

Biosimilar Medicines in the Irish Healthcare setting

Introduction

Biological medicines (or ‘biologics’) are treatments where the active ingredients are proteins such as hormones (erythropoietins, insulins and growth hormones), enzymes that are naturally produced in the human body, or monoclonal antibodies. They may also be blood products, immunological medicinal products and advanced technology products such as gene and cell therapies.¹ As biologic agents are complex molecules the production process is significantly more complicated than that for chemically synthesised medications.

A biosimilar medicine (or ‘biosimilar’) is a biological medicine that is developed to be highly similar to an existing biological medicine in physicochemical and biological terms.² Due to the complex manufacturing process biosimilars are not identical versions of the reference product so they are not considered to be generics. Therefore the issue of interchangeability and equivalence has become an area of intense review both in Europe and worldwide. The Health Products Regulatory Authority (HPRA) and the National Medicines Information Centre (NMIC) have recently produced comprehensive guides to biosimilar medicines, outlining the background, authorisation requirements and the role for biosimilar medicines in clinical practice, including guidance for practitioners.^{3,4}

Background to Biosimilars

The European Union was the first region worldwide to have a legal framework and regulatory pathway for biosimilars and the first biosimilar was approved in 2006.⁵ The European Medicines Agency (EMA) originally issued guidance in 2005 explaining that the approach to biosimilars would be different to generic products due to the complexity of the manufacturing process for biologics and this advice has been updated as recently as July 2015.^{6,7} Following centralised approval of biosimilars by the EMA each country can then adopt their own approaches to pricing, reimbursement and substitution of biosimilars. Depending on the country these issues may be dealt with by legislation or by way of guidelines.⁸ In Ireland the issue of substitution and interchangeability of biosimilars is addressed in legislation through the Health (Pricing and Supply of Medical Goods) Act 2013 which currently prohibits substitution of biological medicines.⁹ Nearly two thirds of countries across Europe have either laws or guidelines in place to prohibit the substitution of biologics.⁸

The biosimilar approval process through the EMA is based on a robust comparability exercise which looks at three specific steps: quality comparability (physicochemical and biological), pre-clinical comparability (in vitro and in vivo studies) and clinical comparability (pharmacokinetics, pharmacodynamics, safety and efficacy).^{3,4} This process is discussed in detail in recent publications by the HPRA and the NMIC.^{3,4} The HPRA notes that quality comparability testing is seen as the cornerstone of biosimilarity and has been in place for many years when authorised biologics undergo changes to the manufacturing process which is common in this scientific area.⁴

Comparability of biological and biosimilar medicines

As biological medicines are large and complex medicines with complicated manufacturing processes there may be a degree of variability in molecules with the same active substance. Most biological medications cannot be exactly reproduced and between batch variations can commonly exist. Individual biological medicines are also likely to be modified several times during their production history due to changes in the manufacturing process. Therefore while biosimilars cannot be deemed “generics” of the originator biological agents it is important to note that significant product variability can also exist between originator product batches.³

This is true, for example, in the manufacturing of the originator of infliximab (Remicade®). There have been approximately 40 listed changes in the manufacturing process for the active substance or the final product in the 12 years after it was first authorised (1999-2011).² The inherent variability of all biopharmaceuticals is tightly controlled by manufacturers and regulators and must remain within accepted and pre-defined limits.

Interchangeability and Substitution

While originators and biosimilars may have the same international non-proprietary name (INN) the inherent variability between products requires clarity on the product being used by individual patients.¹⁰ Substitution of biosimilars is prohibited in Ireland by legislation and to ensure this does not occur at dispensing it is recommended that all biological medicines, including originators and biosimilars, are prescribed by brand name. Adverse drug reaction (ADR) reporting should also include the brand name and batch number of the product to ensure appropriate traceability.^{10, 11}

Benefits of the Introduction of Biosimilars

The introduction of biosimilar medicines, offers the opportunity to reduce costs of these expensive agents both in primary care through the High Tech Drug (HTD) scheme and for hospital budgets. This potential for savings will allow for more treatment with new medicines and therefore getting the best possible value for the medicines budget without impacting on patient safety.

Potential Cost Savings

Competition between originator biological medicines and biosimilar alternatives offers increased treatment options for patients and clinicians and can also offer potential cost savings and improved value for money for biological treatments. Table 1 shows the originator (Neupogen®) and the biosimilar (Zarzio®) and associated reimbursement price for filgrastim in Ireland.

Table 1. Example of potential cost savings from use of biosimilar filgrastim

Filgrastim		
Neupogen® Singleject Syringe 30 Mu	1	€85.23
Zarzio® Soln. For Inj. Or Inf. In Pre Filled Syr 30 MU/0.5ml	1	€74.63 (12% reduction)

The use of the biosimilar Zarzio® would currently offer a 10-12% reduction in cost compared with the originator. In 2013 €2.36million was spent on filgrastim (ingredient cost) with approximately 4,000 prescriptions issued on the high tech drug scheme.¹² Use of a biosimilar alternative such as Zarzio®, could result in a saving of approximately €280,000 per annum. Cost savings for biosimilar

medicines will not offer the same price reductions as generic medicines and this is due to the complexity of the manufacturing process for biological agents, which leads to increased costs.

In 2013 expenditure on erythropoietin (ingredient cost) was approximately €5.16million on the HTD scheme with just under 10,000 items dispensed that year. Erythropoietin was the 13th most frequently prescribed high tech medicine on the HTD scheme that year.¹² The use of the biosimilar Retacrit® offers the potential for cost savings in the acute hospital setting as well as in the community.

Tumour necrosis factor alpha (TNF- α) Inhibitors account for the highest expenditure category on the HTD scheme with a total expenditure of €160.73 million in 2013.¹² Adalimumab and etanercept are the two most frequently prescribed products in the HTD scheme accounting for 21% of all items dispensed under this scheme. The ingredient cost of adalimumab in 2013 was €67.36 million with etanercept accounting for €47.16 million.¹² A biosimilar for etanercept, Benepali® received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in the European Medicines Agency (EMA) in November 2015.¹³ The introduction of biosimilars for these products could result in significant savings.

In the acute hospital setting there is significant expenditure on the TNF- α Inhibitor infliximab. The availability of infliximab biosimilars Remsima® and Inflectra® have the potential to reduce hospital expenditure by up to 50% for this high cost product.

Introduction of Biosimilars

In recent times there has been an increasing range of biosimilar medicines both currently licensed and in development. In the coming years additional biosimilar products will enter the market impacting on the hospital and the community settings. The potential to utilise these therapies in preference to the originator products could significantly reduce drug expenditure and facilitate greater access to such treatments. The HSE-Medicines Management Programme supports the appropriate introduction of these agents into clinical use in Ireland to enable safe and effective prescribing while also promoting cost-effective initiatives.

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