Seirbhís Sláinte Níos Fearr á Forbairt | Building a Better Health Service

Guidance for Biological Medicines in Acute Hospitals

Purpose:	The purpose of the guidance is to provide expert opinion to help improve value and access to biological medicines in acute hospitals.
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Introduction

Biological medicines have greatly advanced the treatment of a wide range of debilitating and life threatening conditions for tens of thousands of patients in Ireland but present significant budgetary challenges to healthcare providers. Although they are proven to be cost-effective their affordability is a potential barrier for patient access to these and other high cost treatments. The introduction of biosimilars in recent years means there is a greater choice of biological medicines for patients and prescribers. They also bring competition to the market and this presents an opportunity for significant improvement in value for patients and healthcare providers; value is maximised if innovative approaches to the procurement and prescribing of biological medicines are adopted. Innovation will benefit all stakeholders as more patients will have access to more treatments and there is potential for healthcare providers to reinvest savings to further develop health services.

The biological medicines market will continue to grow in the coming years as more medicines lose patent exclusivity and new biosimilar medicines are granted marketing authorisations. There has been rapid growth in this area in recent years - as of April 2019 the European Medicines Agency (EMA) have approved over 50 biosimilar medicines, with over half of these approved since January 2017.[1] It is essential that the Health Service Executive of Ireland [HSE] is prepared for this evolving and expanding market to maximise potential benefits.

Background

Biological medicines consistently feature in the "Top 10" of drug expenditure reports in secondary care in Ireland. The projected national annual expenditure for biological medicines with a biosimilar alternative available is approximately €260million for 2018 across the HSE (final expenditure for 2018 not yet available). Expenditure is split between primary care (~€200million) and secondary care (~€60million); the majority of prescribing activity is within secondary care.

There have already been actions taken to improve value with biological medicines in Ireland. The IPHA-HSE Framework on the Supply of Medicines Agreement 2016 includes a clause for patent-expired non-exclusive biological medicines which applies an automatic price reduction of 30% to the reference medicine when a biosimilar comes on the market [a 20% discount plus a 12.5% rebate of the discounted price].[2] In August 2017 a consultation paper was produced by the Department of Health but the final policy is not yet published.[3] The National Cancer Control Programme (NCCP) published guidance on the use of *Biosimilar Medicines in Cancer Treatment*[4] in August 2017 as well as the introduction of a "fixed dose price" for rituximab to encourage more cost effective prescribing of this medicine. The Acute Hospital Drug Management Programme [AHDMP] set a target rate of 50% for biosimilar uptake in February 2018 for biological medicines with a biosimilar available.

Despite these actions the uptake of biosimilars in Ireland remains low. The uptake rates vary widely both nationally and within hospital groups ranging from 0 to 100% for different hospitals. Significant efficiencies are being reported in centres where biosimilars were introduced as a prescribing option compared to sites with little or no uptake. The most significant savings have been achieved where there has been engagement of all key stakeholders [clinical teams, patients, pharmacy, finance, and procurement] and a structured competitive procurement exercise was undertaken involving one or more hospitals. Efficiencies made significantly exceeded those from the IPHA-HSE 2016 framework agreement.

The HSE Medicines Management Programme (MMP) provides guidance on community-supplied biological medicines (including biosimilars) reimbursed on the Primary Care Reimbursement Service (PCRS) High Tech Drug Scheme. In October 2018 the MMP published a draft "*roadmap for the prescribing of best-value biological (BVB) medicines in the Irish healthcare setting*" for consultation with a plan to implement in 2019.[5] The MMP implementation plan will include the identification of a *best-value biological* (BVB) medicine for each of the anti-TNFα agents adalimumab and etanercept; both are prescribed in hospital but community-supplied. Despite biosimilar etanercept being available since 2016 uptake remains negligible. The patent on adalimumab

expired in October 2018 and biosimilar alternatives have been available in Ireland since the end of 2018; there is no biosimilar adalimumab uptake data available at present. Joint working between primary and secondary care will be needed to effectively obtain value in this area.

Contents and Scope

The guidance is divided into four sections:

Section 1: Procurement and tendering
Section 2: Prescribing – interchangeability, switching, and substitution
Section 3: Resources and incentives to facilitate uptake of best value biological medicines
Section 4: Education

This guidance document is only applicable for those biological medicines with at least one biosimilar alternative available. The recommendations in each section apply as follows:

- **Section 1:** Procurement and tendering recommendations apply to hospital-supplied biological medicines with a biosimilar available only; procurement of community-supplied biological medicines is managed by the Primary Care Reimbursement Service (PCRS) High Tech Drug Scheme.
- **Section 2:** The prescribing recommendations include general principles that apply to all biological medicines with a biosimilar alternative available (both community-supplied and hospital-supplied). The HSE Medicines Management Programme (HSE-MMP) provides specific guidance for the selection of the best value biological medicine for community-supplied biological medicines.
- **Sections 3 and 4**: The sections on resources and incentives, and education apply to all biological medicines (both community-supplied and hospital-supplied).

