

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Response to Appraisal Consultation Document

Denosumab for the treatment of bone metastases from solid tumours

Amgen Limited

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Confidential information has been removed 

Summary

Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) for denosumab (issued March 2012).

We welcome the Institute's preliminary recommendation of denosumab for the prevention of skeletal-related events (SREs) in adults with bone metastases from solid tumours. Our comments on the specific aspects of the ACD and Evaluation Report which the Appraisal Committee have asked for are provided in this report. We have also listed some minor factual inaccuracies in the ACD for correction.

Section A – Decision problem

1 Has all of the relevant evidence been taken into account?

We believe all of the relevant evidence has been taken into account.

Section B – Clinical and cost-effectiveness

2 Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

2.1 Clinical and cost-effectiveness of denosumab

We believe that the overall summaries of the clinical and cost-effectiveness in the ACD are reasonable interpretations of the evidence. However we believe that the conclusion reached by the Appraisal Committee that '*denosumab was slightly more clinically effective than zoledronic acid*' is not a reasonable interpretation of the evidence.

The ACD states that '*The Committee noted that the trials consistently showed that denosumab improved skeletal-related event outcomes compared with zoledronic acid, and that zoledronic acid improved skeletal-related event outcomes compared with placebo. The Committee discussed the other outcomes data from the denosumab trials noting that there were no benefits to overall survival for denosumab in comparison with zoledronic acid and that the outcomes for pain, although all favoured denosumab, were not all statistically significant. The Committee concluded that the evidence directly comparing denosumab with zoledronic acid suggested that denosumab was slightly more clinically effective than zoledronic acid in all three cancer groups for which there was trial evidence*' (ACD Section 4.3.8). We agree that the summaries of the clinical-effectiveness are reasonable interpretations of the evidence with respect to SRE outcomes, pain and overall survival for denosumab: Denosumab has demonstrated a superior, statistically significant, clinically meaningful, consistent and robust treatment effect compared with zoledronic acid across the three Phase III studies for the reduction in the occurrence of SREs which is the primary treatment goal for bone-targeted agents i.e. a reduction in morbidity associated with bone metastases. Denosumab has also demonstrated improvements in pain outcomes, although the Phase III studies were not powered to detect significant differences. Finally, denosumab, like bisphosphonates are not expected to provide overall survival benefits in this population. The superior and clinically meaningful benefit of denosumab over existing therapies has been recognised by numerous regulatory agencies including the Committee for Medicinal Products for Human Use (CHMP) which stated '*...the CHMP agreed with the applicant's request for the extension by 1 year of the marketing protection period for*

denosumab since the indication was considered to be new for denosumab and because it would bring a significant clinical benefit in comparison with existing therapies for this indication.¹

In light of the evidence, we are surprised that the Appraisal Committee reached the conclusion that *'denosumab was slightly more clinically effective than zoledronic acid'* since denosumab has demonstrated a superior, statistically significant, clinically meaningful, consistent and robust treatment effect compared with zoledronic acid across the three Phase III studies. We therefore respectfully request that the wording of this final sentence is reconsidered by the Appraisal Committee.

2.2 Network meta-analysis

During the Assessment Report consultation, we provided comments relating to the Academic Group (AG) network meta-analysis (NMA) in breast cancer. We are reassured that the AG were able to identify the misspecification within their NMA and have issued an erratum (with estimates consistent with our NMA findings and the direct head-to-head trial evidence) to allow appropriate consideration of the comparative efficacy of denosumab by the Appraisal Committee.

2.2.1 Breast cancer: Zoledronic acid versus disodium pamidronate efficacy data estimate from Novartis Study 010

During the Assessment Report consultation, we also provided additional information regarding the most appropriate and reliable efficacy estimate for zoledronic acid compared to disodium pamidronate (Section 2.1.4, page 17 of Amgen response to Assessment Report); recommending the use an estimate of HR of [REDACTED] (95% CI [REDACTED]) derived directly from reported estimates, in place of the AG's indirect approach using curve methods HR of 0.97 (95% CI 0.78 to 1.20) within the AG's breast cancer NMA. However this was not incorporated in the AG NMA re-analysis because *'neither the source of the manufacturer's pooled estimate nor the method for combining the results is [was] clear. The AG therefore has no evidence that the AG estimate is less robust than the estimate suggested by the manufacturer'* (Evaluation Report, page 8 of Response to consultee and commentator comments on the Assessment Report from Aberdeen HTA Group).

