ERG comments added

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Denosumab for the Prevention of Osteoporotic Fractures in Postmenopausal Women

Manufacturer identification of factual inaccuracies in the ERG Report Received 24 March 2010

Amgen UK Ltd.

Submitted 31 March 2010

Page in ERG report	Statement from ERG report	Response/clarification	ERG comment
p7	"The submission from Amgen was much longer than recommended in the NICE guidance to manufacturers. The initial submission was about 460 pages long (though that includes about 60-70 pages of text from NICE) with about 600 pages of appendices. Following remonstrations from NICE…"	We do not consider "remonstrations" to be a factual or appropriate description of the discussions between the Institute and Amgen. As explained in the foreword to our restructured submission, the length of our submission resulted from the breadth of the final scope, as set out by the Institute, and the unusually large volume of data for denosumab. The Institute requested that we attempt to reduce the length of the main submission in order to facilitate ERG and Appraisal Committee review. We were happy to oblige.	The length of the revised submission remained far above that requested the guidance which states that; " A submission should be as succinct and informative as possible. It is expected that the main body of the submission will not usually exceed 75 pages. The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but which is considered to be relevant to the submission. Any additional appendices should be clearly referenced in the body of the submission and should not be used to present core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the efficacy section with 'see appendix X'. " NICE provided an explanatory statement which has been used in revision of this section.
p7	"The initial submission contained a large amount of material on trials which had bone mineral density as the outcome. Given that there are trials of denosumab and the key comparators which report fracture rates, data on BMD were not required. In the revised submission, some of the details of these trials was moved to appendices,	BMD data were included in our submission as this was listed as the second outcome in the final scope for this appraisal.	Fair point, and perhaps NICE issued too broad a scope. But the point about length remains valid.

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	but a lot was retained in the main submission, and was not relevant."		
p7	"The [redacted]	The final scope for the appraisal did not discriminate between fracture type, [redacted]. Furthermore, radiographic vertebral fractures were the primary endpoint in the FREEDOM study.	As above, Amgen are arguing that the fault lies with NICE. But as noted, radiographic-only fractures were, correctly, not included in the modelling and were not relevant to this appraisal. The fact that they were the main outcome in the FREEDOM trial is irrelevant.
p8 p38	"The Amgen submission stated that … the place of denosumab would be in women in whom oral BPs could not be used, either because they could not tolerate them, or because of contraindications to use." "Clinical opinion sought by the ERG suggests these drugs (IV ibandronate and IV zoledronate) are currently considered at the same time denosumab will potentially be considered (i.e. in women who have failed to comply with or tolerate oral BPs)"	This is an inaccurate statement. Our evidence submission stated that "denosumab is expected to be an appropriate option for diagnosed patients for whom oral BPs are unsuitable; reasons for unsuitability include inability to comply with the special instructions for administration, a contraindication or intolerance."	We don't see much difference in these statements about contraindications and tolerance. However, text has been amended.
pp8-9 p12	"The drugs used in the indirect comparison were therefore strontium, raloxifene, teriparatide, zoledronate and intravenous ibandronate (with results from a trial of oral ibandronate being assumed to reflect those of IV ibandronate – data from a trial which showed IV ibandronate to be more effective than oral were not used)." "In the indirect comparison, data from a trial of oral ibandronate were used, and assumed to apply to IV ibandronate. However, the DIVA trial of oral versus IV ibandronate showed that the IV form, given at three monthly intervals, was more	Our rationale for the exclusion of the DIVA study (Eisman et al., 2008) and the MOBILE study (Reginster et al., 2006) was made clear in our response to the second round of clarification questions. The ERG does not appear to have taken our response to that question into account in the report.	It was actually in the first round of clarification responses, page 4. It is correct that the DIVA and MOBILE studies recorded fractures only as adverse events, and that they reported "clinical osteoporotic fractures". But the data could have been used to adjust the oral ibandronate efficacy.