Section 1: Procurement and tendering

Procurement of medicines in the HSE must comply with EU legislation [EU Procurement Directive 2014/24/EU][6] and the HSE's National Financial Regulation 01 (NFR01) *Purchase to Pay*.[7] A structured procurement process is essential for achieving value, quality and sustainability with a biological medicine when a biosimilar becomes available. A successful procurement exercise should include input from clinicians, patients, pharmacy, procurement and finance. The involvement of these stakeholders in awarding contracts will ensure the best outcomes are achieved.

The pricing framework for biological medicines in Ireland is set out in the IPHA-HSE 2016 Framework Agreement[2] however tendering can be used in the procurement process to obtain further voluntary price concessions by manufacturers.

The main formats of tendering are:

i. Direct negotiation
ii. Open tenders
iii. Restricted tenders
iv. Competitive negotiation

Direct negotiation with a single supplier is least likely to obtain the best value for the payer and should be limited to very small or emergency purchases and is unlikely to be suitable for biological medicines with more than one manufacturer unless there is a clinical argument to be made for not switching patients. Open tendering does not require prequalification of suppliers and is most likely to provide **lowest cost**. Restricted tendering is limited to suppliers meeting predefined qualifying criteria and this can have a positive impact on **quality** and **sustainability** of the market.[8] Tendering can be undertaken at a single hospital level or aggregated at a regional or national level. Concessions offered by manufacturers are often volume based meaning aggregated tenders are more likely to result in lower prices for the payer. Best practice indicates that maximum value is achieved when there are three or more competitors participating in the tender process. Contracts can be awarded to single or multiple suppliers with single suppliers likely to result in the lowest price to the payer. However, the low prices achieved may come at the cost of removing some manufacturers from

the market and thereby having a negative effect on sustainability.[8] The AHDMP are developing a national procurement strategy for acute hospitals which will assist with successful implementation of tendering processes.

Recommendations:

1. Biological medicines should be procured in compliance with the EU Procurement Directive 2014/24/EU and the HSE's National Financial Regulation 01 (NFR01) *Purchase to Pay*.
2. The tendering process should involve input from all key stakeholders.
3. Hospitals should undertake a formal procurement exercise for hospital-supplied biological medicines where there is at least one biosimilar available; competitive tenders with high volume are likely to deliver maximum value.

Section 2: Prescribing – interchangeability, switching, and substitution

The EMA define interchangeability as "*the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect*". This can apply to replacing a reference medicine with a biosimilar (or vice versa) or replacing one biosimilar with another. **Switching** is when the replacement is prescriber led and **automatic substitution** is when the replacement occurs at the pharmacy level without the prescriber being contacted. The EMA do not make recommendations on interchangeability but the decision is to be made by individual member states.[9]

Clinical evidence is growing to support switching of reference medicines to biosimilars. The NOR-SWITCH study is the largest randomised switch trial to date.[10] NOR-SWITCH results showed that a single switch from reference infliximab (Remicade®) to the biosimilar infliximab CT-P13 (Inflectra®, Remsima®) in inflammatory arthritides, inflammatory bowel disease, and psoriasis was non-inferior in terms of safety, efficacy and immunogenicity. Although specific to infliximab in certain indications, these data are supportive of the framework and scientific principles applied by the EMA in biosimilar development to ensure no significant difference between reference medicines and their biosimilars. Switching to biosimilars has already become routine clinical practice in some hospitals in Ireland and other European countries and, as expected, there have been no new safety signals or reports of loss of efficacy from these "real-world" switches. There is currently a paucity of evidence to make a recommendation on multiple switches but this will be an area of focus in future versions of this guidance document as the evidence base grows.

Recommendations:
(NOTE: The following recommendations only apply to biological medicines with at least one biosimilar available)

4. For a biological medicine with a biosimilar available for the same licensed indication, the best value biological medicine should be prescribed (provided that this is the most clinically appropriate biological medicine for the patient)
    i. All treatment naïve patients should be initiated on the best value biological medicine [whether biosimilar or reference medicine].
    ii. All non-naïve patients currently on treatment with the reference medicine should be considered for a switch to a biosimilar if the biosimilar is the best value biological medicine.
    iii. All non-naïve patients on a break in treatment should be restarted on the best value biological medicine [whether biosimilar or reference medicine] if further treatment is indicated. (The Summary of Product Characteristics should be referred to for precautions required with restarting treatment with biological medicines after a treatment break).
    iv. Switching by a Registered Nurse Prescriber [RNP] is recommended only if it is agreed as part of the RNP's Collaborative Practice Agreement with their Collaborating Medical Practitioner/s **and** agreed as part of local governance arrangements.
    v. Switching by a pharmacist is recommended only if agreed as part of a local protocol or other local governance arrangement and with agreement of the supervising specialist clinician.
    vi. Automatic substitution at pharmacy level [without contacting the prescriber] is not recommended and is not permitted under current legislation.
    vii. There is insufficient evidence to make recommendations on multiple switches at this time.

