Translated from ***Rev Prescrire*** **March 2007; 27 (281): 236-1-1/236-1-3**

Forsteo° compliance programme: just say no

As Chief Pharmacist for Lilly Laboratories I feel I must respond to the editorial entitled 'BigPharma's medication compliance programmes: just say no!' that was published in the January 2007 issue of your journal (French edition 279 pages 61-62, Prescrire Int 87 page 32). I would like to set the record straight concerning the aims, methods and functioning of the assistance programme for patients treated with Forsteo°. Indeed, your article contains many inaccuracies and expresses several opinions that have no basis in fact.

I would like to believe that you did not have all the necessary information at your disposal, and hope that, in future, you will contact us directly to obtain the type of sound and validated information that follows.

This programme was launched in 2004 to promote the correct use of and adherence to Forsteo (teriparatide), a drug administered subcutaneously with an injector pen.

I would like to call your attention to the following two points.

A programme evaluated by the French regulator's Advertising Department. *On the one hand, implementation of this programme was evaluated a priori by the Committee of the French drug regulatory agency (Afssaps) that is responsible for controlling advertising and for distribution of recommendations on optimal use of medicines. Anticipating legislation in this area, the programme integrated all the measures providing the framework for patient compliance programmes adopted on 10 January 2007 by the French Parliament (amendment 29 of the White Paper transposing EU law on human medicines). The programme involves no direct contact between the manufacturer and the patient; it is proposed to patients by their doctors, and patients are free to opt out at any time, unconditionally, simply by making a telephone call.*

'Medical control of healthcare expenditure'. *In addition, as proper adherence to this treatment is necessary for it to be effective, the French Transparency Committee (that assesses the therapeutic value of new drugs) stated in its March 2004 opinion that the use of Forsteo° 'must be accompanied by a patient education programme'. In keeping with the objectives of 'medical control of healthcare expenditure (quality care at optimal cost), the Health Products Economic Committee required us to ensure satisfactory compliance, threatening financial penalties if the minimal duration of exposure to the product required to obtain a therapeutic benefit was not respected.*

As you pointed out in the preamble to your article, compliance has a positive impact on morbidity and mortality. In the specific field of osteoporosis, the article on adherence to treatments for osteoporosis published by Cortet et al. shows that compliance is mediocre, whatever the drug (1).

Afssaps guidelines on drug therapy for postmenopausal osteoporosis, published in January 2006, stressed that 'treatments for osteoporosis, like treatments for all chronic disorders, are only effective if compliance is optimal' (2).

Therefore, in my opinion, it is difficult to challenge, in good faith, the fact that long-term compliance to a treatment determines its success, and that assisting patients helps them to take their treatment as prescribed.

Restricted reimbursement. *In the section of your article entitled 'What is the service offered to women with post-menopausal osteoporosis?', you state that the standard treatment is currently a bisphosphonate (alendronic acid), and that teriparatide is less well assessed (3). In our opinion these allegations are unfounded, for the following reasons.*

The efficacy of Forsteo° has been demonstrated at the vertebral and peripheral levels, based on validated endpoints consistent with current European guidelines (4). Peripheral fractures such as hip fracture are predictive of the subsequent fracture risk. Their importance is again discussed in Afssaps guidelines released in January 2006, in which different clinical situations are considered according to whether there is a risk of vertebral and/or peripheral fracture. These guidelines recommend the use of Forsteo°, among other options, when there is a high risk of peripheral fracture.

May I also remind you that the Transparency Committee granted a level III ASMR score for teriparatide compared to bisphosphonates, signifying that teriparatide meets an unsatisfied medical need (only 14% of products examined in 2004 scored ASMR level III) (5).

Finally, owing to its osteogenic mechanism of action, and its proven efficacy, teriparatide is especially useful for patients with severe osteoporosis, as reflected in the reimbursement conditions, which restrict the use of teriparatide to osteoporotic women with a history of at least two vertebral fractures.

