NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Tolvaptan for treating autosomal dominant polycystic kidney disease

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Standard of care (including routine surveillance) is the comparator in this appraisal; it is also included in the intervention strategy as a background treatment. The company acknowledges there were variations in clinical care received across the study sites in the main trial (TEMPO 3:4). What is standard of care in UK clinical practice for patients with autosomal dominant polycystic kidney disease (ADPKD)?
- The anticipated marketing authorisation of tolvaptan specifies adults with Chronic Kidney Disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease. In the clinical trial, rapidly progressing disease was

defined as meeting modified Ravine criteria, total kidney volume (TKV) ≥ 750 mL and estimated creatinine clearance ≥ 60 mL/min. Does the Committee consider that patients with rapidly progressing disease can be identified in clinical practice?

- The initial daily dose of tolvaptan (60 mg as a split-dose regimen of 45 mg plus 15 mg) is titrated upward to 90 mg tolvaptan (60 mg plus 30 mg) per day and then to a target of 120 mg (90 mg plus 30 mg) per day, if tolerated. Patients may down-titrate to lower doses based on tolerability. There is limited evidence in the company submission to determine whether the efficacy of tolvaptan and the frequency and type of adverse effects are dose-related. What is the Committee's opinion regarding this?
- Data are only available for patients aged between 18 and 50 yet the indication, and the remit for this appraisal, has no upper age limit. The number of patients from the UK included in the clinical trial was 5% (n=73). Only 17% of patients had CKD stage 3 disease. Does the Committee consider that the results of the trial are generalisable for patients in England?
- The primary outcome of the trial was annual rate of change in total kidney volume (TKV). Rate of decline of renal function (the main outcome in the scope) was measured as a secondary outcome in the trial, using the reciprocal of serum creatinine level. It was also assessed by the Chronic Kidney Disease Epidemiology (CKD-EPI) equation. What is the Committee's preferred measure of the decline of renal function?

Cost effectiveness

- The effectiveness of tolvaptan was modelled by adjusting the decrease in annual eGFR decline for tolvaptan by a percentage of that for standard care (31.6% reduction, based on the measure of eGFR in the trial using the reciprocal of serum creatinine).The company considered this approach more appropriate than using the primary endpoint (TKV) as an intermediate outcome. Is eGFR, rather than TKV, the most appropriate outcome for estimation of the relative treatment effect between tolvaptan and standard care?
- In a scenario analysis performed by the company, an alternative measure of eGFR (CKD-EPI) from the trial was used to adjust the percentage decrease in

annual eGFR decline (26.4% reduction compared with standard care). Which assessment of eGFR does the Committee consider to be most appropriate for use in the economic model?

- The model assumed that the relative treatment effect (31.6% reduction in annual rate of eGFR decline) is constant over time. In response to clarification questions, the company conducted analyses showing the effect on the ICER when 50%, 10% or 0% of the treatment effect is assumed after 3 years. In all cases the ICER increases significantly. What is the Committee's preferred assumption for the treatment effect beyond the length of available data, i.e. after 3 years?
- The model assumed a treatment discontinuation rate of 0.5% after 3 years, which the company states to be broadly in line with the trend seen in TEMPO 3:4. The ERG conducted an exploratory analysis using 6.5% after 3 years (equal to that observed in the second year in TEMPO 3:4), which increased the ICER substantially. What is the Committee's preferred assumption for treatment discontinuation rates after 3 years?
- The model assumed that adverse effects of tolvaptan treatment were incorporated in the existing costs and utilities associated with each health state. Only clinically significant kidney pain was modelled separately. The ERG questioned this assumption and applied a 0.0123 utility decrement for tolvaptan treatment. Does the Committee agree with the inclusion of a disutility for tolvaptan treatment, due to adverse effects? If so, is the value of 0.0123 appropriate?
- Drug-induced liver injury (DILI) was not included in the model, however there were 3 Hy's Law cases (see below) reported during the TEMPO 3:4 and TEMPO 4:4 trials. Would it be appropriate to include liver complications based on Hy's law in the model?
- Due to the risk of DILI associated with tolvaptan the company proposed a risk management programme, which includes liver function testing prior starting tolvaptan treatment, then monthly for 18 months and 3 monthly thereafter. The ERG explored the effect of additional costs for 4.4% of patients who might be assumed to have an abnormal result detected through increased monitoring. Does the Committee agree with the ERG's suggestion for increased costs associated with additional monitoring?

- The model utilised mortality rates that were for the general population, due to the lack of ADPKD specific mortality data. The ERG explored a higher mortality risk (using a hazard ratio of 2) in CKD stages 1 to 4. What is the Committee's preferred assumption for the risk of mortality for people with ADPKD?
- Estimates of the base case ICER (company and ERG) are similar (£34,733 and £34,769 respectively). However, some of the exploratory and sensitivity analyses had a significant impact (ERG's assumption of 6.5% treatment discontinuation after 3 years increased the ICER to £42,893; the Company's exploratory analysis using 50% treatment effect after 3 years increased the ICER to £92,051). What is the most plausible ICER?
- Does the Committee consider there are any equalities issues to discuss (no issues have been raised during the appraisal to date)?
- According to the manufacturer tolvaptan represents a 'step change', this is the first drug available for the treatment of ADPKD, in an area of high unmet medical need. Does the Committee agree that tolvaptan is innovative?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal is: To appraise the clinical and cost effectiveness of tolvaptan within its licensed indication for treating autosomal dominant polycystic kidney disease.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with autosomal dominant polycystic kidney disease		N/A	N/A
Int.	Standard care in combination with tolvaptan		N/A	N/A
Com.	Standard care including routine surveillance without tolvaptan (No active treatment)		N/A	N/A
Out.	The outcome measures to be	The outcome measures in the	The primary outcome in the	N/A

	considered: • rate of decline of renal function • symptoms of chronic kidney disease (including pain) • mortality • adverse effects of treatment • HRQL	submission: • rate of decline of renal function (including percentage change in TKV) • symptoms of chronic disease (including pain) • mortality • adverse effects of treatment • HRQL	TEMPO 3:4 trial is TKV, which the company considers a surrogate measure of treatment efficacy, and a prognostic indicator for ADPKD progression. However, TKV is not the main outcome driving the economic model, which is eGFR.	

