Biosimilars still not subject to mandatory substitution

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Both the Medical Products Agency (MPA) and the Dental and Benefits Agency (TLV) (the authority which decides on reimbursement) have long held the position that biosimilars are not interchangeable with their reference products, which has been reiterated in different policy papers since 2007. This position has now been supported by an administrative court of appeal in a case relating to glatiramer acetate products used for the treatment of multiple sclerosis.

Background

In two decisions in 2016 and 2018, respectively, the MPA decided that two Copaxone products of different doses were not substitutable to two Glatimyl (initially called Copemyl) products of the same doses. In its reasoning, the MPA stated that the active substance glatiramer acetate is a mix of synthetic polypeptides consisting of four different amino acids, which could not be confirmed to be identical, but only assumed to be controlled by the manufacturing process (as opposed to chemical compounds, which can be confirmed as identical). Even if the medicinal products can be deemed to be equal on a patient group level (which was the basis for the approval of Glatimyl), it cannot be ascertained that the medicinal products are equivalent in such a way that it would be possible to decide on a possible substitution between the products on an individual level.

The decisions were appealed to the administrative court by the holder of Glatimyl's marketing authorisations (the Glatimyl MA). The appeals were denied by an administrative court, and its cumulative decision was appealed to an administrative court of appeal.

The Glatimyl MAH argued that the product had been marketed in Europe for more than two years and substitution in a number of EU member states had been successful, without any serious adverse events reporting or any other reported problems. Further, it referenced judgments in the Netherlands and Italy on substitution between the products, where no hinder to substitution was deemed to exist.

The MPA argued, among other things, that a decision on substitution is within national jurisdiction and must relate to the specific regulatory framework for substitution of each state. The cases from the Netherlands and Italy that the Glatimyl MAH referred to neither provided information on nor support to the question whether repeated switches were safe. The Netherlands judgment did not concern substitution corresponding to the Swedish set up, where substitution is handled by the pharmacy – instead, it described a one-time switch initiated by the prescribing physician.

Decision

The administrative court of appeal denied the appeal. After a description of the relevant section of the Medicinal Products Act and precedents, the court stated that the assessment of whether products are substitutable raises similar issues as those raised when a product is approved or not, that the assessment of substitutability must be tried without preconditions, and that it is not connected to the assessment made at the approval.

From the evidence on record, the court found that the active substance in Copaxone and Glatimyl (ie, glatiramer acetate) was not fully possible to determine or characterise, and that its composition is controlled by the manufacturing process. It was therefore not shown to the court that the active substances of Copaxone and Glatimyl were identical. Further, it had not been shown that the consequences of repeated switches between different products containing glatiramer acetate had been considered in the approval procedure for Glatimyl. The fact that Glatimyl had been considered

therapeutically equivalent to Copaxone in connection with its approval procedure could therefore not give rise to a presumption for substitution between the products.

The court went on to assess whether the difference between the composition of the two medicinal products would result in such risks in relation to safety and efficacy that the products are not equal products for substitution under the Medicinal Products Act.

Under the Swedish substitution regulatory framework, a prescribed product is subject to mandatory substitution by the pharmacy to the product with the lowest price that month deemed to be medicinally equivalent to the prescribed product. On this basis, the court reasoned that a patient will likely switch between several products in the relevant substitution group during treatment. According to the court, a substitution requirement must therefore be that sufficient safety and efficacy can be assured in the event of frequent and repeated switches between products in a substitution group.

The court then cited the MPA's position – namely, that:

- there is a lack of sufficient knowledge and experience concerning the patient risks that may occur when a patient repeatedly switches between different products containing glatiramer acetate; and
- according to the best knowledge on polypeptides available, it could not be ruled out that the antibody formation when repeatedly switching between medicinal products containing glatiramer acetate could contribute to a heightened risk for treatment failure and adverse effects.

However, the court also concluded that the MPA had not presented any documents to support this position (eg, scientific studies or similar).

The Glatimyl MAH asserted that antibody formation did not contribute to a heightened patient risk in cases of repeated switches between products and presented an expert opinion to the court, which, among other things, stated that in practice, each new dose of either of the products can be considered a substitution even if it is a dose of the same product, since the composition would vary from syringe to syringe. The expert's conclusion was that repeated switches between the two products would not constitute a medical risk, due to available data showing that antibodies that are formed against glatiramer acetate were not neutralising and did not affect the treatment efficacy.

However, the court stated that this was not questioned in the cases, and instead it remarked that neither the expert opinion nor any other evidence provided addressed the issue at hand in the cases – namely, whether the differences in the composition of the active substance between various products containing glatiramer acetate lead to patient risk when switches repeatedly occur.

In conclusion, the administrative court of appeal found that it was not sufficiently clear whether repeated switches between Glatimyl and Copaxone could result in unacceptable risks with regard to safety and efficacy, and thus that the products could not be deemed substitutable.

Comment

This decision confirms the view that biosimilars are generally not included in the Swedish system for mandatory substitution. Biosimilars already available and used for treatment are thus still dependent on prescribing physicians to initiate a switch from the originator to the biosimilar. While this may be seen as a rather harsh stance, it can be explained by the structure of the Swedish system for mandatory substitution.

In Sweden, generic substitution is mandatory between medically equivalent products. Substitution is carried out by the pharmacy, which must dispense the least expensive product included in the benefits scheme (unless the prescribing physician has prohibited substitution for medical reasons). The TLV maintains a list of products in the benefits scheme, where the preferred product is appointed through a monthly action – which means that the product to be dispensed may vary from month to month. Consequently, a patient who is prescribed a specific product may in practice be given a different product each month, which would result in repeated, monthly switches during its treatment depending on which product has been offered to the lowest price. This differs significantly from a system where the patient would only have a one-time switch from originator to biosimilar (perhaps initiated by the prescribing physician).

The judgment has been appealed to the Supreme Administrative Court. At the time of writing, the Supreme Administrative Court has not yet decided whether to grant leave to appeal.

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