KSR Ltd

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ADDENDUM TO
Tolvaptan for treating autosomal dominant polycystic kidney disease

As requested during the PMB teleconference on 18 March 2015, the ERG conducted additional analyses which are presented below.

The Company provided a scenario analysis using the percentage relative reduction in eGFR decline (i.e. treatment effectiveness) based on CKD-EPI (26.4%) instead of based on 1 / serum creatinine (31.6%). The results of this scenario are presented in Table 1.

Table 1: Company's base case (with PAS) using CKD-EPI for the percentage relative reduction in eGFR only

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.44	13.38	£35,755	0.68	0.75	[redacted]

This scenario analysis, presented by the Company, did however not use CKD-EPI as an approximation of eGFR for the "annual change in renal function". The ERG would prefer a scenario analysis using CKD-EPI for both "percentage relative reduction in eGFR decline" and "annual change in renal function". The latter includes annual change in renal function during the first three years (modelled as observed over the trial period) and thereafter (extrapolated using regression equations). This scenario analysis is presented in Table 2.

Table 2: Company's base case (with PAS) using CKD-EPI as an approximation for eGFR

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Standard treatment	[redacted]	16.82	12.68				
Tolvaptan	[redacted]	17.47	13.40	£36,411	0.65	0.72	[redacted]

In the ERG report, the exploratory scenario analysis and additional analyses used 1 / serum creatinine as an approximation of eGFR. The ERG has now also used CKD-EPI as an approximation for eGFR to perform these analyses. Tables 6.1 and 6.2 of the ERG report for these analyses are presented below (Tables 3 and 4). For convenience, the original tables from the ERG containing the exploratory and scenario analyses using 1 / serum creatinine for approximating eGFR are reported in Tables 5 and 6. Note that the exploratory scenario analyses (Tables 3 and 5) now also contain a 'combined' analyses (at the bottom) combining all exploratory scenario analyses. This analysis should however be regarded as a worst case scenario considering the assumptions examined in the exploratory analyses presented in Tables 3 and 5.

Table 3: Exploratory scenario analyses performed by the ERG (with PAS) using CKD-EPI as an approximation for eGFR
(New table, using CKD-EPI as an approximation for eGFR)

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Assuming that 3 out of 10 Hy's Law cases would have a liver transplant at year 1 and would die immediately thereafter							
Standard treatment	[redacted]	16.81	12.68				
Tolvaptan	[redacted]	17.42	13.37	£36,272	0.61	0.68	£53,056
Assuming increased mortality (hazard ratio: 2.0)							
Standard treatment	[redacted]	16.42	12.43				
Tolvaptan	[redacted]	17.02	13.11	£35,031	0.60	0.69	£50,931
Assuming treatment discontinuation of 6.5% after year 3							
Standard treatment	[redacted]	16.81	12.68				
Tolvaptan	[redacted]	17.27	13.19	£30,662	0.46	0.51	£60,652
Assuming increased monitoring costs							
Standard treatment	[redacted]	16.80	12.68				
Tolvaptan	[redacted]	17.46	13.40	£37,787	0.66	0.72	£52,134
Assuming decreased post-transplant costs							
Standard treatment	[redacted]	16.81	12.68				
Tolvaptan	[redacted]	17.47	13.41	£40,199	0.66	0.72	£55,582
Combined scenario analysis (combination of the exploratory scenarios presented above)							
Standard treatment	[redacted]	16.40	12.42				
Tolvaptan	[redacted]	16.77	12.86	£32,095	0.37	0.44	£72,705

ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LY = life year(s); QALYs = quality-adjusted life years

Table 4: Additional analyses performed by the ERG (with PAS) using CKD-EPI as approximation for eGFR
(New table, using CKD-EPI as an approximation for eGFR)

