KSR Ltd

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ERRATUM TO
Tolvaptan for treating autosomal dominant polycystic kidney disease

1. The word [redacted] has been marked as commercial in confidence.
    a. Section 1.4 (page 13): "Hence, the costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per quality-adjusted life year (QALY) [redacted] a PAS.
    b. Section 1.5 (page 13): "The costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS."
    c. Section 1.6 (page 14): "The costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS."
    d. Section 5.4 (page 109): "The costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS."
    e. Section 7 (page 116): "Hence, the costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS."
2. The statement in section 2.2 (page 17) has been amended and now reads:
   "On 5 August 2013 the Food and Drug Administration (FDA) did not approve tolvaptan for the treatment of ADPKD on the grounds of efficacy. In addition, the FDA mentioned a risk of liver injury, with patients potentially requiring liver transplant or leading to death."
3. The statement in section 3.3 (page 22) now reads:
   "In addition, as noted in Section 7 of the ERG report, other management options, such as increased fluid intake and aggressive blood pressure management, might be able to modify the course of disease in early ADPKD."
4. The text in section 5.2.2 (page 76) now reads:
   "The annual probability of significant kidney pain was independent on CKD stage and dependent on treatment (0.05 for Tolvaptan while it is 0.07 without Tolvaptan) for CKD stages 1 to 4. For CKD stage 5 the annual probability of significant kidney pain was independent on treatment (0.07 for both comparators)."
5. The text in section 5.2.2 (page 84) now reads:
   "included CKD specific mortality to approximate mortality for ADPKD patients which is regarded as an preferred alternative by the ERG compared to assuming that mortality risk in ADPKD patients is equal to all-cause mortality. This latter assumption may be in favour of tolvaptan because patients receiving tolvaptan spend more time in CKD stage one to four than patients receiving standard care."
6. The text on page 113 now reads:
    a. "The potential effects on liver-enzyme levels require monitoring."
    b. "Therefore, the trial may not be representative of UK practice."

measurement of outcomes (glomerular filtration rate (GFR), TKV). There are some concerns regarding the safety of tolvaptan, especially regarding the potential of inducing liver injuries.

1.4 Summary of cost-effectiveness submitted evidence by the company

In the systematic review the company did not identify any cost-effectiveness studies relevant to this submission. Therefore a *de novo* economic evaluation was performed.

The model is a patient level state transition model, which the ERG believes is appropriate to model this decision problem. The population in the analysis is consistent with the scope, although it should be noted that the TEMPO 3:4 trial (primary source for the economic model) included only patients aged 18-50 years while no age restriction was included in the final scope and the proposed licensed indication. Moreover, only a small proportion of the TEMPO 3:4 trial population was from the UK (5%; 73 out of 1445). The comparators are standard care with and without tolvaptan, which is in line with the scope. The base case amounted to £34,769 including PAS and to [redacted] excluding PAS. Hence, the costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per quality-adjusted life year (QALY) [redacted] a PAS.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG questioned a number of assumptions underlying the economic evaluation of tolvaptan, and addressed several of these issues in the ERG base case. The ERG base case ICER amounts to £43,280, including PAS. This ICER is higher than the company's base case (£34,769 including PAS). Including the PAS the probability of cost-effectiveness, according to the ERG base case, at a willingness-to-pay threshold of £30,000, £35,000 and £40,000 per QALY gained was 24%, 31% and 42%, respectively. The costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS. However, not all uncertainty is incorporated in these probability estimates; most notably the uncertainty of the extrapolation of the treatment effect. In response to clarification question C13, the company provided a scenario analysis with diminished treatment effect after three years. The ICERs with a 50% reduction of treatment effect after three years show a strong increase compared to the base case: [redacted] excluding PAS and £92,051 including PAS.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

In general the submission was well presented and it should be noted that the company aimed to answer the points raised in the clarification letter. The company searched all required databases specified by NICE. The company's submission provided sufficient detail for the ERG to appraise the searches, which were well documented and easily reproducible. Additional searches of conference abstracts and other resources were undertaken by the company for all sections. The searches were well translated amongst the different resources used. The model structure and approach is appropriate.

1.6.2 Weaknesses and areas of uncertainty

The ERG is concerned about the language bias of restricting the searches to English language only; this is not in line with current best practice.

