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Biosimilar monoclonal antibodies approved for use in the EU

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Two biosimilar TNF- α monoclonal antibody (mAb) products were approved for clinical use in the European Union on 10 September 2013, following a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) in July 2013. The products, with trade names Remsima and Inflectra (INNs infliximab) contain an identical mAb. This approval shows the feasibility of using the biosimilar pathway for mAbs and paves the way for further biosimilar mAb products.

Keywords: Biosimilar, EPAR, infliximab, monoclonal antibody

Monoclonal antibodies (mAbs) have great potential for clinical use *in vivo*. Their specificity and ability to be produced to bind to almost any antigen of clinical interest has established them as potentially probably the largest class of biotherapeutics. Many are now approved for clinical use, many more are in various stages of clinical development and some are considered 'blockbuster' high income products. It would therefore seem reasonable to develop biosimilar mAbs, at least for the higher-usage products.

While it was previously considered that the molecular complexity and relatively large size of mAbs may limit the feasibility of using the European Union (EU) biosimilar approach for them [1], this has now been proven to be not the case, as the first two biosimilar mAb products were approved for use in the EU by the European Commission on 10 September 2013, following a positive opinion in July 2013 by the Committee for Medicinal Products for Human Use (CHMP). The two products, with trade names Remsima and Inflectra have used the TNF- α mAb Remicade as the reference product and the marketing authorizations are held by Celltrion and Hospira, respectively. All three mAbs have the same INN (infliximab), which reflects

their similarity. However, the biosimilars do show some differences in glycosylation and so, according to the INN 'rules' a Greek letter could have been added as an identifier as a second word of the INN, but this option was not considered. The CHMP view was that the small differences in glycosylation were not clinically significant, based on the clinical trial data.

Both Remsima [2] and Inflectra [3] contain an identical mAb and are the same in their pharmaceutical form, strength, composition and route of administration but the packaging size varies.

Despite the approval of both biosimilar mAbs in September 2013, a Remicade patent extension has prohibited their sale in the EU although not elsewhere (Remsima has been marketed in South Korea for some time post approval as a biosimilar by the (then) Korean FDA in July 2012). Resolution of the patent issues will allow the biosimilars to be marketed in the EU later this year or in 2015; precise dates for this will differ between states and also could be affected by other considerations, such as marketing factors.

As per EU biosimilar requirements, the approval application included a detailed

Biosimilars for Healthcare Professionals and thorough characterization of the mAb and an exhaustive quality comparison of the biosimilar with the reference product using state-of-the art methods. This was complemented by comparative non-clinical and clinical studies in a sensitive model to establish and confirm clinical biosimilarity. This comparability exercise data taken together provided an overall 'proof' of biosimilarity and assurance that the safety and efficacy profile of the biosimilar versions matches that of the reference product. This is stressed in the European Public Assessment Report (EPAR) for Remsima [2] which states 'The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that, in accordance with EU requirements, Remsima has been shown to have a comparable quality, safety and efficacy profile to Remicade'. Therefore, the CHMP's view was that, as for Remicade, the benefit outweighs the identified risks. The Committee recommended that Remsima be approved for use in the EU for all therapeutic indications of Remicade. Similar is the case for Inflectra [3].

The very important and often misunderstood issue of clinical comparability is also addressed by quoting data in the EPAR [2], i.e. 'Remsima was studied to show that it is comparable to the reference medicine, Remicade. Remsima was compared with Remicade in one main study involving 606 adults with rheumatoid arthritis. Patients received either Remsima or Remicade in addition to methotrexate for 30 weeks. The main measure of effectiveness was the change in symptoms (measured by ACR20). After 30 weeks of treatment Remsima was as effective as Remicade, with around 60% of patients responding to treatment with either medicine'. The EPAR also contains statements relating to other key similarities found for the biosimilar and reference product, e.g. pharmacokinetics. No unexpected safety issues occurred, and immunogenicity was very similar to that observed for Remicade. For further information, see the EPARs at www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000240/human_med_001023.jsp&mid=WC0b01ac058001d124

It should be stressed that Remsima and Inflectra have been thoroughly characterized to show their biosimilarity to Remicade.

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Unfortunately, this is not the case for what are claimed to be 'biosimilar mAbs' marketed in some non-EU countries, for example, China and India. This problem has been highlighted before [4], but is still continuing as reports describing limited assessment of poorly compared products are still referring to these products as 'biosimilars' although they are clearly not such according to EU (and WHO) definitions [5].

The EU approval of the two biosimilar mAb products not only demonstrates the feasibility of using the biosimilar pathway for relatively large, complex molecules, but also sets a precedent for other biosimilar mAb products to follow. We should expect several more biosimilar mAbs in the near and medium future. Perhaps a biosimilar trastuzumab will be next?

But the real challenge for biosimilar mAbs, at least in the EU will be market penetration. Pricing and uptake of Remsima

and Inflectra throughout the EU will be interesting from this important perspective. Equally, improved communication with physicians [6], payers and patients on the rigorous regulatory approval process should facilitate an increase in the uptake of these types of products.

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