EDITORIAL

Recommendations for an update of the current (2001) regulatory requirements for registration of drugs to be used in the treatment of osteoporosis in postmenopausal women and in men

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Abstract Recent advances in the understanding of the epidemiology of osteoporosis suggest that certain parts of the current European guidelines for the registration of drugs in osteoporosis might be no longer substantiated. The object of this review is to provide the European regulatory authorities with an evidence-based working document providing suggestions for the revision of the "Note for guidance for the approval of drugs to be used in postmenopausal osteoporosis" (CPMP/EWP/552/95). Following an extensive review of the literature

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(1990–2004), the Group for the Respect of Ethics and Excellence in Science (GREES) organized a workshop including European regulators, academic scientists and representatives of the pharmaceutical industry. The outcomes of this meeting reflect the personal views of those who attended and should not, in any case, be seen as an official position paper of any regulatory agency. The group identified a certain number of points that deserve discussion. They mainly relate to the nature of the indication being granted to new chemical entities (treatment of osteoporosis in women at high risk of fracture instead of prevention and treatment of osteoporosis), the requirements of showing an anti-fracture efficacy on all or on major nonvertebral fractures (instead of the hip), the duration of pivotal trials (2 years instead of 3) and the possibility of considering bridging studies for new routes of administration, new doses or new regimens of previously approved drugs. The group also recommends that an indication could be granted for the treatment of osteoporosis in males on the basis of a placebo-controlled study, with bone mineral density changes after 1 year as the primary endpoint, for medications approved in the treatment of osteoporosis in women at high risk of fractures.

Keywords Osteoporosis · Postmenopausal · Registration of drugs

Introduction

Since the release of the latest version of the "Note for guidance for approval of drugs to be used in postmenopausal osteoporosis" document by the Committee of Proprietary Medicinal Products of the European Agency for Evaluation of Medicines (CPMP/EWP/552/95) in January 2001 [1], several new chemical entities (NCE) with original mechanisms of action have been approved for the treatment of osteoporosis (teriparatide, strontium ranelate) as it was the case for new and alternative formulations of previously approved drugs (alendronate and risedronate once weekly dosing formulations) [2–5].

In addition, NCEs exhibiting novel properties with the potential to become potent anti-osteoporotic agents are currently under investigation (e.g., zoledronate, RANKL mAb, cathepsin K inhibitors, calcium receptor antagonists, alternative formulations of parathyroid hormone (PTH) fragments, new generation of selective estrogen receptor modulators (SERMs), and others) [6–7].

This environment of innovation in drug development for osteoporosis, combined with emerging new proposals to identify individual patients at high risk of fractures (World Health Organization {WHO} initiative) [8], has prompted the Group for the Respect of Ethics and Excellence in Science (GREES) to reconvene its "Osteoporosis" section. The objective of this meeting was to evaluate, from an evidence-based perspective, whether the body of science that has emerged in recent years would support a suggestion to the regulatory authorities to revise the current Note for guidance on postmenopausal osteoporosis in women. The following points were considered as of particular interest by the Group:

- Is there a rationale to maintain, as currently formulated, the indication "prevention of osteoporosis" or would it be more productive to consider, instead or in addition to the current wording, an indication targeting postmenopausal women not fulfilling the WHO operational definition of osteoporosis (T-score of bone mineral density [BMD] < -2.5) but presenting with a high risk of experiencing future fractures?
- Is the requirement of a 3-year duration for pivotal studies showing anti-fracture efficacy (prerequisite to be granted the "treatment of osteoporosis" indication), still appropriate?
- When are bridging studies for new formulations or new routes of administration of already approved drugs justified and what would be considered as an acceptable design for such studies?
- What should be the minimal requirements to be granted a marketing indication for the treatment of osteoporosis in males?

Rationale to reconsider the adequacy of the current "Prevention of Osteoporosis" indication

Osteoporosis is defined as a generalized skeletal disorder, characterized by compromised bone strength predisposing an individual to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality. Practically, the WHO opera-

tional definition defines an osteoporotic woman on the basis of a BMD measurement (spine or hip) showing a *T*-score below −2.5 [8].

