



## *The Alliance for Better Bone Health*

Procter & Gamble Pharmaceuticals UK Ltd.,  
Rusham Park Technical Centres, Whitehall Lane, Egham, Surrey TW20 9NW  
Telephone: 01784 474900 Fax: 01784 474722

Dr Cathryn Fuller  
Technology Appraisal Project Manager  
NICE  
MidCity Place  
71 High Holborn  
London  
WC1V 6NA

19<sup>th</sup> August 2005

### *Addendum to Assessment Report*

#### **The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women**

Dear Dr Fuller,

The Alliance for Better Bone Health recognise the importance of the new modelling that has been performed and believe it is important to ensure that all the osteoporosis Guidance documents are harmonised.

We are concerned by some of the modelling assumptions that are present in the Addendum as these are all issues that have arisen in previous Assessment Reports, which have subsequently been rectified in the Appraisal Consultation Document. Thus, we seek reassurance that these issues will be dealt with as on previous occasions. Despite our concerns with some assumptions in the Assessment Report (tabulated below), we feel confident that the Committee will be able to issue the following Guidances (given a willingness to pay threshold between £20 - 30,000 per QALY).

#### **Primary Prevention Guidance**

- 1.1 Bisphosphonates (alendronate, etidronate and risedronate) are recommended as treatment options for the primary prevention of osteoporotic fragility fractures:
- in women aged between 50 and 64 years of age, if they have a very low bone mineral density (T-score of approximately  $-3$  SD or below, or if they have confirmed osteoporosis plus one, or more, additional age-independent risk factor: low body mass index ( $< 22.5$  kg/m<sup>2</sup>); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; certain medical disorders independently associated with bone loss (such as chronic inflammatory bowel disease, rheumatoid arthritis, hyperthyroidism or coeliac disease); conditions associated with prolonged immobility.
  - in women aged 65 and older if the presence of osteoporosis is confirmed by DEXA scanning, and
  - in women aged 65 and older, if they have low bone mineral density (T-score of approximately  $-2$  SD or below) plus one, or more, additional age-independent risk factor: low body mass index ( $< 22.5$  kg/m<sup>2</sup>); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; certain medical disorders independently associated with bone loss (such as chronic inflammatory bowel disease, rheumatoid arthritis, hyperthyroidism or coeliac disease); conditions associated with prolonged immobility.





### *The Alliance for Better Bone Health*

Procter & Gamble Pharmaceuticals UK Ltd.,  
Rusham Park Technical Centres, Whitehall Lane, Egham, Surrey TW20 9NW  
Telephone: 01784 474900 Fax: 01784 474722

- 1.2 In their choice of bisphosphonate, clinicians and patients need to balance the drug's overall proven effectiveness profile against tolerability and adverse effects in individual patients.
- 1.3 Raloxifene and strontium ranelate are recommended as an alternative treatment option, under the circumstances specified in Section 1.1, in women:
- for whom bisphosphonates are contraindicated (see Summaries of Product Characteristics), or
  - who are physically unable to comply with the special recommendations for use of bisphosphonates, or
  - who have had an unsatisfactory response to bisphosphonates, or
  - who are intolerant of bisphosphonates.
- 1.4 Teriparatide is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

