NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Tolvaptan for treating autosomal dominant polycystic kidney disease

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using tolvaptan in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 8) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using tolvaptan in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 26 June 2015

Second Appraisal Committee meeting: 7 July 2015

Details of membership of the Appraisal Committee are given in section 7, and a list of the sources of evidence used in the preparation of this document is given in section 8.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Tolvaptan is not recommended within its marketing authorisation for treating autosomal dominant polycystic kidney disease to slow the progression of cyst development and renal insufficiency in adults who have chronic kidney disease stages 1 to 3 at the start of treatment and evidence of rapidly progressing disease.

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 kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease'. The product had not been launched for use in England when the appraisal consultation document was issued.

2.2 The summary of product characteristics lists the following adverse reactions for tolvaptan: thirst, polyuria, nocturia, pollakiuria (frequent urination), 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 will be 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 cost was provided by the company to NICE. The annual cost of tolvaptan is estimated by the company to be £15,750 per patient. The company has agreed a patient access scheme with the Department of Health. If tolvaptan had been recommended, this scheme would provide 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 would not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 7) considered evidence submitted by Otsuka Pharmaceuticals and a review of this submission by the Evidence Review Group (ERG; section 8).

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 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 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 came from the UK.

3.2 The primary endpoint 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 demonstrated 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). Subgroup analyses of TKV at each CKD stage (1, 2 or 3 at baseline) were presented.

3.3 In TEMPO 3:4 the composite secondary endpoint 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 endpoint 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, 0.62-1.78; P < 0.001), compared with placebo. When GFR was assessed using CKD-EPI, 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 who were receiving placebo in TEMPO 3:4..

3.6 The most commonly reported adverse reactions were thirst, polyuria, nocturia and pollakiuria, occurring in approximately 55%, 38%, 29% and 23% of patients, respectively. Furthermore, tolvaptan was associated with 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 fulfilled 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), which indicates the potential risk for serious drug-induced liver injury. In all cases the abnormalities resolved after stopping treatment with tolvaptan. The percentage of patients who discontinued treatment was 23% in the tolvaptan group and 14% in the placebo group. Health-related quality of life (HRQoL) was not assessed in the TEMPO 3:4 trial.

Cost effectiveness

3.7 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 two 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.

3.8 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.

3.9 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

- 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 3.14)
- 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 sensitivity analysis.

3.10 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, sex, 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.

3.11 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. The company considered this to be more appropriate than adjusting by the primary outcome of the trial (TKV) as an intermediate outcome. The company stated that this was because the relationship between TKV and eGFR (that 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 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 discontinued 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 discontinued.

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 discontinued 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+) 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.

3.16 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. Monitoring costs were applied including liver-function tests (performed 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 perform 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) and
- using a disutility of 0.0123 for being on tolvaptan treatment (ICER with PAS: £40,401 per QALY gained).

3.19 Subgroup analyses were conducted for each CKD stage at treatment initiation. Values for these variables were taken from the TEMPO 3:4 trial. The results of a real-world study called OVERTURE were also explored. 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. The results of the subgroup analyses were marked as commercial in confidence therefore cannot be reported here.

Evidence Review Group

3.20 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 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. In addition, the ERG noted that other treatment options, such as aggressive blood pressure management and increased fluid intake, were not comparators in the scope, but may have an impact on decline in renal function in people with ADPKD.

3.21 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 to 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 receive 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).

3.22 Regarding the outcomes of interest, 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 CKD-EPI equation.

3.23 The ERG noted that 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. In its report the ERG considered TKV as a surrogate endpoint for annual eGFR decline had very limited value. TKV is a good measure of extent of disease because it predicts future decline of renal function. The ERG also criticised the measurement of TKV by the ellipsoid method as potentially unreliable because in ADPKD the kidneys lose their predictable shape.

3.24 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 discontinued treatment because of adverse events in the tolvaptan arm than in the placebo arm of the trial (15.4% compared with 5.0%, respectively).

3.25 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.

3.26 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 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 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.

3.27 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).

3.28 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.

3.29 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 on the tolvaptan and on the placebo arm. 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.

