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**OVERVIEW OF COMMENTS RECEIVED ON
DRAFT GUIDELINE ON THE EVALUATION OF PRODUCTS IN THE
TREATMENT OF PRIMARY OSTEOPOROSIS.**

Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield	UK
2	WHO Collaborating Centre for Osteoporosis Prevention at Geneva	Switzerland
3	International Osteoporosis Foundation	France
4	Francine CAULIN and John KANIS	France – UK
5	National Osteoporosis Society	UK
6	International Menopause Society	UK
7	Novo Nordisk	Switzerland
8	Merck Sharp & Dohme – Europe	Belgium
9	Wyeth Europa	UK
10	Solvay Pharmaceuticals	Belgium
11	Deutsche Menopause Gesellschaft	Germany
12	IGEA	Italy
13	Amgen – Europe	Switzerland
14	Belgian Menopause Society	Belgium
15	International Society of Gynaecological Endocrinology	Italy
16	Italian Society of Gynaecology of the third Age	Italy
17	Portuguese Menopause Society	Portugal
18	European Menopause and Andropause Society	Denmark
19	Swiss Menopause Society	Switzerland
20	Eli Lilly and Company	Europe
21	EFPIA	France
22	British Menopause Society	UK

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield (Professor John A. KANIS)		
GENERAL COMMENTS - OVERVIEW		
We believe (the proposed revision of the CHMP guideline) is a very significant advance for her development and we would strongly support this proposal revision.		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION INTRODUCTION		
Line no. + paragraph no.	Comment and Rationale	Outcome
Page 4 (2 nd paragraph)	It is important, however, to state that the diagnosis of osteoporosis in men is a T-score below minus 2.5 standard deviations of the female reference range.	Included
Page 4 (Section 2)	Forearm fractures are a major osteoporotic fracture and, perhaps, should be included as a major non-vertebral fracture.	Included
GUIDELINE SECTION CLINICAL TRIALS		
Line no. + paragraph no.	Comment and Rationale	Outcome
Page 6, osteoporosis in men	The second sentence might be re-worded as follows “other independent risk factors for fracture have not been as extensively validated in men as in women. It is the applicants responsibility...”	Included
GUIDELINE SECTION STUDY DESIGN		
Line no. + paragraph no.	Comment and Rationale	Outcome
Page 9, 1 st paragraph	The provision for studying catch-up bone loss is welcome	Endorsed

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COMMENTS FROM WHO Collaborating Centre for Osteoporosis Prevention at Geneva (Professor R. RIZZOLI)		
GENERAL COMMENTS - OVERVIEW		
This document constitutes a major step forward, a considerable improvement as compared with the previous version, and this for the particular benefit of the patients involved in clinical trials.		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION INTRODUCTION		
Line no.¹ + paragraph no.	Comment and Rationale	Outcome
Page 4, paragraph 1	The clinical risk factors to be considered are those related to bone.	Included
Page 4, paragraph 3	Calcitonin and vitamin D metabolites should be mentioned.	Included
GUIDELINE SECTION AIM OF TREATMENT		
Line no.² + paragraph no.	Comment and Rationale	Outcome
Page 4, section 2	Risk fracture should be included in the list of major non-vertebral fractures	Included
GUIDELINE SECTION PRE-CLINICAL STUDIES		
Line no.³ + paragraph no.	Comment and Rationale	Outcome
Page 4, last paragraph	The place of preclinical evaluation may be better specified.	Already specified in the original document.

¹ Where applicable

² Where applicable

³ Where applicable

GUIDELINE SECTION CLINICAL TRIALS		
Line no. ⁴ + paragraph no.	Comment and Rationale	Outcome
Page 6 paragraph 4.3.1	"Morphometric and/or semiquantitative" assessment for the evaluation of vertebral fractures.	Included
Page 7, paragraph 4.4	In the analysis of bone biopsy, "degree of mineralization" and "hardness" should be considered.	Included

⁴ Where applicable

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COMMENTS FROM the President's Task Force on Policy of the International Osteoporosis Foundation (Professor P. DELMAS)		
GENERAL COMMENTS - OVERVIEW		
<p>Overall, this document is excellent, it is concise and the Committee of Scientific Advisers of IOF agrees with the views expressed. There are a number of changes in these guidelines data to be welcomed. These include the lack of distinction between prevention and treatment of osteoporosis, the consideration of absolute fracture risks as a criterion for entry to studies and the recognition that factors other than BMD contribute to fracture risk. In addition, recognition of the importance of non-vertebral fractures other than hip fractures and the use of major non-vertebral fractures (including hip) as a primary end-point is a positive change from the previous guidelines.</p> <p>Altogether, the Committee of Scientific Advisers feels that this document is a tremendous improvement compared to the previous version and would like to acknowledge the important contribution made by the CHMP, towards the production of a document that reflects the current understanding of the osteoporosis epidemiology and pathophysiology. The section dealing with the registration of drugs to be used in osteoporotic males is very important and scientifically sound.</p>		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION INTRODUCTION		
Line no.⁵ + paragraph no.	Comment and Rationale	Outcome
Introduction	Hormone replacement therapy is no longer considered as an option for the prevention (or the treatment) of osteoporosis. Most national guidelines indicate that HRT should only be considered for the treatment of climacteric symptoms and used at the lowest dose effective for as short a duration as possible. It might be useful to mention these facts.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .
Page 3, introduction, 5 th paragraph	Some of the independent risk factors listed in the draft guideline differ from those identified in the WHO study.	Corrected

⁵ Where applicable

Page 3, last paragraph	The statement that the incidence of osteoporotic fracture and the predictive value of BMD are low before 65 years of age and increase with age is partially incorrect. Whilst the incidence of fracture does increase with age, the predictive value of BMD becomes weaker, not stronger with age.	Corrected
Page 3, last paragraph	In the parameters reflecting bone quality, it might be wise to include the “degree of mineralisation” and to replace “microfracture” by “microcracks”.	Corrected
Page 4, paragraph 2	Wrist fractures are part of the major osteoporotic fractures.	Included
GUIDELINE SECTION CLINICAL TRIALS		
Line no.⁶ + paragraph no.	Comment and Rationale	Outcome
Page 5, paragraph 4.2	Patients should be selected following an estimation of the fracture risk that has been based on skeletal factors and not on extra skeletal factors.	Specified and corrected
Page 7, paragraph 4.4	It would be useful to give guidance on whether paired or unpaired biopsies should be obtained.	Additional guidance provided

⁶ Where applicable

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
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COMMENTS FROM Francine CAULIN and John A. KANIS	
GENERAL COMMENTS – Francine CAULIN	
There is a special place for considering shorter intervention at the time of abrupt cessation of ovarian function. This, together with the established effect of HRT on fracture risk and the long offset time suggest that short term HRT has a role in the management of osteoporosis, particularly in the years after the menopause.	
SPECIFIC COMMENTS ON TEXT	
GUIDELINE SECTION INTRODUCTION	Outcome
The aim of this report is to support a proposal to include an addition to the draft guideline. We consider that there is a role for intervention at the time of surgical menopause, drug-induced menopause and in women with severe post-menopausal symptoms in whom fracture risk is high.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .

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COMMENTS FROM National Osteoporosis Society UK (Doctor Juliette COMPSTON)		
GENERAL COMMENTS - OVERVIEW		
The National Osteoporosis Society (NOS) welcomes the review of these guidelines. In particular we are pleased to note the consideration of absolute fracture risk as a criterion for entry to studies, the recognition that factors other than BMD contribute to fracture risk and the use of other non-vertebral fractures as well as hip fractures as primary end points.		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION INTRODUCTION		
Line no.⁷ + paragraph no.	Comment and Rationale	Outcome
Page 3, 5 th paragraph and 4.2	The risk factors that are listed do not include tobacco use and alcohol abuse. Sedentary lifestyle is not an independent risk factor for fracture. Only a family history of hip fracture has been shown to be an independent risk factor for fracture.	Corrected
Page 3, last paragraph	The predictive value of BMD actually becomes weaker and not stronger with age.	Corrected
Page 4, section 1 second to last paragraph	The bisphosphonates are now available in daily to 3 monthly dosing formulations as intermittent intra-venous ibandronate has been licensed for use.	Corrected
GUIDELINE SECTION CLINICAL TRIALS		
Line no.⁸ + paragraph no.	Comment and Rationale	Outcome
Page5, paragraph 4.2	The risk factors that are listed do not include tobacco use and alcohol abuse. Sedentary lifestyle is not an independent risk factor for fracture. Only a family history of hip fracture has been shown to be an independent risk factor for fracture.	Corrected
Page 7, paragraph 4.4	It would be useful in this section to give guidance on whether paired or unpaired biopsies should be obtained.	Additional guidance provided

⁷ Where applicable

⁸ Where applicable

GUIDELINE SECTION STUDY DESIGN		
Line no. ⁹ + paragraph no.	Comment and Rationale	Outcome
Page 8, paragraph 5.3	Many ethics committees will feel that the use of placebo-controlled trials is unacceptable since there are several effective interventions. This may mean that recruitment into Phase III studies will be difficult and may not be internationally representative.	Non-inferiority trials vs. 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.

⁹ Where applicable

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COMMENTS FROM the International Menopause Society (Professor Amos PINES)		
GENERAL COMMENTS - OVERVIEW		
The International Menopause Society being committed to the concept of primary prevention of osteoporosis, would like to present the main arguments for maintaining the prevention of osteoporosis as an indication.		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION AIM TREATMENT		
Line no.¹⁰ + paragraph no.	Comment and Rationale	Outcome
Page 4, section 2	The first 5–10 years after menopause are associated with an accelerated rate of bone loss, resulting in a loss of bone architecture and quality. A variety of studies have demonstrated that this is preventable with hormone therapy. Additionally, recent data suggested an improved pharmaco-economic profile for prevention of osteoporosis, specifically with hormone therapy. The draft guideline fails to address the prevention of osteoporosis indication.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .

¹⁰ Where applicable

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COMMENTS FROM Novo Nordisk (Doctor Josef HRUSKA)		
GENERAL COMMENTS - OVERVIEW		
While Novo Nordisk FemCare AG (Novo Nordisk) welcomes the addition of men as a target group, it wishes to express concerns in particular with regard to the deletion of prevention of osteoporosis. Prevention is the “key stone” in management of any disease, and so it should be for osteoporosis which is the underlying condition in women with osteoporotic fracture.		
SPECIFIC COMMENTS ON TEXT		
Line no.¹¹ + paragraph no.	Comment and Rationale	Outcome
	<p>The draft need to retain the following two treatments aims:</p> <ol style="list-style-type: none"> 1. <u>Prevention of osteoporosis</u>, targeted at postmenopausal women deteriorating bone mineral density, but without established osteoporosis. 2. <u>Treatment of osteoporosis</u>, targeted at postmenopausal women with established osteoporosis and/or with history of osteoporotic fracture. <p>Furthermore, the Draft should focus on clear definition of risk factors determining the treatment aim.</p>	The current draft guideline already addresses the issue of women with osteopenia (BMD) T-score between -1 to -2.5 with additional risk factors (i.e. at increased risk of osteoporosis). “Indication “prevention of osteoporosis” for HRT: see above.

¹¹ Where applicable

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COMMENTS FROM Merck Sharp & Dohme – Europe (Mrs Angelika JOOS)			
GENERAL COMMENTS - OVERVIEW			
NONE			
SPECIFIC COMMENTS ON TEXT			
GUIDELINE SECTION Introduction			
Line no ¹² . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Page 3 (Paragraph 6)	<p>“An important predictor of osteoporotic fractures in postmenopausal women without a previous fracture is bone mineral density (BMD)”</p> <p>Unlike a number of other really good predictors mentioned, like age, prevalent fracture, and family history of fracture, BMD is a <i>quantitative</i> predictor of fracture.</p>	Please rephrase: "An important <i>quantitative</i> predictor of osteoporotic fractures in..."	Endorsed
Page 3 (Paragraph 7)	<p>“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...”</p> <p>No data exist that link micro-architecture, damage accumulation, or collagen structure to bone strength or fracture in humans. These parameters are subjects for research and scientists have been trying to link to fracture, but no substantial evidence exists to prove this linkage even after a decade of research.</p>	Please rephrase: "...including bone size and shape, and bone turnover, both of which play a proven role in determining the risk of osteoporotic fractures."	Remains unchanged, since not in agreement with comments from scientific societies.

¹² Where available

Page 4 (first full Paragraph 1)	<p>“Most osteoporotic fractures occur in women because the effect of menopause...”</p> <p>The main reason that women have osteoporosis is that they have lower peak bone mass than men.</p>	Please rephrase: "Most osteoporotic fractures occur in women because <i>they have lower peak bone mass than men</i> , the effect of menopause increases the risk of..."	Corrected
GUIDELINE SECTION 3. Pre-clinical studies			
Line no¹³. + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Section 3.1 Animal Models Page 5	Adult rabbit should be added to the list as an acceptable species. The criteria are that Haversian remodeling exists. Adult rabbit has Haversian remodeling.		Adult rabbit has been added as possible suggestion.
Section 3.2 Methods of Assessing Page 5 (paragraph 2)	<p>“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.”</p> <p>This is too restricted and should allow more flexibility. When it is desired to demonstrate an ability to halt bone loss, it is sufficient to use animals in whom acute estrogen deficiency is induced to cause bone loss. When it is desired to demonstrate an ability to add bone to an osteopenic skeleton, it is recommended to use animals in which oestrogen deficiency has already induced bone loss.</p>		Corrected and enclosed

¹³ Where available

GUIDELINE SECTION 4. Clinical trials			
Line no¹⁴. + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Section 3 Pre-Clinical Studies Page 4 (Paragraph 2)	Text again claims that studies of bone architecture are important. They are interesting, but bone architecture has no proven relationship to fracture.	This requirement should be deleted.	Unchanged. Claims that studies or bone architecture are important are supported by all scientific societies and international literature.
Section 4.2. Population to be studied Page 5 (paragraph 1)	With regards to the patient population to be studied, "...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."	MSD suggests a clarification as to what is considered a "high risk" population e.g. in terms of a range of risk rate that meets the guideline requirements.	Range of risk rates that meets the guidelines requirement has been provided.
Section 4.2 Population to be studied Page 6 (2 nd full paragraph)	<p>"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. ... The definition of a high risk should be based on national and international recommendations."</p> <p>How can we assure that the definition of high risk does not change over time (from recruitment to review of the data)?</p>	Specific reference should be made to national/international definitions of high risk.	The definition of high risk population has been provided, based on the recommendations of the WHO working party.

¹⁴ Where available

Section 4.3.1 Fracture Page 6	“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.” It is not clear what the Guideline means by these endpoints “to be studied separately”. Does it mean that two different studies need to be conducted, one for the study of vertebral fractures, and one for the study of non-vertebral fractures? If these endpoints are studied in <u>one</u> study, with implementation of an appropriate multiplicity adjustment strategy for multiple efficacy endpoints, could results from one study on multiple endpoints be used for filing?	Please clarify that these endpoints should be studied separately, but not necessarily in a separate study, if appropriate statistical measures are applied.	Clarified
Section 5.3.2 Main therapeutic studies Page 9 (paragraph 3)	<p>“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”</p> <p>Conducting placebo control studies in a high-risk population for 5 years may become increasingly difficult for ethical reasons.</p>		Non-inferiority trials vs 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.
GUIDELINE SECTION 5. Study design			
Line no ¹⁵ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Section 5.2 Dose response studies Page 8,	It is interesting to note that the Guideline recommends the use of co-primary endpoints including BMD measured at the spine and/or the hip and appropriate biochemical markers of bone turnover in dose ranging studies. It further states that responders should be assessed, and defines the responders for BMD as patients with changes above baseline at the end of treatment. Nothing is said about the consequences of only meeting one endpoint (say, spine, but not hip) for phase III study designs and for filing/indications.	MSD recommends to clarify the guideline in this respect.	See page 4/10 section 2 “ <i>Aim of treatment</i> ” where this information is provided
Last paragraph of section 5.2 Dose response	“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.”	We suggest moving this in section 3.1. Animal models, where it is more appropriate.	The sentence has been moved in section 3.1 “ <i>Animal models</i> ” and clarification

¹⁵ Where available

studies		Also, clarification is needed as to when the data are required.	has been provided
Section 5.3 Main therapeutic studies Page 8 (paragraph 2)	<p>“In principle, placebo-controlled trials will be requested.”</p> <p>To what extent are PBO-controlled trials ethical in high risk patients (e.g. patients with > 1 prevalent fractures)?</p>	MSD recommends providing guidance with regards to conducting active comparator trials and the possible indications associated with such a study, in case it becomes difficult to recruit a high-risk population for placebo-controlled trials.	Non-inferiority trials vs. 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.
Section 5.3.1 General considerations Page 8	Placebo-controlled trials are still required. Non-inferiority trials versus active comparators could be considered if justification of the margin of non-inferiority can be made before the start of the trial. The study population, as stated on page 5 under Section 4.2, is postmenopausal osteoporosis women or osteoporosis men at “high risk of fracture”. Osteoporosis is defined by the WHO as a T-score <-2.5. It is not clear from the Guideline, however, whether or not the study population could be osteoporotic men and/or women with prior fractures.	Please clarify	Guidance has been provided regarding the definition of “at increased risk” patients.
Section 5.3.2 Main therapeutic studies Page 9 (paragraph 3)	<p>“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”</p> <p>Conducting placebo-controlled studies in a high-risk population for 5 years may become increasingly difficult for ethical reasons.</p>		See above.

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM WYETH EUROPA (Mr John Inman and Mrs Benedicte Chatelard)

GENERAL COMMENTS - OVERVIEW

Revisions to the European guidance regarding osteoporosis have been proposed, which would change the therapeutic indication to the treatment of osteoporosis in patients at high risk of fracture. This proposed guideline is incomplete in that it does not address the prevention of osteoporosis indication.

The proposed revisions have taken into account appropriate medical advances over the past 10 years, of making attempts to streamline the development of new medicinal products, and to extend this therapeutic indication to men with osteoporosis. Our concern is that the proposed guideline will needlessly allow patients to lose bone architecture and quality. As most fractures occur in non-osteoporotic women, the proposed guideline would put postmenopausal women at risk of developing fractures and the end effect would be to increase the economic and social consequences of osteoporosis.

The prevention of osteoporosis is a most important therapeutic indication, which should be continued. Prevention of an initial fracture is paramount to the avoidance of subsequent fractures. Maintaining bone density, architecture and overall bone quality is essential to preventing fractures, which result in the social and economic consequences of osteoporosis. Selection of the appropriate patient population for prevention of osteoporosis should be made primarily on the basis of BMD and other secondary risks of fracture such as markers of bone turnover, age, and a family history of hip fracture.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE: 2. AIM OF TREATMENT			
Line no ¹⁶ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
	The proposed changes, in patient population and in the initiation of treatment only in women at high risk of experiencing fractures, would lead to the elimination of therapy to many osteopenic patients in whom the prevention of osteoporosis is appropriate.	Maintain prevention of osteoporosis as a therapeutic indication for those patients at risk of losing bone architecture and quality as indicated by BMD and bone turnover.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .
	<ul style="list-style-type: none"> • Following menopause there is a rapid loss of bone tissue, which results in declining bone architecture and hence quality. 		
	<ul style="list-style-type: none"> • The changes in bone quality, which are observed in early postmenopausal women and other conditions associated with a loss of bone structure and bone quality lead to an increased risk of fracture. 		
	<ul style="list-style-type: none"> • The proposed changes would result in an increased number of patients with primary fractures and hence an increased number of patients with subsequent fractures. 		

¹⁶ Where available

5.3 Main therapeutic studies	This proposed guideline is incomplete in that it does not address the prevention of postmenopausal osteoporosis	Add a subsection 5.3.5 Prevention of postmenopausal osteoporosis Oestrogen or oestrogen containing products used for the treatment of menopausal symptoms have been shown to prevent bone loss. Therefore, oestrogen or oestrogen containing products may seek an indication for the prevention of osteoporosis, particularly in women with postmenopausal symptoms. For the indication of prevention of osteoporosis, BMD is an appropriate surrogate endpoint. The study duration should be two years.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .
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GUIDELINE SECTION TITLE: 4.2 Populations to be studied

Line no ¹⁷ + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
	BMD testing does not identify those individuals with poor quality bone. Bone turnover is an independent risk factor for fracture, which may be a principal mechanism of antiresorptive drugs for reducing fracture.	Include criteria for the patient population to be studied for the prevention of osteoporosis indication.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .
	<ul style="list-style-type: none"> • We propose that a combination of BMD and bone turnover be used to identify patients at risk of fracture for the prevention of osteoporosis indication. 		
	<ul style="list-style-type: none"> • Clinicians could add other characteristics to identify patients for the prevention of osteoporosis including: age and a family history of hip fracture. 		
	<ul style="list-style-type: none"> • Patients most likely to benefit from the prevention of osteoporosis include those with early or premature menopause and/or rapid or accelerated bone loss, immobilisation, corticosteroid treatment, or any period where the patient is at acute risk of bone loss. 		

