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Interchangeability of Biosimilars – Position of Finnish Medicines Agency Fimea

Interchangeability

This document defines the current position of Fimea towards interchangeability of biosimilars and their reference products approved in the European Union (EU). It is a recommendation to the healthcare system in Finland.

In this document, interchangeability means the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber. This document does not deal with substitution at the pharmacy level.

A switch is a decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent.

Background

The manufacturing process of a biological medicinal product will be changed several times during its life cycle. The change will create a new version of the active substance. Therefore, the manufacturer must always compare the new and old versions and demonstrate to the regulatory authorities that the efficacy and safety of the product have not changed. This is, in most cases, achieved by demonstrating comparability using physico-chemical and structural analyses, sometimes supplemented by in vitro functional assays. The manufacturers and regulators have more than 20 years experience in assessing the comparability of different versions of a given biological medicinal product.

Biosimilars are copies of the reference product (innovator product). According to the current regulatory definition, biosimilars contain a new version of the active substance of its reference product. Thus, the development of a biosimilar is based on the demonstration of comparability of the biosimilar and the reference product. This comparison applies the same principles as the demonstration of the comparability of the old and new versions of the reference product except that the testing is much more extensive, including clinical data.

Twenty one biosimilars were granted marketing authorization in EU by the end of 2014. The first biosimilar in EU was authorized in 2006. Since then, there has been a wide use of biosimilars and the safety profiles of biosimilars have been the same as those of their reference products.

Interchangeability of the biosimilar and its reference product is of utmost importance for the health care system since most of the costs of the biological products are due to chronic treatment.

Interchangeability: potential problems

It has been claimed that the switch from the reference product to the corresponding biosimilar may have an impact on the efficacy and safety. The purpose of this document is to assess these potential risks. The starting point is that the biosimilar meets the current regulatory requirements, including a comparable pharmacokinetic profile as well as comparable safety and efficacy in at least one therapeutic indication.

In theory, changes in safety and efficacy might be associated with a switch from reference product to biosimilar if either of the products has a higher inter-individual variation in pharmacokinetics. Such a difference has not been observed with current biosimilars.

Thus, the remaining potential problem is immunogenicity. A biological product is immunogenic if the immune system of an individual will recognize it as a foreign substance. For body's own substances, there is an immunological tolerance. It is not always possible to avoid immunogenicity of biological medicinal products. A biosimilar is allowed to be as immunogenic or less immunogenic but not more immunogenic than the reference product.

Biosimilars, interchangeability and immunogenicity

Immunogenicity caused by a switch between a biosimilar and its reference product may, in principle, may be caused by two mechanisms. First, the immune system may react to a structural difference between the products. Such a reaction is highly unlikely with licensed biosimilars, since the products have been shown to have comparable structure and immunogenicity in pre-licensing clinical trials. Increased immunogenicity has, in rare cases, been associated with manufacturing changes of a given biological product. In these cases, no immunogenicity studies were performed before transition from the old to the new version.

The other possibility is that the reference product is immunogenic and the immunoglobulin class or specificity will change upon the switch to a biosimilar. In both cases, the activation of T lymphocytes is required. Activation of T-lymphocytes would require recognition of new linear peptide epitopes in the biosimilar. This is unlikely since the active substance of the biosimilar has the same amino acid sequence and a similar post-translational profile as compared to its reference product.

T- and B-lymphocytes may, in rare cases, become activated in an abnormal way by impurities of a biological product. This problem is well known and inferior quality is not allowed to biosimilars.

Risk associated with the switch between non-similar biological products

Examples of switches between two non-similar but related biological products may help to evaluate the risk of switching between two highly similar biological products. According to the literature, switches between insulins and TNF-alfa-inhibitors are not problematic. Patients with haemophilia A are at risk of immunogenicity (inhibitor development) against the Factor VIII products because they lack the immunological tolerance to the intact FVIII. Even in this high risk situation, a switch between structurally different coagulation factors does not markedly increase immunogenicity. Similar experiences have been obtained with switches from products administered intravenously to related products administered subcutaneously – also a potentially risky situation. These examples suggest that the risk of switching two biological products that have been shown to be highly similar is not associated with significant risks.

Risks associated with a switch between the biosimilar and the reference product

Development programs of several biosimilars have included studies in which the reference product has been switched to the biosimilar and, occasionally, back to the reference product. Switches of somatropins, epoetin alfas, and glargin insulins have not indicated a risk for adverse effects. Preliminary results of infliximab do not raise concerns either. This view is supported by the fact that switches between reference products and biosimilars have been commonly associated with hospital tendering processes in some EU Member States. Yet, there is no safety signal associated with such switches in the European EudraVigilance data base for serious adverse effects.

Practical aspects associated with a switch

The patient needs to be informed as of any other change in the medication. Some biosimilars can be administered at home by the patient or a relative by using special administration devices. Training may be needed in such cases. The traceability of biosimilars has been good in adverse effect reports. Nevertheless, the switch should be documented, including the brand name and the batch number, as with any biological product.

Conclusions

The following conclusions can be made on the basis of the above considerations:

- Switches between biological products are common and usually not problematic, e.g. in the context of hospital tendering processes.
- For time being, there is no evidence for adverse effects due to the switch from a reference product to a biosimilar
- The theoretical basis of such adverse effects is weak

- Risk of adverse effects can be expected to be similar to the risk associated with changes in the manufacturing process of any biological product.
- Automatic substitution at the pharmacy level is not within the scope of this recommendation

Therefore, the current position of Fimea is that biosimilars are interchangeable with their reference products under the supervision of a health care person.