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P18 P26	effective with fracture incidence of 4.8% in the IV groups versus 6.2% in the oral group. This difference was at 2 years follow-up and was not statistically significant, but it could be used in a sensitivity analysis." "In the indirect comparison, Amgen include oral ibandronate but not IV ibandronate, on the grounds that (page 105) "no data for iv ibandronate were identified". The DIVA (Dosing Intra Venous Administration) trial compared injected ibandronate, given at 2-monthly or 30 monthly intervals, with daily oral ibandronate. The primary outcome was BMD. However, the 2-year results from Eisman and colleagues (2008) also provide fracture data.[13] The incidence of clinical osteoporotic fractures was lower in the IV groups than in the oral group – 4.8% versus 6.2%, a difference which was not statistically significantly better. However the key point is that IV ibandronate is at least as good as oral ibandronate, and should be regarded as a valid comparator. The BMD results were highly significantly better, and it is likely that longer follow-up and larger numbers would confirm significant superiority in fractures too. However the correlation between BMD and fracture risk is far from perfect (see below)." "No relevant studies, published at the time, were excluded. However the 2-year DIVA trial[13] report was not used in the indirect comparison."		
p9	**"In women unable to take oral BPs, the ERG considered that zoledronate is the main**	Recently published NICE guidance in postmenopausal osteoporosis (TA160/161) recommends that strontium, raloxifene and no	It is correct that zoledronate has not been appraised by NICE, but it has been licensed for use. The fact that NICE has issued

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p10 p18 p18	**comparator to denosumab."** Whilst the ERG recognises that strontium and raloxifene are primary comparators (p17), in line with current NICE guidance, the group argues strongly that zoledronate is the most appropriate comparator on the basis that: Zoledronate is in routine use: "The submission argued that zoledronate and IV ibandronate should not be primary comparators because they were "not standard care" and because they had not been appraised by NICE. However despite not having been appraised by NICE, both have been licensed for some time and are in routine use in the UK." Zoledronate is recommended by SMC "Zoledronate was approved by the Scottish Medicines Consortium (February 2008) for use in patients who are unsuitable for or unable to tolerate oral treatment options for osteoporosis." Zoledronate has similar efficacy and convenience to denosumab: "zoledronate should be regarded as the main comparator, in patients who cannot take oral BPs, on grounds of convenience and similar efficacy."	treatment be used in patients unsuitable for oral bisphosphonates, depending on risk of fracture as defined by a combination of characteristics (age, T-score, prior fracture, number of independent clinical risk factors). Furthermore, IMS data included in our evidence submission demonstrated that strontium and raloxifene had a combined patient share of 5%, which is 7 and 8 times larger than the zoledronate or ibandronate IV market shares, which were 0.7% and 0.6% respectively (see Table A6, page 39 of our restructured submission). Therefore, strontium and raloxifene are the most relevant comparators on grounds of their significantly more frequent use in routine care across the whole of the UK. One of the founding principles of the Institute was to overcome the problem of inconsistent use of medicines across England and Wales, commonly known as 'postcode prescribing'. Zoledronate and ibandronate IV have not been the subject of NICE appraisal, therefore it is highly likely that there is inconsistent use of these products across England and Wales. The IMS data included in our evidence submission is a robust estimate of the average usage of these products in clinical practice in the UK. We would encourage the ERG to consider very carefully the hierarchy of evidence when making assertions on the relevant comparators. Furthermore, as noted by the ERG	guidance on raloxifene and strontium does not imply that zoledronate should not be used. A key difference here is that SMC considers all new drugs, whereas the agenda set for NICE by DH is more selective. Whether there are regional variations in zoledronate use in England and Wales is not relevant. Note that a criterion used within economic evaluation for deciding on the appropriate comparator is that the treatment should be the next best alternative in terms of outcomes. The evidence would appear to indicate that zoledronate is nearer to being the next best option than either raloxifene or strontium. This suggests that zoledronate is an appropriate comparator, irrespective of market share or current guidance, and can even be argued to be the most appropriate comparator. However we have revised the wording and classed zoledronate as a primary comparator

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		themselves, zoledronate and ibandronate IV have been positively appraised by the Scottish Medicines Consortium, and given that the ERG are based in Scotland, we are concerned that the clinical opinion they have sought may not be representative of clinical practice in England and Wales. The IMS data suggests that this is the case. Therefore, an evidence-based consideration strongly points to the primary comparators being strontium, raloxifene and no treatment, and secondary comparators being IV bisphosphonates. Additionally, we find it surprising that the ERG consider it appropriate to cite similarity of efficacy and convenience as grounds for asserting that a product should be considered the main comparator.	
pp9-10	"The submission reported that denosumab…was cost-effective compared to zoledronate with ICERs reported to be around £70,000 in women with no previous fracture and £29,000 in those with."	The reported ICERs are for zoledronate vs denosumab, therefore the incremental cost per QALY gained with zoledronate compared with denosumab is £70,000 and £29,000 in women with no prior fracture and prior fracture respectively.	We have clarified this statement to avoid any confusion.

