NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Tolvaptan for treating autosomal dominant polycystic kidney disease

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Tolvaptan is recommended as an option for treating autosomal dominant polycystic kidney disease in adults to slow the progression of cyst development and renal insufficiency only if:

- they have chronic kidney disease stage 2 or 3 at the start of treatment
- there is evidence of rapidly progressing disease and
- the company provides it with the discount agreed in the patient access scheme.

1.2 People whose treatment with tolvaptan is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Tolvaptan (Jinarc, Otsuka Pharmaceuticals) 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. Tolvaptan has a marketing authorisation in the UK 'to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic

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kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease'.

2.2 The summary of product characteristics lists the following adverse reactions for tolvaptan: thirst, polyuria, nocturia, pollakiuria (frequent urination), serum alanine aminotransferase or aspartate aminotransferase elevation. Hepatotoxicity has been observed in some people having tolvaptan for autosomal-dominant polycystic kidney disease. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Tolvaptan is taken orally, twice daily as a split dose. Doses can be titrated according to tolerability up to a maximum total daily dose of 120 mg. It is available as 15 mg, 30 mg, 60 mg and 90 mg tablets, in 28-day packs of split-dose tablets, at a flat net price of £1208.20, equating to £43.15 per day, regardless of dose. The company provided these costs to NICE because the British National Formulary (BNF) had not listed the price at the time of producing this guidance. The annual cost of tolvaptan is estimated by the company to be £15,750 per person. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of tolvaptan, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Otsuka Pharmaceuticals and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The main source of evidence presented in the company's submission came from 1 phase-III trial, TEMPO 3:4. This trial was an international,

multicentre, double-blind, placebo-controlled, parallel-arm, randomised controlled trial in which 1445 patients were randomised in a 2:1 ratio to either the tolvaptan (n=961) or the placebo (n=484) arm. Patients aged 18–50 years with rapidly progressing autosomal dominant polycystic kidney disease (ADPKD) and an estimated glomerular filtration rate (eGFR) of 60 ml per minute or more and with a total kidney volume (TKV) of 750 ml or more (as measured by MRI) were included in the trial. Tolvaptan and placebo were administered orally, twice daily. The dose was titrated at weekly intervals over a 3-week period, initially administered at doses 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 had the maximum tolerated dose for the remainder of the 36-month treatment period. Patients were monitored every 4 months during the 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, family origin and factors influencing ADPKD progression. The mean age of patients in the trial was 38.7 years. The mean TKV was 1705 ml in the tolvaptan group and 1668 ml in the placebo group. Patients having tolvaptan and placebo were evenly distributed at baseline across the Kidney Disease Outcomes Quality Initiative chronic kidney disease (CKD) stages 1 (34.5% and 35.9%), 2 (48.5% and 46.5%) and 3 (17.0% and 17.4%), respectively. Seventy-three patients were from the UK.

3.2   The primary end point of the TEMPO 3:4 trial was the rate of TKV change from baseline for tolvaptan relative to placebo, as measured by MRI. Data on the rate of decline of renal function (listed in the final scope as an outcome measure) were also available. The results of TEMPO 3:4 showed that tolvaptan had a statistically significant relative reduction of 49.2% on TKV growth over 3 years when compared with placebo (absolute reduction of −2.71% per year; 95% confidence interval [CI] −3.27% to −2.15%; p<0.0001). Post-hoc analyses of TKV in subgroups of

patients at each CKD stage (1, 2, or 3 at baseline) showed a consistent and significant effect favouring tolvaptan across all stages; results were designated as academic in confidence by the company and therefore cannot be reported here.

3.3 In TEMPO 3:4 the composite secondary end point was time to onset of multiple ADPKD outcomes (worsening renal function, new onset hypertension, worsening hypertension, renal pain and worsening albuminuria). 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 (absolute reduction: 3 events per 100 person-years; hazard ratio 0.39; 95% CI 0.26 to 0.57; p<0.001).

3.4 Rate of change in renal function was also included as a secondary end point in the trial, and was assessed by the reciprocal of the serum creatinine level as a measure of change in glomerular filtration rate (GFR). Subsequent analyses used other methods to estimate GFR, including the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Using the first measure, tolvaptan was associated with a statistically significant 31.6% relative reduction in the annual rate of renal function decline (absolute reduction of 1.20 mg/ml^{-1} serum creatinine; 95% CI 0.62 to 1.78; p < 0.001), compared with placebo. When GFR was assessed using the CKD-EPI equation, the relative reduction was 26.4% for tolvaptan compared with placebo (absolute reduction of 2.72 ml/min/1.73 m^2 per year over 3 years; 95% CI 0.60 1.36; p<0.001).

3.5 The company also presented evidence from an ongoing clinical study in which tolvaptan was the intervention of interest. TEMPO 4:4 is an open label, non-randomised extension study of TEMPO 3:4. The study aims to determine whether tolvaptan modifies the progression of ADPKD and if the effects of tolvaptan are sustained over time. The available interim results of this study indicate that the benefit of treatment persisted for patients who continued taking tolvaptan compared with those having placebo in TEMPO 3:4.

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3.6   The company also reported the results of a real-world study called OVERTURE, which is an ongoing, multicentre, prospective, observational cohort study aiming to identify factors that may predict rapid progression toward, or higher frequency of, clinically relevant morbidities in ADPKD.

3.7   The most commonly reported adverse reactions from TEMPO 3:4 were thirst, polyuria, nocturia and pollakiuria, occurring in approximately 55%, 38%, 29% and 23% of patients respectively. Furthermore, tolvaptan was associated with the adverse effects of elevations of serum alanine and aspartate aminotransferases (ALT and AST respectively), with infrequent cases of concomitant elevations in total bilirubin. During the TEMPO studies 3 people met the criteria for a Hy's law case (hepatocellular injury, serum ALT or AST more than 3 times the upper limit of normal, total bilirubin more than twice the upper limit of normal), indicating the potential risk for serious drug-induced liver injury. In all cases the abnormalities resolved after stopping treatment with tolvaptan. The company reported that after the implementation of the TEMPO Steering Committee's recommendation to increase monitoring to monthly intervals, no further Hy's law cases had been identified. In addition, the company noted that liver biochemistry monitoring was relatively infrequent in the TEMPO studies, and that more frequent monitoring would be expected in real-world use, which would further lower the risk of people developing serious drug-induced liver injury. The percentage of patients who stopped treatment was 23% in the tolvaptan group and 14% in the placebo group. Health-related quality of life was not assessed in the TEMPO 3:4 trial.

Cost effectiveness

3.8   The company submitted an economic analysis for the cost effectiveness of tolvaptan, which was a patient-level simulation model. The model used a lifetime horizon of up to 80 years, and a cycle length of 1 year. A half-cycle correction was applied. The model used the perspectives of the NHS and personal social services, and costs and benefits were discounted by 3.5% per year. The model encompassed the disease

pathway through 2 distinct modules: the first module captured the period of ADPKD progression up to the onset of end-stage renal disease (ESRD) and the second module captured the management of ESRD when tolvaptan is no longer given. The ADPKD module encompassed 5 health states (CKD stages 1 to 4, a significant pain health state), and an end state of death. The ESRD module contained 5 health states (CKD stage 5, conservative care, haemodialysis, peritoneal dialysis, transplant) and an end state of death.

