Pharmacosimilars In Obesity Medicine: Informed Choice, Appropriate Choice

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Abstract

Newer developments in endocrine pharmacology have blurred the distinction between biosimilars and generics. The originator semaglutide, for example, is a biologically active compound, but later versions are chemically synthesized generics. Tirzepatide is a synthetic polypeptide. These molecules are marketed in different strengths and delivery devices across the world. The word 'pharmaco-similar' can be used to describe both biosimilar and generic versions of originator peptide-based medications. This communication suggests a useful framework which assists in sharing information and reaching an informed decision regarding choice of anti-obesity medication. This approval process and status, evidence and experience base, economic factors, rules related to interchange/substitution, robustness of cold chain, and availability of uninterrupted supply all influence this decision.

Keywords: Biosimilar, diabetes, generic, GIPRA, GLP1RA, liraglutide, obesity, semaglutide, tirzepatide

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Introduction

Newer peptides are now available for the management of obesity. These include the glucagon-like peptide 1 receptor agonists (GLP1RA) liraglutide and semaglutide, and the dual peptide agonist, tirzepatide.[1] The GLP1RA are biological compounds, as they are based on a biologically active structure. These preparations are available as originator molecules, and also as pharmaco-similar generics in some developing countries.

Newer developments in endocrine pharmacology, however, have blurred the distinction between some of the biosimilars and generics. The originator semaglutide, for example, is a biologically active compound, but later versions are chemically synthesized generics. Even within the 'originator' bracket, there are multiple preparations with differing modes of administration and strength. Tirzepatide, on the other hand, is a synthetic 39 amino acid polypeptide which works as a dual, asymmetric GLP1RA and GIP analogue. Marketted in different strengths and delivery devices by the developer, generic versions are also available in some countries.

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Cause For Concern

While technically, these products may not be regulated by guidance for biopharmaceutical drugs, they do need extra diligence. The existing rules for generic drug manufacture may not suffice for newer molecules. Drugs such as liraglutide, semaglutide and tirzepatide are based on polypeptide chains, which have not only elementary but quaternary protein structures.[2] These structures are associated with functionality as well, and subtle changes may lead to altered pharmacological properties.

It is possible, therefore, that various preparations of the same molecule may differ in their efficacy. As the drugs are based on protein moieties, there is a theoretical risk of antigenicity as well. Medication has to be taken long term for diabetes and obesity, and this enhances to concerns regarding long term safety and tolerability.

Similar issues and concerns have been raised earlier for hormonally active products[3] as well as pharmaco-active herbo-mineral preparations. To address this confusion, we propose using the term 'pharmaco-similar' to describe newer versions of both GLP1RA and dual peptide agonists. This term will also be useful for other peptide agonists that are currently under development.

Making An Informed Choice

In this practice guide, we list and elaborate important points which must be considered while choosing originator or pharmaco-similar medication for obesity management. This provides a practical, and pragmatic template for informed, and shared, decision making with the person seeking therapy.In this manner, it allows one to practice the cardinal rules of person-centred care, i.e., "being respectful of, and responding to"' "the person's references, needs and values"[4] The AEIOU mnemonic (Box 1) builds upon and strengthens earlier attempts at fostering a person-centred approach towards choice of biologically active pharmaceutical products.

Approval Process

While originator molecules undergo a prolonged, comprehensive process for approval, biosimilars and generics follow an abbreviated process. Though the basic pharmaco-equivalence studies are required for both types of preparations, biosimilar manufacturers do not need to conduct long-term clinical outcome studies, and do not have to provide fresh data for extrapolation of indications.[5] It is possible, for example, that a biosimilar GLP1RA has been studied and approved for glycaemic control, and not for chronic weight management, or vice versa. They are obligated, however, to mount vigorous post-marketting trials and maintain pharmacovigilance programmes, to ensure patient safety.

Biosimilar products do have to undergo extra safety studies, which generic molecules may not have to. Thus, various incretin agonist preparations may have taken different routes for approval.[6] Obesity care professionals must be aware of these differences in regulatory process, and should be able to explain these to persons seeking care.