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p11 p73	"[redacted]" "A threshold type analysis, undertaken by the ERG, suggests that denosumab will have to save approximately ~£80 per year in admin/monitoring costs in order to retain cost-effectiveness over zoledronate (based in a WTP threshold of £30,000 per QALY, and assuming that zoledronate has no efficacy for prevention of wrist fractures and other types of fragility fracture)."	The figures stated on p11 are inconsistent with those reported on p73, which states threshold of £80 rather than £90.	This is a typo which has now been corrected in the report. It depends on wrist fracture efficacy.
p11	**Wrist fracture efficacy** "Because of absence of data on the effect of zoledronate on wrist fractures, the modelling assumed that it would not reduce the incidence of those, whereas it was assumed that denosumab would, based on data from the FREEDOM trial (though the 95% CI was 0.64 to 1.11). However given the equivalence, or a non-significant slight superiority of zoledronate to denosumab, the ERG	We addressed this point in response to the second round of clarification questions. [redacted]	We summarised the manufacturers view on this point on page 56 of our original report (now p57) However, from Amgen's indirect comparison, zoledronate appears to have slight superiority (non-significant) over denosumab for prevention of non-vertebral fractures. Form what we understand this category includes hip

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pp42-43	considered it unlikely that zoledronate would have no effect on wrist fractures." "Based on the above assumptions zoledronate was modelled (due to absence of evidence) to have no effect on wrist fractures or other types of fracture, while denosumab was modelled to reduce the risk of wrist fracture by 15.8% … it seems counterintuitive to assign denosumab higher efficacy for the prevention of wrist fractures while assuming neither drug has any effect on other types of clinical fracture."	[redacted]	fractures, wrist fracture and other fragility fractures (page113 of Amgen's submission). Given the similar efficacy of zoledronate and denosumab for prevention of hip fractures, and similar efficacy for prevention of all non-vertebral fractures (hip, wrist and others), it seems counterintuitive to us to assign denosumab (non-significant) efficacy for wrist fractures while assuming zoledroate has no efficacy for wrist or other non-vertebral fractures.
p11 p13 p44	**The care setting and associated administration costs for denosumab** The ERG argues that denosumab will be administered in the secondary care setting on the basis that denosumab is a biological agent and would be likely to require specialist advice or be hospital prescription only. "The ERG considers it unlikely that denosumab would be started in general practice. While it currently appears safe, it is a new biological agent with effects on other body systems than bone, including the immune system, and long-term adverse events cannot be entirely ruled out." "It seems unlikely that general practitioners would start patients on such a new biological agent without specialist advice, and so we would expect at least one OP visit to be required. In many cases, we would expect continued hospital follow-up." "[redacted]	As explained in our response to the second set of clarification questions, [redacted]. Therefore the assumption that this is the case can be considered opinion-based rather than factually correct. [redacted]. Given that both denosumab would be less costly and therefore more cost-effective when administered in primary care; and that [redacted], we	The fact that there is no regulatory requirement for denosumab to be given in secondary care does not mean that trusts and GPs will agree to its administration in primary care. Clinical opinion suggested that new biological agents might be flagged for administration in secondary care only. We accept the manufacturer's point that there are no restrictions on the care setting for denosumab and have now summarised this more fully in our report.

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	[redacted]"	would anticipate that recommendations be made to encourage the administration of denosumab in a primary care setting in order to ensure the most efficient use of NHS resources.	
p11 p13 p14 p44	**Primary care & Local Enhanced Services** "The ERG had doubts as to whether, if primary care staff did administer denosumab, GPs would provide it as part of general medical services. It is more likely that it would be regarded as an enhanced service for which an additional payment would be negotiated. The size of such payment is not yet known. Thus the marginal cost per patient of administering denosumab in primary care may be greater than the average cost of two GP visits per year." "If follow-up was partly or mainly in general practice, we doubt if it would be regarded as part of GMS, and would expect it to be covered by an enhanced service agreement at a negotiated cost (which may work out to be greater than the average cost of two GP visits per patient)." "our expectation is that denosumab might not be seen as part of General Medical Services (GMS), and that practices would regard it as part of an enhanced service. Thus the marginal cost per patient to trusts of implementing such a service may work out to be greater than the average cost of two GP appointments. " "If denosumab were to be administered in primary care, it is still likely that patients would require an annual review in secondary care, and it is also	The question of Local Enhanced Service payments was raised by the ERG in the second round of clarification questions. The ERG does not appear to have taken into account our response in the report. Therefore we are reiterating our response to this issue. Regardless of whether an enhanced service payment would be considered appropriate for the delivery of denosumab in primary care, [redacted]. It is important to distinguish between the costs of resources which are directly utilised in providing denosumab and the funding arrangements for primary care. The model fully accounts for the former – with respect to primary care, this is covered by the acquisition cost of denosumab and the cost of the GP visit to administer the injection. Even if the delivery of denosumab in primary care became an enhanced service, the resource costs incurred by the NHS in providing it to a given patient would remain unchanged to those in the model. The enhanced service arrangements would be used as an additional income stream into general practice but would not alter the resource costs of delivering the service to a patient. Therefore, to include the fee provided	Our point here is that we are uncertain as to whether or not average unit costs of the GP visits will reflect the actual cost to trusts of having GPs provide denosumab as an enhanced service. Opinion sought indicated that it would require negotiation between trusts and GPs to set a price per patient. We are simply making the point that the average unit costs may or may not accurately reflect the per patient costs that NHS trusts would face. We have amended the text slightly to clarify that we view this as an uncertainty; i.e. we are not certain that the average costs of GP visits will underestimate the cost to trusts, but it may be an issue. We acknowledge the manufacturers point of view and had briefly summarised this in our report (page 55). To address their concerns we have presented their arguments fully in the report (see section 5.3.2).