3.9   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). Within each cycle, the movements between CKD stages, the incidence of renal failure (CKD stage 5) and the incidence of all-cause mortality were tracked. In the case of a patient's simulated eGFR falling below 15 ml/min/1.73 m^2, the patient moved on to the ESRD module. Once this stage was reached, patients could have conservative care management, dialysis or kidney transplantation. At the end of each cycle the patient's disease state was assessed and costs and appropriate health-utility decrements 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 the 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 started for the next subject in the cohort.

3.10   In the tolvaptan arm of the model, a treatment effect was applied to the underlying disease progression. This influenced the incidence and timing of ESRD (CKD stage 5) in this group. Further differences between the treatment and placebo groups included the following variables:

- Treatment-related discontinuation: for the first 3 years the discontinuation rates from TEMPO 3:4 were used, and after that a 0.5% treatment discontinuation was assumed.

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- Clinically significant pain events: for CKD stages 1 to 4 an annual probability of 0.05 was assumed for the tolvaptan arm and 0.07 for the placebo arm.

- The incidence of clinically significant kidney pain was modelled separately from disease progression (see section 3.8).

- Treatment utility decrement: in the base case no treatment-related utility decrement was applied, but in the sensitivity analysis a treatment-related utility decrement of 0.0123 was explored; this value was based on Sullivan et al. 2011 and was originally used by the company in its sensitivity analysis.

3.11   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 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. To estimate the treatment effect of tolvaptan (reduction in annual rate of renal decline for tolvaptan compared with standard care), 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. After the first 3 years, the treatment effect was assumed to persist and remain constant at a level of 31.6% for as long as treatment was continued.

3.12   The annual rate of treatment discontinuation observed during the TEMPO 3:4 trial was used in the first 3 cycles of the model (15.3%, 6.5% and 2.9%, for years 1, 2 and 3 respectively). For the remaining modelled years, an annual rate of discontinuation of 0.5% was applied. If a patient stopped treatment with tolvaptan, the natural history of disease

progression was assumed to apply to their disease course. After progressing to the ESRD module, tolvaptan therapy was stopped.

3.13 For identifying health-state utility values, the company conducted a systematic review of the literature. It identified 23 studies, but none of them reported health-state utility value estimates for patients with ADPKD. In the model, health state utility values estimates from Gorodetskaya et al. (2005) were chosen in the base case for CKD stages 1 to 4. Gorodetskaya et al. reported estimates for CKD stages 1 to 4 and 5, using time trade-off methods in a US sample. For the ESRD module health states, the estimates reported by Lee et al. (2005) were used. Lee et al. published EQ-5D data from a UK sample on CKD stage 5 pre-dialysis haemodialysis, peritoneal dialysis and functional transplant. The base-case analysis assumed no disutilities for tolvaptan treatment. The disutility associated with dialysis complications was based on the NICE guideline on chronic kidney disease. The disutility associated with significant pain events was estimated from a study by Dolan et al. (1997). The model used baseline age-adjusted utilities (general population values [Centre for Health Economics]) with utility decrements applied for the various health states in the model.

3.14 Adverse events 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 to 4. For patients who stopped tolvaptan, the probability of clinically significant pain reported in the control arm was applied.

3.15 All-cause mortality was modelled using age- and sex-specific life tables from England and Wales. Patients with end-stage renal disease are subject to a specific mortality risk, based on age-specific (18–64 and 65+ years) observed dialysis survival rates, using a Weibull model. Time-dependent mortality after transplant was based on the NHS Blood and Transplant Organ Donation and Transplantation Activity Report 2012–13.

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The cost of tolvaptan used for the base-case analysis included a patient access scheme discount. Treatment costs were only calculated for the ADPKD module health states, until the year of discontinuation.

3.16   Monitoring costs were applied including liver function tests (done monthly for 18 months and 3-monthly thereafter), 2 additional consultant visits in the first year of treatment and 1 additional consultant visit in the second year of treatment. Additional consultant time was added for reviewing liver function test results and issuing prescriptions. The resource use was based on the NICE guideline on chronic kidney disease and values were based on clinical expert opinion. The costs were calculated on the basis of Unit Costs of Health and Social Care (Curtis, 2014) and NHS Reference Costs 2012–13. Costs for CKD stages 1 and 2 health states included 1 consultant visit, 1 specialist nurse visit, 1 biochemistry test, 1 haematology test and 1 phlebotomy, based on Unit Costs of Health and Social Care and NHS Reference Costs. The resource use was based on clinical expert opinion. Costs for CKD stages 3 to 5 health states were sourced from the NICE guideline on chronic kidney disease. The costs for CKD stage 3 differed from CKD stage 4, based on a ratio published by Chamberlain et al. (2014). The cost of a significant pain event was based on NHS Reference Costs and HRG code. Costs for the ESRD module were based on HRG codes, NHS Reference Costs 2012–13, and the NICE guideline on peritoneal dialysis. Annual costs for dialysis were sourced from a study published by Baboolal et al. (2008). In the case of transplantation, the maintenance cost of the transplant was sourced from Kerr et al. (2012) and NICE technology appraisal guidance on immunosuppressive therapy for renal transplantation in adults. Costs associated with organ donation and transplantation activities were sourced from the NHS Blood and Transplant Organ Donation and Transplantation Activity Report 2013–14.

3.17   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 after correcting a model code error,

which was identified by the ERG during clarification, resulted in a probabilistic mean estimate of the incremental cost-effectiveness ratio (ICER) for tolvaptan compared with standard care of £34,733 (with the patient access scheme) per quality-adjusted life-year (QALY) gained, representing a gain of 0.92 QALYs at a cost of £31,838 (with the patient access scheme).

3.18   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 were given as probabilistic mean values. Therefore the company did not do individual deterministic sensitivity analyses using alternative fixed estimates of model parameters; however, structural sensitivity analyses and scenario analyses were carried out. The 3 most influential scenario analyses were those that incorporated:

- A treatment effect based on CKD-EPI (ICER with PAS: £47,510 per QALY gained).
- Using 'minimum' utility decrements for ESRD (exact utility decrements not specified, ICER with PAS: £40,615 per QALY gained).
- Using a disutility of 0.0123 for being on tolvaptan treatment (ICER with PAS: £40,401 per QALY gained).

Evidence Review Group critique

3.19   The ERG provided a critique of the evidence provided by the company for the clinical and cost effectiveness of tolvaptan. It considered the company's approach to the decision problem was appropriate. However, regarding the comparator in the appraisal, it concluded that because standard care was not defined, there is some uncertainty on what measure comprised standard care and how this could have influenced the overall findings.

3.20   The ERG noted that the generalisability of the results was limited, because only 73 (5%) of the patients included in the trial were from the UK. It also noted that the trial only included patients aged 18-50, therefore

patients over 50 years (when ESRD onset usually occurs) were not included in the trial. It also stated that the number of patients included in the CKD stage 3 subgroup was relatively low (17%) and evidence for this subgroup is limited. In addition, the ERG considered that, from the people considered eligible to have treatment, a high number had not been included, either because they had not met the inclusion criteria (TKV 750 ml or more, and estimated creatinine clearance 60 ml/min or more, n=530) or because they had declined to participate, or had other reasons for not participating (n=147).

3.21 Regarding the outcomes of interest, the ERG highlighted that there seems to be some uncertainty about 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 CKD-EPI equation.