TKV = total kidney volume; eGFR = estimated glomerular filtration rate; HRQL = Health related quality of life; ADPKD = autosomal dominant polycystic kidney disease

2 The technology and the treatment pathway

2.1 Tolvaptan (Jinarc, Otsuka Pharmaceuticals UK) is a selective vasopressin antagonist. By inhibiting the binding of vasopressin to the V2 receptors, tolvaptan reduces cell proliferation, cyst formation and fluid excretion. This reduces kidney growth and protects kidney function. It is an oral preparation which is taken twice daily.

2.2 Autosomal dominant polycystic kidney disease (ADPKD) is an inherited progressive cystic renal disease which is characterised by a build-up of fluid filled cysts in the kidney. In England and Wales, the diagnosed prevalence of ADPKD is estimated as 3.9 per 10,000. ADPKD has a highly heterogeneous disease course; however the majority of patients with ADPKD eventually develop end-stage renal disease (ESRD). By a mean age of 56 to 60 years, patients with ADPKD reach ESRD and require renal replacement therapy (RRT) such as dialysis and transplantation, which have a substantial clinical and economic impact (see section 2.1 of the submission). People with ADPKD should be referred for specialist assessment and monitored to identify evidence of progressive chronic kidney disease (CKD).

2.3 Currently no pharmacological treatments are available that reduce the progression or growth of renal cysts in ADPKD. Current standard care generally targets the symptoms and complications of kidney disease, such as hypertension and includes only monitoring of kidney function and disease progression. Patients receiving tolvaptan would continue receiving standard care, as necessary.

2.4 The anticipated wording of the MA specifies that treatment with tolvaptan should be started when there is evidence of rapidly progressing disease. In the clinical trials, rapidly progressing disease was defined as meeting modified Ravine criteria, total kidney volume (TKV) ≥ 750 mL, estimated creatinine clearance ≥ 60 mL/min. At baseline, patients had an average estimated glomerular filtration rate (eGFR) of 82 mL/min/1.73m^2 (CKD-EPI) with 79% having hypertension and a mean TKV of 1692 mL (height adjusted 972 mL/m).

Table 2 Technology

	Tolvaptan	**Standard care**
Marketing authorisation	Tolvaptan currently does not have a MA. Anticipated wording according to the draft SmPC: 'Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.'	N/A
Administration method	Tolvaptan administered orally. Hepatotoxicity has been observed in some patients receiving tolvaptan for ADPKD, To manage the risk of serious liver injury, liver function testing is required prior starting tolvaptan treatment, then monthly for 18 months and 3 monthly thereafter (see section 4.4 of SmPC)	N/A
Cost information	NHS list price:	Consultant visits (Nephrologist) - £139.0

	£1,208.20 for each 28-day pack (£43.15 per day) Acquisition cost under proposed PAS scheme: [redacted] Tolvaptan 15 mg, 30 mg, 60 mg, and 90 mg tablets (provided in 28-day packs of split-dose tablets). The monthly cost of tolvaptan treatment is [redacted], the yearly cost is [redacted] Dosing: Twice daily (upon waking and 8 hours later). Doses can be titrated according to tolerability. Length of treatment: long term treatment, until onset of ESRD or renal replacement therapy if ESRD has not been reached.	- once a year Consultation with a specialist nurse - £25.00 – once a year Biochemistry test - £1.25 – once a year Haematology test - £3.01 – once a year Phlebotomy - £3.64 – once a year Ultrasound - £51.00- one time only

See summary of product characteristics (SmPC) for details on adverse reactions and contraindications.

ERG comments

2.5 The prevalence of ADPKD is estimated as 3.9 per 10,000 according to the company submission and the undiagnosed prevalence is estimated as 4.3 per 10,000. However the ERG identified a discrepancy in the company submission, since in section 2.1 the company states that the total prevalence was estimated as 4.3 per 10,000. During clarification the ERG has asked the company to define ‘undiagnosed prevalence’ and received the following response; ‘undiagnosed ADPKD refers to those individuals who are anticipated to have ADPKD but have not had any formal diagnosis.’ The ERG also asked the company to provide correct prevalence rates for diagnosed and undiagnosed prevalence, and the company presented that the estimated prevalence of ADPKD is 3.9 per 10,000, the undiagnosed prevalence is estimated as 0.4 per 10,000 and the total prevalence of ADPKD is estimated as 4.3 per 10,000. The ERG noted in their report that the estimated prevalence of

undiagnosed patients could be much higher, because in the past high risk groups might have chosen not to know their disease status due to the lack of therapeutic options. However, if tolvaptan was approved as a therapy for ADPKD these patients might seek diagnosis; therefore the prevalence of ADPKD might increase significantly.

2.6 The ERG noted that currently there is no clear classification system for disease progression; therefore it is difficult to define and identify rapidly progressing ADPKD. According to the recent NICE clinical guideline on chronic kidney disease (CG 182) accelerated progression of CKD is defined as; ‘a sustained decrease in glomerular filtration rate (GFR) of 25% or more and a change in GFR category within 12 months or a sustained decrease in GFR of 15 ml/min/1.73 m2 per year’. The ERG also noted the company’s response to clarification that states ‘an objective definition of rapidly progressing ADPKD has not been agreed within the clinical community’.

3 Comments from consultees

Comments from consultees included 2 submissions from clinical experts, 2 submissions from patient experts, 1 submission from a patient group and 2 submissions from professional groups.

3.1 Consultees emphasised that currently there are no disease-modifying treatments available for ADPKD. Current standard of care aims to manage the symptoms by monitoring kidney function, offering treatment for symptoms or complications and early planning and preparation for renal replacement therapy. Upon disease progression, patients receive renal replacement therapy, which can be either dialysis or transplantation. Tolvaptan is the first drug to slow down disease progression and slow the deterioration of renal function and delays the requirement of renal replacement therapy.

3.2 The patient experts explained that ADPKD is a debilitating and painful disease. Pain usually results from an enlarged kidney, cyst raptures or infections. This results in discomfort, limiting the amount that can be eaten and also increasing the waist line. One third of them reported their general health as fair or poor. They have also reported significant tiredness and fatigue and 70% said that they were limited in their ability to do activities, such as running, lifting or climbing stairs. ADPKD puts a huge mental burden on the patients, because it is a genetic disorder. The biggest advantage of tolvaptan treatment is that it slows down the progression of the disease and enables patients to continue to have a full and active work and personal life.