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	likely that GPs would demand an enhanced service payment for the delivery of this specialist service. Therefore the average unit costs of a routine GP visit may not reflect the true opportunity cost to trusts of implementing this service."	to general practice for any enhanced service as an additional cost in the model would be inappropriate.	
P13	"It should be noted that in addition to its effects of bone, denosumab might affect the immune system, because it acts by inhibiting RANKL which is involved in lymphocyte differentiation .[3] [redacted]	[redacted]. It is inappropriate to associate denosumab with anti-TNF used in RA as denosumab has a different safety profile to that seen with the anti-TNFs used in rheumatoid arthritis. Denosumab does not bind to TNF-α or TNF-β and there is no binding to TRAIL.	The point here is not about how the drug works. The issue is about the desirability of monitoring the safety of new drugs.
p15	"Only one individual trial of zoldedronic acid showed a statistically significant reduction (RR 0.72, 95% CI 0.56 – 0.91).[6]"	The value is a hazard ratio, not a relative risk.	No response required.
p17	The annual cost of oral alendronate is [redacted].	It is unclear where the cost data for oral alendronate was sourced from. The annual cost of oral alendronate in our restructured appendices (Appendix 9.13 Table 5 p702) is £30.68 (daily) and £47.58 (weekly). The annual cost of oral monthly ibandronate is £220.80.	It comes, as stated, from the current BNF i.e. BNF 59. alendronic acid 10 mg, net price 28-tab pack = £2.30. (versus figures in Appendix 9.13 table 5 of 10 mg 28 tabs = £2.35) Alendronic Acid Once-Weekly 70 mg, net price 4-tab pack = £1.16 (versus figures in Appendix 9.13 table 5 of 70 mg 4 tabs = £3.66) Difference in monthly ibandronate cost due to rounding differences
p22	The ERG states that in the economic analysis "no mention is made of persistence with denosumab	This is incorrect. In our restructured submission, we explain how the persistence	Accepted. We made it clear to NICE that because of the length of the submission, we would not be

<table>
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<tr><td></td><td>varying”.</td><td>with denosumab had been varied (see section 6.2.8 pp 170-171 in the submission).</td><td>responsible if occasional things were missed.</td></tr>
<tr><td>P29</td><td>“Hip fractures rates were reduced from 1.2% in the placebo group to 0.7% in the denosumab group, relative risk (RR) 0.60 (95% CI 0.37 – 0.97).

Clinical vertebral fractures were reduced from 2.6% in the placebo arm to 0.8% in the denosumab arm, RR 0.31 (95% CI 0.20-0.47)”</td><td>The values presented are hazard ratios, not relative risk</td><td>No response required.</td></tr>
<tr><td>p30</td><td>Table 1 Direct comparison of each comparator with placebo
<table><tr><th></th><th>Clinical Vertebral RR (95% CI</th><th>Non-Vertebral RR (95% CI)</th><th>Hip RR (95% CI)</th><th>Wrist RR (95% CI)</th></tr><tr><td>Denosumab</td><td>0.32 (0.21-0.48)</td><td>0.81 (0.69-0.96)</td><td>0.61 (0.37 – 1.00)</td><td>0.84 (0.64-1.1)</td></tr><tr><td>Zoledronate</td><td>0.23 (0.14-0.37)</td><td>0.75 (0.65-0.87)</td><td>0.59 (0.42-0.83)</td><td>-</td></tr><tr><td>Raloxifene</td><td>0.45 (0.05-3.82)</td><td>0.66 (0.16-2.65)</td><td>-</td><td>-</td></tr><tr><td>Strontium</td><td>0.65 (0.50-0.84)</td><td>0.88 (0.78-0.99)</td><td>0.89 (0.67-1.2)</td><td>0.98 (0.73-1.31)</td></tr></table></td><td>If rounding consistently to two digits beyond the decimal, three rounding errors were noted in this table (underlined). The correct figures are:
the 95% CI for hip RR for denosumab is 0.37-0.98;
the 95% CI for wrist RR for denosumab is 0.66-1.11;
the 95% CI for strontium is 0.67-1.18.</td><td>The figures from Amgen varied slightly in different parts of the submission and the published paper. Table 2 of Cummings et al 2009 (The FREEDOM trial) gives the “Relative risk of hazard ratio (95% CI) for hip fractures as 0.60 (0.37 to 0.97)”.

