Our Ref: GY/VS/0166

Strictly Confidential

Dr Elisabeth George
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National Institute for Health and Clinical Excellence
MidCity Place
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4th February 2008

By Fax: 020 7067 5930

Dear Dr George

Appeal Panel Decision for Health Technology Appraisals – Alendronate, etidronate, risedronate, and strontium ranelate for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women

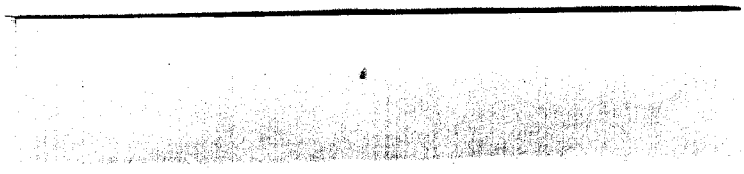
Thank you for your letter of 23rd January 2008 in which you confirm that the Appraisal Committee will now consider the additional GPRD studies submitted by Servier in May 2007 on increased fracture risk in patients receiving concomitant bisphosphonate and acid suppressive medication.

In relation to the issue of confidentiality, the key results from this study are now in the public domain as they have been published in a peer-reviewed abstract (enclosed)[1] This was presented as an oral communication at the National Osteoporosis Society Conference on Osteoporosis on the 28th November 2007. The remainder of the studies have not yet been published and remain academic in confidence, and I have marked up a copy of the letter sent to your office on 21st May 2007 with those sections which remain confidential marked up with the confidential text both highlighted and underlined (also enclosed). However, please inform me if you believe that you would still need to publicly comment on any of the information marked as confidential.
Servier is working towards an anticipated publication of the full study by the end of June 2008, and we would notify you as and when the remaining evidence is published.

However, we suggest that the fact that the key findings of the retrospective study are no longer confidential should allow the Appraisal Committee to produce revised guidance in which it describes how the submitted evidence was considered without revealing any of the as yet unpublished information. We also do not believe that this should affect our right to comment on the Appraisal Committee's consideration of the data that remains confidential.

We look forward to hearing from you as soon as possible whether this satisfies your concerns.

Yours sincerely



Enc.

[1] 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.

SERVIER

Gallions, Wexham Springs, Framewood Road, Wexham, Slough. SL3 6RJ

21 May 2007

Reetan Patel

National Institute for Health and Clinical Excellence (NICE)
MidCity Place
71 High Holborn
London WC1V 6NA

CC: Andrew Stevens; Peter Littlejohns; Ruaraidh Hill; Emma Pugh

Dear Reetan

I write to inform you of important new evidence for inclusion in the development of the guidance for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women.

As highlighted previously in comments to the appraisal committee, evidence is emerging of an association between fracture risk and PPI use, with three independent studies demonstrating statistically significant increases in risk of fracture in patients taking this class of medication[1] [2] [3]. A systematic review of bisphosphonate use carried out on behalf of NICE demonstrated that new bisphosphonate users are up to three times more likely than controls to require acid suppressant agents such as proton pump inhibitors (PPI)[4].

In light of 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). Briefly, this study comprised 67,309 bisphosphonate users, 20.1% of whom had received proton-pump inhibitor therapy and 7.5% had received H_2RA therapy.

[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] Myfanwy Lloyd Jones, Anna Wilkinson. 2006. Adverse effects and persistence with therapy in patients taking oral alendronate, etidronate or risedronate: systematic reviews.

Use of a PPI multiplied the risk of hip fracture by 1.21 (95% CI 1.05-1.38) compared to bisphosphonate alone and,

This research presents evidence that acid-suppressing medication significantly reduces, if not completely negates, the anti-fracture benefits of bisphosphonate treatment. If NICE do not address this issue, current draft guidance will place those bisphosphonate patients requiring an acid-suppressive medication to counteract the adverse gastrointestinal effects of their osteoporosis medication at increased risk of fracture.

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 an 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.
- Patients who are currently being prescribed an acid-suppressive medication and are at risk of an increase in the dose of the acid-suppressive medication to control the gastro-intestinal side effects of a bisphosphonate, should instead be prescribed strontium ranelate.

An appendix is attached detailing the key results for your information. This letter and the attached tables are supplied in strict confidence.

Please do not hesitate to contact me if you require any further information on this matter.

Kind regards,

SERVIER

Appendix 1 Results of ASM + Bisphosphonate Vs Bisphosphonate Alone

Contains commercially confidential information