3.3 It is usual that patients with progressed disease would need a carer; therefore patient experts highlighted that tolvaptan enables two people in the family to stay in the work force for longer and to avoid significant financial burden and loss of earnings.

3.4 There are some major lifestyle challenges which have to be implemented with tolvaptan treatment. These are associated with the fact that they have to drink 6-8 litres of water per day, even during the night and it results in more frequent urination. It affects quality of life due to reduced quality and quantity of sleeping. It also affects a person's social life and daily activities and causes patients to focus on access to water and toilet facilities. However, the discomfort caused by the symptoms during the night can be reduced by changing the time of taking the drug. Overall these side effects are considered manageable and the advantages of tolvaptan outweigh the disadvantages.

3.5 Professional groups explained that implementing this new technology does not require any major clinical challenges compared to the current management of the disease. Tolvaptan would most

likely to be used in secondary care and for implementation ADPKD specific care pathways and should be developed.

3.6 The main disadvantages of the therapy listed by consultees are the challenges of drug tolerability due to side effects, such as thirst and polyuria. It is not clear which patients would benefit the most from treatment with tolvaptan but it is likely to be most beneficial for those patients whose renal function is just starting to decline. The results of the survey conducted by the patient group showed that the importance may be greater for younger patients.

3.7 Consultees suggested that subgroups can be identified by stratification of the patients on the basis of genetic mutations (PKD 1-3 genes). PKD 2 group has a later onset of ESRD and slower progression, so might be a subgroup of interest.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company identified seventeen clinical studies through systematic review that presented information about the safety and efficacy of tolvaptan. In the submission the results of four of these studies were presented; one randomised controlled trial (RCT) was fully presented and three non-RCTs were identified and partially presented.

1. **TEMPO 3:4**: a phase III, multicentre, double-blind, placebo-controlled, parallel-arm trial. Patients were randomised in a 2:1 ratio to tolvaptan (n = 961) administered twice daily in a split-dose, or placebo (n = 484) over three years (Torres *et al*., 2012a (journal article), Torres *et al*., 2012b (supplementary index)).

TEMPO 3:4

4.2 TEMPO 3:4 was a phase III, international, multicentre, double-blind, placebo-controlled, parallel-arm, randomised controlled trial. 1,445 patients were randomised in a 2:1 ratio to either the tolvaptan (n=961) or the placebo (n=484) arm. Patients aged 15-80 years with ADPKD and eGFR ≥ 60 mL/min and with a TKV of ≥ 750 mL (as measured by MRI) were included in the trial. Tolvaptan and placebo were administered orally, twice daily (in the morning and afternoon). The dose was titrated in weekly intervals over a 3-week period, initially administered at a dose of 45 mg and 15 mg, in the morning and afternoon, respectively, and titrated to 60 mg and 30 mg, and then to 90 mg and 30 mg, according to patient-reported tolerability. Following the titration period, patients received the maximum tolerated dose for the remainder of the treatment period. Patients were monitored every 4 months during a 36-month treatment period. Two additional follow-up visits were also conducted 7 to 21 days after month 36 and 7 to 21 days after the first follow-up visit. The baseline demographics were balanced in terms of age, sex, race, and factors influencing ADPKD progression (see section 6.3.2 of the submission and table B6). The mean age was 38.7 years. The mean TKV was 1,705 mL in the tolvaptan and 1,668 mL in the placebo group. Tolvaptan and placebo patients were evenly distributed at baseline across Kidney Disease Outcomes Quality Initiative CKD stages 1 (34.5% and 35.9%), 2 (48.5% and 46.5%), and 3 (17.0% and 17.4%), respectively. 73 patients came from the UK.

4.3 Health related quality of life (HRQoL) was not assessed in the TEMPO 3:4 trial, however it was defined as an outcome in the final scope. Therefore no ADPKD specific EQ-5D health state utility values (HSUV) were available, and the company conducted a literature search for identifying ADPKD or ESRD specific utility values. For further details on modelling HSUV see section 5.15 below.

4.4 The primary endpoint of the TEMPO 3:4 trial was rate of TKV change from baseline for tolvaptan relative to placebo, as measured by magnetic resonance imaging. Data on the rate of decline of renal function (listed in the final scope as an outcome measure) is also available. In TEMPO 3:4 the key composite secondary endpoint was time to onset of multiple ADPKD outcomes (worsening renal function, new onset hypertension, worsening hypertension, renal pain and worsening albuminuria). Out of these outcomes the change in worsening renal function was assessed by means of the slope of the reciprocal of the serum creatinine level as a measure of change in glomerular filtration rate (GFR). Subsequent analyses of the data to estimate GFR (eGFR) used other methods, including eGFR by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI, which is another estimating equation to calculate eGFR (see section 2.1 of the submission).

4.5 After the identification of a signal of serious liver injury in patients with ADPKD participating in a clinical trial with tolvaptan,

[redacted]

Table 3: The characteristics of TEMPO 3:4 trial

Trial	Population	Intervention	Primary outcome	Secondary outcomes
TEMPO 3:4 NCT00428948 Randomised double-blind Phase III (published, Torres et al. 2012)	n=1445, 18-50 yrs with ADPKD and rapidly progressive kidney growth (total volume ≥750 mL by MRI) and a GFR estimated at ≥60 mL/ min	Tolvaptan and placebo, 36 months treatment	Rate of TKV change (%)	Time to onset of multiple ADPKD outcomes (ADPKD outcomes include new onset hypertension, worsening hypertension, renal pain, worsening albuminuria and worsening renal function)

TKV: Total kidney volume

ERG comments

4.6 The ERG noted that based on the information in the submission it is unclear why two of the clinical trials (156-04-248 and 156-04-249) were not presented in the submission, however they would provide additional relevant information to the submission. A third study (156-09-290) could also provide further relevant information, however the study report for this is not yet available, but according to the ERG, interim results might be possible to present. The ERG also raised concerns regarding the searches being restricted to English language only (see section 4.1.3 of the ERG report).

