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**GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE
TREATMENT OF PRIMARY OSTEOPOROSIS**

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EXECUTIVE SUMMARY

This Guideline is intended to provide guidance for the evaluation of new medicinal products in the treatment of primary osteoporosis, principally in postmenopausal women but also in men. This Guideline should be read in conjunction with Directive 2001/83/EC, as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Studies in Support of Special Populations: Geriatrics CPMP/ICH/379/99 (ICH E7),
- Dose-Response Information to Support Drug Registration CPMP/ICH/378/95 (ICH E4),
- Statistical Principles for Clinical Trials CPMP/ICH/363/96 (ICH E9),
- Choice of Control Group in Clinical Trials CPMP/ICH/364/96 (ICH E10),
- Note for Guidance on the Investigation of Drug Interactions CPMP/EWP/560/95,
- Guideline on the Choice of the Non-Inferiority Margin CPMP/EWP/2158/99,
- The Extent of Population Exposure to Assess Clinical Safety for Drugs CPMP/ICH/375/95 (ICH E1A).

This Guideline is intended to assist applicants during the development of antiosteoporotic medicinal products. It is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

1. INTRODUCTION (background)

Osteoporosis is a systematic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.

Osteoporotic fractures cause substantial clinical and economic burden for society. Vertebral and hip fractures have been, for many years, associated with increased morbidity and mortality. More recently, an association has been shown between increased mortality and a collective group of other major non-vertebral fractures (i.e. pelvis, distal femur, proximal tibia, multiple ribs and proximal humerus). Hip, vertebral, forearm and humerus fractures also reduce, to various extents, health-related quality of life with deleterious effects lasting up to several years after the fracture event.

Primary or involutional osteoporosis develops as a result of excessive age-related bone loss. Age and menopause are the two main determinants of osteoporosis. The cessation of ovarian production of oestrogen, at the time of the menopause, results in an accelerated rate of bone loss in women.

Secondary osteoporosis, resulting from immobilisation, diseases (hyperthyroidism, hyperparathyroidism, rheumatoid arthritis) or drugs, especially glucocorticoid therapy and hormonal ablative therapies, should be considered separately and will not be covered in this guideline.

The risk for osteoporotic fractures is determined by several independent factors in addition to the bone mass loss. Age, the existence of previous fractures, a family history of fractures, high bone turnover, low body mass index, sedentarity and propensity to fall are the most important factors to be considered. Genetic and nutritional factors play significant roles.

An important predictor of osteoporotic fractures in postmenopausal women without a previous fracture is bone mineral density (BMD). The WHO operational definition defines an osteoporotic woman on the basis of a BMD measurement (spine or hip) showing a T-score below -2.5. The term “severe or established osteoporosis” habitually denotes a T-score below -2.5 in the presence of one or more fragility fractures. Osteopenia is defined as a BMD T-score between -1 and -2.5.

However, BMD alone has a limited value to predict the risk for fractures and it should be interpreted related to the age. The incidence of osteoporotic fractures and the predictive value of BMD are low before 65 years of age and increase with age. It has become evident that fracture risk is also driven by parameters including bone size and shape, bone turnover, micro-architecture, damage accumulation (micro fracture) or collagen structure, all playing a role in bone strength, and hence in the risk of osteoporotic fractures. Several epidemiological studies showed that a large proportion of incident

fragility fractures occur in postmenopausal women who have a BMD T-score above -2.5. The use of independent risk factors for fractures (e.g. age, family history of fracture, low body mass index, sedentarity, risk for falls, etc.) combined with BMD values provides a global assessment of future fracture risk, allowing to identify women who should benefit from a treatment to prevent the occurrence of osteoporotic fractures.

Most osteoporotic fractures occur in women because the effect of menopause increases the risk of fracture at any given age and because women have a higher life expectancy. However, the life-time risk of fragility fractures in men is also considered as a significant public health issue. No WHO definition for osteoporosis exists for men. However, in clinical practice the same cut-off for the diagnosis of osteoporosis in men, i.e. T-score below -2.5, has been used. Epidemiological studies have shown a similar relationship between BMD and fracture risk in men and in postmenopausal women, i.e. the predictive value of BMD for the occurrence of fractures is similar in men and in women. Prevalent fractures also predict the risk of future fractures to the same extent in both genders. Other independent risk factors have not, however, been validated to the same extent in men than in women. Clinical trials of pharmacological intervention in osteoporotic males have shown BMD increases and changes in biochemical markers of bone turnover similar to those observed in postmenopausal women. The limited available fracture data in men show that, when observed, the degree of reduction in vertebral fractures and height loss in males was consistent with that observed in postmenopausal women.