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Company base case							
Standard treatment	[redacted]	16.82	12.68				
Tolvaptan	[redacted]	17.47	13.40	£36,411	0.65	0.72	£50,524
Correct model code error							
Standard treatment	[redacted]	16.81	12.68				
Tolvaptan	[redacted]	17.47	13.41	£36,779	0.66	0.72	£50,854
Equal kidney pain probability for both arms[a]							
Standard treatment	[redacted]	16.81	12.68				
Tolvaptan	[redacted]	17.47	13.40	£36,901	0.66	0.71	£51,713
Equal CKD-stage costs for CKD-stage 3 as for CKD-stage 4[b]							
Standard treatment	[redacted]	16.81	12.68				
Tolvaptan	[redacted]	17.47	13.41	£38,062	0.66	0.72	£52,628
Disutility of 0,0123 for Tolvaptan treatment[c]							
Standard treatment	[redacted]	16.80	12.68				
Tolvaptan	[redacted]	17.46	13.28	£36,590	0.66	0.60	£60,665
Disutility of 0,02 for HD and PD complications[d]							
Standard treatment	[redacted]	16.81	12.72				
Tolvaptan	[redacted]	17.47	13.43	£36,779	0.66	0.72	£51,226
ERG base case (combination of the scenarios presented above)							
Standard treatment	[redacted]	16.80	12.71				
Tolvaptan	[redacted]	17.46	13.30	£37,956	0.66	0.59	£64,515

ICER = incremental cost-effectiveness ratio; LY = life year(s); QALYs = quality-adjusted life years
[a] Incorporated by adjusting H59:I62 in worksheet 'Control'
[b] Incorporated by adjusting E30:F30 in worksheet 'Cost & Utility Input'
[c] Incorporated by adjusting E92 in worksheet 'Cost & Utility Input'
[d] Incorporated by adjusting E102:E103 in worksheet 'Cost & Utility Input'

Table 5: Exploratory scenario analyses performed by the ERG (with PAS) using 1 / serum creatinine as an approximation for eGFR
(Table 6.1 of the original ERG report, combined scenario analysis added)

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Assuming that 3 out of 10 Hy's Law cases would have a liver transplant at year 1 and would die immediately thereafter							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.54	13.51	£31.341	0.78	0.88	£35,751
Assuming increased mortality (hazard ratio: 2.0)							
Standard treatment	[redacted]	16.36	12.37				
Tolvaptan	[redacted]	17.11	13.23	£29,902	0.75	0.86	£34,754
Assuming treatment discontinuation of 6.5% after year 3							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.32	13.26	£26,922	0.56	0.63	£42,893
Assuming increased monitoring costs							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.57	13.53	£32,744	0.82	0.91	£36,167
Assuming decreased post-transplant costs							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.57	13.53	£35,992	0.83	0.91	£39,264
Combined scenario analysis (combination of the exploratory scenarios presented above)							
Standard treatment	[redacted]	16.36	12.37				
Tolvaptan	[redacted]	16.81	12.92	£29,013	0.46	0.55	£52,741

ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LY = life year(s); QALYs = quality-adjusted life years

Table 6: Additional analyses performed by the ERG (with PAS) using 1 / serum creatinine as approximation for eGFR
(Table 6.2 of the original ERG report)

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Company base case							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.58	13.54	£31,583	0.82	0.91	£34,769
Correct model code error							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.59	13.55	£31,838	0.83	0.92	£34,733
Equal kidney pain probability for both arms[a]							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.59	13.54	£31,964	0.83	0.91	£35,252
Equal CKD-stage costs for CKD-stage 3 as for CKD-stage 4[b]							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.59	13.55	£33,216	0.83	0.92	£36,236
Disutility of 0.0123 for Tolvaptan treatment[c]							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.57	13.41	£31,501	0.82	0.78	£40,401
Disutility of 0.02 for HD and PD complications[d]							
Standard treatment	[redacted]	16.76	12.66				
Tolvaptan	[redacted]	17.59	13.57	£31,838	0.83	0.91	£34,996
ERG base case (combination of the scenarios presented above)							
Standard treatment	[redacted]	16.76	12.66				
Tolvaptan	[redacted]	17.57	13.42	£33,015	0.82	0.76	£43,280

ICER = incremental cost-effectiveness ratio; LY = life year(s); QALYs = quality-adjusted life years
[a] Incorporated by adjusting H59:I62 in worksheet 'Control'
[b] Incorporated by adjusting E30:F30 in worksheet 'Cost & Utility Input'
[c] Incorporated by adjusting E92 in worksheet 'Cost & Utility Input'
[d] Incorporated by adjusting E102:E103 in worksheet 'Cost & Utility Input'