#### **Secondary Prevention Guidance**

1. Bisphosphonates (alendronate, etidronate and risedronate) are recommended as treatment options for the secondary prevention of osteoporotic fragility fractures:
- in women aged 75 years and older, without the need for prior dual energy X-ray absorptiometry (DEXA) scanning
  - in women aged between 65 and 74 years if the presence of osteoporosis is confirmed by DEXA scanning, and
  - in postmenopausal women younger than 65 years of age, if they have a very low bone mineral density (BMD, that is with a T-score of approximately  $-3$  SD or below\*, established by a DEXA scan), or if they have confirmed osteoporosis plus one, or more, additional age-independent risk factor: low body mass index ( $< 19 \text{ kg/m}^2$ ); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; certain medical disorders independently associated with bone loss (such as chronic inflammatory bowel disease, rheumatoid arthritis, hyperthyroidism or coeliac disease); conditions associated with prolonged immobility.
2. In their choice of bisphosphonate, clinicians and patients need to balance the drug's overall proven effectiveness profile against tolerability and adverse effects in individual patients.
3. Raloxifene and strontium ranelate are recommended as alternative treatment options, under the circumstances specified in Section 1.1, in women:
- for whom bisphosphonates are contraindicated (see Summaries of Product Characteristics), or
  - who are physically unable to comply with the special recommendations for use of bisphosphonates, or
  - who have had an unsatisfactory response to bisphosphonates, or
  - who are intolerant of bisphosphonates.





*The Alliance for Better Bone Health*

Procter & Gamble Pharmaceuticals UK Ltd.,  
Rusham Park Technical Centres, Whitehall Lane, Egham, Surrey TW20 9NW  
Telephone: 01784 474900 Fax: 01784 474722

4. Teriparatide is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in women aged 65 years and older who have had an unsatisfactory response to bisphosphonates or intolerance to bisphosphonates, and:
- who have an extremely low BMD (with a T-score of approximately -4 SD or below), or
  - who have a very low BMD (with a T-score of approximately -3 SD or below) plus multiple fractures (that is, more than two) plus one, or more, additional age-independent risk factor: low body mass index (< 19 kg/m<sup>2</sup>); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; conditions associated with prolonged immobility.

Attached are our comments on the Addendum to the Assessment Report. Our comments relate to the assessment of both risedronate (on behalf of the Alliance for Better Bone Health) and also etidronate (on behalf of Procter & Gamble Pharmaceuticals UK Ltd). Whilst we welcome the Addendum to the Assessment Report, we believe that there are several concerns that need to be addressed before NICE can finalise the recommendations. Our concerns relate to both primary prevention and secondary prevention of osteoporosis:

| CATEGORY           | ISSUE   | PAGE NUMBER            | PROPOSED RESOLUTION  |
|--------------------|---|------------------------|--|
| Cost effectiveness | <p><b>Inappropriate inclusion of Raloxifene's breast cancer reducing effect.</b><br/>The inclusion of raloxifene's effect on breast cancer is inappropriate for several reasons:</p> <p>1. It is contrary to the previous Committee decision during the assessment of 'Osteoporosis - secondary prevention', Section 4.3.14, where the Committee noted 'that the breast cancer benefit should not be the sole factor in deciding whether raloxifene is a cost effective option for the treatment of osteoporosis.</p> <ul style="list-style-type: none"><li>• From the evidence presented, raloxifene was not as effective as bisphosphonates for treating osteoporosis.</li><li>• Raloxifene's effect on the prevention of breast cancer has not been assessed by the regulatory authorities.</li><li>• The long-term risks of raloxifene treatment beyond 8 years are uncertain.</li><li>• Full assessment of raloxifene's effect on the prevention of breast cancer and its cost effectiveness in this indication would require consideration of how it compares with other drugs that potentially could be used for the prevention of breast cancer.'</li></ul> | N/A<br>General comment | The effect of raloxifene on breast cancer should not be given further consideration in the assessment of raloxifene's cost effectiveness for osteoporosis. |





*The Alliance for Better Bone Health*

Procter & Gamble Pharmaceuticals UK Ltd.,  
Rusham Park Technical Centres, Whitehall Lane, Egham, Surrey TW20 9NW  
Telephone: 01784 474900 Fax: 01784 474722