Several chemical entities with original modes of action have been approved for the treatment of postmenopausal osteoporosis after demonstration of an anti-fracture efficacy at the level of the axial skeleton (spine) or appendicular skeleton (all non-vertebral, major non-vertebral or hip). These products include bisphosphonates with daily to monthly dosing formulations, selective oestrogen receptor modulators, teriparatide, and strontium ranelate. Some of them have also been approved for the treatment of osteoporosis in males. Studies with these different products demonstrated that the relative reduction of fracture risk does not differ between women with different levels of baseline risk of future fractures. Therefore, there is no rationale to make any distinction in the indication between treatment and prevention or between osteoporosis and established osteoporosis. However, the absolute risk reduction of fractures and hence, the expected benefit of therapy will be different depending on the basal risk for fractures.

These general principles apply to all classes of antiosteoporotic agents including hormone replacement therapies.

2. AIM OF TREATMENT

The aim of the pharmacological intervention is to decrease the incidence of fractures. From the regulatory viewpoint, the therapeutic indication will generally be the treatment of osteoporosis in postmenopausal women at high risk of fracture, or, secondarily, the treatment of osteoporosis in men at high risk of fracture. The applicant will be requested to demonstrate the effect of the investigated medicinal product on both spinal and non-spinal fractures. For non-spinal fractures, either femoral (hip) or major non-vertebral (pelvis, distal femur, proximal tibia, ribs, proximal humerus and hip) fractures should be assessed. This should be done in properly designed and adequately powered studies. The indication may be restricted, e.g. to the effect on the axial skeleton, depending on the results of the clinical trials. The nominal results of the studies will be described in the SmPC section on "Pharmacodynamic properties".

3. PRE-CLINICAL STUDIES

These notes provide guidance for preclinical studies to assess bone architecture and bone strength. In conjunction, other guidelines for normal preclinical testing must be considered, such as Single-dose Toxicity, Repeated Dose Toxicity, Testing of Medicinal Products for their Mutagenic Potential, Carcinogenic Potential and Detection of Toxicity to reproduction for Medicinal Products.

Valid techniques for non-invasive in vivo assessment of bone architecture and strength in humans are currently not available. Documentation of drug-induced effects on these variables in animals is, thus, an important component of the initial efficacy and safety assessment.

3.1. Animal models

There are no completely satisfactory models of human osteoporosis, but a number of useful models exist. For drugs that are aimed for use in the treatment of postmenopausal osteoporosis in women, an evaluation of bone quality should be performed in two species, one of which should be the adult ovariectomised rat and the other an animal with oestrogen deficiency induced by ovariectomy and characterized by evaluable cortical bone remodelling. The primate, sheep or pig are possible suggestions. As a prerequisite to their clinical development, new chemical entities (NCEs) considered for the treatment of osteoporosis in men should be extensively investigated in the relevant animal models to identify potential gender-specific skeletal toxicity and efficacy.

3.2. Methods of assessing efficacy and safety in animals

To allow relevant inference on long-term bone safety in humans, the study duration should take into account the relative rates of bone turnover between animal and human and the proposed regimen. Normally, studies should have a duration of at least 6 remodelling cycles.

The time of initiation of treatment should reflect the clinical indication. Therapy should be started after a period of oestrogen deficiency sufficient to induce osteoporosis.

It is recommended that studies in the adult ovariectomised rat and in the second animal model are timed so as to provide guidance for the Phase II trials and support for the Phase III trials, respectively.

For these studies on bone quality, three exposure levels are normally needed. A low dose should aim at half-maximal response and the middle dose at the optimal response. The high dose should be a reasonable multiple of the middle dose. Where detrimental effects are observed, a clear no-effect dose should be established.

3.2.1. Bone mass/density measurements

Bone mass/density measurements may be made by validated non-invasive methods.

3.2.2. Bone architecture/histology/histomorphometry

The bone histology should be examined using undecalcified histological sections.

3.2.3. Biomechanical testing of bone strength

Validated biomechanical tests should be used. Preferably the same bone should be used for bone density and biomechanical testing. Both long bones and vertebrae should be tested.

4. CLINICAL TRIALS

4.1 General considerations

The studies should aim at defining a treatment schedule, define the optimal effect on the disease progression and explore the safety of the product. Clinical trials should be conducted in patients with characteristics that are representative of those of the population for whom the treatment is intended.

