UK Kidney Association Guidance Commentary:

Tolvaptan for ADPKD (an update)

Final version: XX/XX/XXXX

Review date: XX/XX/XXXX

Authors:

Working Group chair: Professor Albert Ong

Working Group members: Dr Matt Gittus, Helen Haley, Tess Harris, Sarah Borrows, Dr Neal Padmanabhan, Professor Danny Gale, Dr Roslyn Simms, Terri Williams, Aaron Acquaye, Alisa Wong, Dr Melanie Chan, and Eduardo Lee

See appendix for list of previous versions/revisions and working group affiliations.

DRAFT

Endorsements



The National Institute for Health and Care Excellence (NICE) has accredited the process used by The UK Kidney Association to produce its Clinical Practice Guidelines. Accreditation is valid for 5 years from January 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

Method used to arrive at a recommendation

The recommendations for the first draft of this guideline resulted from a collective decision reached by informal discussion by the authors and, whenever necessary, with input from the Chair of the Clinical Practice Guidelines Committee.

Conflicts of Interest Statement

All authors made declarations of interest in line with the policy in the Association's Clinical Practice Guidelines Development Manual. Further details can be obtained on request from the UK Kidney Association.

Acknowledgements

- Dr Jiehan Chong, Consultant Nephrologist, Sheffield Teaching Hospitals Trust
- Ms Nour Ajjan, Specialist Renal Pharmacist, Sheffield Teaching hospitals NHS Trust
- Dr Chenchu Ramu Chimakurthi, Consultant Hepatologist, Leeds Teaching Hospitals NHS Trust

DRAFT

Table of Contents

Executive summary 4

List of abbreviations 7

Introduction, updated evidence and aims 8

Summary of recommendations 11

Section 1: Confirmation of ADPKD diagnosis 14

1.1 DIAGNOSTIC IMAGING 14
1.2 GENomic TESTING 14

Section 2: Confirmation of eligibility for Tolvaptan 16

2.1 AGE 16
2.2 CHRONIC KIDNEY DISEASE STAGES 17

Section 3: Confirmation of rapidly progressive disease or high risk of progression 19

3.1 OVERVIEW FLOWCHART TO ASSESS SUITABILITY FOR TOLVAPTAN 19
3.2 RAPIDLY PROGRESSIVE DISEASE 20
3.3 HIGH RISK OF DISEASE PROGRESSION 21

Section 4: Confirmation of no exclusions to treatment 24

4.1 MANUFACTURER RECOMMENDATIONS 24
4.2 PREGNANCY AND BREAST-FEEDING 25

Section 5: Initiation, titration and drug interactions 26

5.1 TOLVAPTAN DOSING 26
5.2 DRUG INTERACTIONS 27

Section 6: Monitoring during Tolvaptan therapy 29

6.1 MONITORING RESPONSE TO TOLVAPTAN AND THERAPEUTIC EFFICACY 29
6.2 KIDNEY FUNCTION MONITORING 29
6.3 LIVER FUNCTION MONITORING 30

Section 7: Management of side effects and adverse effects 31

7.1 OVERVIEW 31
7.2 AQUARETIC SIDE EFFECTS 32
7.3 DRUG-INDUCED LIVER INJURY 33
7.4 OTHER SIDE EFFECTS 36

Section 8: Considerations from a patient perspective 37

8.1 HELPING PEOPLE TO MANAGE WITH SIDE EFFECTS 37
8.2 OTHER RESOURCES FOR PATIENTS 41

Section 9: Additional recommendations 42

DRAFT

9.1 HEALTHCARE SETTING 42
9.2 IMAGING 42
9.3 GENomic TESTING 43
9.4 THE NATIONAL REGISTRY OF RARE KIDNEY DISEASES (RADAR) 43
Appendices 44
Appendix 1: Unified criteria for ultrasonographic diagnosis of ADPKD[1] 44
Appendix 2: Mayo Imaging Classification of risk of disease progression[25] 44
Appendix 3: PROPKD score[38] 45
Appendix 4: Tolvaptan prescribing checklist for treatment initiation[39] 46
Appendix 5: Drug interactions[43] 48
Appendix 6: Example patient information letter 51
Appendix 7: Example supporting letters for patient use 56
Appendix 8: Working group membership affiliations 57
References 59

DRAFT

Executive summary

Tolvaptan was initially developed as an aquaretic drug with a novel mechanism of action, promoting the excretion of water without affecting the excretion of electrolytes. This occurs through inhibition of the vasopressin type 2 receptor (V2R) which is expressed exclusively in

the kidney. In pre-clinical studies, it was shown to inhibit cystic disease progression in several rodent models of autosomal dominant polycystic kidney disease (ADPKD). Results from the pivotal TEMPO3:4 Randomised Controlled Trial (RCT), conducted in over 1400 patients with ADPKD in 15 countries, demonstrated that Tolvaptan significantly slowed the increase in total kidney volume and the decline in kidney function over a 3-year period. Tolvaptan was subsequently approved by NICE for the treatment of ADPKD patients with rapidly progressive disease in 2015.

Following the NICE decision, the United Kingdom Kidney Association (UKKA), then the Renal Association, issued a commentary on the NICE guidance to facilitate the appropriate prescribing of Tolvaptan for ADPKD patients in adult kidney units across the UK. Since this commentary was written, there has been an extension trial, TEMPO 4:4, which included longer follow-up from TEMPO 3:4 and the REPRISE trial which assessed the impact of Tolvaptan in patients with later stage chronic kidney disease (CKD). These trials have provided confirmatory evidence on its efficacy, tolerability and safety, especially with regard to the continuing need for mandatory monitoring to detect rare idiosyncratic hepatotoxic events observed in TEMPO 3:4.

Tolvaptan has been widely adopted across the UK over the past 8 years and as a community, we have learnt a great deal as to how to best deliver and monitor the drug in different clinical settings. The major aims of this revised commentary are therefore to:

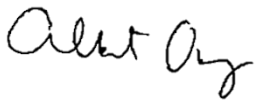
(i) Provide an updated evidence-base for Tolvaptan prescribing in adults with ADPKD, focusing on how best to assess the risk of kidney disease progression and thus patient eligibility

(ii) Support the safe and pragmatic implementation of Tolvaptan in clinical practice informed by practical experience from different models of care and patient perspectives

We offer this evidence and consensus-based update accompanied by recommendations for evaluation of suitability, monitoring, dose selection & titration, management of side effects and practical considerations in the hope of improving its uptake and tolerability in all eligible patients and its continuing safe use across the UK.

I am grateful to all the members of the UKKA working group for giving their time and effort to update this commentary and trust that it will be of use to the entire UKKA community who care for ADPKD patients and their families.

DRAFT



Professor Albert Ong (chair)

Working group members: Dr Matt Gittus, Helen Haley, Tess Harris, Sarah Borrows, Dr Neal Padmanabhan, Professor Danny Gale, Dr Roslyn Simms, Terri Williams, Aaron Acquaye, Alisa Wong, Dr Melanie Chan, and Eduardo Lee.

DRAFT

List of abbreviations

Abbreviations	Definition
ACEi	Angiotensin Converting Enzyme inhibitor
ADPKD	Autosomal Dominant Polycystic Kidney Disease
ANA	Antinuclear Antibody
AMA	Antimitochondrial Antibody
ARB	Angiotensin Receptor Blocker
BNF	British National Formulary
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRISP	Consortium for Radiologic Imaging Study of PKD
CT	Computed Tomography
DILI	Drug Induced Liver Injury
eGFR	Estimated Glomerular Filtration Rate
ESKD	End Stage Kidney Disease
GMSA	Genomic Medicine Service Alliance
htTKV	Height Adjustment Total Kidney Volume
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PCR	Polymerase Chain Reaction
PROPKD	Predicting Renal Outcomes in ADPKD
RCT	Randomised Controlled Trial
REPRISE	Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD
SMA	Smooth Muscle Antibody
SMC	Scottish Medicines Compendium
TEMPO	Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes
TKV	Total Kidney Volume
TSAT	Transferrin Saturation
US	Ultrasound
V2R	V2 vasopressin Receptor

DRAFT

Introduction, updated evidence and aims

INTRODUCTION

The approval of Tolvaptan in 2015 marked a step-change in the management of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Since its approval, it has become an important treatment option for people with ADPKD.

Two randomised controlled trials (RCTs) and post-hoc analysis have shown that Tolvaptan has a beneficial effect on ADPKD-associated estimated glomerular filtration rate (eGFR) decline in those with rapid progression[1-3]. The pivotal TEMPO 3:4 (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) trial demonstrated a significant beneficial effect of Tolvaptan on the rate of total kidney volume (TKV) growth and estimated glomerular filtration rate (eGFR) decline. There was also a treatment-associated reduction in kidney pain and urinary tract infections[2, 3]. However, only a subset of ADPKD patients experience rapid disease progression and will reach early kidney failure due to ADPKD. As there are associated side effects, costs and monitoring requirements, careful patient selection is important to maintain a positive benefit to risk ratio[4].

In October 2015, NICE recommended that Tolvaptan was approved for patients with ADPKD in England and Wales[5]. This was extended to patients in Scotland in January 2016 by the Scottish Medicines Consortium (SMC)[6]. As of February 2023, Tolvaptan has been licensed for people with ADPKD in Australia, Canada, the European Union, Hong Kong, Indonesia, Japan, Korea, New Zealand, Norway, Switzerland, Taiwan, Turkey, the United Kingdom and the United States.

UPDATED EVIDENCE

In 2017, TEMPO 4:4 studied the long-term effect of Tolvaptan after 24 months as an open-label extension study of TEMPO 3:4. This demonstrated that Tolvaptan was effective in maintaining kidney function in the long-term although the effect on TKV was not sustained. These findings may have been influenced by the non-randomised design and unadjusted baseline characteristics[2].

The Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial included people aged 18 to 55 years old with a baseline eGFR 25-65 ml/min/1.73m^2 and people aged 56 to 65 years old with a baseline eGFR 25-44 ml/min/1.73m^2. At 1-year follow-up, Tolvaptan slowed the decline in eGFR by 1.27 ml/min/1.73m^2 in all groups except the non-white, aged over 55 years or early stage CKD[7, 8].

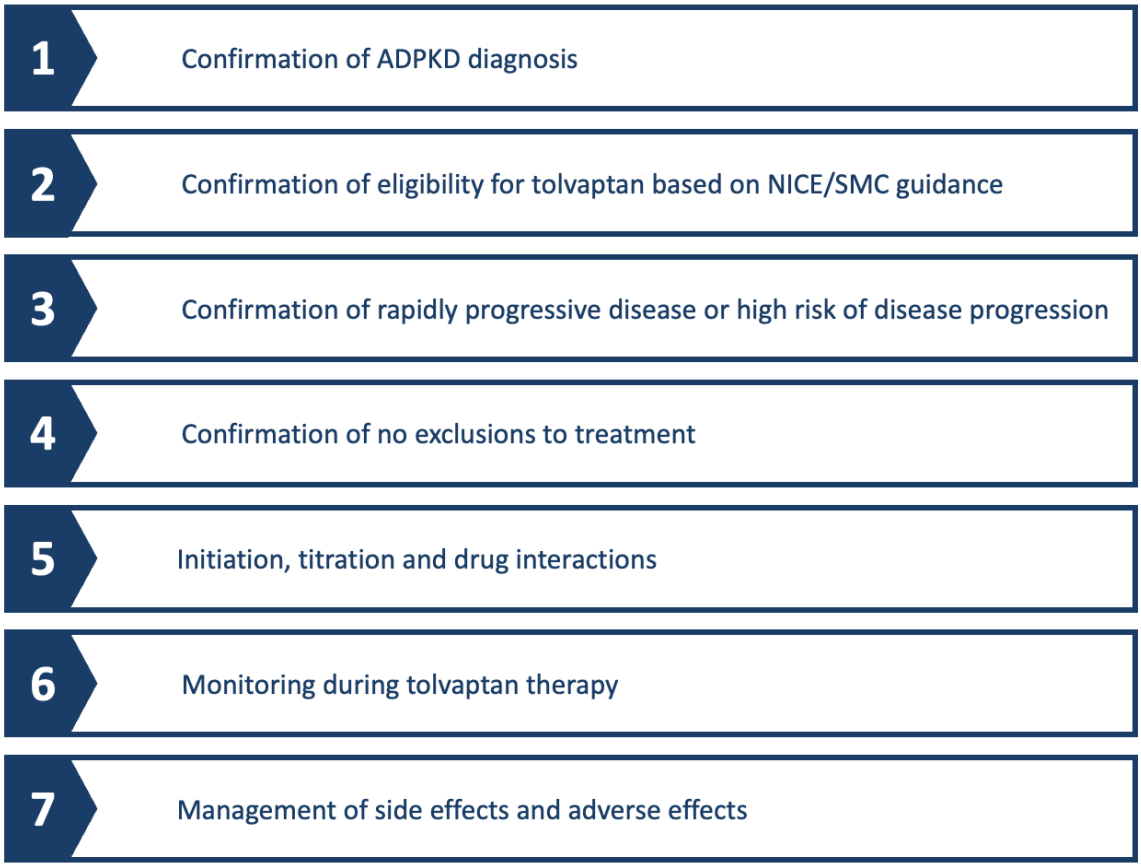
DRAFT

A retrospective analysis of 97 patients at an expert centre provided long-term follow-up data for people with ADPKD treated with Tolvaptan for up to 11 years (median 4 years, range 1.1-11.2). When compared with matched controls from other ADPKD studies, the predicted eGFR decline had a similar effect size to TEMPO 3:4 and REPRISE[8].

In addition to the reported effects on eGFR loss and TKV increase, secondary analysis of the TEMPO 3:4 trial outcomes demonstrated that Tolvaptan decreased the incidence of kidney pain events and urinary tract infections compared to placebo[9].

STEPWISE APPROACH TO TOLVAPTAN

A stepwise approach has been proposed by Chebib et al which we have adapted for patients in the UK[9]. The below diagram provides an overview of the sections within this commentary.



AIMS OF COMMENTARY

Our overriding objective is to provide practical and pragmatic guidance to facilitate the effective and safe use of Tolvaptan in the context of adults with ADPKD. The evidence base used to inform this guidance derives from relevant large-scale randomised trials, post hoc studies and growing practical evidence.

We specifically aim to:

(i) Provide guidance on the use of Tolvaptan in adults with ADPKD, focusing on the potential to modify the risk of kidney disease progression

(ii) Support safe and pragmatic implementation of Tolvaptan into clinical practice in adults with ADPKD

DRAFT

Summary of recommendations

Section 1: Confirmation of ADPKD diagnosis
We recommend that all people with ADKPD being considered for Tolvaptan should have an established diagnosis of ADPKD. This can be established through: • Diagnostic imaging • Genomic testing
Section 2: Confirmation of eligibility for Tolvaptan based on NICE/SMC guidance
We recommend that people with ADPKD being considered for Tolvaptan should be aged 18 and above at the time of treatment initiation.
We recommend initiating Tolvaptan in patients with the following eGFR criteria: • England & Wales: CKD stage 2-3 (30-89 ml/min/1.73m^2) • Scotland: CKD stage 1-3 (eGFR ≥ 30 ml/min/1.73m^2)
Section 3: Confirmation of eligibility for Tolvaptan based on NICE/SMC guidance
We recommend that a definition for evidence of rapid disease progression and eligibility for Tolvaptan is: A sustained decline in eGFR of ≥3 ml/min/1.73m^2 per year (at least 5 measurements over 4 years)
We recommend assessment for risk of disease progression if there is a lack of evidence for rapid disease progression based on eGFR criteria. This evidence can be based on diagnostic imaging and/or genetic testing. Risk of disease progression can be determined by the following methods: • Kidney length ≥16.5cm (≤46 years only) - USS imaging • TKV ≥750ml (≤50 years only) - MRI/CT imaging • Mayo Imaging Class (classes 1C-E) - MRI/CT imaging • PROPKD score (scores ≥6)

Section 4: Confirmation of no exclusions to treatment
We recommend that people with ADPKD should be assessed for potential contraindications/precautions prior to Tolvaptan initiation.
We do not recommend Tolvaptan use in people who are pregnant or breast-feeding. We recommend advising people who may become pregnant of the potential teratogenic risk of Tolvaptan and encourage them to use contraception.
Section 5: Initiation, titration and drug interactions
We recommend a starting dose of Tolvaptan 45mg in the morning and 15mg 6-8 hours after the first dose. We recommend doses should be up-titrated based on healthcare professional preference. Some centres increase doses at 28day intervals in accordance with standard pack sizes of Tolvaptan. We recommend titrating to a maximum dosage of 120mg per day (90mg/30mg) in all patients unless not tolerated or contraindicated.
Special care should be given when prescribing Tolvaptan alongside drugs that interfere with the action of CYP3A4. Tolvaptan dose adjustment should be considered with concurrent use of strong or moderate CYP3A4 inhibitors but not with CYP3A4 inducers.
Section 6: Monitoring during Tolvaptan therapy
We do not recommend any specific monitoring for Tolvaptan treatment response or efficacy.
We recommend measuring kidney function monthly in line with liver function monitoring. An initial decline of 3-9% in eGFR may be expected when Tolvaptan is started which is reversible on cessation. We recommend that Tolvaptan should be stopped prior to the initiation of renal replacement therapy.
We recommend measuring liver function monthly during the first 18 months of treatment then 3 monthly afterwards.

Section 7: Management of side effects and adverse effects
We recommend discussing side effects with patients and providing written patient information prior to initiating Tolvaptan. We recommend withholding Tolvaptan during periods of acute illness due to the increased risk of dehydration. This can be described as “sick day guidance” as advised for ACEi/ARBs.
We recommend carefully counselling patients and provide practical suggestions on minimising problems with aquaretic side effects, especially the reduction of dietary sodium intake, and how to manage this in daily life. This is particularly important for people with earlier stage ADPKD.
We recommend that following the initiation of Tolvaptan, patients should be informed of the rare but potential risk of liver injury and encouraged to self-report symptoms. We recommend withholding Tolvaptan in the event of suspected drug-induced liver injury to allow time to exclude other causes. Liver enzyme levels should be monitored until levels return to normal or their baseline.
Section 8: Practical considerations from a patient perspective
Based on patients’ perspectives of Tolvaptan we recommend that the following factors should be taken into account when Tolvaptan is being considered: • Impact on lifestyle • Occupation • Family planning • Healthcare appointments
Section 9: Additional recommendations
• Initial assessment and follow-up in a dedicated genetic/ADPKD/Tolvaptan clinic • Multidisciplinary team input • An established pathway for patients with ADPKD on Tolvaptan to interact with their kidney unit outside of clinic times • A three-dimensional scan should be performed as part of the initial assessment of a person with ADPKD • All people with ADPKD should be offered genomic testing where available and appropriate as this could inform patient eligibility for Tolvaptan • We encourage the registration and monitoring of people with ADPKD through the UKKA RaDaR registry

Section 1: Confirmation of ADPKD diagnosis

RECOMMENDATION

We recommend that all people with ADKPD being considered for Tolvaptan should have an established diagnosis of ADPKD.

This can be established through:

- Diagnostic imaging
- Genomic testing

1.1 DIAGNOSTIC IMAGING

Ultrasound (US) is the most commonly used imaging modality used to screen individuals at risk for ADPKD. In moderate to advanced disease, it is able to detect the multiple, bilateral renal cysts typical of ADPKD but this may not be obvious at a younger age and/or in earlier stage disease especially in individuals with *PKD2* variants[10]. The Pei-Ravine criteria are widely accepted for the radiological diagnosis of at-risk individuals with a positive family history associated with *PKD1* or *PKD2* variants (Table 1). Diagnostic sensitivity and specificity data for these criteria are included in Appendix 1.