|                               |  |                        |   |
|-------------------------------|--|------------------------|---|
|                               | <p>2. To include such an effect would be out of the original scope and unethical considering that in this patient population there is an inverse correlation between the incidence of breast cancer and that of low BMD.</p> <p>3. In the previous assessment of 'Osteoporosis – secondary prevention' the NICE appeal panel rejected Lilly's appeal that raloxifene's effect on breast cancer should be fully considered as part of the products cost effectiveness in the treatment of osteoporosis.</p>   |                        |   |
| <b>Clinical effectiveness</b> | <p><b>Inappropriate optimal ranking within the bisphosphonate class.</b></p> <p>There are no head to head fracture trials involving bisphosphonates. A thorough analysis of the data from the bisphosphonate studies has shown that the different study designs, heterogenous populations, different Ca/Vit supplementation, different classifications for fractures, dose switching in the alendronate studies and age of the etidronate studies mean that in the absence of robust well designed head to head fracture studies, the existing data is too similar with overlapping confidence intervals to permit any within class optimal ranking. Thus, it would be inappropriate to differentiate between the bisphosphonates in the textual summary or in in-text tables that could be used out of context.</p> <p>In addition it would appear erroneous to rank products when the relative risks for risedronate appear to be incorrect.</p> | N/A<br>General comment | Remove optimal ranking of bisphosphonates in the text and tables and present the data for each product with the caveats that bisphosphonates should be considered as a class. |
|                               | <p><b>Unexplained change in the efficacy estimates for risedronate.</b></p> <p>Without any scientific justification the efficacy estimates (relative risk) for risedronate have been altered from the value of 0.66 used in the assessment report for the prevention and treatment of osteoporosis (2003, pg 56), to 0.74 for the hip, and 0.68 to 0.76 for the wrist.</p>   | Page 3, Table 1        | Provide an explanation and clarification for the change in fracture incidences or correct this error, as this negatively affects the cost effectiveness of risedronate.       |
|                               | <p><b>Exclusion of the effect of etidronate on hip and non-vertebral fractures.</b></p> <p>Etidronate is not credited with the data it has on hip and non-vertebral fracture risk</p>  | Page 3, Table 1        | Due to the age of this product it does not have the comprehensive data package to support it like risedronate and alendronate. However, as with                               |



*The Alliance for Better Bone Health*

Procter & Gamble Pharmaceuticals UK Ltd.,  
Rusham Park Technical Centres, Whitehall Lane, Egham, Surrey TW20 9NW  
Telephone: 01784 474900 Fax: 01784 474722

|  |   |   |
|--|---|---|
|  | <p>reduction, due to a lack of RCT data. However this ignores the decisions of the Committee in the Guidance on Osteoporosis - secondary prevention Section 4.3.7 ie 'The Committee heard from the clinical experts that although an effect of etidronate on non-vertebral fractures is likely, this effect is less pronounced than with alendronate and risedronate, the evidence base is weaker, and the mode of action is slightly different. However, given the lack of direct head-to-head comparisons, the Committee concluded that all of the bisphosphonates were treatment options for women with established osteoporosis who fulfil the criteria for treatment.'</p> | <p>the previous assessment on Osteoporosis –secondary prevention, it is reasonable to assume that since it has comparable vertebral efficacy to the newer bisphosphonates, and has demonstrated hip fracture risk reduction in a large well controlled GPRD study, that etidronate's non-vertebral and hip fracture efficacy estimates should be considered to be broadly similar to the other bisphosphonates.</p> |
|--|---|---|

If you have any questions relating to our comments, please don't hesitate to contact us.

Yours sincerely, on behalf of the Alliance for Better Bone Health and Procter & Gamble Pharmaceuticals,



**Dr Heert Eijkman**  
Medical Director – UK/NL/Ireland  
Procter & Gamble Pharmaceuticals  
Procter & Gamble Technical Centres  
Rusham Park  
Whitehall Lane  
Egham  
TW20 9NW



**Dr Alan Collins**  
NICE Project Manager  
Procter & Gamble Pharmaceuticals  
Procter & Gamble Technical Centres  
Rusham Park  
Whitehall Lane  
Egham  
TW20 9NW



**Mr Mike Baldwin**  
Head of Health Technology  
Appraisals  
Sanofi-aventis  
One Onslow Street  
Guildford  
Surrey  
GU1 4YS