3.22 The ERG noted that the primary outcome of the TEMPO 3:4 trial was outside the final scope and because the trial was powered for this primary outcome it is possible that the relevant outcomes defined in the final scope are underpowered. In its report, the ERG considered that TKV as a surrogate end point for annual eGFR decline had limited value, but that it was a good measure of extent of disease because it predicts future decline of renal function.

3.23 Regarding the adverse events, the ERG emphasised that 2 or more Hy's law cases, which were found in the clinical trial, is an important safety concern. Other adverse events (such as thirst or polyuria) may affect the ability of people to tolerate effective doses of tolvaptan. It was also reported that more people stopped treatment because of adverse events in the tolvaptan arm than in the placebo arm of the trial (15.4% compared with 5.0% respectively).

3.24 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 sex were included in the final models, why sex was included to predict TKV progression despite not being statistically significant and whether alternative models for the data were tested). The ERG highlighted that these analyses assumed that the rates of eGFR decline and TKV growth were constant. This was not tested and because 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 measurement of eGFR might result in uncertainty, but the ERG thought that the approach is justifiable.

3.25   The ERG noted that there is little evidence to substantiate the company's claim that the correlation between eGFR and TKV as observed in patients having 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 cautioned about accepting this assumption because the only longer-term data was 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, in which late onset adverse effects may arise, are not available. Therefore the ERG argued that there is little evidence to conclude whether the treatment effect would persist or decline.

3.26   The ERG stated that there is little evidence available to support the use of a 0.5% annual treatment discontinuation rate after year 3. It also considered the company's sensitivity analyses (0%, 2%) had too small a range and conducted exploratory analysis using a 6.5% discontinuation rate, which was equal to that observed in the second year in TEMPO 3:4. This resulted in an ICER for tolvaptan compared with standard care of £42,893 per QALY gained (with patient access scheme).

3.27   In its report the ERG noted that the way the utilities were included in the model was subject to possible errors and double counting. The model calculated the total utility for a patient at any given time by subtracting the

sum of the disutilities for health state, kidney pain and (in a scenario analysis only) treatment-related disutility from the age-adjusted baseline utility for each patient. The ERG also 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 of a kidney pain event was set to equal for both arms. The ERG also noted that the disutility value (0.06) applied for haemodialysis and peritoneal dialysis complications is exaggerated and favours the tolvaptan arm. The conservative approach would be to set the value of this disutility to 0.02.

3.28   The ERG noted that modelling only clinically significant pain may have introduced a downward bias to the ICER, because of the assumption that the difference in kidney pain as observed in TEMPO 3:4 is independent from the effect of tolvaptan on disease progression. During clarification the ERG pointed out that the results of TEMPO 3:4 show different serious adverse events in the tolvaptan and in the placebo arms. The ERG asked the company to investigate treatment-dependent adverse events 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 stated that a conservative approach would be to apply a 0.0123 utility decrement for tolvaptan treatment; this value was investigated in one of the scenario analyses in the company submission.

3.29   The ERG noted that hepatotoxicity from tolvaptan treatment or other drug-induced liver injury was not included in the model, despite 3 Hy's law cases being reported in TEMPO 3:4 and TEMPO 4:4 collectively. Finding 2 or more Hy's law cases is considered highly predictive that there is a risk of causing severe drug-induced liver injury. Therefore, the ERG did an exploratory analysis, incorporating consequences of tolvaptan-induced hepatotoxicity.

3.30   In its report the ERG noted that using non-ADPKD-specific mortality for CKD stages 1 to 4 can underestimate the mortality risk and this assumption may favour tolvaptan. To account for this the ERG explored a higher mortality (hazard ratio 2.0) in CKD stages 1 to 4 in an exploratory analysis.

3.31   The ERG critiqued the use of additional monitoring costs, noting that although liver function tests and additional consultant visits had been included in the model, the costs of further monitoring for patients who experience an abnormal test result had not been included. Therefore the ERG explored the impact of higher costs in its exploratory analyses. In addition, it did not agree with the cost applied in the model for the CKD stage 3 health state, which was based on the calculated cost for CKD stage 4, adjusted using a reference from a study which the manufacturer acknowledged may not have been fully representative of the population in the UK. The ERG therefore used equal costs for CKD stages 3 and 4 in its exploratory analyses.

3.32   The ERG considered that the lack of 1-way sensitivity analyses was a serious shortcoming and that the justification for excluding sensitivity analyses was not convincing.

3.33   The ERG noted that the company did not explore scenarios considering the extrapolation of the treatment effect, which it considered would probably be one of the most influential uncertainties.

ERG's exploratory analyses

3.34   The ERG criticised the company's assumption that the potential for drug-induced liver injury does not lead to any costs or health losses and did an exploratory analysis incorporating the consequences of it. 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 after. In this exploratory analysis, the ICER

increased from the company's base-case ICER of £34,733 to £35,751 per QALY gained (with the patient access scheme).

3.35 The ERG also explored higher mortality values in CKD stages 1 to 4, because the company's base case used general population results, which might underestimate mortality for ADPKD. The ICER in this scenario increased the company's base-case ICER to £34,754 per QALY gained.

3.36 The ERG conducted an analysis in which it assumed a treatment discontinuation of 6.5% after 3 years. This increased the company's base-case ICER to £42,893 per QALY gained.

3.37 The ERG explored the effects of additional monitoring costs using 2 assumptions. It assumed that patients with serum alanine aminotransferase higher than 3 (4.4%) will need more monitoring, therefore in the exploratory analysis the monitoring was doubled for these patients. It was also assumed that after the second year patients would need an extra consultation visit because of possible adverse events. The results showed that the company's base-case ICER increased to £36,167 per QALY gained.

3.38 The ERG considered that the maintenance costs after 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 per QALY gained.

3.39 After correcting a model code error, the ERG also implemented some changes to the model and calculated a base-case ICER with its preferred assumptions. 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
- applying a disutility of 0.02 for haemodialysis and peritoneal dialysis complications.

This resulted in an ICER for tolvaptan compared with standard care of £43,280 per QALY gained.

3.40 The ERG conducted further analyses to explore the impact on the ICER of using the CKD-EPI equation as an approximation for eGFR for both modelling the disease progression and treatment effect. This change to the model increased the company's base-case ICER to £50,524 per QALY gained. The ERG also re-calculated its preferred base case using the same assumptions as in the exploratory analyses (described in section 3.39) and using the CKD-EPI equation as an approximation of eGFR. This increased the ICER to £64,515 per QALY gained (ERG's preferred base-case ICER using the CKD-EPI equation).

3.41 The ERG also did an exploratory analysis using the worst-case scenarios as described in sections 3.34–3.38. This analysis contained only these scenarios, and did not include any of the ERG's preferred assumptions from the ERG's preferred base-case ICER (section 3.39. When using the CKD-EPI equation as an approximation for eGFR, the combination of these worst-case scenarios resulted in an ICER of £72,705 per QALY gained (ERG's worst-case scenario ICER using CKD-EPI).

3.42 The results of the company's base-case analysis, the ERG's preferred base case and the further analyses using CKD-EPI for assessing eGFR for each of the exploratory analyses described in sections 3.17, 3.40, 3.39, 3.40, and 3.41 are presented in Table 1.

