*The Alliance for Better Bone Health*

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Dear Carole

**Final Appraisal Determination: secondary prevention of osteoporotic fragility fractures in postmenopausal women**

Thank you for the Final Appraisal Determination on alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. The Alliance for Better Bone Health, on behalf of sanofi-aventis and Procter & Gamble (The Alliance), wishes to appeal against this determination and the grounds for our appeal are outlined below.

**Executive summary**

*Appeal Ground 1 (The Institute has failed to act fairly and in accordance with the Appraisal Procedure set out in the 'Guide to the Technology Appraisals Process'):*

1. The focus on initiation of pharmacotherapy is inconsistent with the original scope for the appraisal, and the change in scope introducing this new focus is both inconsistent with the appraisal procedure and unfair.
2. The comparisons between individual bisphosphonates are inconsistent with the appraisal scope, unfair and not sufficiently transparent.

*Appeal Ground 2 (The Institute has prepared guidance that is perverse in the light of the evidence submitted):*

1. The recommendations are perverse because they do not take account of identifiable patient groups who cannot or should not receive alendronate as first line therapy.
2. The recommendations for bisphosphonate treatment are perverse because they are internally inconsistent, inconsistent with other technology appraisals and fail to recognise the clinical value of different dosage forms.
3. The focus on BMD is perverse because it is inconsistent with the remit to advise on "the prevention and treatment of osteoporosis and prevention of osteoporotic fractures" which requires a consideration of treatment effects that cannot be explained by BMD increases alone.

*Appeal Ground 3 (The Institute has exceeded its powers):*

The Alliance does not wish to submit an appeal based on this ground.

1. **<u>Appeal Ground 1</u> (The Institute has failed to act fairly and in accordance with the Appraisal Procedure set out in the 'Guide to the Technology Appraisals Process')**

*The focus on initiation of pharmacotherapy is inconsistent with the scope for the appraisal, and the change in scope introducing this new focus is both inconsistent with the appraisal procedure and unfair.*

- The original scope for the appraisal (August 2002) set the following objective:
  "To establish the clinical and cost effectiveness of SERMS, bisphosphonates, and parathyroid hormone (subject to licensing) for the prevention and treatment of osteoporosis and the prevention of osteoporotic fractures in post-menopausal women, and to provide guidance to the NHS in England and Wales."

  The subsequent scope relating to strontium ranelate (October 2004) set the following objective:
  "To establish the clinical and cost effectiveness of strontium ranelate... for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis, and to provide guidance to the NHS in England and Wales."

- The Institute's letter to consultees of 23rd February 2007 refers to a decision by the Appraisal Committee during the appraisal process to focus on initiation of pharmacotherapy only.

- The Alliance believes that this re-focus of the appraisal constitutes a change to the appraisal scope. We understand that such a change is inconsistent with the 'Guide to the Technology Appraisal Process'. Section 3.5 of the Guide states that the "final" scope is produced following comments on the draft scope and discussions at the scoping workshop. The only allowance for a change to the scope during the appraisal process itself is given in paragraph 6.1.7 of the 'Guide to the Methods of Technology Appraisal' which states that the Appraisal Committee may question the original remit or scope "if evidence is forthcoming during the appraisal". The Alliance has not been made aware of any evidence forthcoming during the recent course of the appraisal that would have supported the change in scope.

- Furthermore, the change in scope is unfair when it is a driver of "significant change" in the appraisal recommendations (Institute letter of 23rd February) and there has been no consultation with consultees regarding that change in scope.

*The comparisons made between different bisphosphonates are inconsistent with the appraisal scope, unfair and not sufficiently transparent.*

- The August 2002 scope stated that head to head comparisons of "classes of interventions" would be undertaken rather than comparisons between interventions within the same class. The recommendation of alendronate over other bisphosphonates is based on a within-class rather than a between-class comparison and is therefore inconsistent with the scope. Furthermore, Technology Appraisal No 87 in the secondary prevention of osteoporotic fragility fractures (January 2005), based on the same original scope, makes recommendations regarding the bisphosphonate class, not individual molecules within that class.

- Paragraphs 4.2.14 and 4.2.15 of the Final Appraisal Determination describe the inclusion of DXA scanning in the cost-effectiveness analysis. In the assessment of treatment alternatives, the inclusion of all scanning costs, rather than only those costs relating to women eligible for treatment, is unfair and inconsistent with the

approach adopted in other technology appraisals (eg. Technology Appraisal No 87 on osteoporotic fragility fractures and Technology Appraisal No 71 on coronary artery stents for ischaemic heart disease).

- Insufficient data have been presented throughout the appraisal process to allow consultees to understand how the recommendations have been reached. In particular, the economic models and the numerous changes to them have not been made available in any format, read-only or otherwise. As stated in the Alliance's response to the Appraisal Consultation Documents of October 2006, although Excel spreadsheets stripped of commercial and academic in confidence material were released, these provided only some of the model outputs upon which the recommendations have been based. As a result, the model has not been open to external scrutiny and the Alliance has not been able to assess the influence of each component of the modelling process and, ultimately, the relevance of those components to the Committee's decisions. We believe that this is inconsistent with reasonable expectations for valid consultation and that the process has therefore been unfair.