Table 1. Age related modified Pei Ravine criteria for at-risk individuals with a positive family history associated with PKD1 or PKD2[11]

Age (years)	Imaging criteria
15-39	≥ 3 cysts (total)
40-59	≥2 cysts (each kidney)
> 60	≥4 cysts (each kidney)

Magnetic resonance imaging (MRI) and contrast-enhanced computed tomography (CT) have increased sensitivity to detect very small cysts (<5mm) compared to ultrasound. This can result in the detection of cysts incidentally, occasionally during the workup of individuals being considered as transplant donors. A total of ≥10 cysts in subjects younger than 30 years of age had a sensitivity and specificity of 100%. Thus, a total of ≥ 10 cysts using any imaging modality can be considered diagnostic for ADPKD for at-risk people aged over 16 years after the exclusion of other forms of cystic kidney disease[10, 12].

1.2 GENOMIC TESTING

Identification of a monoallelic pathogenic variant in a known cystic kidney disease gene (most commonly *PKD1*, *PKD2*, and *IFT140*) can confirm a diagnosis of ADPKD. This is particularly useful in the context of atypical disease or in the absence of a family history (~30%). A

genomic diagnosis has numerous potential clinical applications for patients with cystic kidney disease and their families. This includes identifying individuals with variants associated with a greater risk of disease progression, assisting decision-making around family planning and preimplantation genomic testing,and enabling kidney donation from an unaffected relative[13]. Centrally commissioned whole genome sequencing is available in each of the 4 regions through the NHS Genomic Medicine Service (NHS GMS) in England[14], the Scottish Strategic Network for Genomic Medicine (SSNGM) in Scotland[15], the All Wales Medical Genomics Service (AWMGS)[16] and Belfast City Hospital Clinical Genetics Department in Northern Ireland[17]. Testing is available for any NHS patient with cystic kidney disease where a genomic diagnosis is required to influence management. This test can be requested by nephrologists and clinical geneticists. The NHS GMS and SSNGM provide a national genomic test directory as well as additional resources such as necessary surveillance and family planning options including pre-implantation genetic testing[15, 18]. Wales and Northern Ireland currently use the NHS GMS national genomic test directory in England.

The testing criteria for cystic renal disease (R193) according to the National Genomic Test Directory include[18]:

Patients with non-syndromic cystic renal disease (excluding acquired cystic disease due to chronic or ESKD) which is either:

1) Clinically not characteristic of ADPKD and underlying diagnosis is required for management purposes
2) Clinically symptomatic disease presenting before the age of 18 years
3) Clinical diagnosis of ADPKD where a genetic diagnosis is required to influence management

Resources available:

- **NHS England » National genomic test directory**
- **NHS Scotland » National genomic test directory**
- **NHS England » The structure of the NHS Genomic Medicine Service**
- **QGenome » Genomic referral, risk assessment and testing guidance for clinicians**
- **GeNotes » Genomic notes for clinicians**

DRAFT

Section 2: Confirmation of eligibility for Tolvaptan

The published guidance by NICE in England & Wales and SMC in Scotland described the eligibility of people with ADPKD for Tolvaptan in each nation which is summarised below:

NICE (England & Wales) – TA458[5]

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

- there is evidence of rapidly progressing disease
- they have chronic kidney disease stage 2 or 3 at the start of treatment

SMC (Scotland) – SMC No. 1114/15[6]

To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease stage 1 to 3 at the initiation of treatment with evidence of rapidly progressing disease.

2.1 AGE

RECOMMENDATION
We recommend that people with ADPKD being considered for Tolvaptan should be aged 18 and above at the time of treatment initiation.

It is recommended that patients considered for treatment should be aged 18 and above. In the TEMPO 3:4 trial participants were 18-50 years of age[1]. This age range was extended to 18-65 years in the REPRISE trial which examined Tolvaptan in later-stage ADPKD[3].

It is important to recognise that other chronic conditions can progress with age such as diabetes mellitus, vascular disease and hypertension. Thus, the expected kidney function for a certain age group should be considered in the shared decision-making process with patients[4]. The National Kidney Foundation summarises the average eGFR for each age group in Table 2[19]. We do not recommend any age-related restrictions on the use of Tolvaptan.

Table 2. Average measured eGFR by age group in people without CKD[19]

Age group	Average eGFR (ml/min/1.73m^2)
20-29	116
30-39	107
40-49	99
50-59	93
60-69	85
70 +	75

There have been no large-scale RCTs examining the efficacy and safety of Tolvaptan in children and adolescents. A Phase 3b two-part study was undertaken in subjects aged 4-11 years of age and 12-17 years of age which demonstrated a reduced increase in height-adjusted Total Kidney Volume (htTKV) at 12 months in the Tolvaptan arm compared to the placebo arm (2.6% vs 5.8%, p>0.05). There was a non-statistically significant mean change in eGFR from week 1 to month 12 between the Tolvaptan and placebo arms (1.9 ml/min/1.73m^2 vs -1.8ml/min/1.73m^2, p 0.11)[20]. Although these results are promising there is currently insufficient data to support the use of Tolvaptan for people with ADPKD under the age of 18 years.

2.2 CHRONIC KIDNEY DISEASE STAGES

RECOMMENDATION

We recommend initiating Tolvaptan in patients with the following eGFR criteria:

- England & Wales: CKD stage 2-3 (30-89 ml/min/1.73m^2)
- Scotland: CKD stage 1-3 (eGFR ≥ 30 ml/min/1.73m^2)

Measurements of eGFR should be confirmed by two blood tests, at least 72 hours apart, and without intercurrent illness. In situations where eGFR reporting does not differentiate between CKD stages 1 and 2, it is recommended that the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation should be used.

– **MDCalc » CKD-EPI equations for Glomerular Filtration Rate (GFR)**

Guidance from NICE excludes patients with stage 1 CKD (eGFR ≥90 ml/min/1.73m^2). This was based on the less favourable cost-benefit analysis of Tolvaptan in patients with stage 1 CKD who showed a non-significant eGFR slope despite a significant reduction in TKV increase[5]. We recommend that people with ADPKD and stage 1 CKD should undergo serial risk evaluation with a review of symptoms, family history and age at ESKD as people with stage 1 CKD may be at risk of rapid disease progression. In England, Wales and Northern Ireland the Mayo

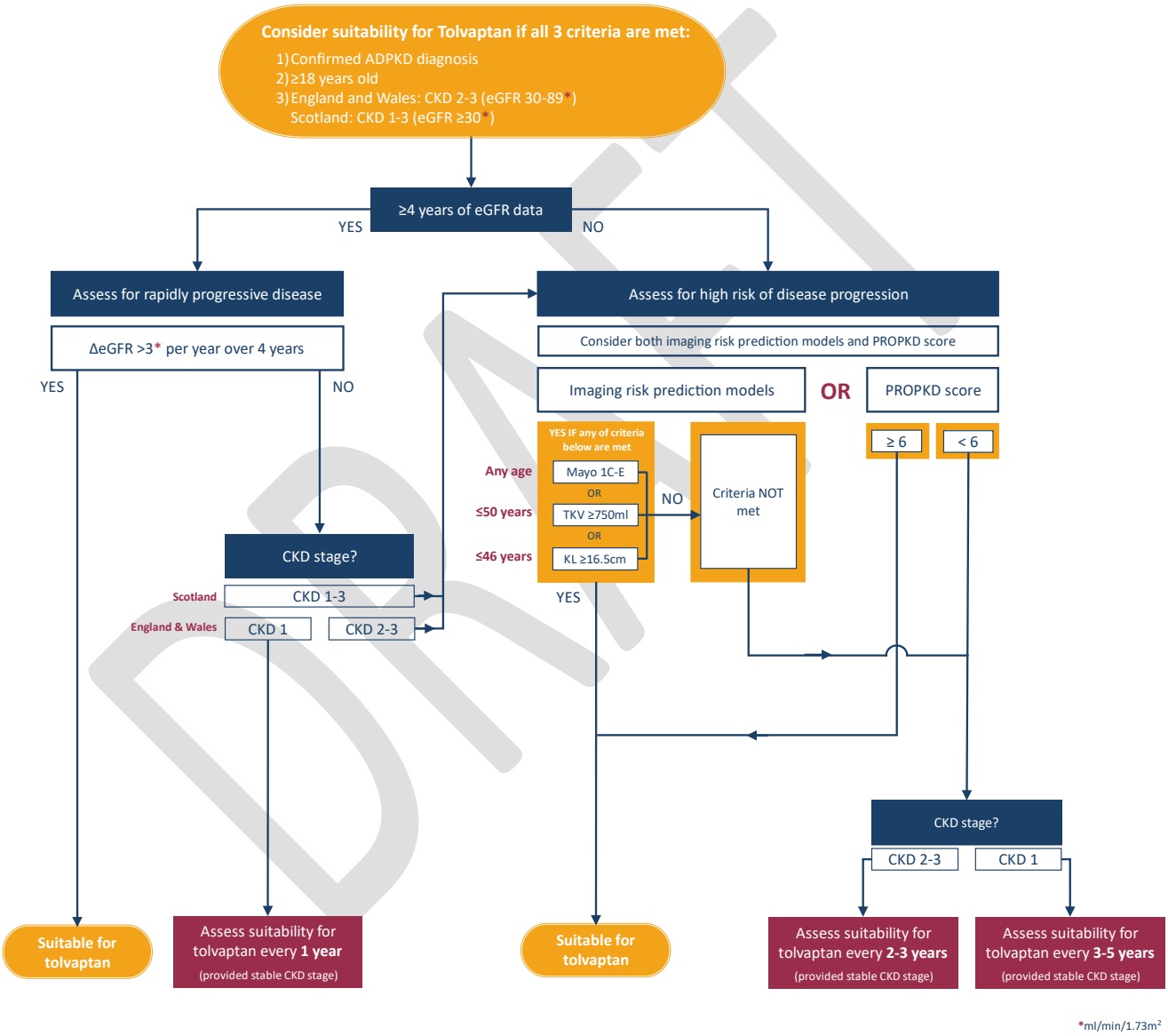
Imaging Classification or PROPKD score could be used to identify rapid progressors prior to the initiation of Tolvaptan when eGFR ≤89 ml/min/1.73m^{2,} see section 3.3. However, in Scotland, people with CKD stage 1 are eligible to receive Tolvaptan under the approval of Tolvaptan by the SMC[6].

