Comments from Novartis on the Assessment Report for the Health Technology Appraisal of denosumab for the treatment of bone metastases from solid tumours

1. Introduction

Thank you for your invitation to comment on the above Assessment Report (AR) prepared by the Aberdeen HTA group. We will highlight that our ability to comment fully on this Assessment Report was limited by the unavailability of the economic model and the heavily redacted AR. Nevertheless we still tried to understand the analysis as much as was feasible without access to the economic model.

2. Summary of mains points

2.1. The Assessment Group (AG) analysis did not fully incorporate the effect of generic price of zoledronic acid on the cost effectiveness (CE) of denosumab for all cancers considered. Novartis believes the impact could be significant given the small QALY gain attributed to denosumab.

2.2. It is not clear why other oral bisphosphonates such as clodronate and ibandronate were excluded from the analysis yet they were included in the NICE scope. The impact of including oral bisphosphonates in the economic analysis is likely to be significant because there are no administration costs associated with these treatments.

2.3. The economic analysis by the AG did not incorporate the reduced dosing frequency of zoledronic acid due to renal toxicity.

2.4. The economic analysis by the AG has overestimated the staff and administration time savings for denosumab.

2.5. The price for pamidronate applied in the model does not reflect the lower generic cost for the drug.

All these factors are likely to have a huge impact on the cost effectiveness of denosumab and Novartis recommends that the AG conduct additional analyses incorporating the above points in the base case analysis. This will enable the Appraisal Committee to make an informed decision on the true cost effectiveness of denosumab compared with zoledronic acid and other bisphosphonates.

3. Detailed discussion of key points

3.1. The future generic price of zoledronic acid

Zoledronic acid will be going off patent (generic) in early 2013 and therefore its price is going to significantly go down after this date. The AG's base case analyses for all the different cancers has shown that the QALY gain for denosumab compared with zoledronic acid is very small ranging from 0.013 in breast cancer, 0.006 in prostate cancer, to as low as 0.003 in

lung cancer. This implies that any slight changes in the incremental costs results in a significant change in the incremental cost effectiveness ratio (ICER). It is therefore not surprising that the ICER for denosumab compared with zoledronic acid changes significantly (from denosumab not cost effective to denosumab dominating) when changes to the cost inputs are made. The economic model adopts a lifetime horizon and therefore the full time horizon includes a significant period when zoledronic acid will be generic and hence far cheaper than the current price applied in the AG model. Given that the QALY gain is so small, the price of generic zoledronic acid will have a massive impact on whether denosumab is cost effective or not. Evidence based on other generic bisphosphonates (ibandronate and pamidronate) shows that at the point of going generic the price could go down by as much as 50% and within six months the price could go down by as much as 80%[1]. The AG acknowledges the impact of zoledronic acid going generic and poses the same question as Novartis by stating the following:

> *To what extent should zoledronic acid coming off patent in 2013 be considered? The anticipated patient benefits from denosumab over zoledronic acid are small. Only a relatively small drop in the price of zoledronic acid would be sufficient to make denosumab not cost effective when judged by conventional thresholds (page 217 of the AR)*

We fully agree with the AG's statement and we are requesting the AG to incorporate a higher reduction in the price of zoledronic acid in the model after a year to reflect the likely price of the drug when it goes generic. The AG should consider a zoledronic price reduction of at least 50% which we believe will be conservative given the percentage fall in price of other generic bisphosphonates when they went off patent. Novartis believes that applying such a discount is crucial because the NHS will not be paying the list price of zoledronic acid from next year and more importantly ignoring this significant generic price drop produces results that might not reflect the true CE of denosumab when compared with zoledronic acid in this setting. As mentioned earlier, the economic analyses both from the manufacturer and the AG have shown that denosumab offers marginal benefit (if any) over and above zoledronic acid. Novartis views it as inappropriate for the economic analysis to consider the list price of zoledronic acid for the lifetime given that the drug will be far cheaper and offering the same benefit as denosumab. Novartis reiterates that the AG incorporates a higher percentage drop in price in the base case analyses.

3.2. Exclusion of some comparators from the analysis

The inclusion and exclusion of some comparators in the analysis is not clear. The final scope of this appraisal specified that all bisphosphonates including oral versions were appropriate comparators. The analysis from the manufacturer and the AG seems not to have fully considered oral ibandronate and clodronate. Novartis market share data shows that oral ibandronate and clodronate have significant market share to warrant consideration as 'stand alone' comparators in the health economics analysis. The market share data further shows that infusional ibandronate is rarely used in clinical practice yet it was considered as part of the comparators.[2] Thus the analysis seems to have broadly excluded oral comparators for inclusion (oral clodronate and ibandronate studies) and concentrated more on infusional or intravenous options some of which are not usual clinical practice in this setting. The NICE

scope for the appraisal specifies these as comparators and their inclusion might have an effect on the cost effectiveness analysis (CEA) given that there are no administration costs associated with the oral treatments. Novartis therefore believes that the true cost effectiveness of denosumab can be established when all the appropriate comparators (both oral and infusional or intravenous bisphosphonates) as per the NICE scope are considered in the analysis. Novartis reiterates that the cost effectiveness of denosumab could easily change given the small QALY gain predicted in both the manufacturer's model and the AG's model and therefore suggests that the AG analyses is updated with oral bisphosphonates as 'stand alone' comparators where appropriate.