'Complexity'. *This assistance programme is therefore intended for a specific therapeutic situation: a chronic disease associated with a risk of complications, in which compliance is mediocre whatever the treatment; and the drug is administered subcutaneously, to elderly people who are often taking several other drugs. Rather than simply being a financial 'rescue' for a problem drug, the Forsteo° programme is justified by the complexity inherent in treatment of chronic diseases, requiring good compliance, in elderly patients, outside of the hospital setting.*

For the past 130 years, Eli Lilly has been encouraging innovation. We seek to enhance mutual understanding through open dialogue with all parties involved. For our part, we are convinced that the joint efforts of all involved parties, focusing together on the patient, within the framework of the assistance programme, will be beneficial:

- *for the patient, whose treatment will be more effective with proper adherence and administration;*
- *for healthcare professionals, who are naturally concerned about the effectiveness of their prescriptions and who often have no way of ensuring good adherence to complex treatments;*
- *for the healthcare system, for which poor adherence to treatments poses a problem;*
- *and, finally, for pharmaceutical companies.*

I hope this information helps to clarify the objectives of our programme and the way in which it is implemented.

Marie-Line Salama-Biard
Chief Pharmacist, Lilly
(our translation from the French)

Contrary to what Marie-Line Salama-Biard asserts in her letter, we did not state that, in general, '*adherence has a positive influence on morbidity and mortality*'. What we stated is that, while in certain situations it has been demonstrated that adherence has a positive effect, this is not the case in many other situations. This is a complex issue with many unknowns, as shown by a recent analysis of 11 systematic reviews by the Cochrane Collaboration (6). And while the study to which Marie-Line Salama-Biard refers does show that treatment adherence is not optimal in osteoporosis, it provides no accurate evidence on the potential clinical consequences of this poor adherence.

Assistance programmes: for whom?
The recent growth in patient assistance programmes concocted and implemented by drug companies raises questions about their appropriateness both for patients and for the public in general.

Conscientious healthcare professionals, patient groups and patients' relatives have always sought to help patients with their treatments, in order to ensure proper usage and adherence, but also for a variety of other reasons. Some drugs are more difficult to administer than others, and healthcare professionals (especially physicians, pharmacists and nurses) are used to explaining to their patients how to inject, inhale or apply treatments.

Top priority: high-quality packaging, delivery devices and good quality patient leaflet. Drug companies do play an important role in ensuring correct use and adherence: by producing well-designed and appropriate drug packaging, delivery devices and patient information. But not through direct involvement with patients.

Is Forsteo° really so difficult to administer? Not really: the drug solution is pro- ►►

► vided in a prefilled cartridge for use with an injector pen that is no more difficult to use than pens designed for many other drugs. The patient leaflet is clear, detailed and well illustrated (7). The only criticism is that the needles required for subcutaneous injection are not provided with the pen.

The Forsteo° injection technique can be explained by all healthcare professionals and does not warrant a specific assistance programme.

Regulatory agencies and compliance programmes. During recent discussions on industry-run compliance programmes, voices were raised – including that of the French health minister, among others – to assert that such programmes were required by various regulatory authorities. Let's examine the example of Forsteo° to see if this is the case.

Nothing in the European agency's public assessment report. Forsteo° was approved by the European Commission, through the European centralised procedure, based on the opinion of the drug licensing committee (CHMP) of the European Medicines Agency (EMEA). The CHMP assessment report (EPAR) on Forsteo° does not mention the need for a patient assistance programme (8).

Nothing in the European Commission's decision. The marketing authorisation mentions no special conditions, except that Forsteo° must be obtained with a medical prescription (9).

Nothing in the SPC. The summary of product characteristics (SPC) annexed to the marketing terms was written by Lilly and approved by the European Commission. The section on the dose regimen and mode of administration states that '*Patients must be trained to use the proper injection techniques*'; it mentions the user manual contained in the box but does not say that patients must be trained by the marketing authorisation holder (10). Unlike the complete EPAR, the EPAR summary released to the public mentions, that patients can inject the product themselves once they have been trained to do so, but simply mentions the user manual (11). Finally, the EMEA website does not mention the need for a 'risk management plan' for Forsteo°. [We have asked the EMEA director general for a list of all ongoing risk management plans and are awaiting a reply.]

Nothing from the French Transparency Committee. In France, the Forsteo° dossier was examined by the Transparency Committee, the bureau responsible for advising the health minister on drug reimbursement by the national health insurance system. In an opinion dated 10 March 2004, the Committee "*subordinates its recommendations* (editor's note: relative to refunding) *to the launch of a follow-up study by the end of 2004, describing: the characteristics of the patients receiving this treatment, their adherence, the duration of treatment and reasons for treatment cessation, and adverse effects*" (12). This type of post-marketing study, like clinical trials conducted before and after marketing, must be coordinated by an outside investigator and has nothing to do with a patient assistance programme: it is simply an observational study on routine use of the drug.