Generalisability of the only identified randomised, controlled trial, TEMPO 3:4, is limited by a) the relatively strict inclusion criteria based on which many patients were excluded; b) the restriction to patient aged 18 to 50 years; c) the low number of UK patients and d) patients in CKD stage 3. There is some uncertainty regarding measurement of GFR and TKV. As best standard care which was provided in both groups (tolvaptan and placebo) was not clearly defined, there is some uncertainty surrounding the potential effect of measures forming best supportive care.

The main weakness of the cost effectiveness analysis presented in this submission is a number of assumptions that potentially favour tolvaptan and are, in the ERG's opinion, unjustified. Most notably, the extrapolation of the treatment effect over the lifetime of the population. Other assumptions and/or model inputs the ERG questioned are:

- Exclusion of adverse events (other than kidney pain)
- Kidney pain being treatment dependent and CKD-stage independent
- The CKD-stage 3 costs
- The disutility for HD and PD complications
- The use of general population mortality (instead of ADPKD-specific mortality)
- The extrapolation of the treatment discontinuation probability
- Monitoring costs

The costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG performed additional scenario analyses exploring the impact of 1) incorporating liver complications based on Hy's Law cases; 2) incorporating ADPKD-specific mortality risks for CKD stage; 3) incorporating more conservative treatment discontinuation probabilities; 4) incorporating increased monitoring costs and; 5) lower transplant costs. The ICERs of these scenario analyses ranged between £34,754 and £42,893 with PAS. Moreover, the ERG constructed an alternative base case wherein 1) a model code error was corrected; 2) the kidney pain probability was assumed equal for both arms; 3) the costs for CKD-stage 3 were corrected; 4) a disutility was applied for being on Tolvaptan treatment and; 5) the disutility HD and PD complications was decreased. This resulted in a base case ICER of £43,280 with PAS.

average, patients in ESRD would be willing to give up 10 years of life on dialysis in exchange for 4 years with normal renal function".[11]

According to page 35 of the CS, *"the age-standardised mortality rate in patients with ADPKD is 60% higher than in the general population.*[12] *Data from a UK cohort study reports that the median age at death for ADPKD patients was 70 years (interquartile range 62-78 years)*[13]*, as compared to the current UK life expectancy of 81.5 years.*[14] *However, the life expectancy in a faster progressing patient population considered in this submission is likely to be even lower."*[2]

ERG comment: ADPKD is associated with a significant reduction in patient health-related quality of life (HRQoL) and life expectancy. Overall, the evidence presented in the CS on this section was in line with the background information given in the final scope[1] and is also consistent with the ERG's understanding of the problem.

2.2 Critique of manufacturer's overview of current service provision

"Tolvaptan does not currently have a UK marketing authorisation for the indication detailed in this submission. A submission for marketing authorisation in the European Union (EU) was made in December 2013 through the European Medicines Agency (EMA) centralised procedure. CHMP positive opinion is anticipated in February 2015".[2]

Tolvaptan was granted orphan designation for the treatment of ADPKD by the European commission on 5 August 2013 but does not currently have a UK marketing authorisation for the population under consideration for this submission.[2] On 26 February 2015, the European Medicines Agency (EMA) has recommended granting a marketing authorisation to tolvaptan.[15]

On 5 August 2013 the Food and Drug Administration (FDA) did not approve tolvaptan for the treatment of ADPKD on the grounds of efficacy. In addition, the FDA mentioned a risk of liver injury, with patients potentially requiring liver transplant or leading to death.[16] However, the drug was approved for the treatment of ADPKD in Japan on 24 March 2014.

"No licensed treatment for ADPKD is currently available that has been demonstrated to delays [sic!] *ADPKD progression; a disease-modifying therapy that delays ADPKD progression is needed to provide a step-change in ADPKD management. Current standard of care is limited to management of the other signs and symptoms of the disease; control of hypertension, and interventions to manage patients as they approach or reach ESRD.*[17, 18] *ESRD is treated by renal replacement therapy (dialysis or transplant), which has substantial health care resource use and economic implications, as well as diminishing patient HRQL".*[19-22]

"The proposed licensed indication states that patients with ADPKD may be initiated on tolvaptan if in CKD stage 1-3 with evidence of rapidly progressing disease. In order to identify patients in CKD stage 1-3, a measure of renal function (in terms of estimated GFR) will be required. This is routinely assessed in ADPKD patients. With respect to evidence of rapidly progressing disease, no objective criteria are defined in the licensed indication meaning this assessment will be more subjective according to specialist clinical judgement.

