College voor zorgverzekeringen

Subject:	**Preferential policy towards biological drugs**
Summary:	CVZ regards biological drugs as therapeutically interchangeable if they are designated as "similar" after being registered by the EMA or the CBG. Based on the system of the *Zorgverzekeringswet* [Zvw, Health Insurance Act], there is no reason for regarding these drugs as having any differences. For first-time users biological drugs with a comparable active ingredient are therapeutically fully interchangeable. In individual cases there may be a reason to opt for a specific biological drug. Based on the registration procedures, the following conditions are described in which existing users may be switched to a different biological drug: · Switching can only take place in consultation with the attending physician and after the latter has given his/her approval (implicit or otherwise). · Switching drugs due to the means of administration and for an indication for which the biosimilar is not registered is not advised, as comparability with the original product was not demonstrated for this indication during registration. · Patients must be treated, as far as possible, with a single biological drug if they respond well to it as far as efficacy and side effects are concerned. If a switch does take place, detailed information about the product (product name and batch) must be recorded in the patient's file in order to guarantee its traceability in the event of problems. · If an alteration in treatment with a biological drug leads to using a different method of administration (for example, an injection pen), it is essential that the patient receives instructions and is clinically monitored in order to guarantee therapy compliance and efficacy of the treatment.
Type of ruling:	AaZ = Request for advice re Zvw
Date:	**29th September 2011**
Issued to:	Health Insurer
Type of care:	Pharmaceutical care

Below are the full text

The *College voor zorgverzekeringen* (CVZ) received your request for advice on 13th August 2010. UVIT asked whether the *Zorgverzekeringswet* (Health Insurance Act) allows health insurers to apply preferential policy in respect of biological medicines, in particular, biosimilars. Providing an answer proved to be more difficult than expected. The stakes involved are high. This had consequences for the time it took me to provide a reply.
I would like to apologise for this.

CVZ does not feel that it would be useful to issue a statement about the question of whether article 2.8, third paragraph of the Health Insurance Decision (*Besluit zorgverzekering*) allows preferential policy in respect of biological medicines. Preferential policy is based on the concept 'the same active ingredient; apparently, in this matter the regulations are not well-adjusted in relation to key aspects of new techniques such as biological medicines. Furthermore, preferential policy cannot be applied to biological medicines in the same way as is currently done for chemical medicines by various health insurers. Under the current preferential policy, the specific characteristics of biological medicines shifts the role of pharmacists (in part) to prescribers, which requires a different apportionment of decision-making powers as well as altering the role of the care-providers involved.

Based on this insight, CVZ approached this matter from the perspective of the basic insurance and examined under which circumstances it is appropriate to replace medicines in general (i.e., both "classic" medicines and "modern" biological medicines).

I Are biological medicines interchangeable based on the system of the Health Insurance Act?

The question we are dealing with is whether, from the perspective of the basic package, biosimilar medicines that are registered for the same indication are interchangeable and if so, under which conditions.

Specific characteristics of biological medicines
Due to the specific way in which they are manufactured, biological medicines are characterised not only by their active ingredient. The final product is also partly characterized by the entire manufacturing process. Nevertheless, if a biosimilar fulfils the requirements of the European registration authorities, then the product is similar, though not identical, to the original product with the same strength, the same pharmaceutic form and the same means of administration. The assumption is that biological medicines which have a comparable (biosimilar) active ingredient are therapeutically interchangeable. It is a fact that all biological medicines (original and biosimilar) are capable of stimulating antibodies and, in rare cases, causing a clinically observable immunological response, which can vary per product and per batch of a product, and which can have a negative effect on its efficacy and safety. CVZ emphasizes the fact that even within a single product the active ingredient can actually differ per batch which means that a given batch is not in fact identical, but can at best be regarded as comparable with respect to other batches of the same product.

Requirements of the European registration authorities for registering biosimilars
Since 2005, when registering biosimilars, the European Medicines Agency (EMA)'s point of departure is that the biosimilar must be comparable ('similar') to the reference product in respect of quality, safety and efficacy.

To this end the EMA has drawn up general guidelines indicating which comparative studies need to be carried out between a reference product and a biosimilar.
The registration authorities make use of, among other things, the following criteria:

- the immunogenicity (incl. a profile of antibodies) and the consequences for efficacy, safety and kinetics must be examined in clinical studies.
- After bringing a medicine onto the market, its safety must be monitored by means of a 'risk management program' or a 'pharmacovigilance plan'.

