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22 April 2008

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Dear Natalie

Thank you for the opportunity to comment on the appraisal consultation documents ("ACDs") for the technology appraisals ***Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women*** and ***Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women*** issued on 25 March 2008.

On behalf of Servier Laboratories UK Ltd I have a number of comments on these documents. The comments are summarised in the box below:-

- Certain patients who would ordinarily have access to alendronate are unfairly denied access to an alternative treatment if they cannot take alendronate
- Etidronate should not be recommended given its weak evidence base
- Risedronate efficacy evidence should not be pooled with that for alendronate
- The analysis of data submitted by Servier Laboratories on increased rate of fracture risk with PPIs should be applied to all bisphosphonates
- Bisphosphonates should not be recommended where the concomitant prescription of a PPI is required
- Alternative bisphosphonates should not be recommended as alternatives to alendronate where a patient is unable to take alendronate as the reasons for not being able to take alendronate apply across the class
- Hip-fracture data for strontium ranelate which was accepted by the EMEA and SMC should be accepted, particularly in the light of further supporting evidence of the treatment effect
- The ICER values and the compliance period for strontium ranelate should be amended to reflect the correct figures
- Clarification of the disutility values used for strontium ranelate should be

provided

- Strontium ranelate should be preferred to raloxifene on the basis of the analysis conducted by the Institute
- All risk factors should be treated equally rather than assigning an arbitrary value to some of them
- Permission to provide copies of the disclosable part of the economic model should be sought so that stakeholders should have access to the model
- The ACDs should be amended to avoid unjustified discrimination which breaches patients' human rights
- Strontium ranelate's innovative status should be recognised in the ACDs

These comments are described in more detail below.

Comments relate to Primary and Secondary Prevention ACDs.

1. Patients Not Able to Take or Intolerant of Alendronate

The guidance in both ACDs discriminates on the basis of a patient's medical condition.

It is clear from section 1 of both ACDs that patients who are contraindicated or cannot take alendronate must satisfy a lower T-score threshold than patients who are not contraindicated to and/or can take alendronate before they qualify for treatment. Similarly, patients who cannot take or do not tolerate other bisphosphonates must satisfy an even lower T-score threshold in order to access strontium ranelate. For example, a 66-year old patient with a T-Score of -2.5 (and who is therefore defined as having osteoporosis) and one clinical risk factor would be entitled to alendronate, but if contraindicated or intolerant of alendronate, would get no treatment at all until she reached 75 years of age and only then if she obtained a further clinical risk factor. Even then, she would only have access to risedronate and/or etidronate, which are unlikely to be suitable for patients who are contraindicated or intolerant of alendronate. This is an unjustifiable discrimination among patients. It is manifestly unfair to restrict access to medicines solely on the basis of whether a patient's physical and medical condition allows them to take the cheapest treatment on offer, when other effective and safe medicines are available.

Clearly, many patients unable to take these drugs due to contraindication or lack of tolerance will be left without access to therapy. The Appraisal Committee should reconsider the guidance for patients unable to take alendronate for reasons of contraindication or lack of tolerance and make alternative agents, including strontium ranelate, available to these patients without having to comply with more restrictive criteria. A failure to do so unfairly disadvantages those patients unable to take one or more medicines solely on the basis of their medical profile. We note that a concern not to unfairly disadvantage patients on this basis is described in paragraphs 4.3.23 and 4.3.22 of the primary and secondary ACDs respectively, which the Appraisal Committee did take into account in that case.

2. Etidronate Recommendation

Section 1 of the ACDs (paragraph 1.2 of both ACDs) recommends the use of etidronate as a first-line treatment option for patients contraindicated to alendronate and as a second line option in patients unable to take alendronate.

This recommendation contradicts the statement on the weak evidence base supporting etidronate in paragraph 4.3.25 in both ACDs. Etidronate has no randomised controlled trial evidence, nor does it have a licence for the prevention of hip fracture. The Appraisal Committee's concern regarding the weak evidence base for etidronate is further demonstrated by the fact that it did not request an evaluation report on the cost-effectiveness of etidronate. It is internally inconsistent and unfair for only some of the recommended medicines to have been appraised with scrutiny.

The Appraisal Committee should remove the recommendation that etidronate should be considered as an alternative first line or second line agent. Even if NICE is minded to recommend etidronate despite the weak evidence base, it should not do so until a full analysis for etidronate has been performed.