4.2. Populations to be studied

Postmenopausal osteoporosis

The clinical significance of osteoporosis lies in the fractures that occur. In order to encompass the complex relationship between BMD, independent risk factors and the individual 10-year fracture risk (as described in section 1), the suitable population for the clinical trials would be postmenopausal women at high risk of experiencing osteoporotic fractures based on the known independent risk factors such as age, BMD, previous low-trauma fracture, high bone turnover, maternal history of fracture, and low body mass index, that result in an increased 10-year probability of fractures, regardless of the time elapsed since menopause.

In order to properly assess the benefit of treatment, the absolute risk for fractures of the included population should be considered. All known factors that determine the fracture risk should be carefully recorded. Predefined levels of risk for fractures should be prospectively established on the basis of

relevant features (BMD, age, prevalent fractures, family history). Consistency of the effects for the whole range of levels of risk should be evaluated.

It is preferable to include in a specific trial patients with a similar basal risk for fractures. All known factors that determine the fracture risk should be carefully recorded and if groups of patients with different levels of estimated basal risk are included, the therapeutic effect should be consistent in all groups.

It is the Applicant's responsibility to provide substantial evidence confirming the validity of the chosen independent risk factor(s) and the characterisation of the population with regard to the absolute fracture risk. Overall, the indication may be expressed as "treatment of osteoporosis in postmenopausal women at high risk of fracture". The definition of a high risk should be based on national and international recommendations

Osteoporosis in men

No WHO definition for osteoporosis exists for men. However, in clinical practice the same cut-off for the diagnosis of osteoporosis in men, i.e. T-score below -2.5 , has been used. Epidemiological studies have shown a similar relationship between BMD and fracture risk in men and in postmenopausal women. However, since the other independent risk factors for fractures have not been extensively validated in men, it is the Applicant's responsibility to justify that the criteria chosen for the inclusion of men in the pivotal study, including BMD, will generate a fracture risk of a magnitude similar to that of postmenopausal osteoporotic women, especially if the indication "treatment of osteoporosis in men at high risk of fracture" is to be granted based on bridging studies (see 5.3.3). Other potential risk factors for fractures could also be taken into account in men.

4.3. Criteria of efficacy and their assessment

All endpoints to assess efficacy in clinical trials must be defined prior to the start of the trial and included in the study protocol.

4.3.1. Fractures

Fractures should be validated according to pre-defined criteria and the site and time of fracture recorded. Data regarding height and deformities also provide important efficacy information. The primary variable should be based on the occurrence of new axial and peripheral fractures (not worsening of previous fractures). Vertebral (clinical or morphometric) fractures and non-vertebral (hip, all non-vertebral or major non-vertebral) fractures are to be studied separately in confirmatory trials. In the analysis the patient (not the fracture) should be the sampling unit. The primary variable should be assessed as incidence of patients with new fractures, which may be expressed as vertebral fractures or as a composite of hip fractures and the rest of major non vertebral fractures.

The baseline number of prevalent fractures/deformities must be recorded.

Serial X-rays, performed once a year, should be used to assess vertebral fractures and deformities. Provisions should be made for additional radiographic examinations to identify symptomatic vertebral fractures. A standardisation of procedures for obtaining X-rays is mandatory in order to minimise differences due to variations in the film to focus distance and to centring of X-rays. Prevalent and incident vertebral fractures/deformities should be determined by using morphometric or semi-quantitative assessments (radiographic assessments). Since it is difficult to assess vertebral fractures accurately, a carefully validated method with predefined criteria for diagnosis of fractures must be used. The assessment should be made at a central facility with blinding to the treatment assignment of the patient. Radiographs should be kept available for possible re-analysis by an independent expert. Patients who wish to withdraw from the study should have an x-ray taken at the time of withdrawal, if more than 6 months have elapsed since the last X-ray.

4.3.2. Bone Mineral Density (BMD)

BMD may be the primary end point in exploratory studies but it is not an appropriate surrogate for fracture reduction. The current usual method for assessing BMD is dual energy X-ray absorptiometry. For all techniques, instrument precision and accuracy are very important. Careful quality control and assurance are required. The use of central BMD quality assurance centers is recommended.

It is desirable to measure BMD in the axial and appendicular skeleton at several different locations, taking into account trabecular and cortical bone. Measurements are mandatory at those sites where osteoporotic fractures most commonly occur, i.e. the spine (measurements can be taken at L₁ to L₄ or L₂ to L₄) and the hip (measurements of total hip and femoral neck BMD). Documentation of the effect on the forearm and/or total body may provide additional valuable information. In elderly subjects, values of spinal BMD should be analysed with caution due to the potential presence of osteophytes. The presence of a fracture in a given vertebra can also affect the analysis of BMD in that region.