Table 1 ERG exploratory analyses (with the patient access scheme)

Technologies	Incremental cost	Incremental QALY	ICER
Company's base case (after correcting a model code error)			
Standard care			
Tolvaptan	£31,838	0.92	£34,733
Company's base case using CKD-EPI as an approximation for eGFR (after correcting a model code error)			
Standard care			
Tolvaptan	£36,411	0.72	£50,524
ERG's preferred base case			
Standard care			
Tolvaptan	£33,015	0.76	£43,280
ERG's preferred base case using CKD-EPI as an approximation for eGFR			
Standard care			
Tolvaptan	£37,956	0.59	£64,515
ERG's worst-case scenario exploratory analyses using CKD-EPI as an approximation for eGFR			
Standard care			
Tolvaptan	£32,095	0.44	£72,705
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ERG, Evidence Review Group; HD, haemodialysis; ICER, incremental cost-effectiveness ratio; PD, peritoneal dialysis; QALYs, quality-adjusted life years.			

Company's submission of additional evidence

3.43   The company submitted additional evidence in response to consultation. In this additional evidence, the company presented a revised base-case analysis for a subgroup with only CKD stages 2 and 3 at the start of treatment and who had evidence of rapidly progressing disease. The updated analysis using the subgroup will be referred to from this point as the company's 'revised base case'.

3.44   In the company's revised base case, the following adjustments were applied to the original model:

- A revised PAS discount on the tolvaptan NHS list price.
- Baseline patient profile adjusted to represent ADPKD patients with CKD stages 2 to 3a.

- Subgroup specific relative reduction in renal function decline using the CKD-EPI equation as an approximation for eGFR.

- Annual change in renal function and percentage TKV change estimated using regression equations instead of data observed for the first 3 years over the trial period.

- Corrected model code.

- Equal costs for CKD stages 3 and 4.

- Utility decrement of 0.02 for haemodialysis and peritoneal dialysis complications.

- Utility decrement of 0.0025 for tolvaptan treatment.

- Treatment discontinuation of 2.9% after year 3 for the remainder for the modelled time horizon.

- Decreased post-kidney transplant costs.

- Increased mortality (hazard ratio: 1.6).

- Increased monitoring costs for the first 2 years while assuming the same monitoring costs as in its original base case for subsequent years.

3.45 From the revisions listed above, the company's revised base case matched the preferred assumptions described by the ERG in its exploratory analyses for the following: corrected model code (see section 3.39); equal costs for CKD stages 3 and 4 (see section 3.31); utility decrement of 0.02 for haemodialysis and peritoneal dialysis complications; decreased costs after kidney transplant (see section 3.38).

3.46 In the company's revised base case, the underlying risk of disease progression was modelled using regression equations to predict the annual change in TKV and eGFR. Baseline characteristics were adjusted from those of the placebo arm of TEMPO 3:4 to reflect a population with CKD stages 2 and 3, which was 48.4% female with a mean age of 44 years, mean eGFR of 60 ml/min/1.73 m^2, and a mean TKV of 2300 ml. These baseline characteristics were used in the regression equation for estimated TKV progression in the first year. Thereafter, the patient

characteristics of the previous cycle were used and updated 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). This was repeated until the lifetime trajectory of TKV and eGFR of each patient was predicted.

3.47   To estimate the treatment effect of tolvaptan for the subgroup (note that only patients with CKD stages 2 or 3a at baseline from TEMPO 3:4 were included in the analysis), the company took the relative reduction in the slope of renal function decline, which was 29.7% for tolvaptan compared with placebo as measured by CKD-EPI. The company then applied this treatment effect to the underlying disease progression. As with the company's original submission, after the first 3 years the treatment effect was assumed to persist and remain constant for as long as treatment was continued.

3.48   The company argued the utility decrement of 0.0123 assumed by the ERG in its original base case (see section 3.39) was overestimated. The company's revised base case assumed a treatment-related utility decrement of 0.0025 which it estimated assuming that the number of QALYs gained because of pain reduction were equal to the number of QALYs lost because of the negative effect of tolvaptan treatment. Regarding serious kidney pain events, the company continued to apply probabilities for people having tolvaptan and placebo of 0.05 and 0.07 respectively. For treatment-related discontinuation, the company continued to use the TEMPO 3:4 trial data for the first 3 years, after which the company then used a treatment discontinuation of 2.9% for the remainder of the modelled time horizon; this was the rate of discontinuation in the third and final year of TEMPO 3:4. All-cause mortality was modelled according to figures specific to polycystic kidney disease from a publication by Florijn et al. (1995) using a hazard ratio of 1.6.

3.49   The company's revised base case assumed that monitoring and administration costs in year 1 and 2 were set at 1.044 times the annual monitoring cost, accounting for doubling the intensity of monitoring for the estimated 4.4% of people with raised serum alanine aminotransferase (ALT) levels. The company stated that the risk across study arms of elevated serum ALT was equal after the first 18 months and therefore it did not assume increased monitoring frequency after year 2.

3.50   In the company's revised base case in the subgroup with CKD stages 2 and 3, the probabilistic mean estimate of the ICER for tolvaptan compared with standard care was £23,503 (with the patient access scheme) per QALY gained.

ERG's critique of the company's submission of additional evidence

3.51   The ERG commented that the company had not adjusted the annual change in renal function and percentage TKV change to reflect the subgroup of people with CKD stages 2 and 3. The ERG noted that it was likely the reduction in renal function would be higher and the percentage TKV change would be lower for the subgroup, which would both have the effect of decreasing the ICER compared with the analyses the company had presented using values for the whole population. Hence, the ERG commented that the company's estimate was conservative. The ERG also commented that it would have preferred the annual change in renal function and percentage TKV change to be informed by the actual trial data for the first 3 years, rather than using regression equations, which it stated the company had not justified and which was not a conservative assumption.

3.52   The ERG noted that it had applied a utility decrement of 0.0025 in its revised base case. The ERG stated that it was unclear why the utility decrement as a result of tolvaptan treatment should 'cancel out' the utility decrement as a result of pain reduction (as argued by the company). In addition, the ERG stated that it was not convinced this assumption was justified given the evidence presented, hence the ERG stated it would

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prefer the use of the conservative utility decrement of 0.0123 for being on tolvaptan treatment.

3.53   The ERG noted that in the company's additional evidence, it had assumed a mortality hazard ratio of 1.6 , and agreed that this was a more plausible estimate than the value of 2.0 the ERG had previously assumed (see section 3.30). The ERG further noted that the company had agreed with the increased monitoring costs applied except for the additional monitoring costs after the second year. The ERG commented that given the serum ALT elevation after 18 months for patients having tolvaptan compared with placebo (as noted by the company, see section 3.49), it was likely that the scenario proposed by the company was more plausible than the increased monitoring costs scenario proposed by the ERG in its exploratory analysis (see section 3.37).