3.30 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 performed an exploratory analysis, incorporating consequences of tolvaptan-induced hepatotoxicity.

3.31 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.

3.32 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.

3.33 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.

3.34 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

3.35 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 performed 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).

3.36 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.

3.37 The ERG conducted an analysis where 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.

3.38 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.

3.39 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.

3.40 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; and 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.

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

£64,515 per QALY gained (ERG's preferred base case ICER using CKD-EPI).

3.42 The ERG also undertook an exploratory analysis using the worst case scenarios as described in sections 3.35–3.39. 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 3.41). When using CKD-EPI as an approximation for eGFR, the combination of these worst case scenarios resulted in an ICER of £72,705 (ERG's worst case scenario ICER using CKD-EPI).

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, 3.41 and 3.42 are presented in Table 1~~Table 1~~~~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;			

3.43 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 family. 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 the disease on 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 family; 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 extreme 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 sufficiently early before going to bed limits the impact 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

currently no pharmacological treatments that can reduce the rate of decline in renal function. The Committee noted that current treatment aims to manage the 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 for this disease area. The Committee concluded that tolvaptan is an important development in the treatment of ADPKD.

4.4 The Committee was aware that the marketing authorisation for tolvaptan is for those 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. The Committee acknowledged that in current clinical practice the disease is not categorised into slow, medium or rapidly progressing disease because there are currently no treatments available even if risk of progression was known. The Committee heard from clinical experts that, potentially, genetic testing and height-adjusted total kidney volume, measured by validated techniques, could help better define those people at greatest risk of progression, but these approaches are not currently used in clinical practice. The Committee concluded that there is no universally agreed definition for rapidly progressing disease exists.

Clinical effectiveness

4.5 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 that compared tolvaptan with placebo. It

noted that there was a high number of patients who had been considered eligible for treatment but who had been excluded from the trial (n=530) because of the inclusion criteria (total kidney volume [TKV] 750 ml or more, and estimated creatinine clearance 60 ml/min or more). The trial included a small percentage of CKD stage 3 (17%) patients. The Committee noted that the average baseline kidney volume was 1692 ml and the average estimated glomerular filtration rate (eGFR) of 82 ml/min/1.73 m^2 (measured with Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]). The Committee considered 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 recalled that in the pivotal trial 5% of the patients were from the UK and 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 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.

4.6 The Committee considered the outcomes in the TEMPO 3:4 trial. 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 representatives that rate of decline in renal function, as assessed by eGFR, was included as a secondary outcome, but that the trial was not powered to detect a statistically significant difference in this endpoint. 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 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.

4.7 The Committee considered the relative benefit of tolvaptan compared with placebo as reported in the TEMPO 3:4 trial. It was aware of a statistically significant reduction in the annual rate of TKV for tolvaptan of 49.2% compared with placebo, (absolute reduction of −2.71% per year; 95% confidence interval −3.27 to 2.15; p<0.0001).The Committee also noted the relative reduction in the annual rate of renal decline of 31.6% measured by the reciprocal of the serum creatinine level and 26.4% measured by CKD-EPI, for tolvaptan compared with placebo. The Committee was aware that data was not available for a large number of people (n = 677, of whom 530 were excluded due to the inclusion criteria) who had been considered suitable for treatment and who may therefore be treated in clinical practice. It considered that this could introduce uncertainty about the size of the treatment effect in clinical practice. It heard from the company that the analyses were performed on all data available, on an intention-to-treat basis. The Committee was aware that the US Food and Drug Administration had raised concerns about the quantity of missing data. The company stated that a new safety and efficacy study had been commissioned, and that this was currently recruiting in order to provide further evidence about the treatment effect of tolvaptan. The Committee concluded that tolvaptan offers some clinical benefit compared with standard care, but there is some uncertainty about the size of the treatment effect as reported in the TEMPO 3:4 trial.

4.8 The Committee was aware of the requirement for liver function testing, as detailed in the summary of product characteristics, for patients taking tolvaptan. It noted that significant abnormal liver-function test results (as determined by Hy's Law, see section 3.6) 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 major concern with tolvaptan treatment, but noted that the effect reversed after discontinuing the drug. 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 per 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 effects, the more serious of which can be avoided through increased monitoring, and some that people can manage without additional clinical assistance.