Evidence And Experience

Originator drugs, in general, will have more evidence published regarding their efficacy, safety, tolerability and long-term outcomes.[7] Biosimilar molecules may have received approval by sharing "data on file", and may or may not have published their findings. Obesity care professionals must be aware of the scientific evidence, both from clinical trials and real-world data, related to a particular preparation. This information should be shared with persons contemplating pharmacotherapy so that they can make in informed choice.

Evidence is buttressed by experience, and professionals do form opinions based upon their personal experience, as well as that of their peers. This should be taken into account during decision making. It must be remembered that results of randomized controlled trials are considered much higher in the hierarchy of evidence than those of individual cases.

Economic Factors

A major factor in decision making, especially in pay from pocket markets, is cost. Economic determinants of health are well known, and these must be considered while offering choices to persons seeking therapy.[8] The relative costs of originators and pharmaco-similar products as well as different delivery devices, if available, should be shared with them.

Implications For Interchange

Obesity care professionals must be aware of rules and regulations regarding switching or interchange of preparations.[5] Ideally, biologically active or hormonal drug preparations should not be interchanged, unless there is a compelling indication. The same approach should be followed with generic versions of semaglutide and tirzepatide. If a particular GLP1RA based preparation is effective, safe and well tolerated, it should not be changed. If dose titration is required, another strength of the same brand should be used.

If, due to unavoidable circumstances, another GLP1RA brand has to be administered, extra monitoring must be ensured. This will include clinical questioning for tolerability, objective auditing for weight-reducing (+ glucose-lowering) efficacy, and inclusion in pharmacovigilance programmes.

Extraneous Obstacles

Extraneous, or environmental factors may play a role in decision making. GLP1RA based drugs are highly temperature sensitive, and need to be transported and stored under cold chain conditions. Such facilities are usually available across South Asia. However, the obesity care professional must confirm that the cold chain maintenance is of optimal standards.[9] This is equally relevant for originator and pharmaco-similar molecules.

Uninterrupted Supply

As switching brands of biological products should be avoided, it is imperative to ensure uninterrupted drug supplies. Availability, accessibility, affordability and acceptance of drugs, as well as drug delivery systems, must be ensured. Ancillary supplies, such as needles, syringes and alcohol swabs, must be bundled with the drug, if needed.

In unforeseen circumstances where change is necessary, a brand closest to the original preparation must be chosen. Persons taking the drug must be counselled about the substitution, about the need for enhanced vigilance, and about future plans for prescription.

Need For Clarity

The term 'hormonal generics' has been proposed for such medicines.[3] Another suitable descriptor, 'hormonoids' can fit drugs such as liraglutide, semaglutide and tirzepatide. These chemical entities do have effects like endogenous hormones, as they act upon hormone receptors. Herein, we suggest the word 'pharmaco-similar' to describe newer brands of incretin-based drugs, irrespective of their method of manufacture.

Apart from the points mentioned in Box 1, an informed choice regarding the preparation of hormonoid drugs should take into account 8Ps: the pedigree of the

Box 1: Aspects of informed choice of anti-obesity medications.

Approval process and status
Evidence and experience;Economic factors
Interchange/substitution
Obstacles, extraneous
Uninterrupted supply

Box 2: Factors to consider in choice of hormonal generics/hormonoid drugs.

- Pedigree of manufactures
- Policies re: cold chain maintenance
- Preparation shelf life
- Precision and comfort of delivery device
- Packaging: environment friendly,
- Published data
- Pocket-friendliness, cost
- Physician's and peer experience

manufacturer, the policies regarding cold chain maintenance, product shelf life, precision of the delivery device, packaging in environment-friendly, person-safe manner, published data regarding efficacy, tolerability and long-term outcomes, pocket friendliness and the prescriber's experience (Box 2).

As the pharmacotherapeutic landscape of obesity becomes more and more complex, health care professionals will need to handle questions and queries regarding choice of preparations and delivery devices. This communication brings clarity and simplicity to this process.

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