3. Risedronate Recommendation

3.1 Efficacy of Risedronate

The Appraisal Committee has meta-analysed the evidence base for alendronate and risedronate and produced a post-hoc analysis as the basis for estimating the efficacy of risedronate. No justification has been provided as to why it could be considered reasonable to pool efficacy data from two different medicines. When questioned at the Appeal Hearing the Appraisal Committee Chairman was unable to provide an adequate explanation. [The statements recorded at paragraphs 23 and 24 of the Appeal Panel Decision on the primary FAD are not adequate justification for this pooling of products with potentially very different effect sizes]. Risedronate has been studied in clinical trials involving over 7000 patients. There is adequate evidence available on its effect on fracture risk. There is no justification for considering the evidence for these two medicines together.

The Appraisal Committee clearly does not believe that risedronate can be pooled with alendronate when it comes to potential adverse effects as risedronate is recommended as an alternative to alendronate where alendronate is contraindicated, poorly tolerated or ineffective. This is inconsistent with the Committee's approach on pooling of data for the purpose of calculating a figure for relative risk.

The base case for the cost effectiveness of risedronate should utilise the relative risk for risedronate on which the license for in the prevention of fractures in patients with osteoporosis was granted.

4. Bisphosphonate Use in Patients at Risk of Concomitant PPI Use

4.1 PPI use and altered fracture risk

As we have highlighted in past consultation phases, there is evidence of increased risk of fracture associated with PPI use with three independent studies, each with different designs that demonstrate statistically significant increases in the risk of fracture in patients taking this class of medication[1,2,3].

In addition to these findings a retrospective cohort study using the GPRD has been conducted to examine fracture risk in patients receiving concomitant bisphosphonate and acid-suppressive medication (ASM)[4]. This research presents evidence that acid-suppressing medication significantly reduces, if not completely negates, the anti-fracture benefits of bisphosphonate treatment.

We are pleased to see that the Appraisal Committee have considered these data in the latest ACDs and now acknowledge that the various studies outlined above show a trend between acid-suppressive medication and fracture risk and conclude that "*caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates*". However, we do not understand why the Appraisal Committee has not also incorporated this conclusion into the overall recommendations in the ACDs.

In support of the Appraisal Committee's decision not to incorporate the trend between acid-suppressive medication and fracture risk into the overall recommendations the Committee refer to an additional analysis that "*included the increase in fracture risk for the proportion of women for whom acid-suppressive medication may be co-prescribed*" (4.3.33 in the primary prevention ACD and 4.3.34 in the secondary prevention ACD). The Appraisal Committee then states, "*this analysis did not decrease the T-scores for alendronate to the T-scores established for strategies including strontium ranelate or raloxifene*". We are unclear as to what analysis is here referred to and we request that the Appraisal Committee provide details on this analysis. As set out above, we also request that the Appraisal Committee apply this analysis to risedronate and etidronate when considered as alternatives to alendronate, as this has been demonstrated to be a class effect across all bisphosphonates.

In addition, we are disappointed by the unbalanced summary covering the data on acid-suppressive medication and fracture risk (4.1.35 in the primary prevention ACD and 4.1.41 in the secondary prevention ACD). We are particularly concerned by

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1 Yu E.W. C. Shinoff, T. Blackwell, K. Ensrud, T. Hillier, D.C. Bauer. Use of Acid-Suppressive Medications and Risk of Bone Loss and Fracture in Postmenopausal Women.

2 Vestergaard, P., L. Rejnmark, L. Mosekilde. 2006 Proton Pump Inhibitors, Histamine H2 Receptor Antagonists, and Other Antacid Medications and the Risk of Fracture Calcified Tissue International Vol 79:76-83.

3 Yang Y-X, J.D. Lewis, S. Epstein, D.C. Metz. 2006, Long term proton pump inhibitor therapy and risk of hip fracture, JAMA, 296:2947-2953.

4 De Vries F, Cooper AL, Logan RF, Cockle SM, van Staa TP, Cooper C. Fracture risk in patients receiving concomitant bisphosphonate and acid-suppressive medication or bisphosphonates alone. Osteoporosis Int. 2007; 18(Suppl 3):S261.

comments on the retrospective cohort study using the GPRD conducted to examine fracture risk in patients receiving concomitant bisphosphonate and ASM.

In response to these comments we have enclosed the full study report (see Appendix A – this report remains academic in confidence and should be treated as confidential). In particular, the Appraisal Committee states that the design of this study is prone to confounding when in fact this study took into account an extensive list of potential confounders (see Table 4 of study report). As highlighted by the Appraisal Committee this study is not yet fully published but the key results from this study are now in the public domain as they have been published in a peer-reviewed abstract[5]. This was presented as an oral communication at the National Osteoporosis Society Conference on Osteoporosis on the 28th November 2007. We are working towards an anticipated publication of the full study by the end of June 2008, and we will notify you as and when this is published.