**2. <u>Appeal Ground 2</u> (The Institute has prepared guidance that is perverse in the light of the evidence submitted)**

*The recommendations are perverse because they do not take account of identifiable patient groups who cannot or should not receive alendronate as first line therapy.*

- Section 1 of the Final Appraisal Determination states that the recommendations do not cover women who are "contra-indicated to or, for whatever reason, have withdrawn from initial treatment". However, some women will be contra-indicated for the recommended treatment (alendronate) but not contra-indicated for risedronate treatment. This includes patients who:

  - Have abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia
  - Are unable to stand or sit upright for at least 30 minutes.

  It is perverse to deny initial treatment to these women by not offering risedronate as an alternative first line treatment.

- In addition, alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min. Risedronate by contrast is contraindicated in renally impaired patients where GFR is less than 30ml/min. It is perverse to deny initial treatment to women with GFR between 30ml/min and 35ml/min.

- The recommendations do not take account of key differences between the bisphosphonates in relation to their side-effects and the importance of these for specific groups of patients. Technology Appraisal No 87 on the secondary prevention of osteoporotic fragility fractures stated that "the choice of bisphosphonate may differ between patients and... clinicians and patients need to balance the individual drug's overall proven effectiveness profile against the tolerability and adverse effect profile when deciding which bisphosphonate to prescribe". There is strong evidence that the gastrointestinal side effect profile of risedronate is superior to alendronate. Not allowing patients who are likely to experience these side effects with alendronate to receive risedronate as an alternative is perverse when the cost-effectiveness analysis assumes the efficacy of the two drugs to be the same.

- The recommendations do not take account of patients who, in the opinion of their physician, would be unlikely to comply with the dosing instructions for alendronate treatment (eg. because of their inability to consume alendronate with the required volume of water, which is greater than for risedronate). This is perverse and inequitable.

*The recommendations for bisphosphonate treatment are perverse because they are internally inconsistent, inconsistent with other technology appraisals and fail to recognise the clinical value of different dosage forms.*

- The Assessment Group has used pooled alendronate and risedronate efficacy data, but the Committee has made recommendations focused on one molecule (alendronate) which is differentiated in the Assessment Group's model by cost alone. This is internally inconsistent (using pooled data to make a molecule-specific recommendation), and inconsistent with the approach adopted by NICE in relation to treatments considered at the class level in other appraisals (eg. Technology Appraisals No 43 for antipsychotics and No 94 for statins). In these other appraisals, consideration was given to acquisition cost but recommendations were not limited to one molecule. In the case of bisphosphonates, there is a narrower spread of prices than there was for statins and there are robust clinical data on different groups of patients that enable the various molecules to be distinguished on clinical grounds. If these data are ignored, it is perverse then to distinguish between the molecules on cost grounds.

- Paragraphs 4.2.16 and 4.2.18 - 4.2.20 of the Final Appraisal Determination refer to the cost effectiveness of alendronate with and without DXA scanning. The conclusions regarding the superiority of alendronate over risedronate are perverse given that the cost-effectiveness results are based on a specific price at which only one dosage form (weekly non-proprietary alendronate) is available. This limitation to the results of the modeling is not spelt out, and the recommendations are consequently misleading.

- In situations where the clinical assessment favours use of any other dosage form (eg. once a day (OAD) or alendronate combined with vitamin D), the costs will be higher than those assumed in the cost-effectiveness modeling and the statement that "risedronate has a greater acquisition cost than alendronate" (para 4.3.17) is untrue. The June 2007 NHS Drug Tariff price for alendronate OAD10mg (28 tablets) is £23.15 and for Fosavance 70mg/70 microgram (4 tablets) it is £22.80. Both these prices are higher than for risedronate 5mg OAD (28 tablets) which is priced at £19.10 and risedronate once a week 35mg (4 tablets) which is priced at £20.30. It is perverse to recommend only one molecule on the basis of cost when it does not offer the "lowest acquisition cost" (para 4.3.15) for clinically important dosage forms. It is equally perverse to restrict the availability of alternative dosage forms without making such a restriction explicit and providing substantiation for such a recommendation.

- Paragraph 4.3.16 of the Final Appraisal Determination refers to possible treatment options when "alendronate is contraindicated at the point of initiation of therapy or when a woman is intolerant to alendronate". The paragraph then states that "all other treatment options (etidronate, risedronate, raloxifene, strontium ranelate and teriparatide) have higher acquisition costs and/or different effectiveness profiles which would reduce the cost effectiveness of preventive therapy". This is perverse in light of the statement that the recommendations specifically exclude women who are contraindicated for initial treatment (para 1), and the fact that the cost effectiveness conclusion is dependent on a specific price at which only one dosage form of alendronate is available.

*The focus on BMD is perverse because it is inconsistent with the remit to advise on "the prevention and treatment of osteoporosis and prevention of osteoporotic fractures" which requires a consideration of treatment effects that cannot be explained by BMD increases alone.*

- Paragraph 3.1 of the Final Appraisal Determination states that "the bisphosphonates alendronate, etidronate and risedronate are inhibitors of bone resorption and increase BMD by altering osteoclast activation and function". It is perverse to focus exclusively on increases in BMD as an end point, given that the Dept of Health remit for the appraisal includes "prevention of osteoporotic fractures". This remit requires a consideration of treatment effects that cannot be explained by BMD increases alone.

**3. <u>Appeal Ground 3</u> (The Institute has exceeded its powers)**

*The Alliance does not wish to submit an appeal based on this ground.*

Yours sincerely

[redacted]
Senior Manager – HTA, sanofi-aventis
*On behalf of the Alliance for Better Bone Health*

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