Cost effectiveness

4.9 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. It understood that the model used an underlying risk of disease progression to which a treatment effect for tolvaptan was applied and acknowledged that the company's base case (including the patient access scheme) resulted in an incremental cost-effectiveness ratio (ICER) of £34,700 per QALY gained, for tolvaptan compared with standard care. To establish the risk of disease progression, 2 regression equations were used: 1 for TKV and 1 for eGFR. The regression equation for eGFR depended on TKV in the previous cycle and therefore TKV was used as an intermediate step in predicting eGFR, the primary outcome of the model. The Committee was mindful of the opinion of the Evidence

Review Group (ERG) that TKV was therefore used as a surrogate measure of eGFR. The company emphasised that, according to the literature, TKV can be used to predict decline in renal function. The Committee questioned why it had been necessary to predict eGFR using TKV as a surrogate, given that eGFR was one of the outcomes directly collected in the trial. The Committee did not agree with using regression equations for modelling the disease progression in the standard care arm and then using direct data from the clinical trial to model the treatment effect of tolvaptan, and therefore concluded it would have been preferable if the economic analyses considered only the eGFR results of the trial. The Committee further concluded that modelling eGFR using TKV as a surrogate endpoint introduced the potential for bias and therefore increased the uncertainty in the results of the model.

4.10 The Committee considered the 2 different means of assessing eGFR (that is, using the reciprocal of the serum creatinine level and CKD-EPI). It was mindful of its discussions about the appropriate measure for the clinical effectiveness of tolvaptan (see section 4.6) and its preference for using CKD-EPI as the appropriate approach to assessing eGFR. The Committee noted that using CKD-EPI to estimate both disease progression and the treatment effect increased the incremental cost-effectiveness ratio (ICER) substantially (from £34,700 per QALY gained to £50,500 per QALY gained, for tolvaptan compared with standard care, in the company's base case). The Committee concluded that the decision about the cost effectiveness of tolvaptan should be based on an analysis that uses CKD-EPI as the means of assessing eGFR for both the underlying disease progression and the treatment effect of tolvaptan. It recognised that the only analyses in which this was carried out were those explored by the ERG in their addendum.

4.11 The Committee discussed the assumptions around treatment discontinuation rates in the model, noting that the company's base case assumed a discontinuation rate of 0.5% for each year in the model after the 3 years for which data were available. It was also aware of the ERG's exploration of the effect of this variable on the ICER, in which a discontinuation rate of 6.5% had been used for each year beyond year 3 of the trial. The Committee noted that increasing the discontinuation rate significantly increased the ICER by about £8000 per quality-adjusted life-year (QALY) gained (see section 3.12). The Committee was aware that a discontinuation rate of 6.5% was described by the ERG as a worst-case scenario, and had been chosen in order to explore the effect on the ICER. The Committee noted that in the TEMPO 3:4 trial the discontinuation rates for years 1, 2 and 3 were 15.3%, 6.5% and 2.9%, respectively. The Committee considered that another option might have been to use the last year for which data were available, that is, the third year, for which the discontinuation rate was 2.9% and that this might have been more plausible than the worst-case scenario as explored by the ERG. The Committee concluded that the value of 0.5% might be an underestimation, whereas 6.5% might be an overestimation of the true treatment discontinuation rate and concluded that the rate beyond the trial data would be between 0.5% and 6.5%.

4.12 The Committee discussed the health-state utility values used by the company in the model. It noted that health-related quality of life (HRQoL) 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). However the Committee was aware that one of the trials for tolvaptan, the OVERTURE trial (see section 3.23~~.23.19~~), had collected EQ-5D data. The Committee questioned the

company on whether these data had been available for use in the economic model. It heard from the company that these data had not been made available for the submission and that only interim data were available. The Committee did not agree that ADPKD-specific HRQoL data should be disregarded because they are only available from an interim analysis and highlighted that the company could have used interim results for modelling HRQoL. The Committee concluded that it would have preferred to see ADPKD-specific health-state utility values used in the model and consequently, the results using the Gorodetskaya utility values were associated with a considerable degree of uncertainty.