4.7 The ERG concluded that the inclusion criteria of the TEMPO 3:4 trial were broadly in line with the final scope. As standard care was not defined, there is some uncertainty on what measure comprised standard care and how this could have influenced the overall findings (see section 4.1.2 of ERG report).

4.8 The ERG noted that the TEMPO 3:4 trial did not provide results for one of the outcomes, which was health-related quality of life. It also concluded that both treatment arms appear well balanced. The generalisability of the results is limited, because only 73 (5%) of the patients included in the trial were from the UK. There is also limited evidence for CKD stage 3 patients, since only 17% of the patients belonged to this subgroup. It also noted that the trial only included patients aged 18-50 years, therefore patients over 50 years, (when

ESRD onset usually occurs) were not included in the trial (see section 4.2.2 of ERG report).

4.9 The ERG highlighted that there seems to be some uncertainty surrounding how GFR should be estimated. In the base case it was estimated by measuring the reciprocal of serum creatinine level and as a secondary measurement it was also assessed by the Chronic Kidney Disease Epidemiology (CKD-EPI) equation (see section 4.2.3 of ERG report).

4.10 The primary outcome of the TEMPO 3:4 trial was outside the final scope and since the trial was powered for this primary outcome it is possible that the relevant outcomes defined in the final scope are underpowered (see section 4.2.1 of ERG report).

Clinical trial results

4.11 The results of TEMPO 3:4 demonstrate that tolvaptan provides a significant relative reduction of 49.2% on TKV growth over 3 years when compared with placebo (absolute reduction of –2.71% per year; 95% CI, –3.27% to –2.15%; P < 0.0001) (see Table 4). Subgroup analysis of TKV at each CKD stage (1, 2, or 3 at baseline) also showed a consistent and significant effect favouring tolvaptan across all stages (see Table 5). In a sensitivity analysis patient profiles from the OVERTURE real world study (CKD stages 1-3) were also explored. The OVERTURE is an on-going, multicentre, prospective, observational cohort study, which aims to identify factors that predict rapid progression toward, or higher frequency of, clinically relevant morbidities in ADPKD.

4.12 The results showed that tolvaptan treatment was associated with a 61% relative reduction in the risk of worsening renal function over 3 years compared with placebo (HR, 0.39; 95% CI, 0.26-0.57; P < 0.001). Patients in the tolvaptan group experienced significantly reduced decline in renal function, compared with the placebo group

(estimated slope of −2.61 mg/mL-1 per year -1 vs. −3.81 mg/mL-1 per year-1, respectively; P < 0.001). Tolvaptan was associated with a significant 31.6% relative reduction in the annual rate of renal function decline, compared with placebo (see Figures B6 and B8 in section 6.5.3 of the submission). When assessed using CKD-EPI, the relative reduction was 26.4% for tolvaptan compared with placebo.

4.13 The percentage of patients who discontinued was 23% in the tolvaptan group and 14% in the placebo group. During clarification the ERG requested the company to provide data about stopping rules, as they were not considered in the submission; despite that it was stated in the final scope that they should be considered if evidence allows. In its response the company stated that for individual patients with ADPKD, the trajectory for the expected decline in renal function and expected increase in TKV cannot be predicted in a validated way, therefore the company was unable to recommend specific stopping rules.

4.14 Subgroup analyses were conducted according to each CKD stage of TKV growth and the results showed a consistent and significant effect favouring tolvaptan across all stages.

Table 4 Rate of change in TKV within the treatment period (see section 6.5.3 of the submission)

Treatment group	N	Mean rate of % growth/year (SD)[a]	Slope reduction (%)	Treatment difference (%) (95% CI)[b]	*P* Value[c]
Tolvaptan	819	2.78 (5.66)	49.2	−2.708 (−3.27, −2.15)	< 0.0001
Placebo	458	5.61 (5.33)			
CI = confidence interval; SD = standard deviation.					

Table 5 Effect of tolvaptan on TKV growth in CKD stages 1 to 3 (see section 6.5.3 of the submission)

Baseline CKD stage by $eGFR_{CKD\text{-}EPI}$ (mL/min/1.73m^2)	N	Slope % (annualised)	Ratio of geometric mean (annualised growth rate)*	95% CI	P

Stage 1 (≥ 90)					
Tolvaptan	267	3.02%	[redacted]	[redacted]	< 0.0001
Placebo	158	5.07%			
Stage 2 (89-60)					
Tolvaptan	402	2.08%	[redacted]	[redacted]	< 0.0001
Placebo	214	5.27%			
Stage 3 (< 60)					
Tolvaptan	147	4.11%	[redacted]	[redacted]	0.0004
Placebo	84	6.83%			

CI = confidence interval; CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration

* By the formula, % change = 100 x (1-ratio of geometric mean), the annual ratio of geometric mean effect size of 0.981 is approximately -1.9% per year change in TKV.

Source: Otsuka responses to EMA Day 120 list of questions 2014: Table 3.2.3.7-1, Table 3.2.3.7-5, Table 3.2.3.6-7 (Otsuka Pharmaceutical Europe Ltd. data on file, 2014); Torres *et al.*, 2014a.

ERG comments

4.15 In its report the ERG stated that there seems to be some uncertainty surrounding how to best to assess and estimate GFR (see section 4.2.3 of the ERG report). It also stated that the number of patients included in the CKD stage 3 subgroup was relatively low and evidence for this subgroup is limited.

4.16 In its report the ERG considered TKV as a surrogate endpoint for annual eGFR decline with very limited value. TKV is a good measure of extent of disease as it predicts future decline of renal function. However due to natural variation between patients and unreliability of measurement TKV is not a reliable measure of treatment effect. The ERG also criticised the measurement of TKV by ellipsoid method, since in ADPKD the kidneys lose their predictable shape, therefore this method has a potential for unreliability.

Adverse effects of treatment

4.17 The potential risk for serious liver injury has been observed during the clinical trials. Three people has met the definition of a Hy's Law case (hepatocellular injury, serum ALT or AST > 3 × upper limit of

normal [ULN], total bilirubin > 2 × ULN). In all cases the abnormalities resolved after stopping treatment with tolvaptan (see section 6.9 of the submission).