4.3.3. Stature/deformity

Secondary endpoints may include stature. Height loss is a well-recognised clinical consequence of vertebral fracture. Measurements of stature should be performed with a validated measuring tool and appropriate quality control.

4.3.4. Biochemical markers

Biochemical markers of bone turnover are used to evaluate the mechanism of action of drugs and the integrated effect on bone. Appropriate biochemical markers of bone turnover include osteocalcin, bone-specific alkaline phosphatase, urine and serum N- or C-telopeptide of type I collagen, and N-propeptide of type I procollagen. In response to treatment, short-term changes (three to six months) in markers of bone remodelling have been demonstrated, along with changes in BMD and/or fractures after a longer period (2 to 3 years). However, the causal link (surrogacy) between the markers and longer term endpoints has not been unequivocally proven. Although BMD and biochemical markers used hitherto are not considered appropriate surrogates in therapeutic confirmatory treatment studies, they should be measured in the pivotal studies, at least in a subset of patients. They should be considered as primary variables in Phase II dose finding trials (see section 5.2).

4.4. Criteria of safety and their assessment

All adverse experiences occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug events, dropouts and patients who died while on therapy. Any information available concerning clinical features and therapeutic measures in accidental overdosage or deliberate self-poisoning should be provided.

Laboratory tests usually performed in the safety evaluation of all drugs should be performed. Serum levels of calcium, PTH, and 25-OH vitamin D, and for some products also calcium excretion in the urine should be followed.

Radiographs or ultrasound examinations to detect soft tissue calcifications may be indicated with certain drugs.

Quantitative bone histomorphometry on undecalcified sections should be performed in a subset of patients in Phase III trials unless there is pre-clinical justification for not doing so. At least a representative subset of patients should be studied with the aim to disclose any potentially negative effects of the drug on bone remodelling as well as in an attempt to characterise its effects on bone remodelling balance or mineralisation. The biopsies should be read at a central facility with appropriate expertise.

5. STUDY DESIGN

5.1. Human pharmacology

Studies involving the first administration of anti-osteoporotic agents do not differ from the first administration of drugs in general.

5.1.1. Pharmacodynamics

The initial studies should determine the general safety of the compound and should provide an indication of doses of potential clinical relevance.

5.1.2. Pharmacokinetics

The pharmacokinetic information required is stated in detail in the guideline on "Pharmacokinetic Studies in Man". Apart from the pharmacokinetic studies in healthy volunteers, studies should be

performed in the elderly (>65 years old) and the very elderly (>75 years old), and in patients with varying degrees of renal dysfunction and hepatic dysfunction.

The difficulty with regard to patients with osteoporosis results from the study of the bone compartment, which varies depending on the state of bone turnover. The possibility that binding of the NCE to bone may not correlate with plasma and urine levels can make interpretation of pharmacokinetic constants difficult.

5.1.3. Interactions

The guideline on the investigation of drug interactions (CPMP/EWP/560/95) should be followed, apprehending that the study population is elderly.

5.2. Dose response studies

A parallel-group, fixed dose, double-blind, placebo-controlled study design should be used in Phase II. Evaluation of at least three doses is recommended. If conclusive data are not obtained, at least two doses should be studied in Phase III studies.

Studies should be designed to allow robust evaluation of dose response. The treatment duration required to evaluate significant effects may vary depending on the drug. The duration of treatment should be clearly justified by the applicant in the protocol and the primary analysis performed at this time point.

It is recommended to use co-primary variables including BMD measured at the spine and/or the hip and appropriate biochemical markers of bone turnover. The variables should be specified in the protocol and the study should be powered to detect significant effects on each variable. The mean change from baseline to the end of treatment is an appropriate primary parameterisation for each variable, but responders should also be assessed. The expected mean differences in BMD between active and control group must be predetermined. For inhibitors of bone resorption, BMD responders are patients with changes above baseline at the end of treatment. For stimulators of bone formation, the primary BMD site should be the spine, with an absence of deleterious effect documented at other skeletal sites including hip, distal forearm, and/or total body. For biochemical markers the definition of responders should be based on robust scientific evidence.

In addition, it is mandatory for stimulators of bone formation to have a preclinical package demonstrating safety of the tested drug in terms of bone biomechanics at the exposure selected for Phase III clinical trials.

5.3. Main therapeutic studies

5.3.1. General considerations

Parallel-group, double blind, placebo-controlled and/or comparator-controlled studies are necessary. The studies must be carefully designed and dimensioned to maintain acceptable power in the face of anticipated dropouts. The use of an active control requires extra precaution in planning and conducting the study (ICH E10).