However, it has become evident that fracture risk is not only driven by the level of BMD but by parameters including bone size and shape, bone turnover, micro-chitecture, mineralization, damage accumulation (micro-fractures) or collagen structure, which play a role in bone strength and, hence, in the risk of osteoporotic fractures. These different parameters are not captured by the assessment of BMD. [9]

This has been confirmed by several epidemiological studies showing that at least half of incident fragility fractures occur in postmenopausal women who have a BMD *T*-score above −2.5 [10–11]. In these populations, using independent risk factors for fractures allows identifying a substantial proportion of women who will experience fragility fractures [12, 15].

Recently, a WHO working party, re-analyzed extensive European, Australian, Japanese and North American databases to better identify individual risk factors for osteoporotic fractures, independently of BMD measurements. The expected outcome of this working group is the production of fracture risk tables, based on the combination of the BMD values and other independent risk factors, including previous fracture algorithms, age, family history of osteoporosis, body mass index and tobacco or alcohol use. High bone turnover has also been repeatedly shown to be an independent risk factor of future fracture risk [16]. These integrated risk assessments predict that approximately one-third of postmenopausal women with *T*-scores between −1 and −2.5 will also experience a fracture within the next 10 years [10].

These findings strongly support the concept that the decision process for initiating a treatment in an individual woman in order to prevent the occurrence of the first osteoporotic fracture should be based on the global assessment of specific clinical risk factors rather than relying on a BMD measurement only. Hence, the theoretical basis to differentiate the osteoporosis prevention indication from the treatment indication as defined in the present Note for guidance does not appear to be substantiated any longer. Decision to treat should be based on a projected 10-year fracture risk rather than on an arbitrary BMD threshold [17].

Patient populations to be included in pivotal clinical trials could include one of the two main subsets: patients with osteoporosis (BMD *T*-score below −2.5 with or without prevalent fractures) and patients at high risk of experiencing a first fracture, defined as postmenopausal women with osteopenia (BMD *T*-score between −1 and −2.5) associated with one or more independent risk factors, that result in a 10-year probability of fracture similar to that of osteoporotic women, regardless of the time elapsed since menopause.

If clinical studies performed in one or both populations demonstrate a reduction in fracture risk, this could lead to an indication labeled "treatment of postmenopausal women at high risk of fracture" or "prevention of the first fracture." This wording better reflects the patients included in the trials than the current wording: "prevention of osteoporosis" and "treatment of osteoporosis."

Duration of pivotal studies required for being granted the indication "treatment of osteoporosis for women at high risk of fracture"

Current guidelines recommend that phase III trials designed to demonstrate the efficacy of a NCE on fracture reduction in osteoporotic patients should usually last 3 years. This recommendation was historically driven by the safety concerns raised in the 1990s by the increase in fracture incidence over time in the sodium fluoride studies and during the third year of the etidronate studies.

However, during the last decade, it has been shown that preclinical (animal) osteoporosis models may significantly contribute to the early detection of potentially deleterious effects of new molecules on bone quality. This has been emphasized both by the WHO and the US Food and Drug Administration (FDA). Actually, for both fluoride and etidronate, preclinical studies did show issues with respect to bone quality that, with current knowledge, would have predicted poor efficacy in clinical studies [18–21]. A better understanding of the mode of action of NCEs and the recent technological advances in bone imaging have significantly improved the robustness of the conclusions derived from the outcomes observed in preclinical studies in osteoporosis. Preclinical (animal) studies are a major determinant of the safety package of a NCE developed for the treatment of postmenopausal osteoporosis.

There is now evidence from NCEs that were granted a marketing authorization in osteoporosis during the last 5 years (i.e., bisphosphonates, SERMs, teriparatide or strontium ranelate) that, in studies appropriately powered and designed, a significant effect on fracture risk reduction can be demonstrated as early as 12–18 months after initiation of therapy [22–25]. In these trials, there was a systematic concordance between the magnitude of the anti-fracture effect seen after this limited period and the final outcomes observed at the end of the requested 3-year studies.