3.54   In response to consultation, the company also submitted additional evidence regarding the treatment of missing data in TEMPO 3:4. In this response, the company presented 'jump to placebo' and 'tipping point' analyses. For the 'jump to placebo' analysis it was assumed that for all patients who withdrew from the TEMPO 3:4 study, there was 100% loss in the efficacy of tolvaptan. In this analysis, the company showed there was still a statistically significant improvement ($p < 0.0001$) in the decline in eGFR for tolvaptan compared with placebo. The 'tipping point' analysis estimated that a 267% drop in the efficacy of tolvaptan was needed before the improvement in eGFR decline was no longer statistically significant. The company argued that based on these analyses, the impact of missing data had not negatively affected the overall conclusions about the efficacy of tolvaptan in ADPKD made from the TEMPO 3:4 study. The company also submitted additional evidence relating to whether TEMPO 3:4 was adequately powered to detect a statistically significant difference in eGFR using the CKD-EPI equation. Using post-hoc power calculations, the company estimated that for a statistical significance of 95%, the TEMPO 3:4 study provided over 99% power to detect a difference of 0.977 in the eGFR slope.

ERG's additional analyses

3.55   After critiquing the company's additional evidence submission, the ERG presented additional analyses using its preferred assumptions for both the intention-to-treat population and the subgroup with CKD stages 2 and 3; these analyses will be referred to as the ERG's 'revised base case' from this point.

3.56   The ERG's revised base case agreed with that of the company's revised base case with the exception of the following assumptions:

- Equal kidney pain probability for both tolvaptan and placebo (company assumed probabilities of 0.05 and 0.07 respectively; see section 3.48).
- Utility decrement of 0.0123 for tolvaptan treatment (company assumed a utility decrement of 0.0025; see section 3.48).
- Assuming that 3 out of 10 Hy's law cases would have a liver transplant at year 1 and would die immediately thereafter (company did not model the possibility of Hy's law cases).

The ERG's revised base case resulted in a probabilistic mean estimate of the ICER for tolvaptan compared with standard care of £43,514 per QALY gained in the intention-to-treat population, and £30,025 per QALY gained in the subgroup with CKD stages 2 and 3.

3.57   Full details of all the evidence are in the [Committee papers](#).

4   Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of tolvaptan, having considered evidence on the nature of autosomal dominant polycystic kidney disease (ADPKD) and the value placed on the benefits of tolvaptan by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1   The Committee heard about the impact of the disease from patient experts. It understood that ADPKD is a genetically inherited disorder that puts a high mental burden on patients and their families. Patients are often aware of how the disease has affected their older relatives as well as living with the condition themselves. The patient experts also explained their feelings of guilt of having potentially passed on the disease to some or all of their children. The Committee noted comments in patient- and professional-group submissions that ADPKD is a debilitating and painful disease. The comments also emphasised that the disease can have a negative impact on family relationships and career progression. The Committee acknowledged the high burden of disease for people with ADPKD and their families; and concluded that having a treatment option is very important.

4.2   The patient experts informed the Committee of the main benefits of treatment with tolvaptan in their experience. The patient experts stated that, given the lack of active treatments for ADPKD to date, the availability of tolvaptan gives patients hope, not just for themselves but also for future generations. The clinical experts stated that this is the first treatment to target the disease rather than manage complications. The Committee noted that the main adverse reaction of tolvaptan is thirst, which significantly affects daily lifestyle, but the patient experts explained how it is possible to adapt to the need to drink a significantly increased volume of water and that it is important to give the body time to adjust to this change. In the patient experts' experience, taking the later dose of tolvaptan sufficiently early before going to bed limits the effects on the quality of sleep. The Committee understood from the patients that on balance, the advantages of tolvaptan and the hope that it brings in terms of slowing disease progression outweigh the disadvantages.

4.3   The Committee considered the management of ADPKD in current clinical practice. It heard from the clinical experts that there are no pharmacological treatments that can reduce the rate of decline in renal function. The Committee noted that current treatment aims to manage the

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symptoms of ADPKD; that is, control blood pressure and hypertension, and provide supportive care for pain, infections and bleeding. The Committee understood from the clinical experts that treatment for ADPKD has not changed for many years and an agent that actively targets disease progression would be a significant development in this disease area. The Committee concluded that tolvaptan is an important development in the treatment of ADPKD.

Clinical effectiveness

4.4   The Committee was aware that the marketing authorisation for tolvaptan is for people with chronic kidney disease (CKD) stages 1 to 3 with rapidly progressing disease. It heard from clinical experts that there is no definition of rapidly progressing disease, but that in clinical practice they were able to identify people at greater risk of rapid decline in renal function using a variety of observations, such as baseline GFR and a person's symptoms and quality of life over time. In addition, clinical experts stated that a person's risk of progression could be assessed according to the experience of progression by family members with ADPKD. The Committee concluded that clinicians would use a combination of clinical variables to identify patients in clinical practice who may be more likely to benefit from tolvaptan when used within its licensed indication.

4.5   The Committee noted that the company's additional evidence submission focused only on a proposed optimised subgroup of people with CKD stages 2 and 3. The Committee heard from clinical experts that this subgroup could be readily identified in clinical practice because CKD stage is routinely recorded in clinical practice. The Committee considered whether it was appropriate to only define the subgroup according to the stage of CKD. It noted that to be eligible for entry into TEMPO 3:4, patients had to have a total kidney volume (TKV) of 750 ml or more and the TKV in the optimised subgroup had increased considerably compared with the intention-to-treat population. It heard from the company and from

clinical experts that TKV is not routinely recorded in clinical practice, and that the most accurate method to determine TKV is MRI, which may be associated with potential access issues. It was also mindful of its previous conclusion that several clinical variables are often used in clinical practice to identify people at risk of rapid progression (see section 4.4). The Committee heard from the patient and clinical experts that they considered it acceptable to narrow the eligible population by excluding people with CKD stage 1. The Committee concluded that CKD stage is routinely recorded in clinical practice, and that it was appropriate to consider tolvaptan for the subgroup of people with CKD stages 2 and 3 as well as for people within the broader licensed indication for tolvaptan.

4.6   The Committee considered whether the evidence for the clinical effectiveness of tolvaptan could be generalised to patients in clinical practice. It was aware that the main evidence in the company's submission came from the pivotal TEMPO 3:4 randomised controlled trial (n=1445) that compared tolvaptan with placebo. The Committee noted that a high number of patients who had been considered eligible for treatment had been excluded from the trial because they did not meet the inclusion criteria (TKV 750 ml or more, and an estimated glomerular filtration rate [eGFR] of 60 ml per minute or more). It was also aware that the trial included a small percentage of CKD stage 3 (17%, n=247) patients. The Committee noted that the average baseline TKV was 1692 ml and the average eGFR was 82 ml/min/1.73 m^2 (measured with Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation). The Committee understood that these factors reflected a population with a greater probability of rapidly progressing disease, as defined by the inclusion criteria for the clinical trial. The Committee noted that for the subgroup presented by the company, the average baseline TKV was 2300 ml and the average eGFR was 60 ml/min/1.73 m^2 (midpoint of CKD stages 2 to 3). It considered that the subgroup reflected a population with an even greater probability of rapidly progressing disease than that of the intention-to-treat population. The Committee recalled that in the pivotal

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trial 5% of the patients were from the UK, although it also noted comments from the company that there were similarities in ethnicity between the trial population and people in England. The Committee noted that the age range of patients included in the trial was between 18 and 50. However, the marketing authorisation for tolvaptan has no upper age limit. The Committee noted comments from clinical experts stating that TEMPO 3:4 reflected UK clinical practice. The Committee concluded that TEMPO 3:4 was relevant to UK clinical practice and that the results could be used for decision making.

