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Commentary

Medicines that are Biologicals, or Maybe Not: The Strange Case of Teriparatide Forsteo® and its Copy Drugs

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COMMENTARY

Forsteo® is the peptide sequence 1-34 of the human parathyroid hormone (PTH) produced in *Escherichia Coli* with recombinant DNA technology, which is identical to the 34 N-terminal amino acid sequence of endogenous human PTH. Further information concerning the product is the following: each dose of 80 µl microliters contains 20 µg of teriparatide. One pre-filled pen of 2.4 ml contains 600 µg of teriparatide (corresponding to 250 µg/ml). The excipients are glacial acetic acid, sodium acetate (anhydrous), mannitol, metacresol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injections. The product is supplied as disposable pens, assembling 2.4 ml of solution in cartridge (siliconised Type I glass) with a plunger (halobutyl rubber) and disc seal (polyisoprene/bromobutyl rubber laminate/aluminium). Forsteo® is available in pack sizes of 1 or 3 pens. Each pen contains 28 doses of 20 µg (per 80 µl). The products should be stored in a refrigerator (2-8°C) at all times. The pen should be returned to the refrigerator immediately after use [1].

Forsteo® was registered in the European Union (EU) by the marketing authorization holder (MAH) Eli Lilly Netherlands B.V., *via* a centralized procedure, which is mandatory for biotechnological drugs (date of first authorization: June 10, 2003). The registration dossier was a full dossier. The section covering clinical evidence included the following: *i)* a dose-ranging study conducted in women; *ii)* a pivotal placebo-controlled study conducted in women [2]; *iii)* two support studies conducted in women, one comparing the product to alendronate [3] and the other to placebo in women treated with replacement hormone therapy; *iv)* a pivotal placebo-controlled study conducted in men [4]. The results of these studies are reported in the summary of product characteristics (SmPC) [5].

Based on the clinical evidence submitted by the Sponsor during the registration procedure, as well as on later variations, currently Forsteo® is recommended under the following conditions: *i)* treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures, but not hip fractures, has been demonstrated; *ii)* treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

Forsteo® patent expired in Europe during 2019. In anticipation of patent expiry some copy drugs were developed, obtaining a marketing authorization (MA). The obvious approach was to copy the innovator Forsteo® in all aspects, including the development and production as biotechnological agents. In fact, two products so far have been developed as biotech drugs, and followed the centralized registration procedure of Comparability Exercise, namely Movymia®, with MAH STADA Arzneimittel AG, and Terrosa®, with MAH Gedeon Richter, both approved by the European Commission (EC) in January 2017. Movymia® and Terrosa® share with the innovator Forsteo® the same active ingredient and excipients, but are supplied as cartridges instead of disposable pens.

Although Forsteo®, Movymia® and Terrosa® are all biotechnological products, the active ingredient teriparatide is a polypeptide in nature; thus, the possibility exists that the molecule can be obtained by chemical synthesis. Indeed, Teva had the idea to develop and produce a copy of Forsteo® by chemical synthesis, *via* the solid-phase peptide synthesis method. In this process, the polypeptides are synthesized in resin, by adding one amino acid at a time according to the primary structure of the natural peptide, starting from the C-terminal domain. At the end of process, the peptide is recovered from the resin block, purified, and isolated. In this specific case, the finished drug product was evaluated via an array of analytical procedures (including ultra-violet and amino acid analysis, mass spectrometry, nuclear magnetic resonance, peptide mapping, chiral gas-chromatography /mass spectrometry, molecular exclusion chromatography, electrophoresis on SDS-PAGE gel) both for the evaluation of the title and the purity of the product, and for the comparison with the physical-chemical structure of the innovator Forsteo® [6].

As a medicine containing an active ingredient obtained by chemical synthesis, the Teva product had no obligation to register in the EU

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through a centralized procedure. Indeed, the product was registered using a decentralized procedure that had Germany as reference member state (RMS) and 16 other European countries (including Spain, Italy, France, and United Kingdom) as concerned member states (CMS). The legal basis of the procedure was Article 10(3) of Directive 2001/83/EC (hybrid application), and the Reference product indicated by the MAH was Forsteo®, 20 µg/80 µl solution for injection in a pre-filled pen.

Was this regulatory approach correct? Seemingly, the regulators made no effort to try to foresee the possible 'regulatory mess' that may ensue to registering a product through an abridged registrative procedure, having a biotech medicine as reference product. Another issue was questionable: according to the Guideline EMA/CHMP/225411/2006 [7], the hybrid application should be adopted in the following cases:

i. when the definition of a generic medicinal product (that is: the same qualitative and quantitative composition of active ingredient when compared to the Reference product, same pharmaceutical form as the Reference product, demonstration of bioequivalence through specific studies) does not apply

ii. when a bioequivalence (BE) study cannot be used to demonstrate BE

iii. when there are modifications relating to the active ingredient, therapeutic indications, dosages, pharmaceutical form, or route of administration of the generic product with respect to the Reference product

However, the Teva product showed none of the changes listed in point *iii)*. Likewise, point *ii)* does not apply as well, because a BE study was performed successfully (see below). By exclusion, use of the hybrid application would have been justified by the fact that the Teva product cannot be defined as a generic medicine (point *i*), because of qualitative and quantitative differences between the Teva product and Forsteo®. This point also appears contradictory, insofar as Forsteo® was used as the Reference product in the BE registrative study (see below).