4.18 According to the SmPC the most commonly reported adverse reactions are thirst, polyuria, nocturia, and pollakiuria occurring in approximately 55%, 38%, 29% and 23% of patients, respectively. Furthermore, tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in bilirubin-total (BT).

4.19 Very common (≥1/10) adverse reactions classified by system organ class and frequency in the clinical trials: polydipsia, headache, dizziness, diarrhoea, dry mouth, nocturia, pollakiuria and polyuria.

ERG comments

4.20 Regarding the adverse events the ERG emphasised that two or more Hy's Law cases, which were found in the clinical trial is an important safety concern. Other adverse events (e.g. thirst, polyuria) may affect the ability of patients to take effective doses of tolvaptan. It was also reported that more people discontinued treatment due to adverse events in the tolvaptan arm, than in the placebo arm of the trial (15.4% vs. 5.0%, respectively).

5 Cost-effectiveness evidence

Model structure

5.1 The company identified one cost-effectiveness study (Erickson et al. 2013), which evaluated the cost-effectiveness of tolvaptan compared with standard care across different ADPKD population in the United States (US), using a Markov model populated with aggregated, published clinical data from the TEMPO 3:4 trial. The company considered the results (a delay in the median time to onset of ESRD with tolvaptan of 6.5 years and an increase in life expectancy of 2.6 years, base case ICER $744,100 per QALY) not to be relevant to decision-making in England and Wales, due to their limited generalisability. The cost of tolvaptan, the resource use and unit costs, the discount rates and the societal perspective which were applied to the model are not generalisable to the NHS in England and Wales (see section 7.12 of the submission).

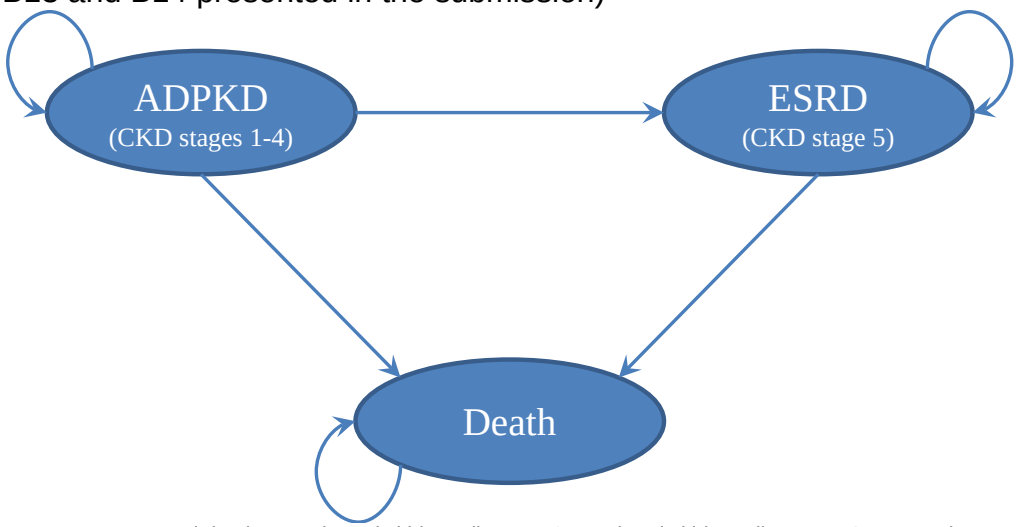
5.2 The company submitted a de novo analysis, which was a patient-level simulation model. The model used a lifetime horizon of up to 80 years, and a cycle length of one year. Half-cycle correction was applied. The model used the perspective of the NHS and personal social services, which were discounted by 3.5% per year. The model encompassed the disease pathway via two distinct modules; the first module captured the period of ADPKD progression up to the onset of ESRD and the second module captured the management of ESRD when tolvaptan or other treatment is no longer given. The ADPKD module used 5 health states; CKD stages 1-4, a significant pain health state, and an end state of death. The ESRD module contained 5 health states of CKD stage 5, conservative care, haemodialysis, peritoneal dialysis, transplant and an end state of death. Further information on these states can be found in the submission in section 7.2.4.

ERG comments

5.3 The ERG agreed with the development of a new model.

5.4 The ERG concluded that the description of the model was overly complicated. The model consisted of three states (ADPKD, ESRD and death) and different patient characteristics (age, sex, eGFR, TKV and CKD stage) were assigned to individual patients and updated at the end of each cycle. Although the description of the model in the submission suggests that this is not a Markov model, the ERG considered it to be an individual-patient Markov model and agreed that this type of model is appropriate.

Figure 1 Model structure by the ERG (adjusted version of the flow diagrams, Figures B13 and B14 presented in the submission)



ADPKD = autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; ESRD = end-stage renal disease

5.5 Regarding model validation, the ERG considered that the model lacked some transparency. This was mainly due to the use of a state-transition model coded in the Macro modules in Excel with parameters that are often redirected and renamed, sometimes multiple times. For further details, see section 5.2.12 of the ERG report.

Model details

Model transitions

5.6 At the start of a simulation, the model generated a patient cohort based on the average baseline characteristics of the TEMPO 3:4 trial. Each patient within the cohort progressed in annual time increments (1 year cycles). At each cycle, the movements between chronic kidney disease (CKD) stages, the incidence of renal failure (CKD stage 5) and the incidence of all-cause mortality are tracked. In case of a patient's simulated eGFR fell below 15 mL/min/1.73m2, the patient moved on to the ESRD module. Once this stage was reached, patients could receive conservative care management, dialysis or kidney transplantation. At the end of each cycle a subject's disease state was assessed and costs and appropriate health utility decrement were applied. Assuming a patient did not die in a given cycle, the simulation continued until the model time horizon (80 years or maximum age of 101 years) was reached. In case of a fatal event, all costs, life years and quality-adjusted life years were accumulated and the simulation ended for that subject. Once the simulation ended, the process begun for the next subject in the cohort.