The system of the Health Insurance Act and interchangeability
Biological medicines can currently be found on both List 1A and List 1B. For inclusion on List 1B, CVZ will have carried out a formal assessment (of the product), whereby CVZ has formed the opinion (regarding its content), based in part on an Outcome of Assessment by the *Commissie Farmaceutische Hulp* (Medicinal Products Reimbursement Committee), that there is a separate place for this biological medicine. Alternative procedures exist for biological medicines that have a comparable active ingredient (e.g., biological medicines that have been derived from a reference product or two innovative products with a comparable active ingredient). For these medicines the Minister does not ask CVZ for advice, but places them in

a cluster on List 1A, without subjecting them to a content-based assessment. The fact that they have a comparable active ingredient makes the medicines interchangeable and provides sufficient guarantee – in the absence of a content-based assessment – that the medicines are mutually interchangeable.

Based on the system of the Health Insurance Act, CVZ regards biological medicines as interchangeable if they were deemed similar to the innovative product after the registration process, and thus automatically places them in the cluster of medicines that are mutually interchangeable with the original product.

As this says nothing about the quality-related conditions for interchangeability, CVZ describes these conditions in the next paragraph.

II Mutual interchangeability of biological medicines in practice

As described above, a biosimilar and the original reference product are, in principle, interchangeable due to the requirements imposed during registration.
This also has consequences for the subsequent procedures that lead to reimbursement via List 1A of the Health Insurance Decision.

However, relevant differences may exist for individual patients. The severity of a disorder or the fact that a medical institution pays close attention to its patients may form a reason for preferring a given biological medicine. For this reason, switching should only take place in consultation with the attending physician and upon their approval.

The CBG also indicates that because biosimilars and biological reference medicines are comparable, but not identical, the decision to treat a patient with a reference medicine or with a 'biosimilar' medicine should be based in part on the opinion of the attending physician. The EMA also states that the decision to treat a patient with an innovative product or a biosimilar should be made by a qualified professional in the field of health care. This makes proper collaboration between the physician, the pharmacist and the patient essential.

In principle, physicians should keep to registered indications when prescribing. Off-label usage is only permitted with no questions asked if the off-label use is described in the guidelines of the professional group. If the guidelines are still in the process of being developed, then consultation between the physician and the pharmacist will in any case be necessary. Switching medicines for a method of administration and an indication for which the biosimilar is not registered is not advised, because comparability with the original product has not been demonstrated during registration.
Extremely small differences in effects and rare side effects between a biosimilar and original products only surface after large groups of patients have been monitored over a long period of time. In principle, it is sufficient to keep to the requirements laid down by the EMA in the risk management plan for biological products following their registration.

Due to the importance of safety when switching between biologicals, it is imperative to be able to *trace* the product (including batch number) administered to a patient when investigating a side effect. It is for this reason that the European Committee wants to accentuate the rules for pharmacovigilance even further with respect to reporting side effects. They have ordered registration authorities to ensure that the specific product given to a patient is traceable. Physicians also need to be aware of the specific product that has been supplied to a patient. This will increase the administrative burden on both physicians and pharmacists.
One problem here is that some side effects only occur after long-term use. If a patient has switched to a different product in the meantime this may result in a lack of clarity about which product is causing (/caused) a side effect. Frequent switching can exacerbate this problem.

The CBG regards the uncontrolled switching of patients from one biological medicine to a biosimilar product (i.e., from an original to a biosimilar, or vice versa), without adequate clinical monitoring, as undesirable. The CBG suggests that where possible patients should be treated with a single biological medicine if they respond well to it as far as efficacy and side

effects are concerned. If switching nevertheless does take place, the patient file should indicate which product and which batch was switched so that the traceability of the product is guaranteed in the event of problems. CVZ agrees with this.

If an alteration in treatment with a biological leads to using a different method of administration (e.g., a pre-filled injection pen), instructions and clinically monitoring the patient are essential in order to guarantee therapy compliance and the efficacy of the treatment.

Conclusion
CVZ regards biological medicines as therapeutically interchangeable if they have been deemed "similar" following registration by the EMA or CBG. Based on the system of the Health Insurance Act, there is no reason for envisaging differences between these medicines.

For *novice users*, biological medicines with a comparable active ingredient are therapeutically fully interchangeable. In individual cases there may be a reason to opt for a specific biological medicine.

With respect to registration, the following conditions indicate in which situations *existing users can* be switched to a different biological medicine:

- Switching can only take place in consultation with the attending physician and following his/her approval (implicit or otherwise).
- Switching medicines for a method of administration or an indication for which the biosimilar is not registered is not advised, as its comparability with the original product has not been proven during registration[1].
- Where possible, patients must be treated with a single biological medicine if they respond well to it as far as concerns efficacy and side effects. If switching does take place, the patient file must record in detail (product and batch) information about the product in order to guarantee its traceability in the event of problems
- If an alteration in treatment with a biological medicine leads to using a different method of administration (e.g., a pre-filled injection pen), instructions and clinical monitoring of the patient are essential in order to guarantee therapy compliance and the efficacy of the treatment.

[1] CVZ describes the principle that off-label use should only be allowed if the off-label use is described in the guidelines of the professional group. If the guidelines are still currently being developed, then consultation between the physician and the pharmacist is necessary.