Therefore, the current recommendations included in the latest ACDs do not go far enough. As we have stated previously, the Appraisal Committee could address this issue by providing guidance that:

- Patients being considered for anti-fracture treatment and at risk of gastrointestinal side effects and use of acid-suppressive medication should be prescribed strontium ranelate.
- Patients who are currently taking a bisphosphonate and are co-prescribed an acid-suppressive medication to control the gastro-intestinal side effects of their bisphosphonate should be switched to strontium ranelate and titrated off the acid-suppressing medication.

4.2 Economic Analysis of PPI risk

Furthermore, it is uncertain from Section 4.3.34 whether or not the new analysis referred to (but not supplied) was undertaken for newly diagnosed patients with and without a risk for developing GI disease and being prescribed a PPI or if patients were prescribed a PPI with certainty.

For patients who have been on bisphosphonate treatment and have suffered a GI side effect and are being considered for a PPI in addition to the bisphosphonate, the elevation of risk as a result of prescription of a PPI cannot be described as 'small'. In this scenario, the treatment effect of the bisphosphonate is virtually negated by the addition of the PPI.

If a patient has not been able to take alendronate without the addition of a PPI the cost-effectiveness of alendronate plus a PPI compared to placebo should be determined. Indeed the same analysis should be conducted for risedronate and etidronate to examine their place in therapy for patients of this type. A comparison with a non-bisphosphonate treatment compared to placebo would then be appropriate.

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5 De Vries F, Cooper AL, Logan RF, Cockle SM, van Staa TP, Cooper C. Fracture risk in patients receiving concomitant bisphosphonate and acid-suppressive medication or bisphosphonates alone. Osteoporosis Int. 2007; 18(Suppl 3):S261.

Once again, we request that the Appraisal Committee make available for consultation the analysis referred to in Section 4.3.34.

In addition, we request that the increased risk of being prescribed a PPI, especially in patients already at elevated risk of fracture, should be a matter noted in evidence, and should be applied to all bisphosphonates. In doing the cost effectiveness analyses, it would be appropriate to apply the elevated fracture risk to the cost and effectiveness of risedronate and alendronate in separate analyses.

5. Strontium Ranelate

5.1 Effect in Hip Fracture

Section 4.3.26 states that strontium ranelate has 'non-significant' evidence of prevention of hip fractures. In fact, strontium ranelate has statically significant and robust evidence that it reduces the risk of a hip fracture by 36% in an appropriate patient population. This evidence was acknowledged by the EMEA and justified a license for the prevention of hip fracture and is further endorsed in the recently published guidelines for the treatment of osteoporosis in Europe[6]European guidance for the diagnosis and management of osteoporosis in postmenopausal women.

The estimate of relative risk of hip fracture used by the Appraisal Committee in the economic modelling was produced in a study that was not powered to detect efficacy in hip fracture. The sub-group analysis produced in co-operation with the EMEA did have the power to adequately assess a treatment effect on hip fracture and this is the appropriate relative risk to use in the economic analysis for this appraisal.

In addition new data have been published that further validates the efficacy in the prevention of hip fracture by strontium ranelate. These data, collected from the TROPOS study, show that patients treated with strontium ranelate were protected from hip fracture five years (which has not been demonstrated for any other treatment) after the commencement of treatment, further reinforcing the data initially presented to the Appraisal Committee. Published peer reviewed abstract are attached in an appendix for your consideration[7].

Therefore, we request that the assumptions on the treatment effect of strontium ranelate in the prevention of hip fracture are amended accordingly.

5.2 ICERs

The ScHARR report from February 2008 appears to contain some errors in reporting the ICER values. The table on page 17 of the report contains the same extremely high

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6 Kanis J.A., N. Burlet, C. Cooper , P. D. Delmas J.-Y. Reginster, F. Borgstrom, R. Rizzoli European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008

7 Reginster JY, K Brixen, C Cormier J Cannata. Strontium ranelate demonstrates vertebral and non-vertebral ANI fracture efficacy including hip fractures over 5 years in post menopausal osteoporotic women. Osteoporosis Int. 2007; 18(Suppl):S5-S27

figure (£391,217) for strontium ranelate for all T scores and clinical risk factors. The same anomalous figure also appears in the table on page 13 for strontium ranelate for patients with a T-score of -3.5 to -4.0 and 2 clinical risk factors. We request that the correct figures are provided.