Hence, in the context of the increasing concerns raised by the design of clinical trials in osteoporotic patients (ethical restrictions when patients at high risk of fractures are exposed to long-term placebo use or practical limitations due to the sample size required to demonstrate non-inferiority in active comparator studies) [26–28], it seems scientifically sound to consider shorter duration for pivotal studies designed to demonstrate the anti-fracture efficacy of NCEs, provided normal bone quality has been demonstrated in preclinical studies.

A proposal for shortening the study duration should primarily take into account the need to convincingly address the regulatory requirements for efficacy and safety. It should also encompass some determinants related to the baseline characteristics of the study population. As previously mentioned, several effective drugs are now available to treat osteoporotic patients, hence, making the design and conduct of placebo-controlled studies of long duration in patients at high risk of fractures ethically questionable [28]. If patients with lower risk of fractures (i.e., patients with a lower expected annual incidence of fractures in the control group) are enrolled in clinical trials, the demonstration of the anti-fracture efficacy of an NCE will require a major increase in the size of the study population that would be logistically difficult, even extremely difficult, over a 3-year period.

As a consequence, a reasonable compromise for the duration of the pivotal studies assessing efficacy and safety of a new drug in osteoporotic patients could be 2 years. This duration would allow the design of a placebo-controlled study, with a realistic sample size in a patient population at low to medium risk (i.e., ethically acceptable) for fracture, and provide sufficient duration of exposure to the NCEs to gather relevant safety data.

However, NCEs with an original and completely new mechanism of action may need to provide longer skeletal and/or extra-skeletal safety data. Sustainability of anti-fracture efficacy is an important consideration, especially for test medicines having a new mode of action. Depending on the NCEs, these long-term safety studies may be submitted after registration.

Bridging study design for new formulations or new routes of administration of approved drugs

The CPMP "Note for guidance for approval of drugs to be used in postmenopausal osteoporosis" issued in 2001 states that, "For compounds having demonstrated anti-fracture efficacy and for which the indication "treatment of osteoporosis" has been previously granted for a specific dose, formulation or route of administration, an extension of the indication "treatment of osteoporosis" could be given for a new dose, formulation or route of administration, on the basis of the demonstration of an equivalence in terms of BMD changes (differences in the means and percentage of responders) between the original and the new doses, formulations or routes of administration in a study of a minimum 2 years." Such studies will be referred to as "bridging studies" in the current manuscript.

A bridging study is aimed at showing that a new regimen is at least as effective as a reference regimen (non-inferiority) through the use of a surrogate marker.

For bridging studies, the original NCE, for which the indication has been granted, will be used as an active control. The prerequisite is the existence of a placebo-controlled trial (i.e., the main therapeutic study(ies) originally submitted to get the marketing authorization) that will be used to set up a clinically relevant delta of non-inferiority or margin of equivalence (i.e., the acceptable (or meaningless) difference in mean BMD changes between the original and the new dose, formulation or route of administration) and to assess the assay sensitivity.

Up to now, the bridging concept has been used successfully to gain approval for the once-weekly dosing regimen of bisphosphonates compared with daily administration regimen [4, 5].

For bisphosphonates, assay sensitivity has been reasonably documented in multiple historical placebo-controlled trials with BMD and fracture endpoints. In addition, and whereas analyses based on individual patient data did not systematically reach similar conclusions [29, 30], several meta-analyses of clinical studies based on mean group values (Poisson regression) provide good evidence of the relationship between BMD increase over time and fracture risk reduction for bisphosphonates [31, 32]. It is thus reasonable to choose BMD as a surrogate endpoint to design non-inferiority or equivalence trials comparing the effect of daily dosing vs less than daily, for bisphosphonates for which a fracture/BMD relationship has been well established for that specific compound. However, when the new formulation leads to less frequent dosing than the original formulation, the impact of the drug-free interval on this fracture/BMD relationship should also be assessed for drug-free intervals longer than weekly. Alternative surrogate endpoints, such as biochemical markers of bone turnover, could be used in bridging studies after a thorough analysis of historical studies showing a good correlation between the pharmacodynamic response and the reduction in fracture risk. The temporal pattern of biochemical marker changes over time should repeat the one observed with the original dosing regimen in order to avoid having to conduct separate fracture studies. This should apply to any surrogate endpoint that is known to be associated with fracture risk, such as BMD or marker.

