Denosumab for the prevention of skeletal-related events (SRE) in adults with bone metastases from solid tumours

[redacted]

Assessment Group response to Amgen comment 2.2 made in response to the Appraisal Consultation Document (ACD).

The Assessment Group (AG) are grateful for the manufacturer's response to the ACD in which they clarify the source of the hazard ratio (HR) used in their network meta-analysis (NMA) for time to first SRE comparing zoledronate to pamidronate.

The manufacturer pooled the HRs published in the FDA report of the Novartis 010 study to combine results from the chemotherapy and hormone therapy groups. The AG is satisfied that relevant data were used by the manufacturer and the method for pooling the HRs was both appropriate and correctly applied. The AG replicated the manufacturer's approach and arrived at a very similar estimate of 0.89 (95% CI 0.72 to 1.10).

The results in the FDA report allow for a pooled HR to be estimated from HRs and confidence intervals presented separately for the chemotherapy and hormone therapy groups, which is a more robust method than estimating the pooled hazard ratio from survival curves. The FDA data were not used in the AG NMA because the FDA report was not identified in the AG search and nor was it referenced in the manufacturer submission. Using the Novartis study published by Rosen, the best estimate of the HR obtainable by the AG required the use of curve methods.

If the FDA data were to be used in a revised AG NMA, the only input that would differ from the NMA in the TAR would be the HR for zoledronate versus pamidronate for time to first SRE. The Novartis study only looked at two treatments (zoledronate and pamidronate) and did not include time to first-and-subsequent SRE as an outcome.

The AG has re-run its NMA model for time to first SRE to examine the effect of replacing the Rosen curve estimate of 0.97 (95% CI 0.78 to 1.20) with the FDA pooled HR of 0.89 (95% CI 0.72 to 1.10). The estimated HR from the revised posterior distribution for denosumab versus pamidronate is slightly lower at 0.73 (95% CI 0.56 to 0.94), compared with 0.79 (95% CI 0.56 to 1.03). The resulting estimates for denosumab versus zoledronate, denosumab versus placebo and zoledronate versus placebo all remain unchanged.

The impact of this change upon the cost utility model estimates is relatively minor.

- For the SRE naïve subgroup denosumab compared to pamidronate was previously estimated to result in 0.177 fewer SREs, a 0.009 QALY gain and a cost saving of

£3,118 when the PAS is included. With the revised HR TTF SRE estimate these increase to 0.249 fewer SREs, a 0.013 QALY gain and a cost saving of £3,205.

- For the SRE experienced subgroup the revised HR TTF SRE estimate does not affect results.
- Across all patients denosumab compared to pamidronate was previously estimated to result in 0.274 fewer SREs, a 0.010 QALY gain and a cost saving of £3,253 when the PAS is included. With the revised HR TTF SRE estimate these increase to 0.317 fewer SREs, a 0.012 QALY gain and a cost saving of £3,305.

Previous errata correction to AG report estimates.

Table 106 Breast cancer AG NMA cost effectiveness results

All Patients	SREs	net	QALYs	net	Tx Costs	net	All Costs	net	ICER
BSC	3.159	-0.988	1.821	0.027				£6,242	£229,547
inc PAS								£4,292	£157,829
Zol. Acid	2.383	-0.211	1.841	0.007				£1,707	£245,264
inc PAS								-£243	Dominant
Denosumab	2.171		1.848						
inc PAS									
Pamidronate	2.445	-0.274	1.839	0.010				-£1,303	Dominant
inc PAS								-£3,253	Dominant
SRE Naive	SREs	net	QALYs	net				net	ICER
BSC	2.807	-0.962	1.850	0.035				£6,308	£181,092
inc PAS								£4,358	£125,109
Zol. Acid	2.031	-0.186	1.876	0.008				£1,747	£209,345
inc PAS								-£203	Dominant
Denosumab	1.845		1.884						
inc PAS									
Pamidronate	2.022	-0.177	1.875	0.009				-£1,168	Dominant
inc PAS								-£3,118	Dominant

The table below shows the impact of revising the deterministic estimate for HR TTF SRE for pamidronate versus zoledronic acid from the 1.031 of the AG NMA fixed effects model to the 1.127 implied by the above revisions due to the adoption of the FDA data. Only the costs and effectiveness estimates for pamidronate is affected. These revisions have no impact upon the results for the SRE experienced group of patients.

Table 106 Breast cancer AG NMA cost effectiveness results (revised)

All Patients	SREs	net	QALYs	net	Tx Costs	net	All Costs	net	ICER
BSC	3.159	-0.988	1.821	0.027	[redacted]		[redacted]	£6,242	£229,547
inc PAS								£4,292	£157,829
Zol. Acid	2.383	-0.211	1.841	0.007	[redacted]		[redacted]	£1,707	£245,264
inc PAS								-£243	Dominant
Denosumab	2.171		1.848		[redacted]		[redacted]		
inc PAS									
Pamidronate	2.488	-0.317	1.836	0.012	[redacted]		[redacted]	-£1,355	Dominant
inc PAS								-£3,305	Dominant
SRE Naive	SREs	net	QALYs	net	[redacted]		[redacted]	net	ICER
BSC	2.807	-0.962	1.850	0.035	[redacted]		[redacted]	£6,308	£181,092
inc PAS								£4,358	£125,109
Zol. Acid	2.031	-0.186	1.876	0.008	[redacted]		[redacted]	£1,747	£209,345
inc PAS								-£203	Dominant
Denosumab	1.845		1.884		[redacted]		[redacted]		
inc PAS									
Pamidronate	2.094	-0.249	1.871	0.013	[redacted]		[redacted]	-£1,255	Dominant
inc PAS								-£3,205	Dominant