

Position statement on use of biosimilars of the *Société de Néphrologie, Société Francophone de Dialyse* and *Société de Néphrologie Pédiatrique*

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The European patent for epoetin alfa (Eprex®/Erypo®[®], Janssen-Cilag) expired in 2004 and the epoetin beta patent (NeoRecormon®, Roche) expired in 2006, meaning it will be possible to market biosimilar – copies of innovator biotech products – epoetins in Europe. The complexity of the processes necessary for producing pharmaceutical products containing biotechnology-derived proteins as active substances and for characterising the physico-chemical properties of these compounds means the guidelines that have been developed for generic drugs cannot be used for approval of biosimilar products. Thus, the EMEA (European Agency for the Evaluation of Medicinal Products) has provided guidelines for the development of biosimilars, including specific guidelines for epoetins. These guidelines do not answer every question raised by the development of biosimilars, however, and in some cases decisions will have to be taken at a national or even local level. This is why the Society of Nephrology (*Société de Néphrologie*), the French-speaking Society of Dialysis (*Société Francophone de Dialyse*) and the Paediatric Society of Nephrology (*Société de Néphrologie Pédiatrique*) have deemed it necessary to take a position on approval and use of biosimilar epoetins.

■ Primary end points used for pivotal clinical studies

EMEA guidelines state that biosimilar epoetins must be tested in at least two efficacy studies which are preferable conducted in CKD patients: a titration study, conducted in erythropoiesis-stimulating agent (ESA)

naïve patients and a maintenance study, conducted in patients already treated with ESA. The first study is likely to enrol non-dialysis CKD patients who will receive ESA subcutaneously while the second is likely to be conducted in haemodialysis patients who will receive the drugs intravenously. These studies will have to demonstrate equivalence between the biosimilar product and the reference product in terms of both efficacy on haemoglobin concentration and epoetin dosage (co-primary end points.) This raises the question of the equivalence margin for both co-primary end points. *All three Societies suggest that the acceptance margin should not be higher than 1 g/dL for haemoglobin concentration and 10% for epoetin dose.*

■ The case of children

All three Societies consider that once efficacy of a biosimilar epoetin product has been established in adults, it will not be necessary to repeat the equivalence studies in children. *However, they also consider it necessary to conduct a study focussing particularly on children, to confirm efficacy, determine the dose needed and assess the tolerability of the biosimilar drug.* These paediatric studies can only be envisioned when all the pivotal studies have been completed in adults.

■ The possibility of replacing innovator drugs with biosimilars

Once biosimilar epoetins have been approved, it is likely that it will be theoretically possible for phar-

macists to automatically substitute a biosimilar drug for an innovator drug, as is the case with generic drugs.

Regarding hospitals and dialysis facilities, all three Societies consider it the responsibility of the *ad hoc* committee(s) to choose which product(s) can be used in these facilities.

Regarding outpatients, all three Societies ask the French regulatory authorities to prohibit any possibility of automatic substitution of an innovator drug with a biosimilar drug that has been approved and marketed for less than two years. During this period of time, retail pharmacists will only be allowed to give the biosimilar drug if it has been explicitly prescribed. This measure is deemed necessary to prevent unnecessary switched from one product to another and to help interpret post-marketing surveillance data. After this two-year period, and provided that exposure to the biosimilar product is sufficient (which will have to be determined by the regulatory authorities), it will be the responsibility of the prescribing physician to explicitly mention that the prescribed innovator drug cannot be substituted, if he/she wants to prevent automatic substitution.

■ Labelling, traceability and post-marketing surveillance

As compared to innovator drugs, biosimilar products will be approved after having been tested in a more limited number of subjects, which raises the question of their safety regarding rare adverse events.

All three Societies consider that accurate traceability of biosimilar drugs will be critical for a fast detection of adverse events, and in particular of anti-erythropoietin antibodies. *They would like traceability of biosimilar epoetins to be guided by rules identical to the ones that have been put in place for blood-derived products.* They also suggest that all phials or prefilled syringes of epoetins should bear a sticker displaying the lot number and this sticker should be stuck in a patient's file. This would allow easier traceability of the injected products.

All three Societies also consider that labelling of phials and prefilled syringes should be such as to allow easy distinction between innovator drugs and biosimilar drugs.

■ Reporting of adverse events

All three Societies recognise that exhaustive reporting of adverse events occurring with both biosimilar and innovator drugs will be crucial in assessing the safety of biosimilar products. Therefore, they are ready to actively support all efforts made by regulatory agencies to promote systematic reporting of adverse effects.

■ Storage of serum samples

For patients sequentially treated with different epoetins and who develop anti-erythropoietin antibodies, having a stored serum sample drawn before the switch from one product to another can be of great value in determining which product occasioned the antibodies. *All three Societies would like the companies that will market biosimilar epoetins to put in place a risk management plan that includes the possibility of storing serum samples.*

This position paper has been drafted by a working group which includes Drs Bouchet, Brunet, Canaud, Chanliau Combe, Deray, Kourilsky, Niaudet, Ortiz, Rossert, Singlas and Verheist. It was amended and approved by the councils of the Society of Nephrology (*Société de Néphrologie*), the French-speaking Society of Dialysis (*Société Francophone de Dialyse*) and the Paediatric Society of Nephrology (*Société de Néphrologie Pédiatrique*).

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