¹⁷ Where available

	<p>The proposed guideline for the treatment of osteoporosis seeks to identify patients for the treatment of osteoporosis on the bases of factors that result in an increased 10-year probability of fracture.</p>	<p>Include the relative weighting of the factors and effects of their interactions in the guidance to ensure selection of the appropriate patient population.</p>	<p>Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i>.</p>
	<ul style="list-style-type: none"> • The relative weighting of the factors and the effects of their interactions, are not specified in the guideline. 		

GUIDELINE SECTION TITLE: 4.3 Criteria of efficacy and their assessment			
Line no ¹⁸ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
	This proposed guideline is incomplete in that it does not address the prevention of osteoporosis indication.	Include criteria for determining the efficacy of therapy for the prevention of osteoporosis indication.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .

¹⁸ Where available

	<ul style="list-style-type: none"> • Data indicate that bone density and the rate of bone turnover can help identify individuals who could benefit from therapy for the prevention of osteoporosis. These parameters can be used as the primary endpoints in clinical trials for the prevention of osteoporosis. 		<p>Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i>.</p>
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**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM SOLVAY PHARMACEUTICALS		
GENERAL COMMENTS - OVERVIEW		
<p>The draft “Guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis” does not make any distinction between treatment and prevention of osteoporosis but accepts exclusively treatment of “primary osteoporosis” defined by the probability of fractures.</p> <p>Osteoporosis is a disorder characterised by loss of bone mass combined with structural changes of the bone, specifically a decrease of connectivity between the trabecules. For pragmatic reasons, osteoporosis is currently defined by low bone mineral density and prevention is indicated for women with osteopenia who are at high risk of future fractures.</p> <p>The proposed indication “treatment of osteoporosis” is characterised by the risk of fractures. However, such risk ill-defined and patients with low bone density in need of prevention of further bone loss and future high risk of fractures may not be eligible to receive treatment. Due to the limited chance to restore bone stability, the indication “prevention of osteoporosis” should be maintained for such patients.</p>		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE: 2. AIM OF TREATMENT		
SPECIFIC COMMENTS ON TEXT		
Line no.¹⁹ + paragraph no.	Comment and Rationale	Outcome
Page 4/10	<p>Due to the currently limited chance to restore bone architecture and stability, bone deterioration should be brought to a stop before fractures occur. For pragmatic reasons, the appropriate patient population should be selected on the basis of bone mineral density as main characteristic for osteoporosis and other risk factors which should be weighted appropriately.</p> <p>As prevention is by definition “any activity by which an individual avoids the development of a disease or condition”, there is a rationale to maintain the distinction between prevention and treatment. The disease to be prevented is osteoporosis and the condition to be prevented is bone fracture.</p>	<p>Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i>.</p>

¹⁹ Where applicable

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PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM DEUTSCHE MENOPAUSE GESELLSCHAFT

GENERAL COMMENTS - OVERVIEW

The proposed revisions to the European guidance in accordance to osteoporosis include a substantial change of the definition of primary and secondary prevention of osteoporosis. If fully converted, this on our behalf would lead to a tremendous change of the therapeutic indication and to the treatment of osteoporosis in patients with a high fracture risk.

We, the German Menopause Society (DMG), believe that it is worthwhile reconsidering aspects in accordance to an optimal management of patients at high risk of fracture. The proposed changes include a limitation to the initiation of treatment only for women with osteoporosis with an extremely high risk to sustain a fracture. Hereby, a significant proportion of women with low bone mass (T-score -1 to -2.5) and risk factors, which in a number of recent studies comprised a high risk of fracture, are unable to receive any effective preventative treatment. We believe that the initiation of a preventative treatment for this group of women is of up most importance.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION: AIM OF TREATMENT		
SPECIFIC COMMENTS ON TEXT		
Line no. ²⁰ + paragraph no.	Comment and Rationale	Outcome
	<p>We therefore suggest reconsidering the current draft of the guidelines. We strongly support the maintenance of the <i>prevention of osteoporosis</i> indication. We believe that the proposed change, both in patient population and in the initiation of treatment only in women at the extreme highest risk of fractures, would lead to the elimination of prevention of osteoporosis in patients with low bone mass (T-score -1 to -2), also at high risk of fracture. Unlike for HT, there are no RCT data suggesting that bisphosphonates or other alternatives reduce fracture risk in these groups of high risk women. On contrary to the intention of the EMEA, these proposed changes would put additional postmenopausal women at risk of sustaining fractures and therefore would increase the economic and social problems of osteoporosis and the effects on the elderly in our societies.</p>	<p>RCT have demonstrated the ability of selective estrogen receptor modulators and strontium ranelate to reduce fracture risk in women with osteopenia. In the guideline, women with BMD T-score between -1 and -2.5 and additional risk factor are considered as “Women at increased risk of fracture” and are considered as deserving a treatment.. Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i></p>

²⁰ Where applicable

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM IGEA (Mrs Francesca de Terlizzi)		
GENERAL COMMENTS - OVERVIEW		
<p>On page 4/10 in the paragraph 2 (<i>Aim of treatment</i>) it is correctly reported that “the therapeutic indication will generally be the treatment of osteoporosis in postmenopausal women at high risk of fracture”. This assertion has gained increased importance since the WHO position regarding the identification of subjects at high risk of fracture has recently changed; the introduction of the concept of 10 years probability of fracture is certainly a great step forward in the successful management of postmenopausal osteoporosis. In fact the concept of 10 years probability is again reported in the EMEA document on page 5/10 (paragraph 4.2), when describing the characteristics of the populations to be studied; the combination of different risk factors in a quantitative evaluation of risk, based on epidemiologic and clinical studies is undoubtedly of high efficacy.</p>		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION: CLINICAL TRIALS		
SPECIFIC COMMENTS ON TEXT		
Line no.²¹ + paragraph no.	Comment and Rationale	Outcome
	<p>To our opinion it should be fair to explain more in detail the concept of 10-year probability of fracture, and report that data are up to now available in the literature for the calculation of 10-year probability of fracture on the basis of clinical risk factors and, in particular, for 2 densitometric techniques:</p> <ul style="list-style-type: none"> - Femoral neck DXA - Phalangeal QUS <p>It is reported on page 6/10, “the definition of a high risk should be based on national and international recommendations”. We would like to point out that the new Italian “Guidelines for diagnosis, prevention and therapy of osteoporosis” [4], approved by several scientific associations (CROI, SIOMMMS, SIMFER, SIMI, SIOT, SIR), promote the use of 10-year probability of fracture by using the algorithms based on the combination of clinical risk factors and densitometric values; the algorithms proposed can be used either for femoral neck DXA or phalangeal QUS.</p>	<p>Dual energy x-ray absorptiometry remains the gold standard for the assessment of BMD. The WHO operational definition, setting up the threshold for osteoporosis at a T-score of -2.5 has been based on BMD measurement with DXA.</p>

²¹ Where applicable

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM AMGEN (Mr E.O. Boyle)			
GENERAL COMMENTS - OVERVIEW			
<p>Amgen welcomes the opportunity to comment on the draft guidance for the treatment of primary osteoporosis. The guidelines are extremely useful and should be updated in view of scientific advances in the field of osteoporosis over the past few years. The revised broader scope of the guidance to include osteoporosis in men is supported, however further guidance on the development of medicinal products for secondary osteoporosis would be recommended.</p> <p>Amgen supports the provision of CHMP guidance (section 5.3.2) that trials of shorter duration i.e. two years with fracture endpoint can provide evidence of safety and effectiveness. There is published literature for several osteoporosis agents showing that a reduction in risk of vertebral fractures was observed as early as one year and the early treatment effect was predictive of the anti-fracture efficacy at 3 years. Therefore, there should be flexibility in the duration of registration trials for the approval of new osteoporosis agents.</p> <p>Guidance on the algorithm for risk factors (WHO ARA) predicting a 10 year fracture outcome should be included (or referenced) as part of the revised guidance. Amgen supports the provision in the guidance for performing randomized placebo-controlled fracture trial (with calcium and vitamin D supplementation to all patients) as long as the patient and physician are informed and appropriate escape clauses are included in the protocol to minimize the risk to an individual patient.</p>			
SPECIFIC COMMENTS ON TEXT			
GUIDELINE SECTION: CLINICAL TRIALS			
SPECIFIC COMMENTS ON TEXT			
GUIDELINE SECTION: INTRODUCTION			
Line no²². + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Pg 4 para 2 line 8	Examples of risk factors in men should be provided as guidance for the appropriate patient populations to be evaluated in clinical trials in men to support the proposed indication ‘treatment of osteoporosis in men at high risk for fracture’.	‘Other independent risk factors (<i>e.g. to be provided.....</i>), have not, however, been validated to the same extent in men than women....’	Included

²² Where available

GUIDELINE SECTION: AIM OF TREATMENT			
Line no ²³ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Pg 4 Para 4 line 4	Amgen supports the provisions in the guidance that a reduction in the risk of non-vertebral osteoporosis fractures should also be evaluated in registration trials and the SmPC should include a description of non-vertebral fracture efficacy by skeletal site.		Already included in the guidelines
Pg 4 Para 4 line 8	Amgen supports the inclusion of non-vertebral fracture data in the Therapeutic Indication section 4.1 and Pharmacodynamic properties section 5.1 of the SmPC.		Already included in the guidelines
GUIDELINE SECTION: CLINICAL TRIALS			
Line no ²⁴ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Pg 5 Para 1 & Para 2	An algorithm of risk factors versus 10 year fracture risk should be provided and / or referenced in the guidance, to ensure appropriate patient populations are enrolled into clinical trials. The impact of those patients enrolled in clinical trials to the therapeutic indication in the prescribing information should be addressed.	‘Predefined levels of risk for fractures should be prospectively established defined on the basis of <i>the established algorithm of risk factors for the 10 year fracture risk</i> (ref Section X in Guidance)’ e.g. (BMD, age, prevalent fractures, family history). Consistency of the effects for the whole range of levels of risk versus <i>risk factors at baseline</i> (as defined by the algorithm) should be evaluated.’	The exhaustive WHO algorithm will not be available before several months (years). Guidance has been provided for the absolute risk defining the population to be included in the trials.