5.7 The tolvaptan arm of the model utilised the same patient cohort data (i.e., baseline demographics and risk factors) as the no treatment arm, but applied a treatment effect to the underlying disease progression (see below sections 5.13 and 5.14 on disease progression). This affected the incidence and timing of ESRD (CKD stage 5) in this group. Other differences between the treatment and no treatment groups existed for the following variables: treatment-related discontinuation (for the first 3 years, the results of the TEMPO 3:4 were used, and after that a 0.5% treatment discontinuation was assumed), clinically significant pain events (for CKD stage 1-4 a 0.05 annual probability was assumed for the

tolvaptan arm and 0.07 for the placebo arm) and treatment-specific costs and health utility decrement (in the base case no treatment related utility decrement was applied, but in sensitivity analysis a 0.0123 treatment related disutility was explored). The incidence of clinically significant kidney pain was modelled separately from disease progression and was simulated based on the annual probability of occurrence (see section 7.2.5 of the submission).

Underlying disease progression

5.8 The underlying risk of disease progression was modelled using regression equations to predict annual change in TKV and eGFR. Baseline characteristics from the placebo arm of TEMPO 3:4 (age, gender, TKV and eGFR) were used in the regression equation for estimated TKV progression in the first year. Thereafter, the patient characteristics of the previous cycle were used for each new cycle. Annual change in TKV was used as an intermediate step to model change in eGFR, which was the primary outcome of the model (eGFR was dependent on TKV in the previous cycle). This was repeated until the lifetime trajectory of TKV and eGFR of each patient was predicted. See section 7.3.2 of the submission for further information.

ERG comments

5.9 The ERG found that the regression analyses for disease progression based on TKV and eGFR were not described in detail (it was unclear to the ERG which covariates were initially examined, why only age and gender were included in the final models, why gender was included to predict TKV progression despite not being statistically significant and whether alternative models for the data were tested). The ERG considered that these analyses assumed that the rates of eGFR decline and TKV growth were constant. This was not tested and as eGFR is predicted from TKV, and TKV is dependent on age, the ERG considered that it was probable that eGFR would not be

fully constant over time. The estimation of eGFR might result in uncertainty, but the ERG thinks the approach is justifiable.

Treatment effect

5.10 To estimate the treatment effect of tolvaptan, the absolute change in eGFR from TEMPO 3:4 from the period between post-titration baseline to the end of the study (3 years) was applied to the underlying disease progression. The company considered this to be more appropriate than adjusting by the primary outcome of the trial (TKV) as an intermediate outcome. This is because the company considered that the relationship between TKV and eGFR (which has only previously been studied in people receiving no active treatment) may be altered by the use of tolvaptan, making TKV an unreliable predictor of eGFR in the treatment group. After the first 3 years, the treatment effect (reduction in annual rate of renal decline for tolvaptan compared with standard care) was assumed to persist and remain constant at a level of 31.6% for as long as treatment was continued (see section 7.3.1 of the submission). During clarification the ERG asked the company to conduct a scenario analysis, in which treatment effect was directly applied to TKV. In its response, the company produced an analysis using a 49.2% constant reduction in TKV growth for tolvaptan using the equations linking TKV and eGFR. This resulted in a significant rise to the ICER, however the company emphasised that the results should be interpreted with caution. The ERG also asked the company to conduct a scenario analysis in which a 50% reduction of treatment effect (that is, 50% reduction of 31,6%) was applied after 3 years, which also resulted in a significant rise to the ICER (£92,051 per QALY gained with PAS, see Table 19 of Clarification response).

ERG comments

5.11 The ERG considered that there is little evidence to substantiate the company's claim that the correlation between eGFR and TKV as

observed in patients receiving no treatment may misrepresent the relationship in tolvaptan patients. The ERG also questioned the assumption that treatment effect persists for the duration of treatment. The ERG urged caution regarding this assumption since the only longer term data comes from an interim analysis from the 5 year TEMPO 4:4 trial which is an open label, non randomised extension study. Data from longer follow up periods, during which time late onset adverse effects may arise, are not available. Therefore the ERG argued that there is a little evidence to conclude whether the treatment effect would persist or decline.

Treatment discontinuation

5.12 The annual rate of treatment discontinuation observed during the TEMPO 3:4 trial was used in the model. In the first three cycle the actual annual rate observed in TEMPO 3:4 trial was used and after that an annual rate of discontinuation of 0.5% was assumed. In case a patient discontinues treatment with tolvaptan, they follow the natural history of disease progression. After progressing to the ESRD module, the therapy is discontinued. For more details on treatment discontinuation see section 7.3.1 of the submission.

5.13 During clarification the ERG asked the company to provide evidence, why stopping rules were not considered in the submission. In their response, the company stated that the company was unable to recommend specific stopping rules and referred back to the clinical trial results. For further details please see section 4.11 above.

ERG comments

5.14 The ERG in their report stated that there is scarce evidence available to support the use of 0.5% annual treatment discontinuation rate after year 3. It also considered the company's sensitivity analyses (0%, 0.2%) too small range and conducted exploratory analysis with 6.5%, which was equal to that observed in

the second year in TEMPO 3:4 . This resulted in a ICER of £42,893 per QALY gained (with PAS).

Utilities

5.15 For identifying health state utility values (HSUV), the company conducted a systematic review of the literature. It identified 23 studies, but none of them reported HSUV estimates for patients with ADPKD. In the model, HSUV estimates from Gorodetskaya et al. were chosen in the base case for CKD stage 1–4. Gorodetskaya et al. reported estimates for CKD stage 1–4 and 5, using time trade-off methods in a US sample. For CKD stage 5 and conservative care, haemodialysis (HD), peritoneal dialysis (PD) ESRD module health states the estimates reported by Lee et al. were used. Lee et al. reported EQ-5D data from UK sample on CKD stage 5 pre-dialysis HD, PD, and functional transplant. The base-case analysis assumes no disutilities for tolvaptan treatment. The disutility associated with dialysis complications was based on NICE clinical guideline on chronic kidney disease (CG125). The disutility associated with significant pain event was estimated from a study from Dolan et al. The model utilised baseline age-adjusted utilities (general population values (Centre for Health Economics)) with utility decrements applied for the various health states in the model (see section 7.4.9 of the submission).

