injection IM 10mg	Consultants Endocrinology & Diabetes, Consultant Gastroenterologists, Consultant Oncologists, Consultant Surgeons, Consultant Palliative Care	MP 149 To dispense from hospitals only			Cardiac Arrythmias, Chronic Heart Failure, Coronary Artery Disease, Malignant Diseases, Pituitary Adenomas
H01CB02	Octreotide Long Acting	Injection IM 20mg;	Consultants Endocrinology &	MP 149 To			Cardiac Arrythmias,

		Injection IM 30mg	Diabetes, Consultant Gastroenterologists, Consultant Oncologists, Consultant Surgeons, Consultant Palliative Care	dispense from hospitals only			Chronic Heart Failure, Coronary Artery Disease, Malignant Diseases, Pituitary Adenomas
Drugs used in hypoplastic, haemolytic, and renal anaemias							
B03XA01	Recombinant Human Erythropoietin	Pre-filled syringe 2000 IU; Pre-filled syringe 3000 IU; Pre-filled syringe 4000 IU	Consultant Gastroenterologists, Consultant Haematologists, Consultant Nephrologists, Consultant Paediatricians	MP 65			Chronic Kidney Disease, Malignant Diseases
Drugs used in neutropenia							
L03AA02	Filgrastim (Rec. Human G-CSF)	Injection 30 MIU	Consultant Oncologists, Consultant Haematologists, Consultant Paediatricians, Consultant Infectious Diseases Physician	MP 69 To dispense from hospitals only			HIV/AIDS and HIV Related Diseases, Malignant Diseases, Primary Immunodeficiency Disorder
Drugs that suppress the rheumatic disease process/ Drugs affecting the immune response							
L04AB04	Adalimumab	Solution for Injection in Pre-filled Syringes 40mg	Consultant Dermatologists, Consultant Gastroenterologists, Consultant Ophthalmologists, Consultant Paediatrician, Consultant Rheumatologists	MP 307			Hidradenitis Suppurativa, Inflammatory Bowel Disease, Psoriasis, Rheumatoid Arthritis, Spondyloarthritis
L04AB01	Etanercept	Injection 25mg; Pre-filled Pen 50mg	Consultant Dermatologists, Consultant Rheumatologists	MP 66			Psoriasis, Rheumatoid Arthritis
Pancreatin							
A09AA02	Pancreatin	Capsules 10 000U; Capsules 25 000U	Consultants				Enzyme Disorders, Malignant Diseases, Cystic Fibrosis

Reference: Health.gov.mt [Internet]. Malta: Government of Malta; c2021 [cited 2024 May 26]. Available from URL: https://healthservices.gov.mt/en/pharmaceutical/Pages/formulary/formulary.aspx