The Transparency Committee's opinion dealing with Forsteo°'s role in the management of patients includes a sentence on the injection technique resembling that found in the summary of product characteristics (SPC): "*Its use must be accompanied by a patient education programme*". This sentence is not included in the Commission's recommendations and is therefore not binding. It is simply intended to remind prescribers, pharmacists and other caregivers to ensure that patients understand how to use the product correctly.

Where is the Health Economics Committee's requirement published? Finally, Marie-Line Salama-Biard mentions a curious requirement by the health economics committee concerning adherence to Forsteo° therapy and mentions financial penalties if the minimal length of treatment is not respected. It is unacceptable that a committee that is solely responsible for conducting financial negotiations with drug companies should interfere in a purely medical issue. And if this committee does make such demands, they should be made public in order to inform healthcare professionals and patients.

End the confusion. None of the authorities involved in the Forsteo° dossier explicitly asked Lilly to create a patient assistance programme. The manufacturer has done its job with respect to the packaging (apart from the lack of needles) and the patient information leaflet. In contrast, treatment monitoring is the responsibility of caregivers, patient groups, and relatives.

In order to avoid a confusion of roles that would have placed drug companies in situations clearly involving conflicts of interest, French legislators deleted on 24 January 2007 the article relating to industry-run compliance programmes in the White Paper on transposition of the European Directive on medicines for human use. Even the health minister, who supported inclusion of this article, agreed that a thorough debate was needed before legislating on this issue. For their part, healthcare professionals unanimously agreed that drug companies, whose role is to produce and sell drugs, are not in a position to assist patients, who must remain free to discuss the advantages and disadvantages of their treatments with caregivers.

Prescrire's assessment on the place of teriparatide remains valid. In our published assessment of teriparatide, we stated that the drug had no proven preventive effect on hip and wrist fractures. This was based on our analysis of available clinical data, and on the conclusions of CHMP and the Transparency Committee (8,12). It also remains true that teriparatide is less well evaluated than alendronic acid, a drug with which we have more experience and which has been more thoroughly assessed. The Transparency Committee did give Forsteo° a score of III for the 'improvement in medical service' it provides. But this is hardly endorsed by the Committee's own statement (our translation): "*Although no direct comparisons have been conducted, and assuming that the populations included in clinical trials of alendronate, risedronate and teriparatide were comparable, teriparatide appears to be slightly more effective, in terms of the reduction in the number of fractures generally observed with bisphosphonates* (...)" (12).

Our conclusion therefore stands: patients' interests are not best served by prescribing teriparatide. There is no proof that teriparatide is any better than alendronic acid: teriparatide is injected whereas alendronic acid is taken orally; teriparatide has to be stored in a refrigerator; and teriparatide costs 10 times more than alendronic acid.

To each player a specific role. It is important to help patients, especially those with chronic disorders requiring years of treatment. But each player in the healthcare arena has a different role to play, and, ultimately, each patient must be in a position to make an informed choice in total independence.

1- Cortet B et al. "Adherence, persistence, concordance: do we provide optimal management to our patients with osteoporosis?" *Joint Bone Spine* 2006; **73** (5): e1-e7.
2- "Traitement médicamenteux de l'ostéoporose postménopausique. Recommandations. Actualisation 2006" Afssaps, January 2006.
3- Prescrire Editorial Staff "Teriparatide" *Prescrire Int* 2005; **14** (75): 5-9.
4- Neer et al. "Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis" *N Engl J Med* 2001; **344**: 1434-1441.
5- Rapport d'activité de la Commission de la Transparence 2004.
6- Santesso N et al. "Overview of Cochrane systematic reviews: interventions directed to consumers for evidence based prescribing and drug use" 22 September 2006: 27 pages.
7- European Commission "Summary of Product Characteristics – Forsteo°": 19 pages.
8- European Medicines Agency "European public assessment report (EPAR) - Forsteo - Scientific discussion" 2003: 22 pages.
9- Commission des Communautés européennes "Décision de la Commission-Forsteo" 10 June 2003: 3 pages + Annex II: 2 pages.
10- Commission des Communautés européennes "Résumé des caractéristiques du produit-Forsteo" 5 September 2005: 9 pages.
11- European Medicines Agency "European public assessment report (EPAR) - Forsteo - EPAR summary for the public" June 2006: 2 pages.
12- Commission de la transparence "Avis de la Commission-Forsteo" 10 March 2004: 7 pages.