ERG comments

5.16 In its report the ERG noted that the way the utilities were included in the model was subject to possible errors and double counting due to applying more disutility estimates additively to the age-adjusted baseline (i.e. absolute utility values were calculated by subtracting the relevant health state disutility from the age-adjusted baseline and if at the given time point other disutilities could be applied, they were applied additively e.g. in case of clinically significant pain events). This may resulted in lower absolute utility values. The ERG

considered that including a disutility only for kidney pain and for no other adverse events (and therefore potentially favouring the tolvaptan arm) was not a conservative approach. Therefore in its exploratory analysis the probability for kidney pain event was set to equal for both arms. The ERG also noted that the disutility value (0.06) applied for haemodialysis (HD) and peritoneal dialysis (PD) complications is exaggerated and favours the tolvaptan arm. The conservative approach would be to set the value of this disutility to 0.02. This has also been explored in an ERG exploratory analysis.

Adverse Events

5.17 Adverse events (AEs) were not explicitly modelled, but were incorporated in the costs and utilities of CKD and ESRD health states. Only clinically significant pain was included. The probability of clinically significant pain was derived from the TEMPO 3:4 study, and applied to CKD stages 1-4. For patients who discontinued tolvaptan the control arm's probability of clinically significant pain was applied.

ERG comments

5.18 The ERG noted that modelling only clinically significant pain may have introduced a downward bias to the ICER, due to the assumption about the difference in kidney pain as observed in TEMPO 3:4 is independent from the effect of tolvaptan on disease progression.

5.19 During clarification the ERG pointed out the results of TEMPO 3:4 trial show different serious AEs emergence on the tolvaptan and on the placebo arm and asked the company to investigate treatment dependent AEs in a scenario analysis. In its response the company argued that the differences are not sufficient to justify more detailed modelling and concluded that more detailed consideration of these events in the economic model would add little value and would not greatly impact the overall results. In its report the ERG concluded

that a conservative approach would be to apply a 0.0123 utility decrement for tolvaptan treatment, as it was investigated in one of the scenario analyses in the company submission.

5.20 The ERG noted that hepatotoxicity due to tolvaptan treatment or in other name drug-induced liver injury (DILI) was not included in the model, despite that 3 Hy's Law cases were reported during TEMPO 3:4 and 4:4 studies. Finding two or more Hy's Law cases is considered highly predictive that there is a risk to cause severe DILI. Also it was reported by the company during clarification, that based on post-marketing surveillance data it cannot be excluded that tolvaptan increases the risk of liver injury (see section 4.3 above). In clarification question C8 the ERG requested the company to conduct a scenario analysis, where the costs and quality of life impacts of DILI are explored. In its response the company stated that besides the proposed risk management programme it is highly unlikely that a patient with severe liver function abnormalities would not be identified and have tolvaptan treatment interrupted. It also argued that no irreversible cases of DILI were identified during the clinical trials; therefore the company had no data to include DILI in the model. In its report the ERG stated that it was uncertain whether the proposed monitoring schedule would totally prevent (severe) cases of DILI as well as costs and health consequences associated with it. Therefore, the ERG performed an exploratory analysis, incorporating consequences of tolvaptan induced hepatotoxicity.

Mortalities

5.21 All-cause mortality was modelled using age and gender specific life tables from England and Wales. Patients in ESRD are subject to a specific mortality risk, based on age-specific (18-64 and 65+) observed dialysis survival rates, using a Weibull model. Time-dependent mortality after transplant was based on the NHS transplant survival report.

ERG comments

5.22 In its report the ERG noted that using a not ADPKD specific mortality for CKD stages 1-4 can be an underestimation of the mortality risk and this assumption may be in favour of tolvaptan. To account for this the ERG explored a higher mortality in CKD stages 1-4 in an exploratory analysis.

Costs

5.23 The cost of tolvaptan used for the base case analysis included a PAS discount. Additional monitoring costs were applied, these included liver function tests (performed monthly for 18 months and 3 monthly thereafter), two additional consultant visits in the first year of treatment and one additional consultant visit in the second year of treatment in addition to the currently standard monitoring, plus additional consultant time was added for reviewing liver function test results and issuing prescriptions. The resource use was estimated based on NICE clinical guideline on chronic kidney disease (CG 182) and on clinical expert assumption. The costs were calculated on the basis of Unit Costs of Health and Social Care (Curtis, 2014) and NHS Reference Costs. Treatment costs were only calculated for the ADPKD module health states, up until the year of discontinuation.

5.24 Costs for CKD stage 1-2 health states were calculated as a sum of one consultant visit, one specialist nurse visit, one biochemistry test, one haematology test and one phlebotomy, based on Unit Costs of Health and Social Care and NHS Reference Costs. The resource use was based on clinical expert assumption. Costs for CKD stage 3 to 5 health states were sourced from NICE clinical guideline on chronic kidney disease (CG182). The costs for CKD stage 3 were smaller than for CKD stage 4, based on a ratio published by Chamberlain et al. 2014. The costs of significant pain event was based on NHS Reference Costs and HRG AB04Z

5.25 Costs for the ESRD module were based on HRG codes, NHS Reference costs, and NICE clinical guideline on peritoneal dialysis (CG 125) and annual costs for dialysis were sourced from a study published byt Baboolal et al. (2008). In case of transplantation the maintenance cost of the transplant was sourced from Kerr et al. 2012 and NICE technology appraisal on Immunosuppressive therapy for renal transplantation in adults (TA85). Costs associated with organ donation and transplantation activities were sourced from NHS Blood and Transplant Organ donation and transplantation. Activity report 2013/14. For further details on costs see section 7.5.1, 7.5.2 and 7.5.6 of the submission.

ERG comments

5.26 The ERG critiqued the use of additional monitoring costs, and explored higher costs in its exploratory analyses.

Company's base-case results and sensitivity analysis

5.27 The model resulted in patients in the tolvaptan group spending less time (approximately 2 years) in ESRD and more time in CKD stages 2 to 4. The company's base case analysis resulted in a probabilistic mean estimate of the ICER of [redacted] (without PAS) and £34,733 (with PAS) per QALY gained, representing a gain of 0.92 QALY at a cost of [redacted] (without PAS) and £31,838 (with PAS). (During clarification the ERG identified errors in the coding of the model. In response to clarification, the company provided an updated excel file and, revised base case results. All results presented here are from the revised base case.) Due to the nature of the model which performs individual patient simulation and probabilistic simulations in a single analysis, all base case and sensitivity results are probabilistic mean values. The probability of cost-effectiveness for tolvaptan at a willingness-to-pay threshold of £30,000 was [redacted] and 36% including the PAS.