²³ Where available

²⁴ Where available

Pg 6 Para 4	Some guidance on what is regarded as risk factors for future fracture in men would be helpful regardless of the validation status, to ensure some consistency between applicants.		Guidance has been provided for the risk in women and it is stated that the fracture risk in men should be of a magnitude similar that of postmenopausal osteoporotic women.
4.3 Criteria of efficacy and their assessment Pg 6 Para 1	Amgen maintains that a demonstration of anti-vertebral fracture efficacy associated with statistical significant increase in BMD and demonstration of normal bone quality is necessary to prove the efficacy of an investigational osteoporosis agent. This standard should apply for approval of any osteoporosis agent (including bisphosphonate, estrogen or estrogen agonist on bone, and bone anabolic agent) even when a prior agent in the same class has been shown to reduce fracture risk.		Requirements are similar for any investigational osteoporosis agents. No exception has been planned for new chemical entities even when a prior agent in the same class has been shown to reduce fracture risk.

4.3.4 Biochemical markers Pg 7 Para 3	The utility of existing and new markers of bone turnover as primary endpoints in clinical trials should also be critically evaluated as scientific advancements in this field continue.		At this stage, biochemical markers are not considered as appropriate primary endpoint for pivotal studies. Future guidelines may reevaluate this position, as scientific advancements in the field continue.
4.4 Criteria of safety and their assessment Pg 7 Para 7	Amgen supports the provision in the guidance that bone histomorphometric and histologic analysis of bone biopsies in a subset of patients demonstrating that bone formed during treatment with the agent is of normal lamellar structure and that there is no evidence of osteomalacia or other bone defects.		Included
	Since treatment induced increases in BMD alone does not account for associated reduction in fracture risk, Amgen recommend the inclusion of newer imaging techniques such as quantitative computed tomography (QCT), peripheral QCT, high-resolution QCT, and micro-computed tomography (μ -CT) as well as other assessments for bone geometry and architecture in preclinical studies and clinical studies. The potential inclusion of such data in prescribing information should be clarified.		These techniques should be further validated before being included and accepted as primary or secondary endpoints.

GUIDELINE SECTION: STUDY DESIGN			
Line no ²⁵ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
5.2 Dose response studies Pg 8 Para 6	The definition of responders re biochemical markers based on <i>robust scientific evidence</i> does not provide guidance to sponsors; further clarification is required in this guideline.		The definition of robust scientific evidence is left at the appreciation of the applicant.
5.3.1 General consideration Pg 8 Para 7 line 2	<p>Amgen supports the view that active-controlled trials comparing the investigational agent to approved therapies are permissible if they can be designed and conducted in ways that sufficiently overcome the interpretive difficulties often associated with such trials. Active-controlled fracture trials, are not typically a viable alternative, because, unless the new treatment is considerably superior to the active control, very large sample sizes will be required to demonstrate non-inferiority or superiority.</p> <p>Therefore, even with the availability of approved therapies for osteoporosis, Amgen proposes that placebo-controlled trials to evaluate the efficacy and safety of new agents are appropriate. In order to address some of the concerns with placebo-controlled trials, the following measures could be incorporated into the study designs:</p> <ul style="list-style-type: none"> • Before signing informed consent, the investigator should consider and discuss alternative treatment options for all potential study participants • Calcium (at least 500 mg to 1 g elemental) and vitamin D (at least 400 IU) supplementation should be provided to all study participants • If the study population includes elderly subjects, serum 25-hydroxy vitamin D levels should be assessed at baseline in all subjects and subjects should be repleted with vitamin D if they are found to be vitamin D deficient • If a subject loses considerable bone mass or exceeds a predefined fracture threshold during the trial, the investigator should discuss alternative treatment options with the subject and should discontinue investigational therapy if deemed appropriate. 		Calcium and vitamin D supplementation has already been planned in the guidelines document. Other suggestions are not part of regulatory requirement and are left at the appreciation of the applicant, when designing the clinical trials.

²⁵ Where available

Pg 8 Para 8 line 6	<p>For novel therapies, (e.g. first in a new therapeutic class), evaluated in placebo controlled pivotal trials, the relevance of comparing both efficacy and safety to currently registered medications would not be based on robust scientific data generated in a controlled clinical study. Therefore, the scientific validity of general comparisons made by the applicant at time of filing is questionable. It is also implied that comparative data might be required in some instances. If this is the expectation, then examples should be provided to clarify this requirement.</p> <p>In the absence of further clarification it is preferable to delete this sentence.</p>		<p>Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i>.</p>
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<p>5.3.2 Treatment of osteoporosis in women at high risk of fracture Pg 9</p>	<p>Amgen supports the provisions in the CHMP guidance (section 5.3.2) that trials of shorter duration i.e. two years with fracture endpoint can provide evidence of safety and effectiveness. There is published literature for several osteoporosis agents showing that a reduction in the risk of vertebral fractures was observed as early as one year and the early treatment effect was predictive of the anti-fracture efficacy at 3 years. Therefore, there should be flexibility in the duration of registration trials for the approval of new osteoporosis agents.</p> <p>A shorter trial duration for a new osteoporosis agent should be considered adequate provided availability of all of the following</p> <ul style="list-style-type: none"> • Sufficient preclinical data at the time of regulatory submission demonstrating that the quality of bone is not negatively affected • Bone histomorphometric and histologic analysis of bone biopsies taken from humans in clinical studies demonstrating that bone formed during treatment with the agent is of normal lamellar structure and that there is no evidence of osteomalacia or other bone defects • Data from biomechanical testing of bones from animals in long-term pharmacology studies demonstrating that the biomechanical integrity of bone is not compromised • Adequate safety data at the time of submission exceeding the target established in ICH guideline (E1A) <p>Amgen supports the extension of the pivotal trial where anti-fracture efficacy is demonstrated at two years, in order to monitor safety. Extension of pivotal trial beyond 3 years and up-to 5 years may be necessary in some instances to assess long-term safety.</p>		<p>These comments are in agreement with the current formulation of the guidelines.</p>
<p>5.3.3 Bridging Studies Pg 9</p>	<p>For agents that have demonstrated anti-fracture efficacy, Amgen believes that BMD should be an acceptable primary endpoint for the</p> <ul style="list-style-type: none"> • Indications in men • Indication of treatment and prevention of glucocorticoid-induced osteoporosis and bone loss due to other therapies (<i>outside the scope of this guidance</i>) • New dosage regimens i.e., once weekly, once monthly • New routes of administration 		<p>These comments are in agreement with the current formulation of the guidelines. Glucocorticoid-induced osteoporosis and bone loss due to other therapies are outside the scope of this guidance.</p>

5.3.4 Minimal requirement to be granted a MA indication for the treatment of osteoporosis in males	Amgen concurs that once an initial marketing authorization has been granted for the treatment of postmenopausal osteoporosis in women, a bridging study with a BMD endpoint should be suitable for the approval of a similar indication in men.		These comments are in agreement with the current formulation of the guidelines.
Pg 9 Para 8 line 5	Amgen would appreciate clarification regarding inclusion of men that have baseline <i>fracture risk</i> of a similar magnitude compared with postmenopausal women. Since a large number of men with osteoporosis have no identifiable risk factor or cause, clarification on the appropriate patient populations to be evaluated in clinical trials to support the proposed indication in males will be useful.		Additional guidance has been provided regarding the threshold of fracture risk acceptable to be considered has “at increased risk for fracture”.
Pg 10 Para 2 line 2	<p>The term ‘globally proportional to the decreased incidence of fractures in treated women’ is confusing, but could be interpreted as a comparison should be made across all internationally conducted clinical trials in post-menopausal women.</p> <p>If this is not the intent then this should be reworded.</p>	‘ the magnitude of the changes in BMD versus placebo is similar to that observed in postmenopausal osteoporotic women treated with the same compound <i>in Internationally conducted clinical trials</i> and is globally proportional to the decreased incidence of fractures.	Accepted and reworded.

Not applicable	<p>In addition to the trial design topics covered in the draft guideline Amgen would appreciate additional guidance on the following additional topics:</p> <p>Study design and statistical considerations for the evaluation of agents for secondary osteoporosis such as glucocorticoid-induced osteoporosis.</p> <p>Further guidance is also requested on combined and sequential use of osteoporosis therapies. Several osteoporosis therapies have been approved to date and there is considerable scientific interest in combination and sequential use of different therapies. It will be helpful if guidance could be provided on trial designs to support statements of sequential or combination use of agents with similar or differing mechanism in the prescribing information in the revised CHMP osteoporosis guidelines.</p> <p>Treatment induced changes in BMD should be considered an adequate endpoint to demonstrate efficacy for sequential and combination use of two osteoporosis agents along with supportive preclinical data. This is based on the assumption that the fracture efficacy in postmenopausal osteoporosis has been or will be demonstrated individually for the osteoporosis drugs being used sequentially (e.g. transitioning from one osteoporosis agent to another) or concomitantly.</p>		These comments are outside the scope of the present guidance.
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**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM THE BELGIAN MENOPAUSE SOCIETY (Professor U. Gaspard)		
GENERAL COMMENTS - OVERVIEW		
<p>The proposed revision (2006) only considers "the treatment of osteoporosis in PMW at high risk of fracture". The suitable population for clinical trials concerning this new unique indication would be PMW at high risk of osteoporotic fractures "<u>based on the known independent factors such as BMD, previous low trauma fractures, high bone turnover, maternal history of fracture and low body mass index, that result in an increased 10-year probability of fracture regardless of the time elapsed since menopause</u>"</p> <p>The concern of the Belgian Menopause Society is that the new proposed guidelines are dropping totally the prevention aspects. In fact, as soon as menopause starts, loss of BMD occurs resulting in decline in both bone mass and quality which will favour osteoporosis. Later installation of the most potent (and also most expensive) treatments do not restore bone architecture when it is lost and PMW will remain at a high risk of fracture.</p>		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION: AIM OF TREATMENT		
SPECIFIC COMMENTS ON TEXT		
Line no.²⁶ + paragraph no.	Comment and Rationale	Outcome
	The Belgian Menopause Society requests that the indication of prevention of osteoporosis be retained in the European guidelines.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .

²⁶ Where applicable

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM INTERNATIONAL SOCIETY OF GYNECOLOGICAL ENDOCRINOLOGY (Professor Andrea Genazzani)		
GENERAL COMMENTS - OVERVIEW		
<p>We strongly believe that the scientific societies should express their opinion on the important issue of prevention mainly in those areas where Public Health by the means of prevention can reduce the high costs of the diseases.</p> <p>To our concern, prevention of osteoporosis means reducing the incidence of osteoporosis and therefore, ultimately reducing bone fractures.</p>		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION: AIM OF TREATMENT		
SPECIFIC COMMENTS ON TEXT		
Line no.²⁷ + paragraph no.	Comment and Rationale	Outcome
	<p>The proposed changes in guidelines would lead to the elimination of therapy in osteopenic patients and would increase the number of patients with fractures. An increase in the number of patients with primary fractures will increase the number of patients with subsequent fractures. It is better to maintain bone quality and strength than to attempt to restore it once lost.</p>	<p>Women with osteopenia and additional risk factors are considered as “at increased risk of fracture” and included in the population to be studied.</p>

²⁷ Where applicable

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM THE ITALIAN SOCIETY OF GYNAECOLOGICAL ENDOCRINOLOGY OF THE THIRD AGE (SIGITE)		
GENERAL COMMENTS - OVERVIEW		
The Italian Society of Gynaecology of the third Age (SIGITE) has considered the proposed changes in the guidelines and would like to present the main arguments for maintaining the prevention of osteoporosis as an indication, without negotiation.		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION: AIM OF TREATMENT		
SPECIFIC COMMENTS ON TEXT		
Line no.²⁸ + paragraph no.	Comment and Rationale	Outcome
	<p>The indication of prevention of osteoporosis is crucial. The major goal in the management of osteoporosis is fracture prevention. The prevention of osteoporosis as indication allows intervention to maintain the skeletal microstructure, architecture, and quality thereby reducing the risk of the first fracture from occurring. Without this clear indication, women who deserve preventive treatment will be deprived of such cure.</p> <p>The SIGITE considers that the elimination of the primary prevention of osteoporosis as indication will lead to an overall increase in fractures, and will impact on women's morbidity, quality of life and mortality. The primary prevention of osteoporosis is the key to prevent osteoporotic fractures and is a most important therapeutic indication, which should therefore be continued in the new European Guidelines.</p>	<p>Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i>.</p>

²⁸ Where applicable

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM PORTUGUESE MENOPAUSE SOCIETY (Professor Mario de Souza and Dr Manuel Neves-e-Castro)		
GENERAL COMMENTS - OVERVIEW		
<p>When one discusses the concepts of “prevention” and “treatment” it is clear that whereas “prevention” is aimed at avoiding the occurrence of a disease, a “treatment” is either aimed at a “restitutio ad integrum” or, if not possible, at symptom relief.</p> <p>In view of the above, one can prevent and treat osteopenia, by increasing BMD and reinforcing the structure of trabeculae in order to avoid their fracture. Conversely, one cannot “treat” osteoporosis because none of the available drugs is capable of restoring fractured trabeculae reliably, with bridge formation between these interrupted structures, despite some publication showing that teriparatide restores perforated trabeculae. But, alternatively, one can prevent new fractures from occurring in an osteoporotic bone with the same drugs used in osteopenia. What will happen is that by increasing the associated low BMD one prevents their compromised, but still intact, trabeculae from becoming weaker up to point of breaking.</p> <p>Thus, (and this is not a question of semantics but rather of concept) one can treat osteopenia but one cannot “treat” osteoporosis. One can only prevent the progression of the associated osteopenia that will lead to fractures and osteoporosis.</p>		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION: AIM OF TREATMENT		
SPECIFIC COMMENTS ON TEXT		
Line no.²⁹ + paragraph no.	Comment and Rationale	Outcome
	<p>If EMEA is a regulatory agency concerned with savings in the Public Health budgets of the member States, any recommendation not to reimburse drugs that have not yet met their proposed requirements to be considered “treatments for osteoporosis” will no doubt result in an increased number of preventable fractures that will more strongly have a negative impact in the Health costs of the member States.</p> <p>In conclusion, we hope that EMEA will reconsider their future recommendations as to the classification of drugs to preserve bone health.</p>	<p>Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i>.</p>

²⁹ Where applicable

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM EUROPEAN MENOPAUSE AND ANDROPAUSE SOCIETY		
GENERAL COMMENTS - OVERVIEW		
<p>In the years following the publication of the WHO definition of osteoporosis in 1994 we have had the concept that osteoporosis is a condition involving reduced bone density and architectural impairment. Although bone density is a continuous variable it was possible to define a threshold level of bone density (t-score -2.5sd) which defined the condition. Following that work the accepted definitions were those of “osteoporosis” defined by the bone density threshold and “established osteoporosis” where fracture had occurred. With these definitions we had the concepts of primary and secondary prevention of osteoporosis depending on whether the bone density threshold for osteoporosis had yet been reached. There was also the concept of primary and secondary prevention of osteoporotic fracture which was determined by whether or not fracture had as yet occurred. Clearly primary and secondary prevention of osteoporosis may be included within primary prevention of fractures.</p>		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION: AIM OF TREATMENT		
SPECIFIC COMMENTS ON TEXT		
Line no.³⁰ + paragraph no.	Comment and Rationale	Outcome
	<p>EMAS would argue that the clinical field is best served by EMEA determining what therapeutic agents are effective in the management of osteoporosis, which will include the prevention of an individual developing osteoporosis. If EMEA provides clinicians with licensed agents that are effective for the different circumstances ranging from the prevention of osteoporosis through to the treatment of established osteoporosis where the fracture risk is especially high, then the field will be well served.</p>	<p>Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i>.</p>

³⁰ Where applicable

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM THE SWISS MENOPAUSE SOCIETY (Professor M. Birkäuser)		
GENERAL COMMENTS - OVERVIEW		
<p>The Swiss Menopause Society agrees with the International Menopause Society that the draft Guideline on the Evaluation of New Medicinal Products in the Treatment of Primary Osteoporosis is incomplete in that, unlike the previous Note for Guidance on Postmenopausal Osteoporosis in Women (2001 Guidance), it fails to address the prevention of osteoporosis indication.</p> <p>Early prevention of osteoporosis is essential because the majority of fractures occur in the non-osteoporotic population. Furthermore, it is well known that individuals who had one osteoporotic fracture approximately double their risk to have another. Although treatment of osteoporosis can reduce the risk for a subsequent fracture, it cannot eliminate the excess risk. It is therefore essential to maintain bone architecture and quality as early as in the peri- and early postmenopause. The Swiss Menopause Society is therefore greatly astonished that EMEA does not maintain the prevention of osteoporosis by oestrogens as a first line medical intervention in women with an increased risk of osteoporosis and bone fractures.</p>		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION: AIM OF TREATMENT		
SPECIFIC COMMENTS ON TEXT		
Line no.³¹ + paragraph no.	Comment and Rationale	Outcome
	<p>It is our view that HRT should be considered a first-line option for the primary prevention of osteoporosis-related fracture in post-menopausal women with increased risk, even if asymptomatic. It should also be available to those older women with increased risk who either have persisting menopausal symptoms or who make an informed choice to use it.</p> <p>The Swiss Menopause Society strongly supports the maintenance of osteoporosis prevention as an indication and likes to emphasize that HRT/ERT are effective and safe treatment options for osteoporosis prevention.</p>	<p>Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i>.</p>

³¹ Where applicable

**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM ELI LILLY AND COMPANY			
GENERAL COMMENTS - OVERVIEW			
SPECIFIC COMMENTS ON TEXT			
GUIDELINE SECTION: INTRODUCTION			
Line no³². + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Section 1. line 6 And Section 2. line 6	<p>In the list of major non-vertebral fractures the distal forearm fracture has been omitted.</p> <p>Fractures of the distal forearm (Colles' fractures) are common among the middle-aged and elderly. The incidence in women increases rapidly from the first five years of the menopause, reaching a peak between the ages of 60 and 70 years. For European women, the lifetime risk of a wrist fracture is approximately 15%, a similar risk than hip fractures, and about 20% of 70-year-old women had at least one wrist fracture. There is an established relationship between low bone mineral density and forearm fractures. Moreover, Colles' fractures carry a high absolute risk for subsequent hip and spinal fractures.</p> <p>Distal forearm fractures are painful, usually require one or more reductions and need 4-6 weeks in plaster to establish union. A proportion of patients do not recapture function without physiotherapy. There is a high incidence of algodystrophy after distal forearm fractures (30%) which gives rise to pain and tenderness, stiffness, swelling and vasomotor disturbances.</p>	Section 1. line 6 And Section 2. line 6	Forearm fracture has been included in the list of major non-vertebral fractures

³² Where available

Section 5.3.4 Line 17 and 18	<p>In the section 5.3.4. where the requirements for granting a marketing authorization for treatment of osteoporosis in males is described the following sentence is included:</p> <p>“If ... , or 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.”</p> <p>Comment: Assuming that CHMP uses the term “hormonal” here in the context of sex hormones, we believe that the actual wording of this sentence is different from its intent.</p> <p>Several osteoporosis agents are derived from natural hormones other than sex hormones (e.g. calcitonin, PTH derivatives, etc). In these cases, gender specific differences in antifracture efficacy are not expected, and there is no rationale for requiring a separate fracture endpoint study in males. Therefore, we suggest to limit this requirement to those NCEs where a gender specific mechanism of action is expected.</p>	<p>"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."</p>	Included in the document
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**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM EFPIA (Mrs Christine-Lise JULOU)

GENERAL COMMENTS - OVERVIEW

EFPIA welcomes the effort of the CHMP and the Efficacy Working Party to revise the guideline on the treatment of osteoporosis in line with current medical and scientific developments. A number of improvements in the draft guideline revision are considered particularly conducive to the improvement of patient care. The shortening of the minimum duration of pivotal fracture trials to two years will considerably shorten the time patients will be allocated to placebo. The possibility of studying a composite non-vertebral fracture endpoint reflects the current advances in the understanding of the importance of different types of fractures. The description of nominal results of efficacy studies in the SPC section on “Pharmacodynamic properties” adds valuable scientific information to prescribers. The shortening of the duration of bridging studies to one year as well as the potential use of biochemical markers of bone turnover as surrogate endpoints are in line with current medical viewpoints on the importance of these respective markers. The addition of overall guidance concerning the development of treatment of male osteoporosis is welcomed, an area where therapeutic alternatives are rare, as well as the specific guidance on BMD bridging studies of one year duration.