We are pleased to provide additional information regarding the methods used by Amgen as requested by the AG.

2.2.2 Amgen efficacy estimate methodology

The Amgen breast cancer NMA used the estimate for time to first on-study SRE for zoledronic acid versus disodium pamidronate presented in the Food and Drug Administration's Statistical Review and Evaluation of Zometa for Novartis Study 010.² This is the only source in the public domain that directly reports the treatment effects for this endpoint, as a HR with 95% confidence intervals.

The Novartis Study 010 enrolled patients with myeloma and breast cancer and was stratified for myeloma, breast cancer treated with hormone therapy and breast cancer treated with chemotherapy. Data from the two breast cancer stratification groups for time to first on-

study SRE were selected for inclusion in the Amgen breast cancer NMA. The HR and the 95% confidence intervals were pooled using the same meta-analysis techniques as for the meta-analysis as part of the NMA in our evidence submission. The original calculation was run in SAS so there is a difference in the rounding between SAS and the results presented below are for illustration purposes:

The pooled log-HR was calculated by taking a weighted average, with inverse variance weights as follows: $\log(\text{HR}) = (\log(\text{HR}_{\text{ZA}_A})/\text{SE}_{\text{ZA}_A}^2 + \log(\text{HR}_{\text{ZA}_B})/\text{SE}_{\text{ZA}_B}^2) / (1/\text{SE}_{\text{ZA}_A}^2 + 1/\text{SE}_{\text{ZA}_B}^2)$.

- (A) Using the data for breast subjects by the chemotherapy strata only in this trial, the HR for zoledronic acid relative to disodium pamidronate was [REDACTED] with 95% CI ([REDACTED]). Similarly, $\log(\text{HR}_{\text{ZA}_A})$ was equal to [REDACTED] and the standard error for $\log(\text{HR}_{\text{ZA}_A})$, SE_{ZA_A} , was equal to [REDACTED].
- (B) Using the data for breast subjects by the hormone strata only in this trial, the HR for zoledronic acid relative to disodium pamidronate was [REDACTED] with 95% CI ([REDACTED]). Similarly, $\log(\text{HR}_{\text{ZA}_B})$ was equal to [REDACTED] and the standard error for $\log(\text{HR}_{\text{ZA}_B})$, SE_{ZA_B} , was equal to [REDACTED].

The results for these two strata were combined to provide an estimate for the breast cancer population. Based on this calculation, the log of the HR for zoledronic acid relative to disodium pamidronate for breast cancer subjects was equal to -0.1186. The pooled standard error for $\log(\text{HR})$, given as $\text{SE} = 1/\text{SQRT}(1/\text{SE}_{\text{ZA}_A}^2 + 1/\text{SE}_{\text{ZA}_B}^2)$, was equal to [REDACTED]. The 95% CI of $\log(\text{HR})$ in the log-scale was ([REDACTED]). By taking an exponential transformation, the HR for zoledronic acid compared to disodium pamidronate in breast cancer was [REDACTED] and its 95% CI was [REDACTED] to [REDACTED].

2.2.3 AG efficacy estimate methodology

The AG breast cancer NMA used an estimate for time to first on-study SRE for zoledronic acid versus disodium pamidronate based on calculated HRs and associated statistics from Kaplan Meier plots published for lytic and non-lytic lesion subgroups of the Novartis Study 010.³ This indirect method for calculating HRs is recognised as being less reliable than using HRs taken directly from a published data source; as stated by Tierney⁴, '*There is a hierarchy in the methods described. The direct methods make no assumptions and are preferable, followed by the various indirect methods based on reported statistics. The curve methods are likely to be the least reliable and it is not yet clear which method of adjusting for censoring is most reliable*'. It is also acknowledged in the Assessment Report (page 61), that this method for deriving treatment effects adds a further layer of uncertainty.