4.13 The Committee discussed whether a utility decrement should be applied to the tolvaptan arm of the model. It noted that although the results of the trial show different serious adverse effects in the tolvaptan and placebo arms, the company did not apply a utility decrement for the tolvaptan group in its base case analysis. The Committee heard from the ERG that a utility decrement of 0.0123 had been used by the company in a scenario analysis and that it had originally come from a paper by Sullivan et al. (2011). It noted that applying a utility decrement increased the ICER significantly. The Committee concluded that it was appropriate to include a utility decrement for tolvaptan treatment and in the absence of any further evidence to suggest a different utility decrement, accepted the rate that had been used within the exploratory analyses performed by both the company and the ERG.

4.14 The Committee discussed the additional exploratory analyses performed by the ERG in its preferred base case. These included:

- correcting the model code error
- applying an equal probability of kidney pain to both treatment groups

- assuming equal costs for CKD stages 3 and 4
- applying a lower disutility of 0.02 for dialysis complications.

The Committee was aware that the effect of the model code error on the ICER was minimal and that the change was not contested by the company. It therefore considered this change to the model to be appropriate. Regarding the probability 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 exploratory analysis by the ERG was very small, and recognising some of the uncertainty in this variable, it accepted the ERG's approach as conservative. Regarding equal costs for CKD stages 3 and 4, the Committee concluded that the ERG's assumption to apply equal costs seemed to be reasonable (as in NICE's guideline on chronic kidney disease) and it noted that this scenario had a minor effect on the ICER. Regarding the disutility value for dialysis complications, the company accepted that 0.06 in the submission was an error and that the correct figure is 0.02, as in NICE's guideline on peritoneal dialysis. Therefore the Committee accepted the corrected figure of 0.02 and noted that this scenario had a minor impact on the ICER. The Committee acknowledged that the preferred base-case of the ERG resulted in an ICER of £43,300 per QALY gained and concluded that all these amendments should be incorporated in any estimation of the ICER for tolvaptan. The Committee further noted that when its preferred approach to assessing eGFR (that is, using CKD-EPI rather than the reciprocal of serum creatinine, see section 4.10) was used with these assumptions, the ICER increased to £64,500 per QALY gained.

4.15 The Committee considered the remaining exploratory worst case scenario analyses carried out by the ERG in which they assumed:

- that all Hy's Law cases would have a liver transplant at year 1 and would die immediately after
- increased mortality, instead of the general population mortality data (hazard ratio 2.0)
- a treatment discontinuation rate of 6.5% after year 3
- increased monitoring costs for being on tolvaptan treatment, using the proposed monitoring schedule in the summary of product characteristics
- decreased post-transplant costs.

The Committee accepted the ERG's approach to model the Hy's Law cases and concluded that it should be included in the model but was aware that this scenario had a minor impact on the ICER. Regarding applying an increased ADPKD-specific mortality, the Committee concluded that it had a minor impact on the ICER and recognised there was a lack of available data on ADPKD-specific mortality in the literature. Regarding the treatment discontinuation rate after year 3, the Committee had already discussed this assumption and concluded that 6.5% would most likely be an overestimate of the true discontinuation rate (section 4.11). Regarding monitoring costs, the Committee accepted the ERG's estimate, which was based on the proposed monitoring schedule in the summary of product characteristics. It was also aware that this scenario had a minor impact on the ICER. Regarding the decreased post-transplant costs, the Committee accepted the ERG's reasoning that including maintenance costs and background management costs may lead to double counting, therefore subtracting the background management costs from the maintenance costs was appropriate (see section 3.39). It was aware that this scenario increased the ICER substantially. The Committee acknowledged that cumulating these assumptions resulted in an ICER of £52,700 per QALY gained. It concluded that,

with the exception of the discontinuation rate of 6.5% after 3 years, these assumptions were all plausible scenarios and as such, should be considered when deciding on the most plausible ICER for tolvaptan. The Committee also acknowledged that using CKD-EPI as an approximation for eGFR increased the ICER for these combined scenarios to £72,700 per QALY gained.