It is important that more detailed guidance on the use of risk factors to guide selection of patients for clinical studies is provided. It is suggested that an appropriate algorithm should be included or referenced. As a result of a lack of clarity on the use of risk factors to determine patients at risk of fracture, the guideline is currently unclear as to which patients may be included in clinical studies (e.g. osteopenic patients). This, along with the proposed indication statement, may limit treatment to patients who are considered osteoporotic in terms of BMD rather than osteopenic patients where a large proportion of fragility fractures occur. As a result, the removal of the prevention claim is an issue. As most fractures occur in non-osteoporotic women, the proposed guideline would put postmenopausal women at risk of developing fractures and the end effect would be to increase the economic and social consequences of osteoporosis. Prevention of an initial fracture is paramount to the avoidance of subsequent fractures. In addition, the need to specify ‘high’ risk of fractures is questioned; such undefined categorisation of risk is of no clinical relevance in practice and is likely to cause confusion in the marketplace between existing and future registered osteoporosis treatments.

Further guidance on the development of medicinal products for secondary osteoporosis is recommended.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION: EXECUTIVE SUMMARY			
Line no ³³ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
General p.3/10	The WHO Report with definition of Osteoporosis should be included in the list of references.		The WHO Report has been referenced in the text
GUIDELINE SECTION: INTRODUCTION			
Line no ³⁴ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Paragraph 4 p.3/10	<p>It is noted that the draft Guideline is intended to cover primary osteoporosis only, and specifically excludes secondary osteoporosis arising from immobilisation, diseases (hyperthyroidism, hyperparathyroidism, rheumatoid arthritis) or drugs, especially glucocorticoid therapy and hormonal ablative therapies.</p> <p>Although it is agreed that the cascade leading to osteoporosis may be different from one disease to the other, the final outcome on the bone is still osteoporosis. Consequently, it is suggested that some of the conditions leading to secondary osteoporosis should also be included within this Guideline.</p>		Secondary osteoporosis is not within the scope of the present guidance document.

³³ Where available

³⁴ Where available

Paragraph 5 p.3/10	<p>Clarity is required on the definition of fracture risk. The text mentions how multiple risk factors contribute to the total risk of fractures, but does not give guidance how the risk can be quantified or which minimal risk factors should be taken into account as inclusion criteria.</p> <p>In addition, the set of independent risk factors for osteoporotic fractures varies between different sections of the guideline.</p>	<p>It is recommended that a core set of primary risk factors should be consistently used throughout the guideline, and that this set would include the following risk factors:</p> <ul style="list-style-type: none"> • Low BMD • Age • Family history of susceptibility to osteoporosis • Previous low-trauma fracture • Low Body Mass Index 	<p>The core set of primary risk factors has been revised and consistently used throughout the guideline document.</p>
Paragraph 7 Lines 7-11 p.4/10	<p>A set of lifestyle-related risk factors such as low dietary calcium, vitamin D or protein, smoking and excessive alcohol consumption have no longer been considered in detail in the current guideline draft. It may be important to consider these secondary risk factors as well in a consistent manner.</p>		<p>Secondary factors and life habits have not been included as primary risk factors but calcium and Vitamin D are mentioned in the <i>Introduction</i>.</p>
Paragraph 9 p. 4/10	<p>Calcitonin is missing in the list of products that are registered for the treatment of osteoporosis, with demonstrated anti-fracture efficacy. The sentence should be amended as indicated.</p>	<p><i>“These products include bisphosphonates with daily to monthly dosing formulations, calcitonin, selective oestrogen receptor modulators, teriparatide, and strontium ranelate.”</i></p>	<p>Calcitonin has been included in the list of products that are registered for the treatment of osteoporosis.</p>

<p>General p. 4/10</p>	<p>The proposed indication statement, “<i>the treatment of osteoporosis in postmenopausal women at high risk of fracture</i>”, would lead to the elimination of therapy to many osteopenic patients in whom the prevention of osteoporosis is appropriate.</p> <p>Following menopause there is a rapid loss of bone tissue, which results in declining bone architecture and hence quality. The changes in bone quality, which are observed in early postmenopausal women and other conditions associated with a loss of bone structure and bone quality lead to an increased risk of fracture.</p> <p>The proposed changes would result in an increased number of patients with primary fractures and hence an increased number of patients with subsequent fractures.</p>	<p>Unless further detail is provided on the use of risk factors to determine patients at risk of fracture (see Section 1. Introduction, and Section 4. Clinical Trials), and the indication statement amended as proposed below (Section 2. Aim of Treatment), prevention of osteoporosis must be retained as a therapeutic indication for those patients at risk of losing bone architecture and quality as indicated by BMD and bone turnover.</p>	<p>Further guidance has been provided for the range of risk considered as acceptable.</p>
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1 Introduction + 2 Aim of Treatment p.3-4/10	<p>The old guidance exempted oestrogens from the general rule that a drug must be approved for treatment of osteoporosis first before it can be submitted for prevention of osteoporosis. The reasons for this exemption are obvious:</p> <p>Oestrogen depletion is the main physiological factor for the development of postmenopausal osteoporosis and oestrogen treatment results in clinically relevant increases in BMD and decreases in bone turnover. Since the former guideline was adopted by the CPMP, the data for estrogens is even stronger. The Women's Health Initiative Study clearly demonstrated fracture prevention at the spine, the hip and other non-vertebral sites. Despite this strong evidence, the new guideline increases the regulatory hurdles for oestrogens. It is considered that the request to show anti-fracture efficacy in a large clinical trial for every new oestrogen preparation unscientific and unethical.</p>	As in the old guideline, oestrogens should be exempted from the need to show anti-fracture efficacy.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .
GUIDELINE SECTION: AIM OF TREATMENT			
Line no ³⁵ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Line 1-4 p.4/10 (and section 4.2 final paragraph p.6/10)	<p>The proposal for the indication statement is considered potentially problematic. The proposed terms may confuse prescribers.</p> <p>In contrast with the intention of the revised guideline, the proposed indication statement may be interpreted by prescribers to mean that only a subset of osteoporotic patients with a particularly high risk of fracture may be eligible for treatment with the given drug, e.g. those with particularly low BMD. "High" is a relative term which is subject to interpretation and is of no clinical relevance. In order to ensure that prescribing physicians are aware that a product is intended for the treatment of patients who meet the WHO criteria for both osteopenia and osteoporosis, it is recommended that the indication statement does not refer to the "treatment of osteoporosis" but instead to the treatment of patients "at risk of fragility and osteoporotic fractures."</p> <p>A definition of the risk for osteoporotic fracture, such as the one under preparation by the WHO, should be provided in section 5.1 of the SPC of all medicinal products with this indication.</p>	<p>"From the regulatory viewpoint, the therapeutic indication will generally be the treatment <i>of postmenopausal women at increased risk of osteoporotic or fragility fracture</i>, or, secondarily, the treatment of men <i>at increased risk of osteoporotic or fragility fracture</i>."</p>	Endorsed and corrected in the guidelines.

³⁵ Where available

Line 4 p.4/10	The guideline appears to require that an effect of the investigated medicinal product on both spinal and non-spinal fractures be demonstrated and is considered problematic when taking into consideration the effect of the proposal on clinical trial design, size and duration. If the intention of the guideline is that the effects of the medicinal product on both spinal and non-spinal sites should be “investigated”, rather than “demonstrated”, this should be clarified (see proposed change).	It is proposed that the sentence should be amended to read “ <i>The applicant should investigate the effect of the medicinal product on both spinal and non-spinal fractures</i> ”	In order to get the full indication, the applicant should demonstrate the effect...
Line 6 p.4/10	Please use the non-spinal fracture categories that can be studied consistently throughout the guideline. Section 4.3.1 states that “vertebral (clinical or morphometric) fractures and non-vertebral (hip, all non-vertebral or major non-vertebral) fractures are to be studied.” Whereas, sections 2. and 4.2 make no reference to the “all non-vertebral” fracture grouping.		“All non-vertebral fractures” have been removed from section 4.3.1
Line 6 p.4/10	In the list of major non-vertebral fractures, the distal forearm or wrist fracture has been omitted. Fractures of the wrist (Colles’ fractures) are common among the middle-aged and elderly. For European women, the lifetime risk of a wrist fracture is approximately 15%, a similar risk than hip fractures, and about 20% of 70-year-old women have had at least one wrist fracture. Moreover, Colles’ fractures carry a high absolute risk for subsequent hip and spinal fractures. Distal forearm or wrist fractures are painful, usually require one or more reductions and need 4-6 weeks in plaster to establish union. A proportion of patients do not recapture function without physiotherapy. There is a high incidence of algodystrophy after wrist fractures (30%) which gives rise to pain and tenderness, stiffness, swelling and vasomotor disturbances.	Include wrist fractures in the list of major non-vertebral fractures in Section 1. line 6 and Section 2. line 6 “...major non-vertebral (wrist , pelvis, distal femur, proximal tibia, ribs, proximal humerus and hip)...”	Forearm fractures have been added to the list of major non-vertebral fractures.