In principle, placebo-controlled trials will be requested. However, if properly justified, non-inferiority trials versus active comparators could be considered if a clear justification of the margin of non-inferiority (CPMP/EWP/2158/99) is provided before the trial has started. In this case, the differences in target populations, the consistency of the effect size, and the assay sensitivity should all be taken into account. Consequently, a placebo arm might be needed. The choice of the comparator should be adequately documented and justified. Similarly, in case of a placebo-controlled superiority trial, the relevance of the findings, compared to currently registered medications, might have to be established.

Sample size calculation must provide assurance that the study will enrol enough patients for the hypothesis (superiority or non-inferiority) proposed. Any supplementation with calcium and/or vitamin D should be consistent in all patient groups and should be clearly documented. Dietary and relevant life style factors should be summarised.

5.3.2. Treatment of osteoporosis in women at high risk of fracture

The population to be studied and the criteria of efficacy and safety and their assessment have been detailed above. The primary variable should be the incidence of patients with new fractures. BMD from areas studied for fracture incidence usually provides important secondary efficacy data. Measurements of suitable biochemical variables reflecting bone turnover could be included among secondary efficacy variables.

Treatment to prevent fractures may be regarded as a long term treatment although efficacy demonstration will depend on clinical trials of shorter duration. In order to provide fracture and bone safety data, a duration of randomised treatment of at least two years is usually appropriate. The efficacy at first year should be considered as a secondary variable and the maintenance of the effect during the second year should be addressed.

With long term treatment, loss of effect on fracture prevention due to altered bone structure or other changes is a matter of concern. The maintenance of prevention of fractures with treatment after the second year (e.g. 3-5 years) should be studied, although data may be submitted after registration.

Catch up bone loss after withdrawal of treatment has been described with some drugs. Data that show what occurs after withdrawal are necessary.

5.3.3. Bridging studies

For compounds having demonstrated anti-fracture efficacy and for which the indication “treatment of osteoporosis in postmenopausal women at high risk of fracture” has been previously granted for a specific dose, formulation or route of administration, an extension of the indication could be given for a new dose, route of administration or formulation on the basis of the demonstration of non-inferiority 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 minimum one year. Alternative surrogate endpoints like biochemical markers of bone turnover should also be used in bridging studies after a thorough analysis of historical studies showing a good correlation between pharmacokinetic exposures, the pharmacodynamic response and the reduction in fracture risk. To avoid having to conduct separate fracture studies, the time-course of changes in surrogate markers should recapitulate the time-course observed for the original dosing regimen. This should apply to any surrogate endpoint that is known to be associated with fracture risk, such as BMD or a biochemical marker.

Equivalence or non-inferiority can be tested in a bridging study. Equivalence or non-inferiority margins need to be clinically meaningful and should be selected carefully as described in the Guideline on the Choice of the Non-Inferiority Margin (CPMP/EWP/ 2158/99).

5.3.4. Minimal requirement to be granted a marketing indication for the treatment of osteoporosis in males

Taking into consideration the different pathophysiology of osteoporosis in males and in females and the limited knowledge of the mechanism of action of products that have demonstrated efficacy in women, the gold standard for being granted a marketing authorisation for the treatment of osteoporosis in males remains the demonstration of anti-fracture efficacy (spine and/or non-spine fractures) during a 2-year minimum, placebo-controlled, prospective study. However, once an initial marketing authorisation has been granted to a NCE for the treatment of postmenopausal osteoporosis in women at high risk of fracture, a separate bridging study of the same NCE, using the same formulation, dose, and route of administration in male osteoporotic patients could be sufficient for being granted a marketing authorisation with the indication “treatment of osteoporosis in men at high risk of fracture” provided that:

- the duration of the study is at least one year;
- the dosage is justified;
- the applicant justifies that the cut-off of BMD, age and any other risk factor chosen for the inclusion of men in the pivotal study will generate a fracture risk of a similar magnitude compared with postmenopausal women that were recruited in the studies used to obtain the

indication “Treatment of postmenopausal osteoporosis in women at high risk of fracture” (see 4.2 – Populations to be studied);

- the magnitude of the changes in BMD versus placebo is similar to that observed in postmenopausal osteoporotic women treated with the same compound and is globally proportional to the decreased incidence of fractures in treated women.

If these conditions are not fulfilled, or if the mechanism of action of the NCE is gender specific and/or hormonal, a bridging strategy will not be acceptable and a therapeutic study with fracture endpoints will be required in a separate trial in men.