Despite these apparent discrepancies, the legal basis for a hybrid application was deemed acceptable by all the countries involved in the procedure. Although the hybrid and generic applications are both considered abridged applications, and both are included in Article 10 of Directive 2001/83/EC, the hybrid application differs from the generic application since 'appropriate pre-clinical tests and clinical trials' are required [7]. In this regard, the European Public Assessment Report (EPAR) of Teva product reports a BE study conducted on 72 healthy volunteers, with a 3-arm crossover scheme comparing teriparatide Test with Forsteo® marketed in Europe and with another formulation by the same MAH available on the United States market (Forteo®). The RMS only assessed the comparison between the first two products, and the BE was found to be demonstrated [6].

Thus, some critical issues might have been raised; nevertheless, the procedure was completed successfully, granting Teva a MA for its product in all CMS. At this point, we had an unprecedented situation in Europe, involving a common biotech Innovator, i.e. Forsteo®, having at the same time two copy drugs registered as biosimilars through centralized procedures, and one copy drug registered as a generic through a decentralized hybrid application. What have been the consequences of such unique situation, when it came to discussing price and reimbursement of these products at the national levels? The CMS Spain, despite the fact that it shared the positive outcome of the procedure, it subsequently felt the need to issue a rule that prevented automatic replacement of Forsteo® with Teva's teriparatide, considering the automatic replacement as a drawback of the registration on a legal basis of hybrid application.

Something trickier happened in Italy. There, so-called 'transparency lists' were introduced in 2002. Drugs registered on the legal basis of generic applications are included by default in the transparency lists; the same occurs with products registered on the legal basis of hybrid applications. Interestingly, the transparency lists include all products sharing the same active ingredient, i.e. the innovator together with its corresponding equivalent products, once the innovator's patent has expired. Most important, the primary function of transparency lists is to establish that automatic replacement can be applied among all products included in the lists that share the same active ingredient. Besides, the price reimbursed by the Italian National Health System for each active ingredient corresponds to the price of the cheapest generic sharing that active ingredient.

Within the above-described regulatory framework, once Teva teriparatide was licensed in Italy in keeping with the EC decision, an assessment was set by the *Agenzia Italiana del Farmaco* (AIFA) offices to establish the inclusion of Teva product in the transparency lists. It was an unusual task: at that time, only one out of 312 active ingredients included in the transparency lists was of a peptide nature, namely octreotide (that is, the innovator Sandostatina® Novartis Farma and its generics). The AIFA officers were bearing well in mind that 'Teva's teriparatide' had been registered on the legal basis of a hybrid application, through a decentralized procedure having Italy among the CMS. Moreover, the techniques available for analysis and determination of the physical and chemical characteristics of the molecules allowed to establish the essential similarity of relatively complex molecules (such as peptides or polysaccharide polymers) with a high degree of confidence. On the whole, considering comparative physical and chemical analyses that guaranteed the essential similarity of the Teva product as compared to the Innovator, and in view of the registration on the legal basis of hybrid application (which warrants inclusion by default in the transparency lists), the AIFA offices decided to include the Teva product in the transparency lists, along with the innovator Forsteo®.

While such decision might be agreed as far as the Teva product is concerned, a number of 'unwanted side effects' ensued to the parallel, automatic inclusion of the innovator Forsteo® in the transparency lists. Firstly, Forsteo® was the first biotechnological drug ever to be included in the transparency lists. Secondly, the Forsteo® copy drugs that -similarly to the Innovator - were developed and produced as biotech drugs (i.e. Movymia® and Terrosa®) could not be included in the lists, since these drugs are biosimilars of Forsteo® but they are not the innovators of Teva product. Thus, the anomalous situation was created of a biotechnological Innovator included in the transparency lists, but not its biosimilars. Under these conditions, Forsteo® can be automatically replaced only by the Teva product, but not by its biosimilars; nor could the latter be replaced automatically by Teva teriparatide. Moreover, the reimbursement mechanism (i.e. the alignment of price to that of Teva teriparatide) would apply to Forsteo® but not to its biosimilars, because of their exclusion from the transparency lists.

Thus, the decision of AIFA offices to include both Teva teriparatide and its innovator Forsteo® in the lists of transparency (without foreseeing the possible scenarios ensuing to such decision) turned out to be what we have previously defined as a 'regulatory mess'. Facing the above described inconsistencies and contradictions deriving from the first decision, AIFA was somewhat forced to start a second wave of evaluation, and eventually removed Forsteo® (as well as Teva teriparatide) from the lists of transparency [7].

What is the lesson to be learned from the case of teriparatide copy drugs? There is no doubt that a part of the regulatory tangle we have reported in this paper was due to specific Italian rules. Nevertheless, the main source of possible regulatory issues lies in the fact that teriparatide is a 'borderline' product, meaning that the drug can be produced *via* two different technologies. A cautious regulatory approach should be adopted every time one such borderline product is under scrutiny. This is the case, for example, with the many biotech products that have an equivalent of extractive nature or vice versa, if you prefer.

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