In the natural history of ADPKD, there is often initial compensatory glomerular hyperfiltration leading to eGFR changes occurring later in the disease process[21, 22]. Thus, eGFR should be determined after control of blood pressure (usually with renin-angiotensin system blockade in this patient group). In the early stages of ADPKD, eGFR may not be sufficiently sensitive to measure any change[21, 23]. TKV usually increases prior to any changes in eGFR thus representing a potential prognostic marker[21].

DRAFT

Section 3: Confirmation of rapidly progressive disease or high risk of progression

3.1 OVERVIEW FLOWCHART TO ASSESS SUITABILITY FOR TOLVAPTAN



3.2 RAPIDLY PROGRESSIVE DISEASE

RECOMMENDATION
We recommend that a definition for evidence of rapid disease progression and eligibility for Tolvaptan is: A sustained decline in eGFR of ≥3 ml/min/1.73m^2 per year (at least 5 measurements over 4 years)

ADPKD is typically considered a slowly progressive disease with the development of end-stage kidney disease (ESKD) occurring over many decades. However, there is marked intra and interfamilial heterogeneity in the rate of progression[24].

We propose that historical changes in eGFR over time provide the most robust evidence of disease progression. Rapid disease progression in ADPKD can be defined as a sustained decline in eGFR of ≥ 3 ml/min/1.73m^2 per year with at least 5 measurements over the course of 4 years. The Mayo Imaging Classification system reported that people with typical ADPKD have an annual decline of 2.63 ml/min/1.73m^2 for men and 2.43 ml/min/1.73m^2 for women[25]. Furthermore, TEMPO 3:4 and REPRISE reported an average decline of 3.5 ml/min/1.73m^2[1, 3]. As a result, we recommend that rapid disease progression can be defined by an annual decline of 3 ml/min/1.73m^2 when this decline can be attributed to ADPKD progression. Due to the day-to-day fluctuations in eGFR, this decline in kidney function requires measurement over a period of follow-up[26]. There is also a small sub-group of people with ADPKD that have non-linear eGFR loss[27]. Consequently, we suggest obtaining at least five serum creatinine values over a period of ≥4 years. In people who may become pregnant, the baseline in kidney function should only be taken from 3 months post-partum to take the physiological changes associated with pregnancy into account[28].

When eGFR loss points towards rapid disease progression in elderly patients, it is important to exclude other causes other than ADPKD. In younger patients, reduced kidney function in the absence of known factors leading to acute fluctuations is likely to be the result of ADPKD itself and reflect disease progression[4].

In the previous commentary on the NICE guideline on Tolvaptan for treating autosomal dominant polycystic kidney disease, evidence of rapid disease progression was defined as a decline in eGFR >5 ml/min/1.73m^2 over 12 months based on the KDIGO definition of "rapidly progressive CKD"[29]. However, this acute decline is rarely seen among people with ADPKD in clinical practice and acute causes other than ADPKD progression should be considered. For this reason, this potential criterion has been removed from the updated commentary[1-3].

3.3 HIGH RISK OF DISEASE PROGRESSION

RECOMMENDATION

We recommend assessment for risk of disease progression if there is a lack of evidence for rapid disease progression based on eGFR criteria. This evidence can be based on diagnostic imaging and/or genetic testing.

Risk of disease progression can be determined by the following methods:

- Kidney length ≥16.5cm (≤46 years only) - USS imaging)
- TKV ≥750ml (≤50 years only) - MRI/CT imaging
- Mayo Imaging Class (classes 1C-E) - MRI/CT imaging
- PROPKD score (scores ≥6)

A number of markers have been associated with a more severe disease course in ADPKD so may predict kidney outcome prior to any decline in eGFR. Some markers have been incorporated into different prediction models including age, sex, htTKV, variant type and clinical complications[30, 31]. Patients who lack evidence of previous rapid eGFR loss should be assessed for their risk of disease progression. This evidence can take the form of genetic, clinical or imaging prognostic markers.

3.3.1 Risk prediction using imaging modalities

A. Kidney length (KL)

The CRISP studies suggest that a cut-off kidney length of 16.5 cm, measured by US or MRI, predicts the development of CKD stage 3a over a period of 8 years (sensitivity 85% and specificity 92%). The comparison of US and MRI demonstrated a similar ability to predict disease progression through kidney length. Given that US is more readily available, more cost-effective and does not have any restrictions in terms of metallic clips or other implanted devices, there should be a preference for USS over MRI when measuring KL[32]. Therefore, we recommend that an average kidney length of greater than 16.5cm in those aged 46 or younger (upper age limit of CRISP) is regarded as evidence of high risk of rapidly progressive disease.

It is important to note that kidney length cannot reliably differentiate between ADPKD-*PKD1* and ADPKD-*PKD2* which have different risks of disease progression. Furthermore, the use of kidney length alone may delay treatment initiation for younger people with ADPKD with a kidney size smaller than 16.5cm who might be at high risk for progression[33]. Thus, using a finding of a kidney length of <16.5 cm alone may not be an adequate method to exclude those with high risk for progression[34]. The use of kidney length alone might also misclassify people with atypical ADPKD (Mayo Class 2), which is often focal with few but large kidney cysts, as rapid progressors[33]. Thus, we suggest that the best use of kidney length as a predictor of rapid progression is in those with typical ADPKD (class 1).

B. Total kidney volume (TKV)

The extended observations of the CRISP study demonstrated that participants with a TKV ≥600ml/m predicted the risk of developing ESKD[35]. Following this, the TEMPO 3:4 and REPRISE trials included a minimum TKV of 750ml and an age less than or equal to 50 years as an inclusion criterion for participation in these trials[1, 3]. Other countries have utilised a TKV ≥750ml as an approved indication of Tolvaptan for people with ADPKD in Japan[36]. Therefore, we recommend that a TKV ≥750ml can be used as a marker of disease burden and high risk of disease progression in individuals aged 50 years or younger.

In the previous commentary on the NICE guideline on Tolvaptan for treating autosomal dominant polycystic kidney disease, there was the inclusion of >5% per annual change in TKV with 3 measurements over 2-3 years. However, this is difficult to measure in clinical practice and anecdotally very few patients have been started on Tolvaptan for this indication.

C. Mayo classification

If MR or CT imaging has been performed in an individual, this can be used to determine their Mayo Imaging Class (MIC). This uses a single measured or estimated TKV based on MR/CT imaging adjusted for age and height. It has been validated as a sensitive prognostic marker for people aged 15 to 80 years with "typical" ADPKD predicting their risk of disease progression to kidney failure[25]. The MIC has also been validated in several independent cohorts and compares favourably to models based on genetic information[37]. The definition of "typical" (Class 1) which describes the majority of people with ADPKD is somewhat subjective but is defined as "bilateral and diffuse distribution, with mild, moderate or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV". The 4-9% of people with ADPKD not fitting this description are classified as "atypical" (Class 2) and are not further classifiable in this imaging scheme[25]. The Mayo Imaging Classification is included in Appendix 2.

People with ADPKD classified as Class 1C-E according to the MIC are at risk of rapid disease progression[25]. If height measurements are not available, a single TKV based on MR imaging ≥750ml can be used as a predictor of rapid disease progression in people with ADPKD aged 18-50 years[24]. People with ADPKD classified as Class 1A-B, Class 2 and TKV <750ml are considered to have a low risk of progression[25].

3.3.2 Risk prediction using genomic and clinical factors

Knowledge o the underlying pathogenic variant in an individual may be useful in predicting their risk of disease progression. Genomic analysis in multiple large cohorts in several countries has shown that there is a strong association between the type of genomic change responsible for ADPKD and the expected (or median) age at kidney failure. Protein truncating variants in *PKD1* were the most common and associated with the most severe prognosis,

median age at kidney failure 55 years. This is compared to a median age of kidney failure for missense *PKD1* variants at 67 years and *PKD2* variants at 79 years[38].

A scoring system, PROPKD Score, that incorporates genomic, sex and other clinical information (presence of hypertension or symptomatic cyst haemorrhage/infection/pain before the age of 35) has performed well at identifying the risk of early-onset kidney failure. A score of <4 had an 81.4% negative predictive value and scores >6 had a >90% positive predictive value for kidney failure before 60 years old. Therefore, we recommend that scores of 6 or more constitute evidence of high risk for rapidly progressive disease[38]. This is summarised in Table 3 and more details are provided in Appendix 3.

An online calculator is available which calculates the PROPKD Score and provides information on the risk of progression to ESKD.

- **ADPKDsim » PROPKD Score**

Table 3. PROPKD score[38]

	PROPKD score	Points
Sex	Female	0
	Male	1
Hypertension < 35 years	No	0
	Yes	2
First urological event < 35 years*	No	0
	Yes	2
Variant type	PKD2	0
	PKD1 non-truncating	2
	PKD1 truncating	4

* A urological event is defined by frank haematuria, cyst infection or flank pain related to cysts

DRAFT

Section 4: Confirmation of no exclusions to treatment

RECOMMENDATION
We recommend that people with ADPKD should be assessed for potential contraindications/precautions prior to Tolvaptan initiation.

4.1 MANUFACTURER RECOMMENDATIONS

Recommendations of information to discuss with patients prior to prescribing Tolvaptan and a checklist of contraindications and precautions associated with comorbidities have been prepared by Otsuka, Appendix 4. The main components are summarised below.