ERG comment: The table above seems to be based on the draft scope issued by NICE. Overall, the ERG is convinced that the population is in line with the final scope. However, the available evidence from the TEMPO 3:4 trial only includes participants up to 50 years of age (see Section 4.2.1 of the ERG report).

3.2 Intervention

The intervention described in the CS ('tolvaptan') matches the intervention described in the final scope. According to page 23 in the CS, *"The initial dosage of tolvaptan in ADPKD is 60 mg per day (split-dose 45 mg and 15 mg). This is to be titrated upward to 90 mg per day (split-dose 60 mg and 30 mg), then to a target of 120 mg per day (split-dose 90 mg and 30 mg) if tolerated, with at least weekly intervals between titrations. Patients may down-titrate to lower doses, based on tolerability"*.

Tolvaptan (brand name Jinarc®) is a selective vasopressin antagonist, which specifically blocks the binding of vasopressin to the V2 receptors of the distal portion of the nephron. Tolvaptan tablets are to be taken twice daily as a split dose titrated upward from 60 mg to a maximum tolerated daily dose of 120 mg. Patients continue to have a long-term treatment and are withdrawn at the onset of the end-stage renal disease (ESRD).[2]

ERG comment: The intervention in the CS matches the intervention described in the final scope.

3.3 Comparators

The comparator defined in the NICE scope was, *"Standard care, including routine surveillance without tolvaptan"*. Standard care was not fully defined in the final scope.[1] According to the CS, the standard care does not involve any active treatment for ADPKD.

The justification given by the CS in Section 5 was that *"currently, there are no pharmacological treatments indicated for ADPKD. Patients with ADPKD receive best supportive care or standard care to control symptoms and complications associated with the disease, irrespective of the choice to initiate tolvaptan. Patients receiving tolvaptan will continue to receive best supportive care, as necessary"*.[2]

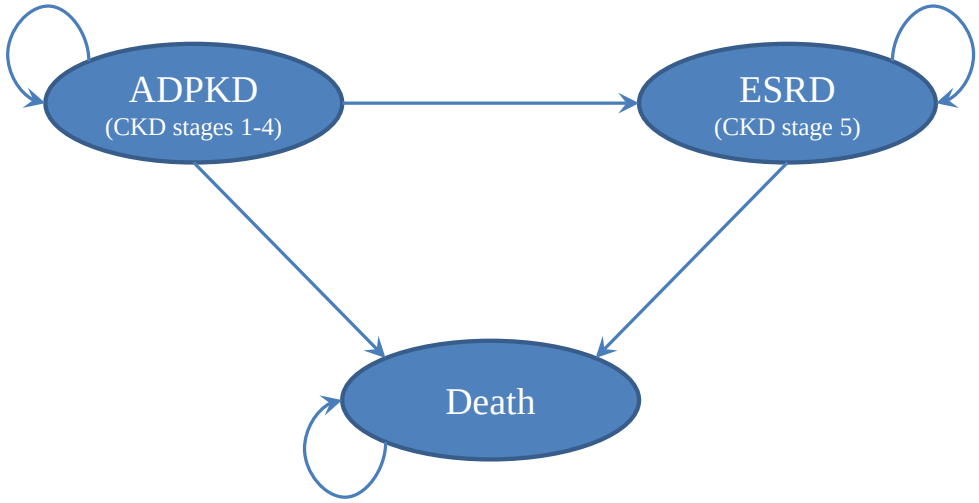
ERG comment: Overall, the ERG was satisfied with the justification provided by the company. However, it should be noted that given that *"standard care"* was not clearly defined, some variation in treatments received is possible.

In addition, as noted in Section 7 of the ERG report, other management options, such as increased fluid intake and aggressive blood pressure management, might be able to modify the course of disease in early ADPKD.

3.4 Outcomes

ERG comment: All outcomes defined in the final scope are reflected in the decision problem defined in Section 5 of the company's submission. However, as discussed in Section 4.1.2 of the ERG report HRQoL has not been included in Section 6.5 of the CS.

