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Dear Arran,

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

The Evidence Review Group (ERG) Aberdeen Health Technology Assessment Group and the technical team at NICE have now had an opportunity to take a look at submission received on the 22nd January 2010 by Amgen. In general terms they felt that it is well presented and clear. However, due to the extensive volume of the submission, neither the ERG nor the technical team have been able to review the submission in depth. Therefore we are sending this letter which contains an initial set of clarification questions relating to the clinical and cost effectiveness data. It may well be necessary to request your response to further formal clarification questions after receipt of the restructured submission that Amgen have agreed to submit to NICE by 15th February 2010.

Both the ERG and the technical team at NICE will be addressing these issues in their reports. As you will only receive the evidence review group report 5 days prior to the Appraisal Committee meeting, you may want to respond to the points raised and provide further discussion from your perspective at this stage. Responses to the initial clarification questions should be provided in a separate clarification response document – not addressed by putting new analyses or making changes in the restructured submission. If any responses to clarification questions refer to sections that are already in your submission, these references should be to the page and section numbering in the restructured submission.

We request you to provide a written response to this letter to the Institute by **17:00, 25th February 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. Based on the alendronate arms of the clinical trials, please provide information on whether there are any differences in baseline characteristics (and hence fracture risk) of patients who could and could not tolerate oral bisphosphonates.

A2. The manufacturer's submission states that there are no trials of IV ibandronate versus placebo with fractures as the outcome (page 24). Please provide the rationale for not including the trials of oral ibandronate versus placebo (BONE), and IV ibandronate versus oral ibandronate (DIVA), in an indirect comparison of IV ibandronate with denosumab via oral ibandronate and placebo.

Section B: Clarification on cost-effectiveness data

Probabilities and model calculations

B1. Please clarify whether the baseline risk of fracture increases over time in the modelling. If so, is such an increase in baseline fracture risk linked to decreasing BMD or linked to increasing fracture prevalence? Please clarify how this was calculated.

B2. When running the model for a population with no prior fractures, please clarify whether fracture risk increases if the modelled women experience a fracture, and whether this is dependent upon the site of fracture.

B3. Please clarify how the "below threshold" risks of fracture were estimated.

B4. Please clarify how the sub-group analysis for different T-score thresholds were conducted (i.e. were all the subgroup analyses conducted using "below threshold" risks, or were any done using at threshold risks?). Please also clarify whether analysis was carried out by band (2.5 to 2.9, 3.0 to 3.4, etc).

B5. When running the model over the lifetime of younger cohorts, relative fracture risks cease to update with age after 30 years. For example, when running the model for a 50 year old cohort, the relative risk of a hip fracture at age 90 is equal to the relative risk at age 80, despite the fact that age dependent relative risks are held up to age 100 (Worksheet titled "RR below"). Please provide the rationale for this approach.

B6. The relative risk of fracture at a given age appears to depend on the start age of the cohort (i.e. the relative risk for hip fracture associated with osteoporosis in a 70 year old varies depending on the start age of the cohort). Please clarify the rationale for this approach, and whether it is assumed that T-scores become worse over time.

B7. The reproduction of the Freedom trial validates the structure of the model but not the risk equations used to derive baseline risks in the osteoporotic population. Please clarify how well the risk equations predict the three year incidence of fractures observed in the placebo arm of the Freedom trial (when age, T-score, and fracture prevalence are set to match the average characteristics of participants in the Freedom trial).

B8. The mortality risk calculations following fracture are not clear. Please provide further details on how the relative risks of mortality were arrived at and how they are used in conjunction with the baseline mortality risks to estimate mortality following fractures (as in worksheet “Model data”: AQ - AU).

Utilities

B9. Health-related quality of life losses continue over the life time of all patients post hip fracture. Please clarify whether the utility multipliers are valid for the baseline population of the model (i.e. were these multipliers derived from populations of similar age with similar likelihood of admission to nursing homes following hip fracture).

Costs

B10. Please clarify whether applying costs for excess bed days was done using the trim points for specific healthcare resource groups (HRGs). Please also clarify the assumption relating to the 2 day trim point used to inflate the HRG costs.

Section C: Textual clarifications and additional points

Model functionality

C1. Please clarify whether or not the “at threshold” risk estimation control should be functional in the model, as the internal calculations all seem to reference the “below threshold” risks.

C2. Please provide a version of the model in which the FRAX algorithm is enabled.