Contraindications[32]

If any of the following apply to the patient then they should not be treated with Tolvaptan:

- Elevated liver enzymes
- Hypersensitivity to the active substance or any of its constituents
- Volume depletion
- Uncorrected hypernatraemia (> 145 mmol/L)
- Inability to perceive or respond to thirst
- Pregnancy
- Breastfeeding
- Anuria

Precautions[32]

If any of the following apply to the patient then Tolvaptan may be prescribed with caution along with appropriate monitoring:

- Severe hepatic impairment (Child-Pugh class C)
- Cirrhosis
- Limited access to water
- Dehydration
- Partial obstruction of urinary outflow
- Fluid and electrolyte imbalance
- Serum sodium abnormalities
- Anaphylaxis
- Lactose and galactose intolerance
- Diabetes mellitus
- Elevated uric acid concentration
- Use of medicines likely to interact with Tolvaptan

DRAFT

4.2 PREGNANCY AND BREAST-FEEDING

RECOMMENDATION
We do not recommend Tolvaptan use in people who are pregnant or breast-feeding.
We recommend advising people who may become pregnant of the potential teratogenic risk of Tolvaptan and encourage them to use contraception.

Tolvaptan has been demonstrated to be teratogenic in animal models at maternally toxic doses, approximately 1-4 times the recommended dose of 90mg/30mg once daily. Thus, the manufacturer recommends that Tolvaptan is contraindicated during pregnancy[39]. They recommend using contraception for at least four weeks before starting and for four weeks after stopping Tolvaptan. We recommend that people who may become pregnant should be advised of the risks and encouraged to use contraception[41].

It is unknown whether Tolvaptan is excreted in human milk, what effects there are on the breast-fed infant or the effects on milk production. Animal studies have shown the excretion of Tolvaptan in milk[39]. The manufacturer advises people not to breastfeed while taking Tolvaptan and to delay breastfeeding for four weeks after stopping Tolvaptan[40].

DRAFT

Section 5: Initiation, titration and drug interactions

5.1 TOLVAPTAN DOSING

RECOMMENDATION
We recommend a starting dose of Tolvaptan 45mg in the morning and 15mg 6-8 hours after the first dose. We recommend doses should be up-titrated based on healthcare professional preference. Some centres increase doses at 28day intervals in accordance with standard pack sizes of Tolvaptan. We recommend titrating to a maximum dosage of 120mg per day (90mg/30mg) in all patients unless not tolerated or contraindicated.

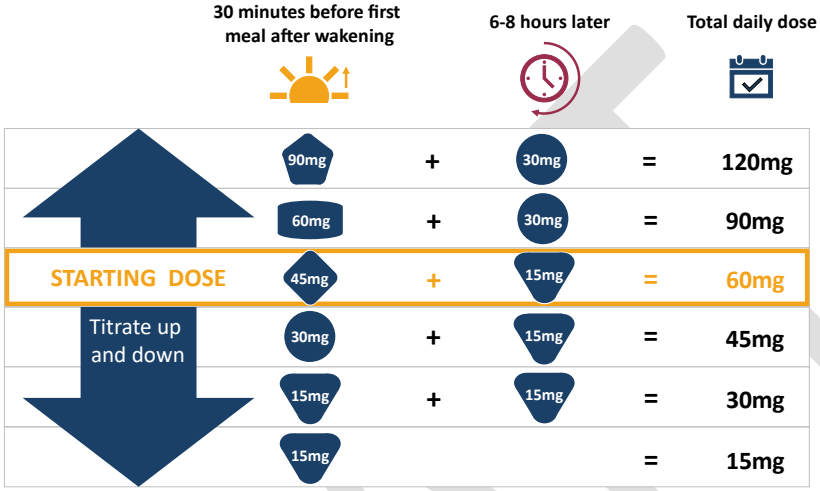
Tolvaptan for ADPKD is taken as a split dose due to its half-life with a maximum daily dose of 120mg based on the TEMPO 3:4 trial where 90mg/30mg was the highest tolerated dose[1]. Tolvaptan is available in 15mg, 30mg, 60mg, 90mg preparations.

It is recommended that Tolvaptan is initiated at a 60mg daily dose split into 45mg in the morning and 15mg 6-8 hours after the first dose. It is advised that Tolvaptan is taken as early as possible to ensure that the second dose is as far away from bedtime as possible. People taking Tolvaptan aim to try and take the final dose before 5pm to reduce nocturnal symptoms. Please note that these times should be adjusted for people working non-traditional working patterns to align with their waking times whilst maintaining the specified time interval between doses. There is currently no published advice on the optimal titration regime.

The Summary of Product Characteristics (SPC) for Jinarc, the brand name for Tolvaptan, states that co-administration with a high-fat meal increases the peak concentration of Tolvaptan. This has been shown for only 90mg doses and not 30mg or 60mg doses. This food effect is unlikely to be clinically significant but this finding has led the manufacturer to advise that the morning dose be taken under fasted conditions (30 minutes before the morning meal). Other clinical information sources such as the BNF, Martindale and Lexicomp do not give this advice. Furthermore, this morning timing of Tolvaptan doses was not undertaken in clinical trials. Finally, patients having to awaken 30 minutes earlier in the morning can have a considerable impact on patients who already have disturbed sleep due to nocturnal aquaretic effects. We recommend a pragmatic approach to this issue and provided the patient is not having a very high-fat meal they may take this morning dose with or without food.

Tolerability can be dose-dependent: in the TEMPO 3:4 study, an initial titration was included to allow patients to slowly adjust to the effects of the drug or to continue at a lower dose depending on tolerability[41]. We recommend up-titrating to the maximum daily dose of 120mg at 28 day intervals since Tolvaptan is generally supplied as a 28 tablet pack size. Tolerability may be higher in those with a lower eGFR as demonstrated in the TEMPO3:4 trial[1]. In those who do not tolerate the starting daily dose of 60mg (45mg/15mg) a reduction in dose can be considered if the alternative is cessation. This approach is summarised in Figure 3.

Figure 3. – Dosing regime and titration steps for Tolvaptan



5.2 DRUG INTERACTIONS

RECOMMENDATION
Special care should be given when prescribing Tolvaptan alongside drugs that interfere with the action of CYP3A4. Tolvaptan dose adjustment should be considered with concurrent use of strong or moderate CYP3A4 inhibitors but not with CYP3A4 inducers.

The British National Formulary (BNF) lists the drug interactions that can occur with concurrent use of Tolvaptan. These recommendations are included in Appendix 5. Tolvaptan is metabolised by the microsomal P450 drug-metabolising enzyme known as CYP3A4, so Tolvaptan levels can be influenced by inhibitors and inducers of this enzyme[42].

Medications can interact with Tolvaptan with four main consequences:

A. Increase exposure to Tolvaptan
B. Decrease exposure to Tolvaptan
C. Increased risk of hyperkalaemia
D. Tolvaptan increases exposure to other medication

A. Increase exposure to Tolvaptan (CYP3A4 inhibitors)

The manufacturer advises reducing the dose of Tolvaptan with concurrent use of strong and moderate CYP3A4 inhibitors. The advised adjustments are indicated in Table 4.

Table 4. Tolvaptan dose adjustments for strong and moderate CYP3A4 inhibitors[43]

		Dose adjustment	
		Strong inhibitors	Moderate inhibitors
Total daily dose	120mg	30mg (potential reduction to 15mg)	60mg
	90mg	30mg (potential reduction to 15mg)	45mg
	60mg	15mg	30mg

B. Decrease exposure to Tolvaptan (CYP3A4 inducers)

The manufacturer does not advise dose adjustment of Tolvaptan with concurrent use of strong or moderate CYP3A4 inducers[43].

C. Increased risk of hyperkalaemia

Tolvaptan is associated with an acute reduction of extracellular fluid volume which could result in an increased serum potassium. Certain medications can increase the risk of hyperkalaemia especially when combined with ACEi/ARBs.

D. Tolvaptan increases exposure to other medication

Tolvaptan may increase the effects of the following medications: digoxin, dabigatran, sulfasalazine and metformin. Due to its mechanism of action, Tolvaptan may also reduce the effect of vasopressin analogues such as desmopressin which is used to increase clotting factors or control urine output/bedwetting[44].

DRAFT

Section 6: Monitoring during Tolvaptan therapy

6.1 MONITORING RESPONSE TO TOLVAPTAN AND THERAPEUTIC EFFICACY

RECOMMENDATION
We do not recommend any specific monitoring for Tolvaptan treatment response or efficacy.

There are no currently validated markers that monitor or predict the effect of Tolvaptan on GFR or TKV at an individual level. Effective blockade of the V2 receptor may be assessed by measuring urine osmolality. Although the lowering of urine osmolality and increased aquaresis reflects adherence, there is insufficient evidence for this to be a marker of treatment efficacy since it may be affected by fluid intake[45]. The increase in copeptin associated with Tolvaptan use suggests it's potential role as a biomarker though there is currently insufficient data to recommend it's use in clinical practice[46]. Changes in eGFR and TKV on Tolvaptan treatment have been compared with trends in pre-treatment data or with predictions based on the Mayo imaging classification. However, the validity and sensitivity of these approaches have not been established so they are not currently recommended for use in individual patients[1-3].

6.2 KIDNEY FUNCTION MONITORING

RECOMMENDATION
We recommend measuring kidney function monthly in line with liver function monitoring. An initial decline of 3-9% in eGFR may be expected when Tolvaptan is started which is reversible on cessation. We recommend that Tolvaptan should be stopped prior to the initiation of renal replacement therapy.

A decline of 3-9% in eGFR may occur following the initiation of Tolvaptan but is reversible on cessation of treatment[1-3]. This degree of decline in eGFR depends on the baseline kidney function. This is comparable to the acute decline in eGFR observed on starting angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs). We recommend that kidney function should at least be checked on the same schedule as for liver function test monitoring monthly for the first 18 months then every 3 months.