The use of these indirect estimates for zoledronic acid compared to disodium pamidronate (instead of the recommended directly reported estimates) has altered the comparative efficacy findings within the AG's NMA for denosumab compared to disodium pamidronate. Whilst we estimated that denosumab significantly delayed the time to first on-study SRE (HR = [REDACTED], 95% CI [REDACTED], [REDACTED]), the AG estimated a non-significant delay (HR = 0.79, 95% CI 0.61, 1.03). We feel that the AG's indirect approach is more complex and less reliable than the use of direct efficacy estimates taken from the primary strata of Novartis Study 010 and

available in the public domain and therefore unnecessarily adds to the uncertainty associated with evidence synthesis through NMA methods.

We recommend that the breast cancer NMA for time to first SRE is re-conducted using the data and methods described above based on updating the pair-wise direct meta-analysis of zoledronic acid versus disodium pamidronate. This will provide the Appraisal Committee with appropriate information to allow a reasonable interpretation of the comparative efficacy of denosumab compared to disodium pamidronate. A summary of the Amgen and AG selected values, methods and meta-analysis findings are provided in Table 1.

Table 1. Time to first on-study SRE estimates for zoledronic acid versus disodium pamidronate derived from Novartis Study 010

NMA	Outcomes	Measures	Values	Source	Method	Meta-analysis
AG NMA	Time to first SRE (breast lytic)	Median days	ZOL 310 days PAM 174 days	Rosen 2004 ³	Indirect estimation of hazard ratio and 95% confidence intervals from Kaplan-Meier plots and subsequent meta-analysis of subgroups	0.97 (0.78, 1.20) [Assessment Report, page 61]
	Time to first SRE (breast non-lytic)	Median days	ZOL Not reported PAM Not reported	Rosen 2004 ³		
Amgen NMA	Time to first SRE (breast hormonal therapy)	Hazard ratio (95% CI)	0.83 (0.62, 1.12)	FDA SREZ (Table 1.3.4) ²	Hazard ratios reported directly and subsequent meta-analysis of subgroups	[Redacted] ([Redacted]) [Amgen submission, Appendix 6, table 17]
	Time to first SRE (breast chemotherapy)	Hazard ratio (95% CI)	0.96 (0.70, 1.32)	FDA SREZ (Table 1.3.4) ²		

Abbreviations: AG, Academic Group; SRE, skeletal-related event; ZOL, zoledronic acid; PAM, disodium pamidronate; FDA SREZ; Food and Drug Administration, Statistical Review and Evaluation of Zometa (zoledronic acid)

2.3 Factual inaccuracies

We would also like to take this opportunity to indicate some factual inaccuracies in the ACD (Table 2).

Table 2. Appraisal Consultation Document: Factual Inaccuracies

ACD Section	Current Text	Comments	Proposed Amendment (underlined)
3.1	Denosumab (Xgeva, Amgen) is a fully human monoclonal antibody...	We wish to indicate that the branded name of denosumab is written in uppercase.	Denosumab (<u>XGEVA</u> [®] , Amgen) is a fully human monoclonal antibody...
4.1.5	Likewise disodium pamidronate was associated with fewer skeletal-related events (including hypercalcaemia) than placebo (2.4 compared with 3.7; p < 0.001).	We wish to indicate that the event rate for disodium pamidronate versus placebo was exclusive of hypercalcaemia.	Likewise disodium pamidronate was associated with fewer skeletal-related events (<u>excluding hypercalcaemia</u>) than placebo (2.4 compared with 3.7; p < 0.001).
4.1.23	In the same trial, time to development of moderate or severe pain was longer for denosumab than zoledronic acid (median 57 days compared with 36 days; HR 0.91, p = 0.1092).	We are unclear what publication these numbers are taken from and if they refer to the overall solid tumour patient population or a subgroup of patients. We recommend the presentation of the data for the pain endpoint in other solid tumours for patients with no or mild pain at baseline as presented in the ACD for breast cancer (4.1.8) and prostate cancer (4.1.16). ⁵	In the same trial, in <u>patients with no or mild pain at baseline</u> , the time to moderate or severe pain was longer for denosumab than zoledronic acid (median <u>144</u> days compared with <u>112</u> days; <u>HR 0.81 (0.66-1.00) p = 0.0499</u>).
4.1.25	The trial comparing denosumab with zoledronic acid in other solid tumours also reported data on a subgroup of patients with non-small cell lung cancer (n = 402).	We wish to indicate that this trial (Study 20050244) reported data on 702 patients with non-small cell lung cancer.	The trial comparing denosumab with zoledronic acid in other solid tumours also reported data on a subgroup of patients with non-small cell lung cancer (n = <u>702</u>).
4.1.26 (and AR Section 8.2.4, page 95)	The incidence of skeletal-related events was lower in the zoledronic acid group (42% with an event), compared with placebo (45% with an event; p = 0.007).	We wish to indicate that the p-value for this outcome was 0.557. ⁶	The incidence of skeletal-related events was lower in the zoledronic acid group (42% with an event), compared with placebo (45% with an event; p = <u>0.557</u>).