Line 8 p.4/10	<p>The therapeutic indication granted should not be restricted by the specific efficacy fracture endpoint data demonstrated in the clinical trials.</p> <p>Osteoporosis can be summarised as a generalised skeletal disorder which is not skeletal site specific and an indication for postmenopausal osteoporosis or male osteoporosis cannot therefore be further defined by skeletal site and nor, therefore a treatment for postmenopausal osteoporosis be skeletal site specific.</p> <p>The example of the bisphosphonate class illustrates that fracture efficacy is likely to exist at vertebral and non-vertebral sites, even if it has only been demonstrated at one specific site. The bisphosphonates have all been shown to increase bone mineral density (BMD) at multiple skeletal sites and reduce the risk of vertebral fractures. Although many studies of bisphosphonates fail to demonstrate non-vertebral or hip fracture efficacy in the overall population, sub-analyses of high-risk cohorts indicate efficacy at these sites (McClung et al, 2003; Reginster et al, 2005; Chesnut et al, 2004). These results indicate that the effects of any bisphosphonate upon bone are not limited to one site and that the overall population analysis can be misleading.</p> <p>Accordingly, the demonstration of anti-fracture efficacy at, at least, one site (spinal or non-spinal) and no deleterious effect, in terms of either BMD or anti-fracture efficacy, shown at another skeletal site(s) should therefore be sufficient for the approval of an unrestricted indication for the treatment of postmenopausal/male osteoporosis.</p> <p>The inclusion of site specific efficacy endpoint data in the SPC section on “Pharmacodynamic Properties” is supported.</p>		The wording has been amended
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GUIDELINE SECTION: PRE-CMINICLA STUDIES			
Line no ³⁶ . + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Section 3.1 Lines 2-5 p. 5/10	The guideline states that “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 adults ovariectomised rat and the other an animal with oestrogen deficiency” The choice of animal models should be left to the applicant.	“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 animal models, one of which could should be the adult ovariectomised rat and the other an animal with oestrogen deficiency”	Adult ovariectomised rat remains a mandatory model
Section 3.1 Line 5 p.5/10	The sheep is not considered a suitable animal model. To our knowledge, it has not proven of much usefulness so far except with Fluor. In addition, sheep bone metabolism is subject to seasonal variation which makes it an idiosyncratic model		The sheep has been considered as an appropriate model in some particular cases.
Section 3.1 Line 7 p.5/10	Paragraph 3.1, last sentence: the word "extensively" should be deleted as it does not add value except, perhaps, in toxicology studies.		Removed.
Section 3.2 Paragraph 1 p.5/10	Paragraph 3.2: requesting studies of at least 6 remodeling cycles may not be relevant in the rat for this species does not have remodeling cycles.	The sentence could read: “ <i>Studies should be of a long enough duration to ensure their objectives are fully met e.g. 6 remodeling cycles in relevant species.</i> ”	Accepted.

³⁶ Where available

Section 3.2 Paragraph 3 Lines 6-7 p.5/10	<p><i>“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.”</i></p> <p>Same comments as for section 3.1 above: The choice of animal models should be left to the applicant.</p>		See above.
GUIDELINE SECTION: CLINICAL TRIALS			
Line no³⁷. + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Section 4.2 Paragraph 1 Line 2 p.5/10	Reference is made to “the individual 10-year fracture risk”. The individual 10-year fracture risk in section 1 should be defined and the relative weighting of risk factors clarified. The use of, or reference to, an appropriate algorithm is recommended.		Further guidance has been provided for the range of risk considered as acceptable.
Section 4.2 Paragraph 1 Lines 3-7 p.5/10	<p>The definition of patients at high risk of fracture as it is expressed in the current draft is incomplete. The burden of choosing the appropriate criteria is fully on the applicant. A more clear and consistent definition of the criteria is considered to be an important piece of guidance which should be included in the revised guideline. Such guidance is in preparation by the WHO and its inclusion into the final guideline text is recommended.</p> <p>The set of independent risk factors for osteoporotic fractures varies between different sections of the guideline (see comment to section 1).</p>	A core set of primary risk factors should be consistently used throughout the guideline (see section 1).	A core set of primary risk factors has been consistently used throughout the guidelines and further guidance has been provided for the range of risk considered as acceptable.
Section 4.2 Paragraph 2 p.5/10	<p><i>“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).”</i></p> <p>The text mentions how multiple risk factors contribute to the total risk on fractures, but does not give guidance how the risk can be quantified or which minimal risk factors and their proper quantification should be taken into account as inclusion criteria.</p>		See above

³⁷ Where available

Section 4.2 Paragraph 2 & 3 p.6/10	The draft guideline requires that patient populations studied should be stratified according to their basal risk for fractures and “consistency of the effects for the whole range of levels of risk should be evaluated.” It is not clear whether the requested inclusion “in a specific trial [of] patients with a similar basal risk for fractures” should be based on the presence of a similar set of risk factors, or on a similar calculated overall fracture risk. Confirmation of the range of levels to be investigated is sought; along with the inclusion criteria for each risk level. For instance, would the demonstration of comparable efficacy in two risk level populations be acceptable to gain a broad treatment claim?		This has been clarified in the guidelines.
Section 4.2 Paragraph 4 Line 1 p.6/10	The draft guideline states that “it is the applicants responsibility to provide substantial evidence confirming the validity of the chosen independent risk factor(s)”. Depending on the algorithms used to define a risk of fracture, individual risk factors may be weighted differently. Further information on the measures/substantial evidence required to confirm the validity of the risk factors chosen by the applicant are requested, along with an indication of which risk factors are currently considered validated by the CHMP.		A core set of primary risk factors has been consistently used throughout the guidelines.
Section 4.2 Paragraph 4 p.6/10	<p>The reference to “national and international recommendations” is not helpful, as such recommendations may not be available, be subject to change, or be contradictory. It is expected that one such fracture risk index will be validated by the WHO in 2007. However, this index may not be available or finalised to guide clinical studies up to its release.</p> <p>The lack of a unified definition of factors constituting a high fracture risk is considered especially problematic in respect to its regulatory outcomes, and in respect to medical and reimbursement practice.</p> <p>As the definition of a valid set of risk factors is left to the applicant, differing definitions of “high risk populations” are likely to result. This in turn may lead to poorly comparable populations being studied by different applicants. This is not only a concern in respect to the validity of the results of a given trial. It is also of concern if and how the population that has been studied will be reflected in the labelling.</p> <p>It is recommended that a definition of the risk for osteoporotic fracture, such as the one under preparation by the WHO, be provided in section 5.1 of the SPC of all medicinal products with this indication.</p>		A core set of primary risk factors has been consistently used throughout the guidelines and further guidance has been provided for the range of risk considered as acceptable.

Section 4.3 General p.6/10	As the draft guideline is currently worded (lack of sufficient detail on the use of risk factors and the proposed indication statement), the omission of the prevention of osteoporosis indication is an issue.	Unless further detail is provided on the use of risk factors to determine patients at risk of fracture (see Section 1. Introduction, and Section 4. Clinical Trials), and the indication statement amended as proposed below (Section 2. Aim of Treatment), prevention of osteoporosis must be retained as a therapeutic indication for those patients at risk of losing bone architecture and quality as indicated by BMD and bone turnover.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication. The issue of ERT/HRT has been considered in the <i>Introduction</i> .
Section 4.3.1 Paragraph 1 Line 4-6 p.6/10	The requirement to study vertebral and non-vertebral fractures separately in confirmatory trials in the current guideline draft could be expressed more clearly. According to guideline CPMP/EWP/908/99, Points to Consider on Multiplicity Issues in Clinical Trials, multiple primary variables may be studied to demonstrate all clinically relevant treatment benefits. Clarification is needed on whether various types of fractures should be studied separately in <i>one trial</i> (as multiple primary variables) or separately in <i>separate dedicated trials</i> . It is recommended that both options be open to the applicant.	“Vertebral (clinical or morphometric) fractures and non-vertebral (hip, all non-vertebral or major non-vertebral) fractures are to be studied <i>as</i> separate <i>endpoints</i> in <i>a</i> confirmatory trial, <i>or in separate confirmatory trials</i> .”	This has been clarified in the document.

Section 4.3.1 Paragraph 1 p.6/10	The following change to the description of how the primary variable should be expressed is proposed.	“The primary variable should be assessed as incidence of patients with new fractures, which may be expressed as vertebral fractures, hip fractures or as a composite of hip fractures and the rest of all or major non vertebral fractures.”	This has been clarified in the document.
Section 4.3.2 Line 2-3 p.6/10	<p><i>“The current usual method for assessing BMD is dual energy X-ray absorptiometry. For all techniques, instrument precision and accuracy are very important.”</i></p> <p>New techniques that have become available, such as pQCT and micro-CT, may be more informative than DEXA and should be included as options.</p>	<i>“The current usual method for assessing BMD is dual energy X-ray absorptiometry, although alternative technologies such as pQCT and micro-CT may be used. For all techniques, instrument precision and accuracy are very important.”</i>	BMD remains, in the opinion of the Agency, the appropriate technique to measure bone quantity.

GUIDELINE SECTION: STUDY DESIGN			
Line no ³⁸ + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Outcome
Section 5.2 Paragraph 1 Line 1 p.8/10	<p>“A parallel-group, fixed dose, double-blind, <u>placebo-controlled</u> study design should be used in Phase II....”</p> <p>Placebo-controlled studies in this patient population are often not considered acceptable from an ethical point of view.</p>	<p>Placebo-controlled studies should only be conducted if justified. Therefore, the following wording is proposed: “A <i>parallel-group, fixed dose, double-blind study including at least three doses of active should be used in Phase II.</i> <i>Whenever possible, the study should be placebo controlled.</i>”</p>	Placebo-controlled study remains the gold standard in Phase II
Section 5.2 Paragraph 3 Lines 9-10 p.8/10	The definition of responders re biochemical markers based on robust scientific evidence does not provide guidance to sponsors; further clarification is requested.		Defining a responder in biochemical markers, based on robust scientific evidence, is left at the appreciation of the applicant.

³⁸ Where available

<p>Section 5.3.1 Paragraph 1 Line 1 & Paragraph 2 Line 1 p.8/10</p>	<p><i>“Parallel-group, double blind, <u>placebo-controlled</u> and /or comparator-controlled studies are necessary.... In principle, <u>placebo-controlled</u> trials will be requested. However, if properly justified, non-inferiority trials versus active comparators could be considered if a clear justification of the margin”</i></p> <p>Placebo-controlled studies in this patient population are often not considered acceptable from an ethical point of view. In addition, this requirement is especially problematic in the context of non-vertebral fracture studies. A placebo-controlled study design to measure hip fracture reduction is no longer acceptable because it would involve putting patients at high risk of non-vertebral, including hip fracture on placebo when there are several effective medications approved. On the other hand, a non-inferiority trial including an active treatment with proven hip fracture efficacy as a comparator would not be feasible as it would require tens of thousands of high-risk patients to be enrolled. Indeed, there are examples of products currently approved for the treatment of post-menopausal osteoporosis, where post-hoc analyses have been applied to demonstrate fracture efficacy at non-vertebral sites. Examples of these are subgroup analyses in patients at high risk for hip fractures or pooling of hip fracture data between doses and or studies.</p>	<p>Non-inferiority studies are considered the better choice in this case and the following wording is therefore proposed:</p> <p><i>“... In principle, placebo-controlled trials should be performed whenever possible. Non-inferiority trials versus active comparators should be considered if a clear justification of the margin...”</i></p> <p>Given the challenges outlined above of conducting adequately controlled clinical trials to demonstrate efficacy at non-vertebral sites, properly conducted post-hoc analyses are considered to be an appropriate alternative to fulfil this requirement.</p>	<p>Included in the document.</p>
<p>Section 5.3.1 Paragraph 2 Lines 6-7 p.8/10</p>	<p>The draft guideline states that “in case of a placebo-controlled superiority trial, the relevance of the findings, compared to currently registered medications, might have to be established”. The Notice to Applicants, Volume 2B and associated CHMP and ICH guidelines require the applicant to demonstrate the safety and efficacy of the product and to provide support for the proposed indication and prescribing information. An assessment of the benefits of the product in comparison to competitors is not stipulated. Hence notwithstanding the comments made previously, where placebo-controlled superiority trials have been performed, an ad-hoc evaluation of the results compared to competitor trials should not be a requirement for registration.</p>	<p>The following sentence “Similarly, in the case of a placebo-controlled superiority trial, the relevance of findings, compared to currently registered medications, might have to be established” should be deleted.</p>	<p>Maintained in the document.</p>