The REPRISE trial demonstrated that Tolvaptan is effective down to the lower eGFR limit of 25 ml/min/1.73m^2. At present, there have been no published trials on eGFR levels below 25

ml/min/1.73m^2. The BNF suggests stopping Tolvaptan at CKD stage 5 (eGFR <15ml/min/1.73m^2). We recommend that Tolvaptan should be stopped prior to the initiation of renal replacement therapy. This may lead to an associated small increase in eGFR on cessation of Tolvaptan[1-3].

6.3 LIVER FUNCTION MONITORING

RECOMMENDATION
We recommend measuring liver function monthly during the first 18 months of treatment then 3 monthly afterwards.

Liver function tests are mandated prior to the initiation of treatment and monthly for 18 months then 3 monthly after that. This is based on the finding of the REPRISE trial that nearly all cases of treatment-associated liver abnormalities occurred within the first 18 months[1, 4]. See section 7.3 for specific advice regarding the management of elevated liver enzymes.

DRAFT

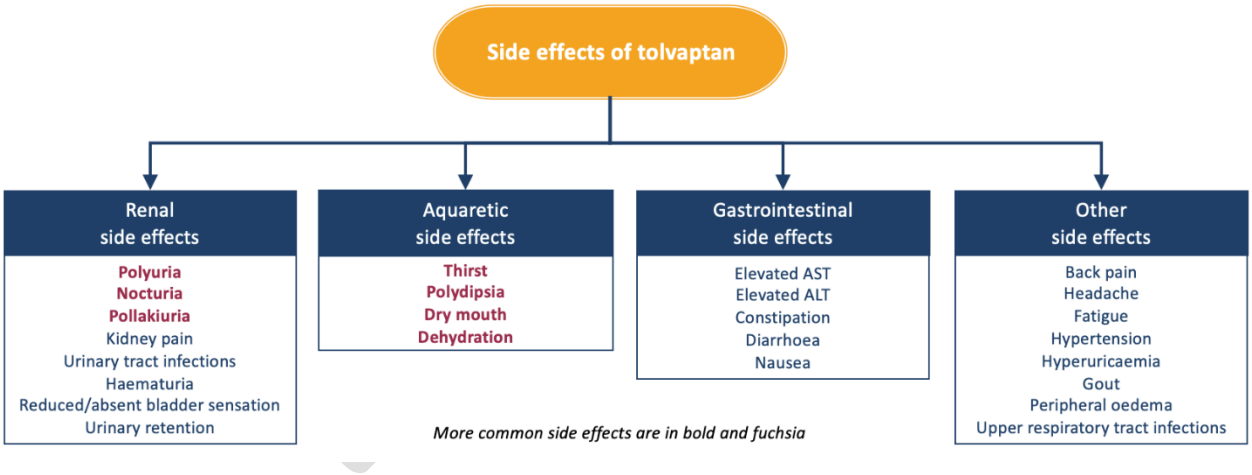
Section 7: Management of side effects and adverse effects

7.1 OVERVIEW

RECOMMENDATION
We recommend discussing side effects with patients and providing written patient information prior to initiating Tolvaptan.
We recommend withholding Tolvaptan during periods of acute illness due to the increased risk of dehydration. This can be described as "sick day guidance" as advised for ACEi/ARBs.

The use of Tolvaptan in people with ADPKD is associated with common and rare side effects[1, 3]. The side effects reported in the TEMPO 3:4 and REPRISE trials are included in Figure 1 which has been adapted from Raina et al[47]. These side effects observed when taking Tolvaptan have been observed to change in frequency depending on the dose of Tolvaptan. Generally aquaretic side effects (polyuria/pollakiuria/nocturia), fatigue and dizziness increase with an increase in Tolvaptan dose (total daily dose 30mg to 60mg)[48].

Figure 1. Common side effects of Tolvaptan by category[47]



Patients should be advised to hold Tolvaptan and to increase hydration in the setting of acute illness that could lead to dehydration or interfere with adequate hydration, when insensible water loss is increased in warm weather or when water access is restricted[9]. In the case of acute illnesses, this can be described to patients as "sick day guidance" as for other medications such as ACEi/ARBs[49]. We recommend advising people with ADPKD taking Tolvaptan to restart taking Tolvaptan 24 hours after recovering from the acute illness. Tolvaptan should be held for 24-48 hours before elective surgeries and not restarted until patients are able to maintain adequate hydration[9].

7.2 AQUARETIC SIDE EFFECTS

RECOMMENDATION
We recommend carefully counselling patients and provide practical suggestions on minimising problems with aquaretic side effects, especially the reduction of dietary sodium intake, and how to manage this in daily life. This is particularly important for people with earlier stage ADPKD.

Tolvaptan is a selective V2 vasopressin receptor antagonist. It prevents the normal binding of vasopressin to V2R which would lead to aquaporin channel translocation[50]. Thus, Tolvaptan prevents this process leading to the loss of free water and commonly experienced side effects of polyuria, nocturia, pollakiuria, polydipsia, thirst, dehydration and dry mouth. Most commonly experienced are aquaretic side effects such as polyuria, nocturia and polydipsia most frequently which are not known to decline with time[51]. Tolvaptan leads to maximally dilute urine. In the later stage ADPKD, there is impaired urine concentrating capacity which will lead to lower 24hr urine volume on treatment compared to early-stage disease. Nonetheless, people in the earlier stage of ADPKD have the most to gain from taking Tolvaptan but will likely experience more aquaretic side effects influencing tolerability[52].

Some measures may make the aquaretic side effects more manageable:

- Time-dependent attenuation
- Dietary changes
- Pharmacological

7.2.1 Time-dependent attenuation

It is recommended that people with ADPKD are advised to start Tolvaptan on a weekend or when they are not at work to help them adjust to the aquaretic response[9]. The timing of the second dose (not too late in the afternoon) may help to prevent excessive nocturia. A reduction of the second dose may be considered if nocturia remains a significant issue but this may reduce treatment efficacy.

7.2.2 Dietary changes

Dietary changes that reduce osmolar loads, such as a moderate reduction in salt and protein intake, may help to reduce the aquaretic effect of Tolvaptan[53, 54]. Low sodium intake in people with ADPKD receiving Tolvaptan reduces natriuresis and resultant diuresis volume in addition to the effect on blood pressure[52, 54]. We recommend advising patients to avoid foods with high salt content. These include tinned foods, instant mixes, condiments, snack foods, pre-prepared foods, soft drinks and fast food. People taking Tolvaptan should be advised to read food labels and aim to eat less than 5 grams of sodium per day[54-56]. We recommend a low

sodium diet, especially later in the day, to potentially address some of the aquaretic side effects associated with Tolvaptan.

In general, people with CKD are recommended to avoid extremes in protein intake with current KDIGO guidelines suggesting 0.8 g/kg/day in adults with an eGFR <30 ml/min/1.73m2 at risk of progression[57]. There are many guidelines that give differing and somewhat conflicting guidance on protein intake[58]. A low protein diet (<0.6 g/kg/day) has not been shown to slow the rate of ADPKD progression and may increase the risk of malnutrition[56, 59]. At the 2015 KDIGO controversies conference on ADPKD, there was no specific recommended protein intake for ADPKD[29]. Theoretically, a low osmolar diet may reduce aquaretic side effects[53]. However, there is no evidence to support this at the current time. We would recommend a moderate protein intake of 0.8-1.0 g/kg/day for people with ADPKD including those on Tolvaptan.

Caffeine is a known stimulus for AMP accumulation and is associated with hypertension[33]. However, the effects of caffeine on natriuresis and diuresis are not fully understood. We recommend a moderate caffeine intake, especially later in the day, to potentially address some of the aquaretic side effects associated with Tolvaptan. This should in particular influence the severity of nocturia.

7.2.3 Pharmacological

Thiazide diuretics have been demonstrated to be effective in reducing polyuria by up to 50% in people with nephrogenic diabetes insipidus; the mechanism behind this paradoxical antidiuretic effect has not been fully elucidated[60]. A small-scale trial has suggested that the mechanism of action of thiazide diuretics may be an option to improve the tolerability of Tolvaptan and adherence in the management of ADPKD[61]. However, at present there is insufficient evidence to recommend their use in practice.

7.3 DRUG-INDUCED LIVER INJURY

RECOMMENDATION
We recommend that following the initiation of Tolvaptan, patients should be informed of the potential risk and encouraged to self-report symptoms of liver injury. We recommend withholding Tolvaptan in the event of suspected drug-induced liver injury to allow time to exclude other causes. Liver enzyme levels should be monitored until levels return to normal or their baseline.

Idiosyncratic drug-induced liver injury (DILI) is an unpredictable type of liver injury following exposure to medication within the recommended dose. Onset can occur from a few days to

months post-exposure. It encompasses the whole spectrum from asymptomatic elevation in liver enzymes to acute liver failure[62]. Thus, it is important to educate people taking Tolvaptan on the potential symptoms of liver injury as these could occur between clinic visits. Healthcare teams should aim to review patients with signs or symptoms of liver injury within 48 hours. In the TEMPO 3:4 trial, DILI was a rare side effect in people taking Tolvaptan[1]. The approach to monitor liver enzymes monthly for the first 18 months followed the finding of no cases of severe DILI after 18 months[2]. The degree of elevation of liver enzymes does not accurately reflect the severity of the liver injury or predict clinical outcomes[63].
Thresholds to define DILI include (adjusted Hy's law)[64, 65]:



The most critical step is the timely recognition of liver injury and withdrawal of Tolvaptan. Alternative diagnoses should be excluded whilst Tolvaptan is withheld[62]. This should include an initial clinical assessment considering other causes of elevated liver enzymes and a standard liver aetiology screen[66].