Table 6 Mean discounted base-case results per patient (probabilistic mean estimates, including PAS)

Technologies	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Standard care	[redacted]	12.63			
Tolvaptan (non PAS)	[redacted]	13.55	[redacted]	0.92	[redacted]
Tolvaptan (PAS)	[redacted]	13.55	£31,838	0.92	£34,733
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Company scenarios

5.28 The company did not perform individual deterministic sensitivity analyses using alternative fixed estimates of model parameters due to the nature of the model. However, structural sensitivity analyses and scenario analyses were carried out (see tables B48 and B49 in section 7.6.2 of the submission for further details). The three most influential scenario analyses were those that incorporated 1) a treatment effect based on CKD-EPI (ICER with PAS: £47,722); 2) using 'minimum' utility decrements for ESRD (exact utility decrements not specified, ICER with PAS: £40,819) and; 3) using a disutility of 0.0123 for being on tolvaptan treatment (ICER with PAS: £39,959).

Subgroup analyses

5.29 Subgroup analyses were conducted for each CKD stage at treatment initiation, since each group had a different set of TKV, eGFR, age and gender characteristics (which are used in the modelling of the underlying disease progression). Values for these variables were taken from both the TEMPO 3:4 trial and an observational study (OVERTURE, see section 4.9 above). For the analysis incorporating the PAS, the results varied between £18,168 (CKD stage 3b group, using OVERTURE data) and £47,983 per QALY gained (CKD stage 1 group, OVERTURE data).

ERG comments

5.30 The ERG presented the base case results of the corrected model in its report. It noted that after updating the model, the acceptability curve had very minor changes.

5.31 The ERG considered that the lack of one way sensitivity analyses was a serious shortcoming and that the justification for excluding sensitivity analyses was not convincing.

5.32 The comparison of the subgroup analyses based on the TEMPO 3:4 and OVERTURE data shows that the ICERs are sensitive to differences in patient characteristics at initiation of therapy (eGFR, TKV, age, gender), even within a CKD stage. In this respect, it should also be noted that eGFR and TKV are highly variable among patients in the same CKD stage and within patients over time.

5.33 Crucially for the ERG, the company did not explore scenarios considering the extrapolation of the treatment effect, which the ERG considered would probably be one of the most influential uncertainties.

ERG's exploratory analyses

5.34 The ERG critiqued the company's assumption that hepatotoxicity does not lead to any costs or health losses (see above in section 5.20). Therefore, it perfomed exploratory analysis, incorporating for the consequences of hepatoxicity. For this exploratory analysis, a worst case scenario was adopted assuming that all Hy's Law cases would need a liver transplant at the end of year 1 and would die immediately thereafter. In this exploratory analysis, the ICER rose from the company's base case ICER of £34,733 to £35,751 per QALY gained (with PAS).

5.35 The ERG also explored a higher mortality values in CKD stages 1-4, since the company's base case used general population results,

which might underestimate mortality for ADPKD. The results in this scenario increased to £34,754 per QALY gained.

5.36 The ERG conducted an analysis, where it assumed a treatment discontinuation of 6.5% after three years. This increased the ICER to £42,893.

5.37 The ERG explored the effects of additional monitoring costs using two assumptions. It assumed that patients with ALT>3 (4.4%) will need more monitoring, therefore in the exploratory analysis the monitoring was doubled for these patients. It was also assumed that patients after the second year would need an extra consultation visit due to possible AEs. The results showed that the ICER increased to £36,167.

5.38 The ERG considered that the maintenance costs for post kidney transplants are likely to be overestimated, therefore it subtracted the background management costs from the maintenance costs for all years, which resulted in an ICER of £39,264.

5.39 After correcting the model code error, the ERG also implemented some changes to the model and calculated an ICER with its preferred scenario. The assumptions were: equal probability of kidney pain for both arms, equal CKD stage costs for CKD stage 3 and CKD stage 4, applying a disutility of 0.0123 for tolvaptan treatment and applying a disutility of 0.02 for haemodialysis and peritoneal dialysis complications. This resulted in an ICER of £43,280 per QALY gained.

The results of each of the above described exploratory analyses scenarios are presented in Table 7 below.

Table 7 ERG exploratory analyses (with PAS) [see section 6 of the ERG report]

Technologies	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Assuming that 3 out of 10 Hy's Law cases would have a liver transplant at year 1 and would die immediately thereafter.					
Standard care	[redacted]	12.63			
Tolvaptan	[redacted]	13.51	£31,341	0.88	£35,751
Assuming increased mortality (hazard ratio: 2.0)					
Standard care	[redacted]	16.36			
Tolvaptan	[redacted]	17.11	£29,902	0.86	£34,754
Assuming treatment discontinuation of 6.5% after year 3					
Standard care	[redacted]	12.63			
Tolvaptan	[redacted]	13.26	£26,922	0.63	£42,893
Assuming increased monitoring costs					
Standard care	[redacted]	12.63			
Tolvaptan	[redacted]	13.53	£32,744	0.91	£36,167
Assuming decreased post-transplant costs					
Standard care	[redacted]	12.63			
Tolvaptan	[redacted]	13.53	£35,992	0.91	£39,264
ERG's preferred base case					
Standard care	[redacted]	12.66			
Tolvaptan	[redacted]	13.42	£33,015	0.76	£43,280
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Innovation

5.40 The company noted that tolvaptan represents a 'step-change' in the management of ADPKD and also demonstrates original and creative properties, as this is the first drug available for the treatment of ADPKD.

5.41 The company emphasised the high unmet need of people with ADPKD and that the disease burden of ADPKD can be extremely high to patients. In its submission it noted that tolvaptan has a significant and substantial impact on health-related benefits.

5.42 The company also noted that tolvaptan could delay time to ESRD and reducing the strain on renal replacement therapy.

6 Equality issues

6.1 No equality issues raised.

7 Authors

Boglarka Mikudina

Technical Lead

Joanne Holden

Technical Adviser

with input from the Lead Team: Gillian Ells, Alexander Dyker and Tracey Cole.

[redacted]