Dear Kate,

Thank you for the opportunity to comment on the appraisal consultation document (ACD) for the single technology appraisal of ***denosumab for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women*** issued on 11th June 2010 .

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

1. Strontium ranelate is not an appropriate primary comparator for this technology appraisal

2. The economic model has been populated with inappropriate and misleading data and therefore confidence intervals around the cost effectiveness figure are much larger than demonstrated.

3. The cost effectiveness profile of denosumab shows inconsistency and a wide degree of variability when the economic model is subjected to sensitivity analysis and this raises further issues with confidence in the outputs.

4. Denosumab has not demonstrated quality of life benefits over placebo

5. The amalgamation of all oral bisphosphonates into a single group for the purposes of this guidance is inconsistent with Technology Appraisal 160/161 and it will result in the inefficient use of UK health resources

Data

1. Strontium ranelate is not an appropriate primary comparator

As concluded by the Expert Review Group (ERG) in section 3.29 of the denosumab ACD, Servier asserts that strontium ranelate is not an appropriate primary comparator for this economic analysis.
Zoledronic acid is the natural primary comparator for denosumab by virtue of its similar method of administration (via injection), similar frequency of dosing (yearly vs. 6 monthly) similar place of administration (i.e. a secondary care setting) and similar mode of action of the two treatments (pure antiresorptive effects on the bone through osteoclast inhibition).

2. Inappropriate and misleading data has been used in the economic analysis

The manufacturers of denosumab use a figure of 0.89 (section 3.6)
as the point estimate relative risk of hip fracture for strontium ranelate vs. placebo to populate their economic model and make an efficacy comparison. This figure has not been accepted by NICE for the Technology Appraisals 160 & 161 for osteoporosis

and hence it cannot be relied upon or deemed acceptable for this analysis or STA. Servier assert the true relative risk of hip fracture in comparison to placebo is 0.64 over 3 years (or 0.57 over 5 years) as accepted by the European Medicines Agency (EMA). The decision by NICE in Technology Appraisals 160 & 161 to reject data submitted by Servier supporting the figure of 0.64, and NICE's conclusion that the correct estimate is 0.85, was recently ruled unlawful by the Court of Appeal *NICE on the basis that NICE had failed to give adequate reasons for rejecting that data (and thus for rejecting the estimate of 0.64). A* reappraisal of that part of the Technology Appraisals has been ordered by the Court, but currently no figure has been definitively concluded in the reappraisal. The figure of 0.89 proposed by the manufacturers of denosumab therefore represents an inaccurate comparison and thus the outputs of their economic analysis cannot be relied upon.
In addition, incorrect methodology has been used by the manufacturers of denosumab to calculate the figure of 0.89 as the Relative Risk from the TROPOS 5 year study and hence any economic result based on this figure is misleading, and underestimates the true treatment effect of strontium ranelate. The calculation conducted by the manufacturers of denosumab takes no account of the incidence and differential timing of hip fractures between the strontium ranelate and placebo groups in the TROPOS 5 year study. The most appropriate statistical analysis, described in the TROPOS 5 year study publication, is a Cox proportional hazard model, which corresponds to a comparison of two Kaplan-Meier survival curves and takes into account the time of onset of events and censure. Importantly, adjusting the Relative Risk of hip fracture for strontium ranelate in the economic model, to a figure that reflects its actual efficacy, has significant effects on the overall cost effectiveness in its comparison to denosumab.

Model and assumptions.

3. Uncertainty of the true cost effectiveness figure

Section 3.24 states "the results of the manufacturer's probabilistic sensitivity analysis showed that denosumab had an approximately 50% probability of being considered cost effective at a willingness-to-pay threshold of £30,000 per QALY gained compared with the primary comparators (strontium ranelate, raloxifene and no treatment) in the base-case population of women aged 70 years with a T-score at or below −2.5 SD and no prior fracture." From this result it can be concluded that there is an equal (50%) chance of denosumab showing cost effectiveness or not for primary prevention against primary comparators. Indeed, also in primary prevention, there is only a 60% chance of cost effectiveness being demonstrated against secondary comparators and this further undermines the confidence in the cost effectiveness conclusions for denosumab.
When the economic model is subjected to deterministic and sensitivity analysis over plausible ranges, large differences and a wide degree of variability emerges between these results and those used by the manufacturer to argue cost effectiveness (section 3.23). This reduces confidence in the cost effectiveness conclusions derived from the analysis submitted by the manufacturers of denosumab.
The model is particularly sensitive to changes in assumptions concerning the place (and therefore cost) of administration of denosumab (section 3.23), argued by the manufacturers to be in primary care and predominantly by patients. The ERG state