Standard liver aetiology screen[66]:

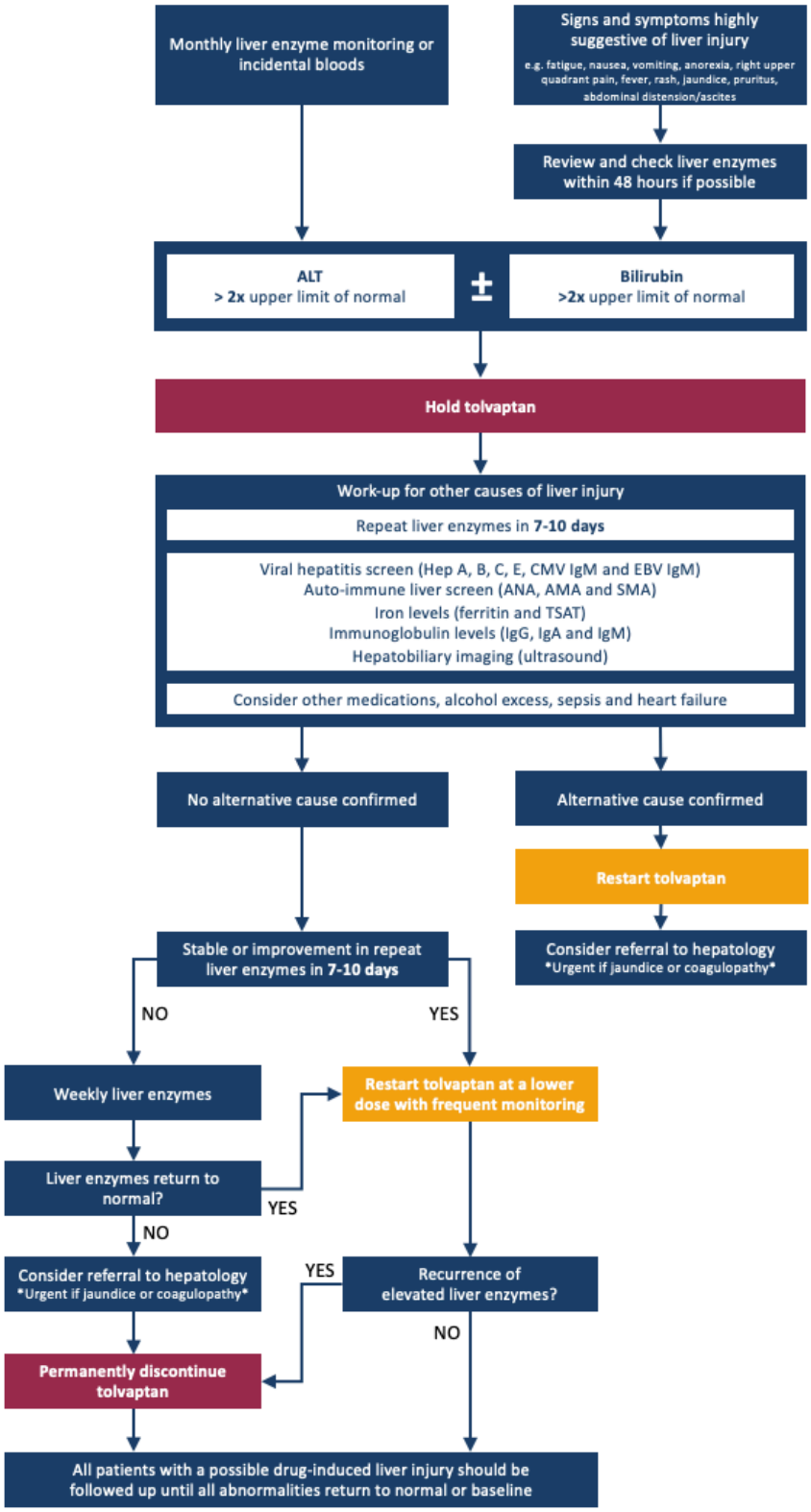
Viral hepatitis screen:	Hepatitis A virus antibody (IgM), Hepatitis B virus surface antigen (Anti-HBs), Hepatitis C virus antibody (with PCR if positive), Hepatitis E virus antibody (IgM), CMV antibody (IgM), EBV antibody (IgM)
Autoimmune screen:	Antinuclear antibody (ANA), Antimitochondrial antibody (AMA), Smooth muscle antibody (SMA)
Iron studies:	Ferritin, Transferrin saturation (TSAT)
Immunoglobulins:	IgA, IgG, IgM
Ultrasound imaging	

The increase in liver enzymes is generally reversible following cessation of Tolvaptan and severe drug-induced liver injury is rare[1]. In people with ADPKD who are found to have DILI after reinitiation, Tolvaptan should be stopped and re-exposure should not be attempted[9]. A stepwise algorithm to suspect, diagnose and manage idiosyncratic DILI in association with Tolvaptan is proposed in Figure 2. A more conservative upper limit for ALT has been chosen to indicate when Tolvaptan should be held with monitoring and work-up for other causes.

We recommend that blood tests should be repeated within 48-72 hours in line with the clinical trials. However, it may take up to 7-10 days for any changes in liver enzymes to take affect based on the half-life of liver enzymes. The half-life in circulation for ALT is 47 hours, ALP is around 1 week and initially fast then slow decline in bilirubin levels (bimodal)[67]. However, this interval between blood tests should be shortened if the presenting individual's clinical condition warrants a quicker response.

DRAFT

Figure 2. Recommendations for evaluation and management of suspected drug-induced liver injury (adapted from Chebib et al[9] and British Society of Gastroenterology[66])



Abbreviations: *Alanine phosphatase (ALP), Alanine transaminase (ALT), Antinuclear antibody (ANA), Antimitochondrial antibody (AMA), Smooth muscle antibody (SMA)*

7.4 OTHER SIDE EFFECTS

7.4.1 Gout

Urate levels can be elevated following the initiation of Tolvaptan[50]. However, this is rarely clinically significant in clinical practice. In the event of recurrent gout, we would recommend introducing dietary changes and considering starting allopurinol. If recurrent gout persists, it may be appropriate to reconsider continuing Tolvaptan.

7.4.2 Skin cancer

In the TEMPO 3:4 trial, a higher number of people with ADPKD who received Tolvaptan reported skin cancer compared to placebo, predominantly basal cell carcinoma (0.8% versus 0.2%)[1]. However, a causal relationship has not been established and the incidence was less frequent in the TEMPO 4:4 trial[68]. At present there is insufficient evidence to recommend routine monitoring or screening in the absence of clinical signs or symptoms of skin cancer.

7.4.3 Glaucoma

In the TEMPO 3:4 trial, there was an unexpected signal in the adverse events for glaucoma amongst people who received Tolvaptan compared to placebo (0.7% versus 0.4%)[1]. Following the trial, the manufacturer engaged an independent expert in ophthalmology and no clear or consistent pattern was identified that would attribute these events to Tolvaptan[68]. For this reason, we do not recommend any changes to the NHS recommendation that the general population have their eyes checked every 2 years by an optician. This frequency could change if an abnormality is detected or advised to do so by their opticians or opthalmologist[69].

DRAFT

Section 8: Considerations from a patient perspective

RECOMMENDATION
Based on patients' perspectives of Tolvaptan we recommend that the following factors should be taken into account when Tolvaptan is being considered: ▪ Impact on lifestyle ▪ Occupation ▪ Family planning ▪ Healthcare appointments

When discussing the benefits of starting Tolvaptan the discussion should include:

- Slowing of kidney function decline in those at risk of rapid progression
- Delayed onset of kidney replacement therapy
- Impact on kidney pain and infections

A shared decision-making approach between physicians, people with ADPKD and their caregivers is important prior to initiating Tolvaptan. When discussing potential side effects, it is important to try and present a balanced overview as well as discuss ways to help manage them. Some patients report that it is helpful to have supporting documents from their medical team to help them advocate for themselves, especially early in their journey on Tolvaptan.

8.1 HELPING PEOPLE TO MANAGE WITH SIDE EFFECTS

It is important that the medical team informs people with ADPKD of the potential side effects that can occur with Tolvaptan whilst reassuring them that they can help them to manage these side effects. This balanced approach to describing Tolvaptan is important as both patients and doctors can be affected by framing effect[70-72]. This can include timing, lifestyle, employment and healthcare adjustments.

The following advice has been provided in conjunction with expert patient opinions and those from the Tolvaptan community support group.

8.1.1 Initiation

- People with ADPKD who start on Tolvaptan report almost immediate changes in the frequency of urination and thirst necessitating increased fluid intake
- Tolvaptan should preferably be started on a day when the person with ADPKD is not at work or required to travel long distances to help them adjust to the immediate aquaretic response[9]

DRAFT

- Many people who are taking Tolvaptan have found that they do adjust and they can have an almost “normal” life with aquaretic side-effect becomes more tolerable over time (usually a few days to a few months)
- Sometimes it is just not the right time for an individual to start or continue taking Tolvaptan e.g. temporary mobility issues (e.g. injury or fractured bone) or caring for very young children
- These issues may limit their ability to manage side effects or the need to attend frequent appointments
- In the case of people of childbearing age, they may wish to delay starting Tolvaptan until after they have had children and/or after breast-feeding is complete
- People with ADPKD should be given the opportunity to restart Tolvaptan in the future if they remain eligible when reassessed

8.1.2 Timing of doses

- Take the morning dose as early as possible so the second dose (taken 6-8 hours later) is as far away as possible from bedtime e.g. 7am and 3pm
- Avoid taking the second dose of Tolvaptan after 5pm
- A pragmatic approach to the Otsuka advice of taking the morning dose 30 minutes before food should be taken; provided the morning meal is not a high-fat meal then this dose can be taken with or without food