4.16 The Committee considered the most plausible ICER for tolvaptan compared with standard care for people with ADPKD CKD stages 1 to 3 with rapidly progressing disease. Given its preference for the use of the CKD-EPI equation to estimate GFR for both the underlying disease progression and the treatment effect (section 4.10), the Committee considered the 2 ERG exploratory ICERs which had used this approach, that is, the ERG exploratory preferred base case of £64,500 per QALY gained (section 4.14) and the ERG remaining exploratory scenario ICER of £72,700 per QALY gained (section 4.15). The Committee was aware that these exploratory analyses were not cumulative and did not take into account uncertainties relating to the utility values (section 4.12**Error! Reference source not found.**~~**Error! Reference source not found..**~~). The Committee therefore concluded that these factors may lead to an underestimation of the most plausible ICER. However, the Committee was also mindful of its conclusion relating to the discontinuation rate (section 4.11) which may lead to an overestimation of the most plausible ICER. The Committee thought it likely that, on balance, these factors would take the ICER higher than the exploratory estimate of £72,700 per QALY gained, but the Committee was unable to say with certainty how much higher than £72,700 the most plausible ICER would be. Despite this, the Committee was confident that the ICERs as presented by both the company and the ERG were sufficient for the purpose of the decision to be made. The

Committee concluded that the ICERs were above the range usually considered a cost-effective use of NHS resources. It therefore further concluded that it could not recommend tolvaptan for treating ADPKD, to slow the progression of cyst development and renal insufficiency in adults who have chronic kidney disease stages 1 to 3 at the start of treatment and evidence of rapidly progressing disease.

4.17 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 management of 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; tolvaptan has a significant and substantial impact on health-related benefits, and it can delay time to ESRD and reduce the strain on renal replacement therapy. The 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. However, the Committee noted that it had not been presented with evidence for these potential beneficial attributes of treatment which may not have been captured in the measurement of QALYs, or for how these benefits might affect cost effectiveness. 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. However, the Committee did not consider that this should alter the conclusion that tolvaptan cannot be recommended, given the high ICERs presented in section 4.16.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Tolvaptan for treating autosomal dominant polycystic kidney disease	Section
Key conclusion		
Tolvaptan is not recommended within its marketing authorisation for treating autosomal dominant polycystic kidney disease to slow the progression of cyst development and renal insufficiency in adults who have chronic kidney disease stages 1 to 3 at the start of treatment and evidence of rapidly progressing disease. The Committee considered that the relative benefit of tolvaptan treatment compared with placebo as reported in the TEMPO 3:4 trial was associated with some uncertainty. It also noted that the incremental cost-effectiveness ratios (ICERs) were above the range usually considered a cost-effective use of NHS resources, therefore the Committee could not recommend tolvaptan for treating autosomal dominant polycystic kidney disease (ADPKD).		1.1 4.7 4.16
Current practice		

Clinical need of patients, including the availability of alternative treatments	Currently there are no pharmacological treatments available for treating 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.	4.2 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. However, it had not been presented with evidence for these benefits, which may not have been captured in the measurement of quality-adjusted life years (QALYs).	4.2 4.3 4.17
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 excessive 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.	4.5 – 4.7
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 in the UK.	4.5

Uncertainties generated by the evidence	The Committee considered that the following factors introduced uncertainty into the evidence base for the clinical effectiveness of tolvaptan: • The outcome of interest for the appraisal, rate of decline in renal function, was not the primary outcome of the trial. • The rate of decline in renal function, measured by the estimated glomerular filtration rate in the trial, used the reciprocal of the serum creatinine rather than the Chronic Kidney Disease Epidemiology Collaboration measure, which is accepted by the clinical community and is recommended in the NICE guideline on chronic kidney disease.	4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Subgroup analyses were conducted for each CKD stage.	3.2

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The results of TEMPO 3:4 showed that tolvaptan demonstrated a significant relative reduction of 49.2% on total kidney volume growth over 3 years when compared with placebo. It also showed a statistically significant 31.6% relative reduction in the annual rate of renal function decline, when estimated glomerular filtration rate (eGFR) was assessed by using the reciprocal of the serum creatinine level. Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) for the measurement of eGFR resulted in a relative reduction of 26.4% for tolvaptan compared with placebo.	3.2 3.4
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee used the company's economic model and the critique of this by the Evidence Review Group (ERG) to inform its discussions.	4.9