Figure 5.1: Model structure
(adjusted version of the flow diagrams, Figures B13 and B14 presented in the CS[2])



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

At the start of the model simulation, individual patient characteristics (age, gender, TKV and eGFR) are sampled from pre-defined distributions (Table 5.5). The eGFR value is subsequently used to update patients' CKD stage (Table 5.6). Patients' characteristics and CKD stage are updated at the end of each cycle. In case of CKD stage 5 (eGFR < 15 ml/min/1.73 m^2), patients transit from ADPKD to ESRD. Clinically significant kidney pain was the only complication explicitly incorporated and occurred in all CKD stages (except after kidney transplantation). The annual probability of significant kidney pain was independent on CKD stage and dependent on treatment (0.05 for Tolvaptan while it is 0.07 without Tolvaptan) for CKD stages 1 to 4. For CKD stage 5 the annual probability of significant kidney pain was independent on treatment (0.07 for both comparators). The Company justified the exclusion of other complications given the lack of evidence supporting a difference in effect on these outcomes.

Table 5.1: Distributions to sample baseline patient characteristics

	Mean	Standard error	Distribution	Source
Current age (years)	38.70	0.19	Normal	TEMPO 3:4 trial
Sex (% female)	48.4%	1.3%	Beta	TEMPO 3:4 trial
eGFR (ml/min/1.73 m^2)	81.61	0.57	Normal	TEMPO 3:4 trial
TKV (ml)	1692.30	23.82	Normal	TEMPO 3:4 trial

eGFR = estimated glomerular filtration rate; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume

Moreover, renal replacement therapy (RRT) would start at eGFR < 8.5 ml/min/1.73 m^2. RRT consists of conservative care (management to prolong kidney function and control symptoms of ESRD), haemodialysis (HD; either hospital HD, satellite HD or home HD), peritoneal dialysis (PD; either ambulatory or continuous ambulatory PD) or kidney transplantation (either from a living or deceased donor). The model allows for different RRT in subsequent cycles (although switching between dialysis modalities was not possible) and dialysis complications (for both HD and PD) in terms of both costs and disutilities were incorporated.

treatment with tolvaptan. As part of the risk management programme, patients will have LFTs monitored every month for the first 18 months and then will have LFTs monitored every 3 months. If LFT abnormalities are seen then treatment with tolvaptan will be interrupted. In addition, in the clinical trial programme and post-marketing experience, there have been no cases of fulminant hepatic failure nor patients who have required liver transplantation as a consequence. Therefore it is very unlikely that a patient who may progress to severe LFT abnormalities or liver disease would ,not be identified and have treatment with tolvaptan interrupted while they are managed further. As there have been no irreversible cases of liver damage in the tolvaptan study programme we have no data upon which to base a model with the occurrence of DILI".[9]

The ERG believes that the assumption that hepatotoxicity does not lead to any costs or health loss is unsustainable. At least two of the Hy's Law cases were admitted to hospital, two weeks and 36 days, respectively.[29] It is uncertain whether the proposed monitoring schedule will totally prevent (severe) cases of hepatoxicity as well as the costs and health consequences associated with this. Therefore, the ERG performed an exploratory analysis, incorporating consequences of hepatoxicity as a result of tolvaptan (see Section 5.3).

Mortality was not ADPKD specific for CKD stages 1-4, this could be an underestimation of the mortality risk. In response to clarification question C10[9], the company gave the following justification for this: *"…no [mortality] data was identified that was considered appropriate to model ADPKD specific mortality. The study by Florijn et al.*[68] *in the Netherlands provides some standardised mortality ratios (SMR) for ADPKD patients. However, there are a number of limitations to this data:*

- The estimates are based on five large families with chromosome 16 linked ADPKD.
- There were only 83 deaths in the 10,279 person years.
- The time horizon for the mortalities, and the SMRs, spanned from 1889 to 1992. Substantial medical developments have been made in this period including antibiotics, antihypertensive therapy, dialysis and renal transplant.[68] An analysis of 50-59 year olds over time revealed a continuous mortality decline, particularly after 1970.
- The mortality estimates do not distinguish between patients in end stage renal disease (ESRD) (and receiving treatment) and those not. As a result the mortality rates would be a double count of ESRD mortality for ESRD patients and overly pessimistic for patients in CKD stages one to four.