4.7   The Committee considered the most appropriate outcomes in the TEMPO 3:4 trial for measuring the progression of ADPKD and the relative treatment effect of tolvaptan. It was aware that the primary outcome was TKV, but that the NICE scope for the appraisal listed the rate of decline in renal function as the main outcome. The Committee understood from the company that rate of decline in renal function, as assessed by eGFR, was included as a secondary outcome, and it noted the post-hoc power calculations presented by the company in its additional evidence submission that suggested it was very likely that the trial was adequately powered to assess this outcome. The Committee considered the approach to assessing eGFR in the trial, and noted that this had been undertaken using the reciprocal of serum creatinine in the primary analysis and was also estimated using the CKD-EPI equation formula. The Committee heard from the clinical experts that CKD-EPI is the accepted method in the clinical community for measuring eGFR and understood that this was the preferred measure for diagnosing, staging and estimating treatment effect in NICE's guideline on chronic kidney disease. The Committee concluded that the preferred measure of both the progression of ADPKD and the relative treatment effect of tolvaptan is eGFR as estimated using the CKD-EPI formula.

4.8   The Committee considered the relative benefit of tolvaptan compared with placebo as reported in the TEMPO 3:4 trial. The Committee noted the relative reduction in the annual rate of renal decline, measured by CKD-

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EPI, for tolvaptan compared with placebo of 26.4% for the intention-to-treat population. It also noted that the equivalent rate for the subgroup with CKD stages 2 and 3a was 29.7%. The Committee was aware that, out of 2122 patients that were assessed for eligibility in the trial, 677 patients (32%) had been excluded (530 of which were excluded due to the inclusion criteria). The Committee expressed concern that data were not available for a large number of people for whom tolvaptan could have been considered suitable in clinical practice. The Committee accepted, however, from the 'tipping point' and 'jump to placebo' analyses (see section 3.54) presented by the company that the impact of missing data had not negatively affected the overall conclusions about the efficacy of tolvaptan based on the TEMPO 3:4 study. The Committee concluded that tolvaptan offers clinical benefit compared with standard care in both the intention-to-treat population and in the subgroup with CKD stages 2 and 3a.

4.9 The Committee noted that in the company's additional evidence submission, it presented clinical effectiveness evidence for only those people with CKD stages 2 or 3a, and that people with CKD stage 3b had been excluded. It understood from the company that this was an oversight and that the subgroup should have contained people with CKD stages 2, 3a and 3b. The Committee understood that for people with CKD stage 3, eGFR ranged from 30 to 59 ml per minute, and that this group could be subdivided into CKD stages 3a (eGFR of 45 to 59 ml per minute) or 3b (eGFR of 30 to 44 ml per minute). The Committee accepted that the company had submitted evidence showing that the difference in treatment effect when people with CKD stage 3b were added to the population was marginal, and that it improved the cost effectiveness of tolvaptan. The Committee was mindful that the ERG had not had an opportunity to review this evidence, nevertheless it concluded that when considering the company's revised base case it was appropriate to consider all patients with CKD stages 2 and 3 (including stages 3a and 3b).

4.10   The Committee was aware of the requirement for liver function testing for patients taking tolvaptan, as detailed in the summary of product characteristics. It noted that significant abnormal liver-function test results (determined by Hy's law; see section 3.7) were recorded for 3 people across the TEMPO 3:4 and TEMPO 4:4 trials. The Committee considered the potential for serious liver injury to be a concern with tolvaptan treatment, but noted that the effect reversed after discontinuing the drug. The Committee also noted comments from the company in its additional evidence submission that there had been no cases of severe drug-induced liver injury (Hy's Law) since the frequency of monitoring had been increased after the initial Hy's law cases, although it understood that the possibility of future Hy's law cases could not be ruled out. The Committee was aware from the patient experts that the main adverse reaction is thirst, and that in the patients' experience it is necessary to drink at least 6 litres of water each day to overcome this thirst. The patient experts stressed that, over time, people can adjust to drinking this quantity of water. The Committee concluded that tolvaptan is associated with adverse reactions and effects, the more serious of which can be avoided through increased monitoring, and that some people do not need additional clinical assistance.

Cost effectiveness

4.11   The Committee discussed the economic model developed by the company for this appraisal. It considered that the model was acceptable for assessing the cost effectiveness of tolvaptan. The Committee noted that in the additional evidence submission the company had provided analyses for the optimised subgroup, but had not provided analyses for the intention-to-treat population. It noted that in the ERG's critique of the additional evidence submission it had carried out additional exploratory analyses to understand the cost effectiveness of tolvaptan in the intention-to-treat population. In these exploratory analyses, the ERG reported the incremental cost-effectiveness ratio (ICER) for tolvaptan

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compared with standard treatment of £43,500 per quality-adjusted life year (QALY) gained (with the patient access scheme; see section 3.56).

4.12   The Committee considered the company's additional evidence containing the revised base case (including the revised patient access scheme) for a subgroup with CKD stages 2 and 3, acknowledging that the company's analyses resulted in a base-case ICER for tolvaptan compared with standard treatment of approximately £23,500 per QALY gained (see section 3.50). The Committee noted that the ICER incorporating the ERG's preferred assumptions was approximately £30,000 per QALY gained (see section 3.56). The Committee understood that there were several differences in the assumptions adopted by the company in its additional evidence submission compared with those preferred by the ERG in its critique of the company's additional evidence, including assumptions relating to: treatment-related utility decrement for tolvaptan; probability of kidney pain for tolvaptan and placebo; and Hy's law events. The Committee discussed each of these in turn.

4.13   The Committee noted that the company used a utility decrement for tolvaptan treatment of 0.0025 whereas the ERG's revised base case used a value of 0.0123. The Committee noted the ERG's view that the value of 0.0123 was conservatively incorporated because no adverse events other than kidney pain were incorporated in the model. The Committee understood that the company had estimated the utility decrement of 0.0025 by assuming the QALYs gained because of pain reduction were equal to the QALYs lost because of the negative effect of being on tolvaptan. The Committee was not convinced that this was a valid assumption; however, it was also aware that there was little evidence to support the utility decrement of 0.0123 applied by the ERG. The Committee heard from the patient experts that although they experienced some treatment-related adverse reactions, their bodies had adapted to the drug and therefore it had a small effect on their quality of life. The Committee also heard from patient experts that people who have a large reduction in their quality of life as a result of tolvaptan would be likely to

stop treatment and therefore the quality of life decrement would be relatively small for long-term patients. The Committee concluded that the true utility value decrement as a result of tolvaptan treatment was unknown, but that it was likely to be less than 0.0123 and may diminish over time.

4.14 Regarding the probability of kidney pain, the Committee noted that in the company's additional evidence for its revised base case it had not applied an equal probability of kidney pain for tolvaptan and placebo (see section 3.48) because it had stated that this contradicted the findings of TEMPO 3:4. The Committee also noted the ERG's comments that the company's assumption inferred that the difference in kidney pain as observed in TEMPO 3:4 was independent from the effect of tolvaptan on disease progression. The Committee noted the ERG's view that pain was a known symptom of chronic kidney disease, increasing with disease progression, and that the separate modelling of pain may have led to double counting (that is, the higher utility for lower CKD stages may have already been captured by the effect of kidney pain). The Committee noted comments from clinical experts that kidney pain is not necessarily reflective of CKD stage and that reduction in pain could be seen as an effect of the drug because of the reduction in kidney size. The Committee was aware that the effect of this assumption was very small (see ERG exploratory analysis in section 3.27). The Committee concluded that the conservative approach incorporating an equal kidney pain probability for both arms was appropriate for the base case.