(section 3.30) that this approach, taken by the manufacturers, has the effect of making the treatment much less costly than what the ERG find is the most appropriate primary comparator, zoledronic acid. As denosumab is likely to be initiated and continued in secondary care, much like zoledronic acid, resource usage for denosumab will therefore be underestimated.
In addition, even if denosumab were to be used in primary care the ERG (section 3.36) believe this is unlikely to be part of general medical services but would be provided as an enhanced service requiring additional payment and therefore costs. These have not been accounted for in the initial analysis and could be significantly higher than the manufacturer's assumption of the average cost of 2 GP visits per year.

4. Denosumab does not show quality of life benefits over placebo

The FREEDOM study demonstrated no significant difference between the denosumab and placebo arms of the study with respect to health related quality of life outcomes (section 4.12). This is a cause for concern as it could be postulated that any benefits shown with regards to hip fracture rate reduction are offset by a worsening of some other unascertained component of quality of life that is impacting on patients and would therefore impact on overall cost effectiveness. This possibility has not been recognised in the ACD.
Section 4.12 states "The Committee heard from the ERG that the number of fracture events with associated EQ-5D scores was low and that there was insufficient information for cross-checking". This is a pivotal point that in our view does not justify the omission of this data from the economic analysis. Considering section 3.10 "when a fracture occurred, women were modelled to remain in the respective fracture state for two cycles (1 year)", it follows therefore that for EQ-5D to be associated with an event it need only be measured within 12 months of the fracture. It is our view that the Committee have been given insufficient information to be persuaded that the manufacturer's approach to modelling Quality of Life was acceptable. Firstly the definition of association (4.12) should be provided to the committee and, secondly, the EQ-5D data should be requested from the manufacturer for the purpose of cross-checking.

Guidance.

5. Inappropriate grouping of all oral bisphosphonates with inefficient resource use

The Appraisal Committee comment that it is reasonable and acceptable for the manufacturers of denosumab to focus on a population of post menopausal women for whom oral bisphosphonates are unsuitable. This is because the manufacturers claim that denosumab is not expected to compete with oral bisphosphonates. In addition the manufacturers also cite the reason for such a positioning after oral bisphosphonates as the need to make efficient use of UK resources (section 4.4). The ACD guidance therefore indicates denosumab should be used after any oral bisphosphonate for both primary and secondary prevention of fractures.
This is quite different and inconsistent with guidance from Technology Appraisals 160 and 161. Here there is clear stratification of the oral bisphosphonates based on cost and clinical factors (e.g. tolerability) and the 3 technologies are not regarded as homogeneous. Technology Appraisals 160 and 161 clearly advocate the use of

alendronate first followed by etidronate or risedronate and only after these technologies are alternative treatments recommended.
The manufacturer states (section 3.7) that only 6.8% of the current osteoporotic drug use would be eligible for denosumab because this is the percentage of osteoporotic drug use that does not involve oral bisphosphonates. It is claimed this would represent efficient use of UK resources. As the current ACD stands it is likely that denosumab could be used in those patients who cannot take alendronate, which would include the 6.8% of drug use stated above **AND** at least a further 15.8% (currently the usage of risedronate) because of intolerance to the first oral bisphosphonate. This amount is far greater than what the manufacturers of denosumab have submitted and quite different from the original intention of the guidance; to allocate the use of UK resources efficiently.
This current ACD also has the effect of unfairly disadvantaging those technologies appraised in guidance 160/161 who are recommended for use after alendronate, and then either risedronate or etidronate, not just an oral bisphosphonate. Therefore any recommendation for denosumab should follow the stratification developed for non-oral bisphosphonates in guidance 160/161.

Conclusion

Considering the data inaccuracies and lack of confidence in the wide range of cost effectiveness values we believe that the cost effectiveness of denosumab has not been proven against an appropriate comparator. Additionally any guidance should be consistent in positioning and wording with existing NICE osteoporosis guidance TA160/161.

Yours sincerely,

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