In light of the factors above we do not feel it is possible to include robust ADPKD specific mortality rates in the model and conduct the requested analysis".[9]

The ERG agrees that evidence regarding ADPKD specific mortality is scarce. However, the cost-effectiveness study by Erickson and colleagues[61] included CKD specific mortality to approximate mortality for ADPKD patients which is regarded as an preferred alternative by the ERG compared to assuming that mortality risk in ADPKD patients is equal to all-cause mortality. This latter assumption may be in favour of tolvaptan because patients receiving tolvaptan spend more time in CKD stage one to four than patients receiving standard care. The ERG explored a higher mortality in CKD stages 1-4 in an exploratory analysis (Section 5.3).

Moreover, the company's base case used general population mortality and is therefore most likely underestimating mortality for ADPKD (see Section 5.2.6 and clarification question C10)[9], which is probably not a conservative assumption. Therefore, mortality for ADPKD was multiplied with a hazard ratio of 2.0 to explore the impact of this assumption. This increased the ICER to £34,754.

Treatment discontinuation after three years was assumed to be 0.5%. This assumption was however not explored in scenario analyses. Scenario analyses conducted by the ERG showed that this was an assumption that has a noticeable impact on the ICER. When assuming a treatment discontinuation of 6.5% (equal as the second year), this ICER increased to £42,893.

Increasing monitoring costs did not have a substantial impact on the ICER: the ICER increased to £36,167.

Finally, the maintenance costs for post kidney transplants are likely to be overestimated as total costs for this state include both management costs and maintenance costs. The ERG showed that this was an assumption that has a noticeable impact on the ICER. Subtracting the background management costs from the maintenance costs for all years increased the ICER to £39,264.

Besides these additional exploratory scenario analyses, the ERG would prefer to apply the following changes to the base case analysis (as mentioned in previous sections):

1. Correct model code error (see Section 5.2.9)
2. Equal kidney pain probability for both arms (see Sections 5.2.6 and 5.2.7)
3. Equal CKD-stage costs for CKD-stage 3 as for CKD-stage 4 (see Section 5.2.8)
4. Disutility for tolvaptan treatment (see Section 5.2.7)
5. Disutility of 0.02 for HD and PD complications (see Section 5.2.7)

The company's base case results in an ICER of £34,769, correcting the model code error slightly decreased this ICER to £34,733.

5.4 Conclusions of the cost-effectiveness section

In a systematic review the company did not identify cost-effectiveness studies relevant to this submission. Therefore a *de novo* economic evaluation was performed. The model is a patient-level state-transition model, which the ERG believes is appropriate to model this decision problem. The population in the analysis is consistent with the scope, although it should be noted that the TEMPO 3:4 trial (primary source for the economic model) included only patients aged 18-50 years while no age restriction was included in the final scope and the proposed licensed indication. Moreover, only a small proportion of the TEMPO 3:4 trial population was from the UK (5%; 73 out of 1,445). The comparators are standard care with and without tolvaptan, which is in line with the scope. The base case amounted to £34,769 including PAS and to [redacted] excluding PAS. The costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS.

The model transparency was hampered by an overcomplicated description and model code, as well as errors in the code. The face validity checks seemed appropriate, apart from the

7 OVERALL CONCLUSIONS

This appraisal looks at the clinical and cost-effectiveness of standard care in combination with tolvaptan versus standard care including routine surveillance without tolvaptan for treating autosomal dominant polycystic kidney disease. The company submission is mainly based on one randomised controlled trial, the TEMPO 3:4 trial. In this phase 3, multicentre, double-blind, placebo-controlled, three year trial, 1,445 patients, 18 to 50 years of age, who had ADPKD with a total kidney volume of 750 ml or more and an estimated creatinine clearance of 60 ml per minute or more, were randomly assigned in a 2:1 ratio to receive tolvaptan or placebo. The trial found that tolvaptan, when given over a period of three years, slows the increase in total kidney volume and the decline in kidney function in patients with ADPKD. However, the potential benefit is not without risks. Thirst, polyuria, and related adverse events may affect the ability of some patients to take effective doses of tolvaptan. The potential effects on liver-enzyme levels require monitoring.

In the remainder of this chapter we will discuss the main strengths and limitations of the TEMPO 3:4 trial. First of all, the TEMPO 3:4 trial is not a UK trial, most of the 1,445 included patients came from the USA (n=379), Japan (n=177) and Germany (n=157); only 73 patients came from the UK. During the scoping workshop, clinical experts commented that the UK has approximately 70,000 ADPKD patients, most of whom are managed in primary care. Therefore, the trial may not be representative of UK practice.