Section C – Implementation

3 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

We believe the Appraisal Committee's preliminary recommendations for denosumab as an option for preventing SREs in adults with bone metastases in breast cancer, prostate cancer and other solid tumours are a sound and suitable basis for guidance to the NHS.

We would, however, like to indicate that the additional criteria pertaining to the use of denosumab in the other solid tumours population may not be suitable to the NHS in all instances. The Appraisal Committee's preliminary recommendation in other solid tumours (recommendation 1.3) states that:

'Denosumab is recommended as an option for preventing skeletal-related events in adults with bone metastases from solid tumours other than breast and prostate if:

- *zoledronic acid is indicated for them **and***
- *if the manufacturer provides denosumab with the discount agreed as part of the patient access scheme.'*

Zoledronic acid is the only bisphosphonate licensed, and with evidence of efficacy, across all solid tumours. It has been indicated as the main bisphosphonate used in clinical practice by clinical experts throughout this appraisal. However market share data for treated patients indicated that disodium pamidronate is used off-license in approximately 20% of the other solid tumour population (Table 14, page 33 of the manufacturer main submission). As a consequence, we included a comparison of denosumab with disodium pamidronate as part of the economic evaluation in accordance with these treatment patterns findings. This pair-wise cost-effectiveness comparison, using bestowd efficacy data for disodium pamidronate in breast cancer in the economic model, indicated that denosumab dominated disodium pamidronate in patients with painful bone metastases and a history of a prior SRE, when including the Patient Access Scheme. Whilst we appreciate that this analysis was not presented by the AG to the Appraisal Committee, we think it is highly likely that this finding would have been shared by the AG if they had undertaken the analysis, since both Amgen and the AG's estimates of the cost-effectiveness of denosumab were highly consistent elsewhere for other comparators and populations.

We kindly request that the criteria for the use of denosumab in solid tumours other than breast and prostate are carefully reconsidered by the appraisal committee and consideration be given to amending the criteria to reflect clinical use of disodium pamidronate in some patients with other solid tumours as per current UK clinical practice. Thereby issuing guidance suitable for implementation by all NHS providers treating bone metastases (recommended amendment marked in underlined text):

'Denosumab is recommended as an option for preventing skeletal-related events in adults with bone metastases from solid tumours other than breast and prostate if:

- *A bisphosphonate is indicated for them **and***
- *if the manufacturer provides denosumab with the discount agreed as part of the patient access scheme.'*

4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We do not believe that there are any particular equality-related issues needing special consideration in this appraisal.

References

1. European Medicines Agency. Summary of opinion (initial authorisation): XGEVA (denosumab). Available at: www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002173/WC500106521.pdf.
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3. Rosen LS, Gordon DH, Dugan W, Jr., Major P, Eisenberg PD, Provencher L et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004;100:36-43.
4. Tierney JF, Stewart LA, Gherzi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8.
5. Fallowfield L, von Moos R, Patrick D, et al. Pain outcomes in a randomized phase phase 3 clinical trial of denosumab vs. zoledronic acid in patients with solid tumours and bone metastases. *ECJ.* 2011; 47s (Suppl): Abstract 7004.
6. Rosen LS, Gordon D, Tchekmedyian S, Yanagihara R, Hirsh V, Krzakowski M et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;21:3150-7