The statistical analysis plan for bridging studies should include both a per protocol and ITT analyses. In active comparator studies, the per protocol analysis is the most conservative approach; however, consistency between both analyses is an important criterion of validity.

Equivalence or non-inferiority can be tested in a bridging study. Equivalence or non-inferiority margins need to be clinically meaningful and, in the case of osteoporosis, a non-inferiority margin of 30% of the smallest BMD (using a confidence interval of 95%) difference vs placebo documented in the original pivotal studies has been suggested as acceptable [28].

Bridging studies can be performed in postmenopausal osteopenic and osteoporotic patients regardless of their baseline risk of fracture and results can be extrapolated to the overall postmenopausal osteoporotic patient population. While a similar fracture/BMD relationship

has not yet been unequivocally established so far in male patients with osteoporosis, currently available data indicate a strong biological plausibility that allows the use of data issued from studies performed in postmenopausal osteoporosis to be considered as the reference for bridging studies designed in this indication, provided the mechanism of action is not gender-specific.

One-year duration for bridging studies can be accepted for a given compound, provided there is sufficient evidence to support a good correlation between early changes in the chosen surrogate endpoint (e.g., BMD or biochemical markers changes)and long-term (up to 3 years) fracture risk reduction. However, safety studies with longer duration may be needed.

Minimal requirements to be granted a marketing indication for the treatment of osteoporosis in males

Whereas, twofold to threefold lower than in women, the lifetime risk of fragility fracture in men is also widely considered as a major public health issue. Osteoporotic fractures occur at the same locations in both genders, but men experience these events 10–15 years later than women do [33–35]. Furthermore, although only one-third of fractures occur in men, adjusted for BMD, men and women have the same incidence of vertebral fractures [36].

Epidemiological studies have clearly established a similar relationship between the level of BMD and fracture risk in men and in postmenopausal women, i.e., the probability of experiencing an osteoporosis-related fracture is identical in men and in women, for a given absolute threshold of BMD. Prevalent osteoporotic fractures also predict the risk of future fractures, to the same extent in both genders [36–41].

Clinical trials of alendronate and teriparatide performed in osteoporotic males have shown BMD increases and changes in biochemical markers of bone turnover similar to those observed in postmenopausal osteoporotic women [42–44]. These studies were not initially designed and powered to assess the effect of these drugs on fracture risk reduction in men. However, in men with osteoporosis, alendronate significantly increased spine, hip, and total-body BMD and prevented vertebral fractures and height loss with a magnitude consistent with the effect observed in postmenopausal women [45, 46]. One study has also shown identical BMD response to 1-year alendronate, when directly comparing men and women with primary and secondary osteoporosis to controls in the same study [46]. The effects of teriparatide on BMD [48, 49] and fracture rates [50] observed in men are also of similar magnitude to those described in women [48, 49].

These similarities in the natural course of osteoporosis and risk factors for fracture in men and postmenopausal women, combined with the similar magnitude of the BMD and anti-fracture effects observed after pharmacological interventions in both patient populations, allow considering the use of BMD changes as primary endpoint in clinical trials designed to demonstrate the efficacy of NCEs in the treatment of osteoporosis in men, provided the applicant has unequivocally demonstrated the anti-fracture efficacy of the NCE in postmenopausal women.

As a prerequisite to their clinical development, NCEs considered for the treatment of osteoporosis in men should, however, be extensively investigated in the relevant animal models, to identify potential gender-specific skeletal toxicity.

Once an initial marketing authorization has been granted to an NCE for the treatment of postmenopausal osteoporosis or women at high risk of fracture, a study of 1-year's duration in male osteoporotic patients showing changes in BMD versus placebo of similar magnitude to those observed in postmenopausal osteoporotic women should be deemed sufficient for being granted a marketing authorization in the indication "treatment of osteoporosis in men." However, this bridging procedure will not be acceptable if the mechanism of action is gender-specific and/or hormonal. The effect of a new drug in male patients with osteoporosis due to secondary causes (e.g., men on androgen-deprivation therapy for carcinoma of the prostate) should be assessed in separate studies.

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