In addition, the inclusion criteria were quite specific and also limit the representativeness of the trial for the total population of UK ADPKD patients:

- The trial included patients aged between 18 and 50 years. Therefore, the trial provides no evidence for patients over 50 years as well as for children and adolescents.
- Most patients in the trial were CKD stage 1 (35%) and 2 (48%). Therefore, there is limited evidence for CKD stage 3 patients (17%).
- Patients with a TKV of ≥ 750 ml ≥ 14 days before randomisation (as measured by MRI) were included. Normal kidney volume is around 250 ml, which means that included patients had TKV at least three times more than normal.

Before randomisation, 530 patients were excluded because they did not meet inclusion criteria for the trial (TKV of ≥ 750 ml (370 patients excluded), creatinine clearance of ≥ 60 ml per minute as estimated by means of the Cockcroft–Gault formula (119 patients excluded)). That also means results are not generalisable to all ADPKD patients.

The NICE final scope[1] mentions standard care without tolvaptan as the comparator. However, standard care is not defined. At the scoping workshop clinical experts agreed that standard care will vary depending on each patient and that it is not possible to define the standard of care treatment for this condition. The NICE final scope does state that *"therapies currently used aim to control symptoms and associated complications of kidney disease, such as pain, cyst infections, urinary tract infections and high blood pressure"*.[1] Therefore, standard treatment is not defined but includes monitoring of renal function, blood pressure control and treatment of complications (pain, urinary tract infections). It is not clear from the trial

approximately 8% of participants, mostly within the first month. Adverse events related to aquaresis in previous clinical trials of tolvaptan for hyponatremia or heart failure were similar to those observed in the current trial, but the higher frequency of liver enzyme elevations was not observed in the previous trials.[114-117]

In response to adverse events related to the liver, the U.S. Food and Drug Administration (FDA) has determined that tolvaptan *"should not be used for longer than 30 days and should not be used in patients with underlying liver disease because it can cause liver injury, potentially requiring liver transplant or death. Samsca is used to treat low sodium levels in the blood. An increased risk of liver injury was observed in recent large clinical trials evaluating Samsca for a new use in patients with autosomal dominant polycystic kidney disease (ADPKD)"*.[118]

The ERG questioned a number of assumptions underlying the economic evaluation of tolvaptan, and addressed several of these issues in the ERG base case. The ERG base case ICER amounts to £43,280, including PAS. This ICER is higher than the company's base case (£34,769 including PAS). Hence, the costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS. Including the PAS the probability of cost-effectiveness, according to the ERG base case, at a willingness-to-pay threshold of £30,000, £35,000 and £40,000 per QALY gained was 24%, 31% and 42%, respectively. However, not all uncertainty is incorporated in these probability estimates; most notably the uncertainty of the extrapolation of the treatment effect. In response to clarification question C13, the company provided a scenario analysis with diminished treatment effect after three years. The ICERs with a 50% reduction of treatment effect after three years show a strong increase compared to the base case: [redacted] excluding PAS and £92,051 including PAS.

7.1 Implications for research

Long term follow-up of the effects of tolvaptan is warranted, including clinical benefit and liver complications. Evidence regarding health-state utilities and mortality in ADPKD patients is scarce.

On page 8 of the CS it was emphasised that *"tolvaptan is the first treatment to delay renal progression in AKPKD"*.[2] According to page 13 of the CS, *"tolvaptan is a selective vasopressin antagonist that specifically blocks the binding of vasopressin to the V2 receptors of the distal portion of the nephron. Inhibition of vasopressin binding to V2 receptors leads to reduction of cell proliferation, cyst formation and fluid excretion"*.

The ERG is not aware of factors which might suggest differences in effectiveness between blocking the V2 receptor with tolvaptan and stimulating it by inhibiting arginine vasopressin release by increasing the fluid intake, e.g. by drinking more water. Post-hoc analyses of TEMPO 3:4 data suggested that participants with lower urine osmolality had lower increases in TKV and within the tolvaptan group the patients whose urine osmolality decreased the most (i.e. who increased their water intake most) were most likely to maintain stable renal function.[37] As detailed above, Spital commented to that effect in a letter[108] in response to the main trial publication in the New England Journal of Medicine[24]. He also highlighted a