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee considered that the following factors introduced uncertainty into the evidence base for the cost effectiveness of tolvaptan:	4.9
	• TKV was used as surrogate measure of eGFR to model disease progression, whereas treatment effect was modelled using eGFR results directly from TEMPO 3:4. However, it would have been preferable if the economic analyses considered only the eGFR results of the trial.	4.9
	• The approach used to measure eGFR was the reciprocal of the serum creatinine level, but the Committee concluded that CKD-EPI would be the appropriate approach for both disease progression and treatment effect.	4.10
	• The true value of the rate of treatment discontinuation would be between the assumption used by the company (0.5%) and the value used by the ERG in its scenario analysis (6.5%).	4.11

	• No ADPKD-specific utility values were available, therefore other values from the literature were used. Interim data were available from one of the ongoing studies, therefore the Committee concluded that it would have preferred to see ADPKD-specific health-state utility values used in the model. • A utility decrement value, taken from literature, was applied for the treatment of tolvaptan in the absence of any further evidence to suggest a different utility decrement.	3.13, 4.12 4.13
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?	Health-related quality of life (HRQoL) was not assessed in the TEMPO 3:4 trial, therefore for identifying ADPKD-specific health-state utility values, the company conducted a systematic review of the literature. However, the Committee was aware that one of the ongoing trials for tolvaptan, the OVERTURE trial, had collected EQ-5D data. It heard from the company that only interim data were available. The Committee concluded that it would have preferred to see ADPKD-specific health-state utility values used in the model. No other health-related benefits have been identified that were not included in the economic model.	3.13, 4.12

Are there specific groups of people for whom the technology is particularly cost effective?	The Committee was aware of the exploratory subgroup analyses for each CKD stage at treatment initiation that were conducted by the company, and which were presented as commercial in confidence.	3.19
What are the key drivers of cost effectiveness?	The Committee considered that the key drivers for cost effectiveness were the cost of tolvaptan, the methodology used for measuring eGFR and therefore the underlying disease progression, and also the treatment effect of tolvaptan.	4.14, 4.15

Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered the 2 ERG exploratory ICERs which had used CKD-EPI to estimate eGFR, that is, the ERG exploratory preferred base case of £64,500 per QALY gained and the ERG remaining exploratory scenario ICER of £72,700 per QALY gained. The Committee was aware that these exploratory analyses were not cumulative and did not take into account uncertainties relating to the utility values. The Committee therefore concluded that these factors may lead to an underestimation of the most plausible ICER. However, the Committee was also mindful of its conclusion relating to the discontinuation rate which may lead to an overestimation of the most plausible ICER. The Committee thought it likely that, on balance, these factors would take the ICER higher than the exploratory estimate of £72,700 per QALY gained, but the Committee was unable to say with certainty how much higher than £72,700 the most plausible ICER would be. Despite this, the Committee was confident that the ICERs as presented by both the company and the ERG were sufficient for the purpose of the decision to be made.	4.16

Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. If tolvaptan had been recommended, this scheme would provide a simple discount to the list price of tolvaptan with the discount applied at the point of purchase or invoice.	2.3
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	No equality issues were raised.	

5 Related NICE guidance

Details are correct at the time of consultation 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 clinical guideline 182 (2014).
- Peritoneal dialysis: Peritoneal dialysis in the treatment of stage 5 chronic kidney disease. NICE clinical guideline 125 (2011).
- Guidance on home compared with hospital haemodialysis for patients with end-stage renal failure. NICE technology appraisal guidance 48 (2002).

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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
May 2015

7 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

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

Dr Malcolm Oswald

Lay member

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
Technical Lead

Joanne Holden
Technical Adviser

Kate Moore
Project Manager

8 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 UK

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 are invited to comment on the ACD.

- Professor Albert Ong, Professor of Renal Medicine, University of Sheffield, nominated by Otsuka, the PKD Charity and the Renal Association – clinical expert

- Professor Bruce Hendry, Professor of Renal Medicine, King's College London, nominated by Otsuka – 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 UK