Section 5.3.2 General p.9/10	It is proposed that the title of this section is changed in line with comments made on Section 2. Aim of treatment.	The title should be “Treatment of postmenopausal women at increased risk of osteoporotic or fragility fracture”.	Endorsed and corrected.
Section 5.3.2 Paragraph 1 Line 2 p.9/10	The draft guideline states that “the primary variable should be the incidence of patients with new fractures”. The guideline should clarify that this is specific to the target site (e.g. vertebral fractures) and that additional sites (e.g. all non-vertebral fractures) can be secondary endpoints.	The following is recommended: “The primary variable should be the incidence of patients with new fractures at the target site(s) (e.g. vertebral fractures). Fractures at additional sites (e.g. all non-vertebral fractures) and BMD from areas studied for fracture incidence are important secondary variables”	See above
Section 5.3.2 Paragraph 3 Lines 2-3 p.9/10	<i>“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.”</i> It should be clarified if the follow-up data is required for both vertebral and non-vertebral data, or if only non-vertebral data is sufficient.		Amended in the document.
Section 5.3.2 Paragraph 4 p.9/10	The need for data on bone loss after withdrawal of treatment is noted. It is proposed that this is performed in a subset of patients and that this data may be submitted after registration. These data are generally generated from long term observation of pivotal trial populations. A requirement to submit these data at the time of filing may lead to delays in access to innovative treatments to patients	“Catch up bone loss after withdrawal of treatment has been described with some drugs. Data that show what occurs after withdrawal <i>may be submitted after registration.</i> ”	Clarified.

Section 5.3.3 General p.9/10	<p>For agents that have demonstrated anti-fracture efficacy, BMD should be an acceptable primary endpoint for the</p> <ul style="list-style-type: none"> • Indications in men • Indication of treatment and prevention of glucocorticoid-induced osteoporosis and bone loss due to other therapies (<i>outside the scope of this guidance</i>) • New dosage regimens i.e., once weekly, once monthly • New routes of administration 		Secondary osteoporosis falls outside the scope of this guidance.
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<p>Section 5.3.3 General p.9/10</p>	<p>Bone biochemical markers should be clearly identified as acceptable end points in bridging studies for compounds with demonstrated anti-fracture efficacy.</p> <p>Although bone biochemical markers such as urine or serum c-telopeptide of type I procollagen (CTX) have not clearly demonstrated surrogacy in terms of a causal link for long-term endpoints, their predictive value is considered not to be inferior to the accepted marker, BMD, for compounds with established efficacy and clinically established change patterns of these markers during therapy.</p> <p>Significant correlation between the reduction of bone turnover as assessed by bone biochemical markers and fracture reduction was seen with various antiresorptive treatments, showing even higher fracture predictive value for these markers than for BMD. After 6 months of raloxifene therapy, changes in bone turnover markers were associated with the risk of subsequent vertebral fracture, whereas changes in BMD were not [Bjarnason 2001]. During risendronate therapy, changes in bone biochemical markers after 3 and 6 months explained 50–70% of the reduction in vertebral fractures and 54–74% of the reduction in nonvertebral fractures [Eastell 2003]. A study of alendronate found that the risk of vertebral fractures over nearly 4 years was significantly correlated with 1-year decreases in bone biochemical markers [Bauer 2002]. On the other hand, markers of increased bone turnover (which is interpreted as referring to biochemical markers) are accepted as being indicative of fracture risk throughout the guideline text. (see section 1).</p>	<p>It is recommended that section 5.3.3. be rephrased as follows:</p> <p>5.3.3. Bridging studies</p> <p>For compounds having demonstrated anti-fracture efficacy and for which the indication <i>“treatment of postmenopausal women at increased risk of osteoporotic or fragility fracture treatment of osteoporosis in postmenopausal women at high risk of fracture”</i> 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 are also acceptable in bridging studies after a thorough analysis of historical</p>	<p>The initial wording is kept.</p>
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Section 5.3.3 Paragraph 1 Lines 1-6 p.9/10	<i>“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, 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..... in a study of a minimum one year”.</i>	<i>“For compounds having demonstrated anti-fracture efficacy and/OR for which the indication “treatment of osteoporosis in postmenopausal women at high risk of fracture” has been previously granted for a specific dose, 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..... in a study of a minimum one year”.</i>	<u>And</u> is the appropriate wording.
Section 5.3.4 Bullet 4 p.10/10	The term ‘globally proportional to the decreased incidence of fractures in treated women’ is confusing, but could be interpreted as a comparison should be made across all internationally conducted clinical trials in post-menopausal women. If this is not the intent then this should be reworded.	‘ the magnitude of the changes in BMD versus placebo is similar to that observed in postmenopausal osteoporotic women treated with the same compound in Internationally conducted clinical trials and is globally proportional to the decreased incidence of fractures.	Corrected

<p>Section 5.3.4 Last paragraph p.10/10</p>	<p>In the section 5.3.4. where the requirements for granting a marketing authorization for treatment of osteoporosis in males is described the following sentence is included:</p> <p><i>“If ... , or 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.”</i></p> <p>Assuming that CHMP uses the term “hormonal” here in the context of sex hormones, we believe that the actual wording of this sentence is different from its intent.</p> <p>Several osteoporosis agents are derived from natural hormones other than sex hormones (e.g. calcitonin, PTH derivatives, etc). In these cases, gender specific differences in antifracture efficacy are not expected, and there is no rationale for requiring a separate fracture endpoint study in males. Therefore, it is suggested that this requirement is limited to those NCEs where a gender specific mechanism of action is expected.</p>	<p><i>"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."</i></p>	<p>Corrected.</p>
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**SUBMISSION OF COMMENTS ON GUIDELINE ON THE EVALUATION OF NEW MEDICINAL PRODUCTS IN THE TREATMENT OF
PRIMARY OSTEOPOROSIS (CPMP/EWP/552/95 REV.2)**

COMMENTS FROM THE BRITISH MENOPAUSE SOCIETY		
GENERAL COMMENTS - OVERVIEW		
	Comment and Rationale	Outcome
	It is accepted that bone mineral density (BMD) is only one of the risk factors for the development of osteoporosis and osteoporotic fracture. Other factors should be considered, such as age, family history, and previous medical conditions or medications. The WHO instrument for identification of individuals at increased risk for osteoporotic fracture is awaited, which may improve such identification.	Included.
	Stratification of BMD values according to age may be of some help in this identification, but practical considerations are also necessary. There seems little point in determining a 10-year fracture risk in individuals aged 80 years whose life expectancy may be very limited. The concept of only instigating treatment in those who have developed the disease, and in many cases have demonstrated the clinical manifestations, namely osteoporotic fracture, runs counter to good medical practice, irrespective of potential financial savings. Patients who have sustained an osteoporotic fracture are at much higher risk of new fracture than those who have not. But equally, intervention with therapy in those who have sustained a fracture does not reduce the risk of new fracture to that level seen in those who have not yet sustained any fracture. Thus all current treatments for established osteoporosis are not ideal. The burden of suffering from new fractures will continue. Hence prevention of osteoporosis, before fracture has occurred, is paramount.	This reasoning is embraced in the guideline. Both patients with and without prior fractures can be included in clinical trials. Various risk factors should be taken into account.
	An analogy is found in hypertension. Blood pressure measurement is a weak surrogate for risk of clinical events such as myocardial infarction and stroke, both of which increase with age. However, it is not acceptable practice to wait for the occurrence of such clinical endpoints in patients with hypertension before instigating treatment. Nor is it acceptable practice to delay treatment in hypertensives of younger age just because their absolute risk of clinical events is lower.	This comment is noted.
	The indication of prevention of osteoporosis is still essential, and this is particularly relevant in patients with increased risk for the disease, and hence future fracture, irrespective of age. Whilst the major goal in the management of osteoporosis is fracture prevention, reduction in bone structural quality due to disruption of the bone micro-architecture must be prevented as this leads to the increased risk of fracture. For example, a reduction in bone density of two standard deviations, even if BMD remains above the T-score threshold of osteoporosis, may indicate severe disruption of the micro-architecture and loss of trabecular structures irrespective of age. An example of this could be seen in women with premature menopause, who are then at increased risk for future fracture. The prevention of osteoporosis indication	This argumentation to maintain the “prevention” indication is not accepted. What matters is the level of risk of fracture.

	allows intervention to maintain the skeletal microstructure, thereby reducing the risk of the first fracture from occurring. This in turn reduces the overall risk of fractures. Without this indication, women who warrant preventive treatment, such as those with premature menopause, will be denied such treatment by clinicians who are not familiar with the issues involved.	
	Treatments for osteoporosis must be demonstrated to result in prevention of fractures, and preferably osteoporotic fractures at all skeletal sites. Appropriate studies can be designed to demonstrate this, as recommended in the proposals. Treatments for prevention of osteoporosis must be demonstrated to prevent bone loss, and preferably reduce fracture incidence at all sites. Again appropriate studies can be designed to demonstrate this. Failure to retain the prevention of osteoporosis indication will lead to an overall increase in fractures, and will impact on both quality of life and duration of life in those with an otherwise meaningful life expectancy duration.	This argumentation to maintain the “prevention” indication is not accepted. What matters is the level of risk of fracture.
	The British Menopause Society requests that the indication of prevention of osteoporosis be retained without compromise.	Since the aim of any anti-osteoporosis intervention is to reduce fracture, it has been considered inappropriate to maintain prevention of early postmenopausal bone loss as an indication.