4.15 The Committee discussed the health-state utility values used by the company in the model. It noted that health-related quality of life was not assessed in the TEMPO 3:4 trial and the company used health-state utility values from a study published by Gorodetskaya et al. (2005), identified from a literature search (see section 3.13). The Committee noted that the utility values published by Gorodetskaya et al. were not ADPKD specific, and consequently, it agreed that the results using these utility values were associated with a considerable degree of uncertainty. However, in a late

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submission that the ERG did not have the opportunity to critique, the company presented an analysis using EQ-5D data from patients with ADPKD from the OVERTURE trial (details of the OVERTURE study are presented in section 3.6; however, details of the utility values are not presented since these were designated confidential by the company). In these analyses, health-state decrements were modified in the model for CKD stages 1 to 4. The results of these analyses found there was only a small effect on the ICER, which the company stated was in line with the low degree of sensitivity demonstrated in scenario analyses on the health state utility decrements for CKD stages 3 and 4 provided in the company's original submission. The Committee concluded that although the analyses presented had not yet been critiqued by the ERG, they were persuaded that the ADPKD-specific EQ-5D data from OVERTURE were unlikely to significantly alter the outcome of the revised base case analysis.

4.16   The Committee considered whether it was appropriate to model the Hy's law cases, noting comments from the ERG that the possibility of future Hy's law cases cannot be eliminated. However, the Committee was mindful of its previous conclusion that the possibility of such adverse effects could be reduced by increased monitoring, The Committee also understood that liver biochemistry monitoring was relatively infrequent in the TEMPO studies, and that more frequent monitoring would be expected in clinical practice, which would further lower the risk of liver failure. The Committee concluded that the ERG base case reflected a 'worst-case' scenario and with the additional monitoring measures in place it was reasonable not to include Hy's law cases in the base case.

4.17   The Committee considered the most plausible ICER for tolvaptan compared with standard care for adults with CKD stages 1 to 3. It noted that the company had not presented an estimate of the ICER for this population in its revised base case, and that the ERG had estimated an ICER of £43,500 per quality-adjusted life year (QALY) gained (see section 3.56). The Committee was aware that this estimate had not included all of its preferred assumptions, but even accounting for this, the

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Committee considered that the most plausible ICER was still not in the range normally considered to be a cost-effective use of NHS resources and concluded that it could not recommend tolvaptan for people with CKD stages 1 to 3. The Committee considered the most plausible ICER for tolvaptan compared with standard care for adults with CKD stages 2 to 3. The Committee noted that in the ERG's additional exploratory analyses, it had presented an ICER for tolvaptan compared with standard treatment of approximately £30,000 per QALY gained. The Committee estimated that this ICER was likely to have overestimated the most plausible ICER for 3 reasons:

- the incorporation of Hy's law, which it estimated had increased the ICER by at least £2500 per QALY gained
- the incorporation of a treatment-related utility decrement of 0.0123, which the Committee regarded as a worst-case scenario, and
- the fact that the company had not adjusted the annual change in renal function and percentage TKV change to reflect the subgroup of people with CKD stages 2 and 3.

The Committee therefore considered the most plausible ICER for adults with ADPKD CKD stages 2 to 3 with rapidly progressing disease was likely to be most closely represented by that reflected in the company's revised base case of approximately £23,500 per QALY gained.

4.18   The Committee noted comments from the company in its submission and from the clinical experts about tolvaptan being an innovative treatment. The company stated that tolvaptan represents a 'step-change' in managing ADPKD, because this is the first drug available that slows cyst growth and reduces the decline in renal function. The company emphasised that this is an area of high unmet medical need and the burden of the disease can be extremely high for people. The company further stated that tolvaptan has a significant and substantial impact on health-related benefits, and it can delay time to end-stage renal disease and reduce the strain on renal replacement therapy resources. The

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Committee heard from clinical experts that tolvaptan represents a step-change in treatment and from the patient experts that it may also have a positive psychological benefit for people with ADPKD. The Committee understood the importance of such benefits, which may be difficult to capture in measures of health-related quality of life in addition to those already included in the QALY calculations. The Committee concluded that tolvaptan is an innovative treatment and it is the first treatment that has been shown to specifically impact on the progression of ADPKD. The Committee considered that the most plausible ICER for adults who have CKD stages 2 to 3 was approximately £23,500 per QALY gained. Taking all of these factors into account, the Committee concluded that tolvaptan represented a cost-effective use of NHS resources in adults who have CKD stages 2 to 3. The Committee therefore recommended tolvaptan as an option for treating ADPKD to slow the progression of cyst development and renal insufficiency only in adults who have CKD stages 2 to 3 at the start of treatment and evidence of rapidly progressing disease.

4.19   The Committee considered whether there were any equality issues associated with recommending tolvaptan for people with CKD stage 2 and 3, considering that people with CKD stage 1 would not get access to treatment, and whether this could be considered unfair. It heard from clinical and patient experts that this was not an equality issue, and that people with CKD stage 1 would eventually progress to CKD stages 2 and 3 and therefore would become eligible for treatment. The Committee also heard from patient experts who considered it fair to exclude people with CKD stage 1 so that people with CKD stages 2 and 3 could gain access to the treatment. The Committee considered that people with CKD stage 1 did not differ from people with CKD stage 2 and 3 as far as any protected characteristics are concerned. It concluded that there was no unfairness or unlawful discrimination, and as a result there were no equality issues associated with recommending tolvaptan for use in patients with CKD stages 2 and 3 with high risk of progression.

4.20   The Committee considered whether it should take into account the consequences of PPRS 2014, and in particular the PPRS payment mechanism, when appraising tolvaptan. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view on the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not applicable when considering the cost effectiveness of tolvaptan.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Tolvaptan for treating autosomal dominant polycystic kidney disease	Section
Key conclusion		
Tolvaptan is recommended as an option for treating autosomal dominant polycystic kidney disease in adults to slow the progression of cyst development and renal insufficiency only if: • they have chronic kidney disease stage 2 or 3 at the start of treatment • there is evidence of rapidly progressing disease and • the company provides it with the discount agreed in the patient access scheme.	1.1
The Committee concluded that CKD stage is routinely recorded in clinical practice, and that it was appropriate to consider tolvaptan for the subgroup of people with CKD stages 2 and 3 as well as for people within the broader licensed indication for tolvaptan.	4.17
The Committee considered that the most plausible incremental cost-effectiveness ratio (ICER) for tolvaptan compared with standard care for adults with CKD stages 1 to 3 was not in the range normally considered	

to be a cost-effective use of NHS resources and concluded that it was not possible to recommend tolvaptan for people with CKD stages 1 to 3.

The Committee considered that in adults with ADPKD CKD stages 2 to 3 with rapidly progressing disease, the most plausible ICER for tolvaptan was £23,500 per quality-adjusted life year (QALY) gained. The Committee concluded that for this subgroup, tolvaptan represented a cost-effective use of NHS resources. The Committee therefore recommended tolvaptan as an option for treating ADPKD to slow the progression of cyst development and renal insufficiency only in adults who have chronic kidney disease (CKD) stages 2 to 3 at the start of treatment and evidence of rapidly progressing disease.