Table B21 of the industry submission gives “Relative risk or hazard ration of hip fracture 0.61 (0.37 to 0.98)”

Table B22 of the submission gives “hip fracture RR = 0.605 (0.373 t0 0.983)” and “wrist fracture RR = 0.842 (0.638 to 1.110)”.

But these differences are trivial.</td></tr>
<tr><td>p35</td><td>“Initial clarifications sought from the manufacturer”</td><td>[redacted]</td><td>This table lists the requests for clarifications relating to the cost-effectiveness model. The second round was a request for additional</td></tr>
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		[redacted].	analysis, and we have attempted to summarise the manufacturers responses to these requests at the appropriate points throughout the report. Additional text has been added to more fully convey the manufacturers point of view where they feel their case has not been represented (see section 5.2.6).
pp42-43	The ERG report states that "zoledronate has if anything slightly higher efficacy for prevention of non-vertebral fractures".	This statement is incomplete as in order to be factually correct it needs to highlight the lack of statistical significance in the indirect comparison results of denosumab versus zoledronate efficacy. This could be confusing to the reader.	The statement in the ER was based on the data from the Amgen indirect comparison, and it is correct that the slight superiority of zoledronate was not statistically significant. But the words "if anything" imply uncertainty. We have now explicitly stated that this is non-significant.
p44	"Clinical opinion sought by the ERG suggested that if denosumab were to be initiated and administered in secondary care, it would require an annual review to check bone markers and vitamin D status as well as an outpatient/day case appointment to administer the drug.	As explained in our response to the second set of clarification questions, there is no rationale for bone turnover markers to be reviewed. We are disappointed that the ERG has not taken our response into account in the report.	It is correct that there is no requirement for bone markers to be checked. But we think they would often be checked. This would also apply to zoledronate. Our additional sensitivity analysis did not include additional costs to check bone markers.
p53	In Table 10 the ICER for teriparatide vs. low-cost comparator is written as ",073,082"	The ICER for teriparatide vs. low-cost comparator is £2,073,082.	This typo has been amended.
p54	The ERG incorrectly concludes that the cost-effectiveness of denosumab versus strontium and raloxifene is inconsequential because strontium	The point that strontium and raloxifene do not compare favourably with no treatment is irrelevant since denosumab has demonstrated cost-effectiveness versus both these	We were making the point here that in many subgroups within the base case cohorts, strontium and raloxifene are not cost-effective and not recommended by NICE (particularly in

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	and raloxifene are themselves not cost effective.	comparators and no treatment in the basecase analysis (age 70yrs, T-score ≤-2.5. Recently published NICE guidance in postmenopausal osteoporosis (TA160/161) recommends that strontium and raloxifene be used in patients unsuitable for oral bisphosphonates, depending on risk of fracture as defined by a combination of characteristics (age, T-score, prior fracture, number of independent clinical risk factors). The fact that strontium and raloxifene are recommended by NICE in patients unsuitable for oral bisphosphonates secures their relevance as comparators for the appraisal of denosumab. Moreover, the cost-effectiveness of strontium and raloxifene is not within the scope of this appraisal.	women with no prior fragility fracture). Thus interpretation of the base case comparisons with raloxifene and strontium requires caution. We have amended the text to clarify this point.
p72	"Denosumab only remains cost-effective compared with no treatment in women with a prior fragility fracture. Zoledronate dominates denosumab in women with and without prior fragility fractures with these costing assumptions."	[redacted]. Recently published NICE guidance in postmenopausal osteoporosis (TA160/161) recommends that strontium and raloxifene be used in patients unsuitable for oral bisphosphonates.	All the ICERs are presented in Tables 19 and 20. Addition clarifications have been added to the text. The analysis was conducted to account for advice from a trust in England which suggested that denosumab might be flagged for administration in secondary care only.