3.3. Zoledronic acid dosing frequency

Within the denosumab trials intravenous therapy could be withheld due to elevated creatinine. This affects the average dose received within the zoledronic acid arm. It appears possible that since exposure to zoledronic acid could only be resumed once creatine levels had returned to acceptable levels, some of these incident patients may have had more than one dose withheld. The AG reports that there was no attempt to correct for doses of zoledronic acid being withheld due to renal toxicity (page 181 of the AR). It is clear that the number of doses of zoledronic acid withheld can have an impact on cost of treatment. The zoledronic acid SPC[3] lists both renal impairment and raised blood creatinine as common side effects, defined as an incidence of between greater than 1 in 100 and less than 1 in 10. It is therefore surprising that the AG have decided to exclude the reduced dose of zoledronic acid in a proportion of patients in calculating the costs of treatment. This is more so when you consider the fact that the adverse event costs associated with renal toxicity were included in the AG model. The impact of this approach is to favour denosumab at the expense of zoledronic acid. Novartis suggests that the AG incorporates the reduced doses of zoledronic acid in its base case analyses to be consistent with the inclusion of renal toxicity AE costs and more importantly to reflect the actual costs of zoledronic acid treatment. Novartis considers that this update to the analysis will have a significant impact on the ICER for denosumab.

3.4. Staff time and drug administration costs

The manufacturer of denosumab used median instead of mean in estimating the costs of staff time and drug administrations from the micro-costing study. We agree with the AG's conclusions that the requirement to make this adjustment might suggest that the micro-costing study that was used to inform the estimates was not reliable. In addition, we do not believe that denosumab will result in staff time savings and administration cost savings as implied in the micro-costing study. Section 6.6 of the denosumab SPC[4] states that when taken from the fridge, the denosumab vial should reach room temperature before use, while zoledronic acid can be used straight from the fridge. In addition denosumab requires special storage conditions of between 2 and 8 degrees, i.e. refrigeration (section 6.4 of SPC), while zoledronic acid requires no special precautions for storage (section 6.4 of SPC). This extra preparation time for denosumab needs to be taken into account when estimating the staff time saving and administration time saving. Furthermore zoledronic acid has recently been launched as a new Ready to Use (RTU) formulation which means there is no drug

preparation time, compared to the previous concentrate formulation which had to be added to a 100ml bag dilutent before being administered intravenously. We therefore suggest that the AG updates its base case analysis and assume no staff time and pre-administration time saving for denosumab. Novartis considers this to be a conservative assumption because it is more likely that zoledronic acid will result in staff and administration time savings if the points discussed above are considered.

3.5. Price for pamidronate

The AG has applied the list price for pamidronate for the purposes of the economic analyses. Novartis is of the opinion that relying on the BNF for the cost of a drug that is generic is misleading and will not reflect the actual cost effectiveness of new compounds such as denosumab. There is evidence showing that the actual reference price of pamidronate is far lower than the BNF list price. Novartis contacted three major generic manufacturers of pamidronate and the average price was approximately more than 50% lower than the list price. In addition Novartis' market research showed that the NHS is paying as low as £20 for a 28 tablet pack of pamidronate and in other NHS organisations, the price is even lower.[5] The pamidronate price is therefore inflated and using a lower price (reflecting the price the NHS is paying for the drug) may have a huge impact on the final results given the small QALY gain associated with denosumab.

4. Conclusion

The AG economic analysis excluded some factors (discussed earlier) that are likely to have a significant impact on the cost effectiveness of denosumab. These factors are very important given that the QALY gain for denosumab is very small and any slight changes to the cost inputs could render denosumab cost ineffective. It should be borne in mind that the main motivation for conducting cost effectiveness analysis in this instance is to establish whether denosumab is a cost effective use of NHS resources. This notion is not reflected in the current economic analysis where several important factors have not been fully taken into account. Novartis suggests that the AG update its analyses to incorporate the points discussed in this document in order to reflect the true cost effectiveness of denosumab compared with zoledronic acid and other bisphosphonates.

References

[1] Novartis data on file
[2] Novartis market research data on file
[3] http://www.medicines.org.uk/EMC/medicine/25058/SPC/Zometa
[4] http://www.medicines.org.uk/EMC/medicine/24755/SPC/XGEVA
[5] Novartis market research data on file