Current practice		
Clinical need of patients, including the availability of alternative treatments	Currently there are no pharmacological treatments available for treating autosomal dominant polycystic kidney disease (ADPKD) and the current standard of care aims to manage the symptoms. Tolvaptan is the first treatment to target the disease rather than manage complications. The Committee understood from the clinical experts that treatment for ADPKD has not changed for many years and an agent that actively targets disease progression would be a significant development for this disease area.	4.3
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The proposed benefit of tolvaptan is to slow disease progression by reducing the rate of decline in renal function and kidney growth. Given the lack of active treatments for this genetically inherited disease, the availability of tolvaptan gives hope for people with ADPKD and also for their children and family. The Committee concluded that tolvaptan is an innovative treatment and it is the first treatment that has been shown to specifically impact on the progression of ADPKD.	4.2 4.18
What is the position of the treatment in the pathway of care for the condition?	Tolvaptan treatment would replace current clinical practice, which aims to manage the symptoms of ADPKD.	4.3
Adverse reactions	The main adverse reactions of tolvaptan were thirst, polyuria, nocturia, pollakiuria and alanine aminotransferase or aspartate aminotransferase elevation. The Committee understood from the patient experts that the main adverse effect is thirst, which considerably affects their daily lifestyle, but it is possible to adapt to this and, for them, the advantages outweigh the disadvantages.	2.2 4.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee considered evidence for the TEMPO 3:4 trial, which was a randomised controlled trial that compared tolvaptan with placebo. It also considered evidence within this	4.6

	trial for the subgroup with CKD stages 2 and 3.	
Relevance to general clinical practice in the NHS	The Committee concluded that the generalisability of the trial results may be limited because of differences in the trial population compared with people with ADPKD seen in routine clinical practice, but overall it was satisfied that TEMPO 3:4 was relevant to UK clinical practice.	4.6
Uncertainties generated by the evidence	The Committee was aware that data were not available for a large number of people for whom tolvaptan had been considered suitable and considered that this could introduce uncertainty about the size of the treatment effect in clinical practice. However, the Committee concluded that the impact of missing data had not negatively affected the overall conclusions about the efficacy of tolvaptan.	4.8
	The Committee considered the potential for serious liver injury to be a concern with tolvaptan treatment, and understood that the possibility of future Hy's law cases could not be ruled out. However, the Committee concluded that the more serious adverse events associated with tolvaptan treatment could be avoided through increased monitoring.	4.10

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The subgroup with CKD stages 2 and 3.	4.9
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The relative reduction in the annual rate of renal decline, measured by CKD-EPI, for tolvaptan compared with placebo was 26.4% in the intention-to-treat population of TEMPO 3:4, and was 29.7% for the subgroup with CKD stages 2 and 3a	4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee used the company's original economic model, its revised economic model, and the critique of these by the Evidence Review Group (ERG) to inform its discussions.	4.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee concluded that the true utility value decrement as a result of tolvaptan treatment was unknown, but that it was likely to be less than 0.0123 and may diminish over time. The Committee noted that the utility values used in the company's model from the published study by Gorodetskaya et al. (2005) were not ADPKD specific, and consequently, it agreed that the results using these utility values were associated with a considerable degree of uncertainty.	4.13 4.15

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	Utility values used in the company's model were from the published study by Gorodetskaya et al. (2005). The Committee concluded that although the health-related quality-of-life analyses presented by the company for OVERTURE had not yet been critiqued by the ERG, they were persuaded that the ADPKD-specific EQ-5D data from OVERTURE were unlikely to significantly alter the outcome of the revised base-case analysis.	4.15
Are there specific groups of people for whom the technology is particularly cost effective?	The subgroup with CKD stages 2 and 3.	4.18

Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that in the additional evidence submission the company had not provided a revised base case for the intention-to-treat population. It noted that in the ERG's critique of the additional evidence submission it had carried out additional analyses and presented a revised base case for the intention-to-treat population, and that the ICER for this was £43,500 per QALY gained (with the patient access scheme). The Committee considered the most plausible ICER for the subgroup with CKD stages 2 to 3 was likely to be most closely represented by that reflected in the company's revised base case of approximately £23,500 per QALY gained (with the patient access scheme).	4.11 4.18
Additional factors taken into account		
Patient access schemes (PPRS)	The Department of Health and Otsuka Pharmaceuticals have agreed that tolvaptan will be available to the NHS with a patient access scheme which makes it available with a discount.	2.3
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	The Committee concluded that there were no equalities issues associated with recommending tolvaptan for use in patients with CKD stages 2 and 3 with high risk of progression.	4.19

5   Implementation

5.1   Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2   The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3   When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has ADPKD and the doctor responsible for their care thinks that tolvaptan is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4   The Department of Health and Otsuka Pharmaceuticals have agreed that tolvaptan will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

5.5   NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.

- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6   Related NICE guidance

Details are correct at the time the final appraisal determination goes out for appeal and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care](#). NICE guideline CG182 (2014).
- [Peritoneal dialysis: peritoneal dialysis in the treatment of stage 5 chronic kidney disease](#). NICE guideline CG125 (2011).
- [Guidance on home compared with hospital haemodialysis for patients with end-stage renal failure](#). NICE technology appraisal guidance 48 (2002).

7   Review of guidance

7.1   The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Gary McVeigh
Chair, Appraisal Committee
August 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Gary McVeigh (Chair)

Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)

GP, West Coker Surgery, Somerset

Dr Aomesh Bhatt

Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black

GP, Mortimer Medical Practice, Herefordshire

Professor David Bowen

Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley

Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell

Honorary Consultant Physician, Llandough Hospital, Cardiff

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Susan Dutton

Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, Newcastle University

Mrs Gillian Ells

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh

Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Professor John Henderson

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Dr Tim Kinnaird

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Mr Warren Linley BSc

Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

Dr Malcolm Oswald

Lay member

Professor Femi Oyebode

Professor of Psychiatry & Consultant Psychiatrist, The National Centre for Mental Health

Dr Mohit Sharma

Consultant in Public Health, Public Health England

Dr Murray Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Boglárka Mikudina and Chris Chesters

Technical Lead

Joanne Holden and Fay McCracken

Technical Adviser

Kate Moore

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Review Ltd (UK):

- Wolff R, Joore MA, Ramaekers B et al. Tolvaptan for treating autosomal dominant polycystic kidney disease: a single technology appraisal, March, 2015.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Otsuka Pharmaceuticals

II. Professional/expert and patient/carer groups:

- British Kidney Patient Association
- British Renal Society
- British Society for Histocompatibility and Immunogenetics
- Kidney Research UK
- PKD Charity
- Renal Association
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on tolvaptan by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

- Professor Albert Ong, Professor of Renal Medicine, University of Sheffield, nominated by Otsuka Pharmaceuticals, the PKD Charity and the Renal Association – clinical expert
- Professor Bruce Hendry, Professor of Renal Medicine, King's College London, nominated by Otsuka Pharmaceuticals – clinical expert
- Dr John Sayer, Senior Clinical Lecturer in Nephrology, nominated by PKD Charity – clinical expert
- Simone Goren, nominated by the PKD Charity – patient expert
- Theresa Williams, nominated by the PKD Charity – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Otsuka Pharmaceuticals