5.3 Compliance

Paragraphs 4.1.39 and 4.1.34 of the secondary ACD should acknowledge that the compliance rates reported were after 3 years of treatment with strontium ranelate rather than at 1 and 2 years reported for other drugs. Please amend this section with this information.

5.4 Strontium ranelate recommended for patients who are intolerant of alendronate and risedronate

It is inappropriate to recommend strontium ranelate only for patients who are unable to tolerate both alendronate **and** risedronate. PEM studies[8] have established that the tolerability profiles of both alendronate and risedronate are similar. Therefore, it is likely that a patient who cannot tolerate alendronate is unlikely to tolerate risedronate.

The Appraisal Committee should recommend strontium ranelate as the alternative medicine for patients unable to tolerate alendronate. Indeed, the effectiveness of strontium ranelate has been demonstrated in patients who have received prior bisphosphonate treatment[9].

5.5 Disutility value

We previously raised concerns regarding the disutility values applied to the various medicines under review in a letter of 3 March 2008 (a copy of which is enclosed with this letter). This letter was not forwarded to the Appraisal Committee meeting. It is still unclear whether the disutility of side effects for strontium ranelate was the same as that for bisphosphonates, which was set to 10-times the value of that based on the patient event monitoring study identified by ScHARR. The ScHARR report from February 2008 suggests, at page 9, that the disutility for strontium ranelate has also been set to this level, despite the fact that strontium ranelate is not associated with the same serious side-effects observed for the bisphosphonates, and it is inappropriate to use the same disutility value for strontium ranelate as has been used for the bisphosphonates. The ACDs do not clarify whether the same ten-times multiplier used for the bisphosphonates has or has not been used for strontium ranelate.

Servier Laboratories requests that the ACDs are amended to make clear that a disutility for bisphosphonates has not been applied to strontium ranelate and, if not,

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[8] Barrera BA, Wilton LV, Harris S, Shakir SAW. 2005. Prescription event monitoring study on 13,164 patients prescribed risedronate in primary care in England. Osteoporos Int., 16, 1989 1998; Biswas PN, Wilton LV, Shakir SAW. 2003. Pharmacovigilance study of alendronate in England. Osteoporos Int., 14, 507-514

9 Busse B et al. J Bone Miner Res. 2007; 22 (Suppl 1):S484-S485

that the analysis of the relevant medicines is repeated to take into account the correct disutility figures (with appropriate explanations).

6. Positioning of Raloxifene in the secondary prevention ACD

Raloxifene has no evidence for the prevention of hip fracture. Therefore, raloxifene clearly offers less potential utility as a treatment for patients with postmenopausal osteoporosis. Strontium ranelate has a license for the prevention of vertebral and hip fractures in patients with postmenopausal osteoporosis. Furthermore, although cost-effectiveness analysis was produced for raloxifene, indicating that it should not be prescribed except in those patients with extremely low T-scores (even lower than those for which strontium ranelate can be prescribed), the secondary prevention ACD recommends raloxifene simply as an alternative to strontium ranelate in all patients who could be recommended strontium ranelate. It is entirely inconsistent to produce a hierarchy of alternative treatments to alendronate based upon the ICER values for those treatments and then allowing one treatment to, in effect, take the benefit of the cost-effectiveness of another. If this is the case, strontium ranelate should be considered as an equal alternative to etidronate and risedronate, or even alendronate, without all the additional T-score, age and clinical risk factor requirements for treatment of a patient with strontium ranelate.

In the light of these facts, strontium ranelate should be preferred to raloxifene in any treatment algorithm in the secondary prevention ACD.

7. Assumption of 50% Effect on Other Risk Factors

The assumption of reducing the treatment effect on fracture risk for clinical risk factors other than age, fracture status and BMD status by 50% is totally without evidence base. There is no reason to believe that medications do not lower fracture risk independently associated with risk factors other than age, BMD and fracture status.

In the clinical trials of these licensed medicines randomised patients were enrolled with many risk factors apart from low BMD, older age and previous fracture. For example, the clinical trials of strontium ranelate included patients in both arms of the study with *familial history of a hip fracture, smoking* and patients with a distribution of body mass indices. *Propensity to fall* was not measured and so, through randomisation, would have been distributed between study treatment arms. A recent examination of the strontium ranelate studies demonstrated that the anti-fracture efficacy of strontium ranelate is independent of baseline risk factors[10], a copy of which is enclosed.

