4 March 2010

NHS
National Institute for Health and Clinical Excellence

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Dear Arran,

Re: Single Technology Appraisal – Denosumab for the prevention of osteoporotic fractures in postmenopausal women

The Evidence Review Group Aberdeen Health Technology Assessment Group and the technical team at NICE have now had an opportunity to take a look at the restructured submission received on the 15 February 2010 by Amgen. Further to my letter of 11 February 2010, we request further clarification relating to the clinical and cost-effectiveness data.

We request that you provide a written response to this letter by **17:00, 10 March 2010**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Fay McCracken – Technical Lead (Fay.Mccracken@nice.org.uk) Any procedural questions should be addressed to Kate Moore – Project Manager Kate.moore@nice.org.uk in the first instance.

Yours sincerely

Helen Chung
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. Please clarify why studies with open label design were excluded from the meta-analysis (figure B2). The usual reason for such exclusion is the possibility of bias by observers aware of allocation, but that should not be a problem if clinical fractures such as hip or wrist are used, or if outcomes are assessed by a reporter unaware of the allocation.

A2. Please clarify why the percentages of drugs used (Table A6) appear to be different to the data from GPRD (page 127). For example, table A6 says that 1.5% of patients recieve etidronate but page 127 reports 29%. Please provide a table showing the GPRD data with percentages receiving each drug.

A3. Please provide persistence data for IV ibandronate and zoledronate (as is provided in Table B28 for oral therapies).

Section B: Clarification on cost-effectiveness data

B1. Please provide results of the modelling with tables showing ICERs by bands of both age and T-score (see table below). Previous analyses conducted for NICE appraisals have used predicted risk at the central point in T-score bands to represent the average risk within the band (e.g. risk at – 2.75 is used to model the average risk for individuals in T-score band -2.5 to -2.99). Please provide a repetition of the type of analysis presented in B76 of the amended submission, for all the age groups of interest.

	T-score 2.5-2.9	**3.0-3.4**	**3.5 – 3.9**	**4.0 or worse**
Under 65				
65-69				
70-74				
75-79				
80-84				
85 and over				

B2. In addition to B1 above, please provide subgroup analysis for patients with none, one and two or more independent clinical risk factors (within each sub-group defined by age and T-score) and present results for all relevant comparators (i.e. strontium, raloxifene, teriparatide, zoledronate and IV ibandronate, but not the oral BPs).

B3. Please provide comment and clarification on the following with regard to cost assumptions, providing sensitivity analyses where appropriate:

- The assumed cost of administration of denosumab (i.e given during the course of a normal consultation) appears to be unrealistic, given that denosumab is a new and specialist drug. The decision to start it would be taken in secondary care, so at least one hospital appointment would be necessary.

- If treatment with denosumab was continued in primary care, it is expected that GPs would not regard it as part of GMS, but would require an enhanced service payment.

- The submission states (section 1.12) that no extra follow-up would be necessary, but it is expected that before each dose, bone marker estimation would be required. If low/very low, the next dose might be postponed.

- The submission notes the lack of wrist fracture data for zoledronate, and then assumes no reduction, thereby imposing an extra cost of hospital care compared with denosumab. The comparison of efficacy for reducing other fractures shows that denosumab and zoledronate have similar effect, so it is implausible to assume that zoledronate has no effect on wrist fractures. Please provide the modelling with the assumption that denosumab and zoledronate have the same effect on wrist fractures.

B4. The modelling does not appear to include any reduction in breast cancer with raloxifene – please confirm that this is the case.

Section C: Executable model

C1. Response C2 to the previous request for clarification says that an executable version of the model with FRAX enabled would be supplied, but the revised version does not seem to have FRAX fully enabled. Please contact us to ensure we have a fully executable model.