5. All biological medicines must be prescribed by brand name rather than by International Non-proprietary Name (INN) [e.g. Flixabi®, Inflectra®, Remicade® or Remsima® rather than infliximab] to avoid accidental substitution. **(EMA recommendation).**

6. For community-supplied biological medicines:
    a. Refer to the relevant HSE-MMP guidance for specific recommendations on the selection of the best value biological medicine.
    b. The patient (or their carer) must be made aware of the brand of biological medicine prescribed to avoid accidental substitution.
    c. The patient (or their carer) must be counselled on the new device, if appropriate, with a focus on any different administration or storage requirements.

7. There are no specific safety requirements for biosimilars; monitoring requirements are the same as for the reference medicine. **(EMA recommendation)**.

8. All biological medicines [biosimilars and reference medicines] authorised by the EMA after 01 January 2011 are "black triangle" medicines and any suspected adverse drug reactions should be reported to the HPRA with the brand name and batch number of the medicine. **(EMA recommendation)**.

9. Clinical trials that include a biological medicine with a biosimilar available should permit the use of either a biosimilar or the reference medicine depending on local practice; unless there is clinical justification for brand specific prescribing.

Section 3: Resources and incentives to facilitate uptake of best value biological medicines

Any positive incentives, such as gain sharing, should be based on the resources required to support the uptake of best value biological medicines and not overall savings. A priority for the HSE is removing disincentives to prescribing biosimilar products. Where individual hospitals have resources funded by monies external to the HSE [e.g. nursing staff funded by a pharmaceutical company] it will be a priority to move these resources to hospital funding.

Implementation of any form of incentives requires monitoring and reporting of prescribing and dispensing data. To facilitate these processes there is a need for prompt and accurate data reporting from prescribing centres to payers. Prescribing trends will be assessed and reported back locally in the context of regional and national trends to monitor performance.

Recommendations for incentives to facilitate uptake of best value biological medicines

10. Disincentives to prescribing best value biological medicine should be removed.
11. Any positive incentives should be based on resources required to facilitate uptake of best value biological medicines and not overall savings.

Section 4: Education

Education of stakeholders is essential to improve the understanding of biological medicines and ensuring there is equal confidence in biosimilars and reference medicines among prescribers and patients. The Acute Hospital Drugs Management Programme will provide educational material for both healthcare professionals and patients. Hospital Drugs and Therapeutics Committees will be requested to support dissemination of educational material at a local level.

The HPRA and EMA also have educational materials and further information about biosimilars and can be found at:
http://www.hpra.ie/homepage/medicines/special-topics/biosimilar-medicines
https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview

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Appendix I - Members of the National Steering Committee for Biological Medicines in Acute Hospitals:

Chair: Dr Vida Hamilton, National Group Advisor and Clinical Lead for Acute Operations.
Co-chair: Paul Gilvarry, Pharmacist - Value in Biological Medicines, Acute Hospital Drug Management Programme.
Prof Anne Marie Tobin: Dermatology Clinical Lead, National Clinical Lead & Consultant Dermatologist, Tallaght University Hospital.
Prof Glen Doherty: Gastroenterology Clinical Lead, Consultant Gastroenterologist, St. Vincent's University Hospital.
Ms Patricia Heckmann: NCCP Oncology and Haematology Clinical Representative, Chief Pharmacist, NCCP.
Prof David Kane: Rheumatology Clinical Lead, National Clinical Lead & Consultant Rheumatologist, Tallaght University Hospital.
Ms Fionnuala King: Chief Pharmacist, Acute Hospital Drugs Management Programme.
Mr Bernard Duggan: Senior Pharmacist, Medicines Management Programme.
Dr Roisín Adams, National Centre for Pharmacoeconomics.
Mr Gerry Greville: Finance Lead, General Manager, Acute Hospital Finance.
Mr Ciaran Halleran: Hospital Pharmacist, Chief Pharmacist, Mercy University Hospital.
Mr Paul Tighe: Hospital Pharmacist, Chief Pharmacist, St Vincent's University Hospital.
Mr Martin Quinlivan: Procurement, Asst. Head Sourcing and Contracts, HBS Procurement.
Mr Shaun Flanagan: Chief Pharmacist, PCRS.
Ms Aoife Kirwan: Lay Representative**.**
Ms Helen Byrne: Assistant National Director, Acute Operations.