If medicines are less effective or not effective in reducing fracture risks cited by the Appraisal Committee then they should, consequentially, be more effective than

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[10] Roux *et al* 2006Vertebral Fracture Risk Reduction With Strontium Ranelate in Women With Postmenopausal Osteoporosis Is Independent of Baseline Risk Factors. Journal Of Bone And Mineral Research. Volume 21, Number 4

demonstrated in the clinical studies in reducing risk associated with BMD, previous fracture and age. These medicines have demonstrated relative risks in trials where they have been burdened with being tested in populations with fracture risks that they could not, in fact, affect.

Since we only have information on the effect of treatments in populations with all the fracture risk factors identified, it is logical to include all the fracture risk factors that patients are exposed to in the tested and licensed population and to assume that fracture risk reductions are consistent with those demonstrated in the clinical studies. To do otherwise significantly reduces the cost effectiveness of medical treatment unfairly and perversely restricts access to patients who could otherwise benefit from treatment.

8. Access to the Economic Model

Thus far, the Appraisal Committee has not granted access to the economic model. We note that the Appeal Panel directed the Institute to request permission of the World Health Organisation ("WHO") to release the Institute from its undertakings in respect of the economic model. Please let us know whether this has been done, and supply a copy of the WHO's response and a copy of what is disclosable from the model. It remains our position that the stakeholder should be supplied with the economic model, in read only form if necessary, such that consultees can view and critique the assumptions made.

You will, no doubt, be aware of the economic analysis published recently by Kanis et al which detailed the differences between the ICERs demonstrated by the model endorsed by the Appraisal Committee and one using a different set of assumptions[11].

The results of this analysis demonstrate that medicines for osteoporosis, including strontium ranelate, are more cost effective than characterised by the Assessment Group model. It is obvious that differences in assumptions are a key driver of the cost effectiveness analyses results. It is incumbent upon the developers of the economic model produced by the Assessment Group to address and justify differences in the results of these two analyses. To have one model not visible to stakeholders makes this discussion impossible

To continue to deny access to the economic model adds to the lack of transparency of this appraisal and removes confidence that the decisions taken are fair to all parties.

9. Human rights

By refusing access for some patients to publicly-funded medicines, the ACDs breach those patients' human rights. Therefore, the Institute has failed to comply with its duties as a public authority and its own Equality Scheme (the NICE Equality Scheme and Action Plan 2007-2010). In the Equality Scheme, the Institute commits to

[11] Kanis, J.A., Adams, J., Borgström, F., Cooper, C., Jönsson, B., Preedy, D., Selby, P., Compston, J., The cost-effectiveness of alendronate in the management of osteoporosis Bone 2008 42 4–15

ensuring that it complies fully with duties contained in the equalities and anti-discrimination legislation.

It is a breach of a patient's right to life for the State (through NICE) to refuse to fund medicines for that patient where other patients with the same condition do receive funded medicine, in the absence of strong justification.

In addition, selecting patients who qualify for access to treatment on the basis of age, the Appraisal Committee has produced ACDs that discriminate against patients on the sole basis of their age. Furthermore, the amended ACDs now also discriminate between patients based solely on whether they are contraindicated, or intolerant of, alendronate, i.e. based on their medical condition. Certain patients are thus discriminated against based on their age and/or their medical condition.

The Institute has recognised that it has a responsibility for ensuring the elimination of discrimination on age *and other grounds* (page 12 of NICE's Equality Scheme). In the absence of a legal justification for this discrimination, the Appraisal Committee should remove restrictions to patients disqualified because of their age and/or their ability to take alendronate.

10. Innovation

It is incumbent upon NICE to account for innovation in decisions about access to medicines. Strontium ranelate is a totally different class of medicines to standard therapy in this condition and is an innovation especially for patients unable to take currently available medicines. Strontium ranelate is the only treatment that has been demonstrated to have a dual role in not only preventing bone resorption, but also promoting bone growth. The benefit of this innovative action has been demonstrated by the further analysis of evidence from the TROPOS study, indicating a protective effect five years later, as outlined above. The Appraisal Committee should acknowledge this innovation and grant access to strontium ranelate to patients denied it as a result of this guidance.

11. Conclusion

We request that the Appraisal Committee take the points raised above into consideration and amend the ACDs accordingly. We remain available to discuss any questions you have or clarifications that you may need.

I should be grateful if you would continue to direct all correspondence in this matter to me.