8.1.3 Fluid intake

- Drink water instead of drinks with high sugar or fat content, e.g. soft drinks, juices and milk, to avoid excessive caloric intake
- Cold infuse teabags in water bottles can help people who find drinking plain water difficult
- Cold water from a fridge and sparkling water can help to quench excessive thirst more than room temperature water, especially in the summer months
- In warm and humid weather, water intake can increase by 20-30% so it is important to ensure that additional water supplied is readily available
- When drinking alcohol it is important to remain hydrated and drink more water than usual as alcoholic beverages may appease some of the thirst sensation
- As a vague rule patients should be matching their fluid intake to their urine output, the average urine output for people taking Tolvaptan is 6-8L per day
- Recognising dizziness, light-headedness and pain as indicators of dehydration and a need to drink more water

8.1.4 Dietary adjustments

- Avoid processed foods, takeaways and cook from scratch where possible (batch cook and freeze) to manage salt intake as people taking Tolvaptan report that a high salt intake can significantly impact thirst, particularly at night

DRAFT

- Having the main meal of the day at lunchtime and a light meal in the evening has been reported to help reduce water consumption during the night
- Avoid or reduce red meat particularly in the evening meal due to the potential increased need for water consumption during the night

8.1.5 Sleep patterns

- Large volumes of water should be available on the bedside table or similar to enable easy drinking of water overnight (approximately 2L)
- Patients should try to get an early night as nocturia can reduce the quality and amount of sleep with knock-on effects on mental and physical wellbeing
- Avoid putting the light on when going to the toilet during the night to make it easier to return to sleep
- Avoid looking at clocks, watches and mobile phones when getting up to go to the toilet during the night to make it easier to return to sleep

8.1.6 External activities – travel, day-to-day life, entertainment venues, sports events

- Patients should bring a letter from their nephrologist stating that they need to carry large amounts of water at all times and have access to facilities (minimum 2 litres)
- If patients have long-distance flights or a travelling long distances via motorways, it will not be possible to bring the volume of water needed or attend toilet breaks as required so they should be advised to "miss the dose" for the day of the trip
- When planning long car journeys patients should factor in regular bathroom breaks
- Female patients should consider wearing skirts/dresses when driving on motorways in case of unplanned traffic jams where there may not be easy access to toilets for some time
- Having a good supply of wide-opening vessels, such as old sports water bottles, "just in case" in their vehicle coupled with such clothing enables easier and more discreet urination if "caught out"
- Other "emergency" items to be kept in the car could include paper towels, additional bottles, bucket, blankets for privacy etc
- Suggest patients buy a "**Radar key"** so they can access disabled toilets if necessary
- Suggest patients obtain a "**Just can't wait**" card from the Bladder and Bowel community to show to personnel who may be able to help with emergency access to toilets e.g. staff bathrooms (this is now available in a downloadable version to mobile phones)

8.1.7 Medical care/Procedures/Drug interactions/Dental care

- As Tolvaptan is a specialised medication, people with ADPKD on Tolvaptan often have questions that cannot be answered by their community team
- Patients report that it is helpful for them to have an established plan of whom they could contact outside of clinic times for example should they develop a new symptom or are unsure about potential medication interactions
- Ensure that each patient has an up-to-date list of medications and fruits that are contraindicated with Tolvaptan

DRAFT

- In the case of temporary medications without any alternatives, e.g. antibiotics, it may be best for people with ADPKD to temporarily withhold Tolvaptan during the duration of the temporary medication
- Patients should have the contact details for their renal nurse if they have any doubts about other medications prescribed to them whilst on Tolvaptan
- Patients should be aware of the need to check with their nephrologist, specialist pharmacist or renal nurse before taking herbal remedies and "supplements"
- If the patient is undergoing an operation with a general anaesthetic it would be advisable not to take Tolvaptan for at least 3-4 days before the operation to ensure that Tolvaptan has fully left their system due to the dehydration risk whilst fasting
- The side effects listed by manufacturers and patient information leaflets were based on those reported in the clinical trials but new symptoms may be described by patients
- An overview of all the suspected adverse drug reactions reported through the Yellow Card Scheme in the UK for Tolvaptan can be accessed on the MHRA website
- It is important to register any suspected adverse drug reactions on the MHRA Yellow Card reporting site
- Suggest patients attend their dentist twice per year to monitor their gum health as Tolvaptan leads to significant dry mouth

8.1.8 Employment/Finances

- Due to the monitoring requirements, people with ADPKD who start taking Tolvaptan need to attend regular appointments which can have an impact on their employment, finances and quality of life
- Patients should be aware of local and national support e.g. social services, Kidney Care UK grants
- Despite the Equality Act 2010 to protect people from discrimination, some people with ADPKD can experience a lack of understanding or difficulties in the workplace[73]. This is likely related to the clinical features of ADPKD and Tolvaptan therapy not being immediately obvious[13]
- Some reasonable adjustments are more obvious such as the need for access to water and bathroom facilities. Others are less obvious such as nocturia affecting the length and quality of sleep which can be difficult for jobs that involve driving or operating heavy machinery
- Patients often benefit if given a letter from their nephrologist which explains the need for regular water access and toilet facilities. Two example letters are included in Appendix 7.
- Simple adjustments could include:
    - Ensuring easy access to refreshment facilities such as water in the workplace
    - Ensuring bathroom facilities are easily accessible and there is no restriction on "bathroom breaks"
    - Allowing employees to have flexible working hours if they experience nocturia that affects the quality and duration of their sleep

DRAFT

- Doing things another way such as allowing someone on Tolvaptan to have their desk nearer to the bathroom facilities instead of hot-desking

8.1.9 Drug holidays

- "Drug holidays" should be discussed with people with ADPKD when starting Tolvaptan as they can be useful on long journeys, holidays or when access to bathrooms may be limited.
- Frequent or prolonged "drug holidays" should be discouraged as it would mean the person with ADPKD would not be getting the full benefit of Tolvaptan
- Where possible appointments should be supported through drop-in or drive-through phlebotomy services and remote appointments in virtual or telephone clinics.

8.1.10 Patient information/Supporting letters

- Most kidney units will have a local patient information leaflet on Tolvaptan, for those that do not have one a sample leaflet has been included in this commentary, Appendix 6
- Patients benefit from having letters from their medical team explaining the reasons for the adjustments required when taking Tolvaptan
- This is often more useful if signed by the most senior doctor possible
- Two letters have been included in Appendix 7 with the second including a reference to the Equality Act in 2010

8.2 OTHER RESOURCES FOR PATIENTS

- **PKD Charity » Treatment options patient information summary**
- **PKD Charity » Learn more about Tolvaptan with Dr Grahame Wood (August 2020)**
- **PKD Charity » Tolvaptan Q&A Live with Professor Danny Gale (July 2022)**
- **PKD Charity » Tolvaptan the experience so far with Dr Matt Gittus and Sarah Kebbell (November 2022)**
- **UHL NHS Trust » Tolvaptan for PKD**
- **Kidney Care UK » Financial support**

DRAFT

Section 9: Additional recommendations

RECOMMENDATION

- Initial assessment and follow-up in a dedicated genetic/ADPKD/Tolvaptan clinic
- Multidisciplinary team input
- An established pathway for patients with ADPKD on Tolvaptan to interact with their kidney unit outside of clinic times
- A three-dimensional scan should be performed as part of the initial assessment of a person with ADPKD
- All people with ADPKD should be offered genomic testing where available and appropriate as this could inform patient eligibility for Tolvaptan
- We encourage the registration and monitoring of people with ADPKD through the UKKA RaDaR registry

In a 2018 survey on Tolvaptan prescribing practices in the UK, 93% (41 of 44 centres) of the kidney centres surveyed used Tolvaptan in the management of people with ADPKD. Tolvaptan was delivered by a mixture of multi-disciplinary teams, a single responsible clinician and multiple independent clinician models. Assessment methods for Tolvaptan eligibility in the responding kidney centres included eGFR slope (100%), mean US kidney length (82%), MRI TKV (53%) and genotype (24%). It is important to note that this survey did not include responses from all kidney units in the UK[34]. Furthermore, since this survey the landscape of ADPKD management has changed through the more widespread availability of genetic testing in the NHS.

In this section of the commentary, we describe what best practice in the provision of Tolvaptan to people with ADPKD could look like in the UK.

9.1 HEALTHCARE SETTING

As mentioned in the aforementioned survey, there exist a variety of models used in the delivery of Tolvaptan as part of ADPKD care[34]. We recommend that best practice is likely to involve an initial assessment and follow-up undertaken in a kidney unit at a secondary or tertiary centre. Ideally, this should be under the supervision of nephrologists with a special interest in ADPKD or genetic kidney diseases in general. We recommend that care, where possible, should be multi-disciplinary in nature.

9.2 IMAGING

The same survey demonstrated that not all kidney units had access to MRI assessment[34]. We recommend that where possible, an initial three-dimensional MRI or CT scan should be

performed as part of the initial assessment of a person with ADPKD in order to have a reliable baseline radiological evaluation of the kidneys and to obtain a total kidney volume (TKV). Considering the small changes in kidney volume between follow-up appointments, volumetric evaluation should not be performed more frequently than every 12 months unless clinically indicated.

9.3 GENOMIC TESTING

In the aforementioned survey, it was indicated that a limited number of kidney units had access to genomic testing[34]. However, this is likely to have changed given the widespread availability of genomic testing now. All people with ADPKD should be offered genomic testing where appropriate. Genomic testing has the potential for an earlier diagnosis to inform lifestyle changes, initiation of Tolvaptan, family planning and living donation information. However, there are potential important legal, insurance and psychosocial issues that can arise from disease diagnosis that should be discussed with people suspected of having ADPKD and those close to them[13].

9.4 THE NATIONAL REGISTRY OF RARE KIDNEY DISEASES (RADAR)

The National Registry of Rare Kidney Diseases (RaDaR) was developed to collate information from people with certain rare kidney diseases. There are potential benefits for the individual with ADPKD as well as the ADPKD community as a whole for patients to be registered with RaDaR. These include access to relevant information, the potential to contribute to new knowledge, become involved in research studies and attending information events. We recommend that interested people with ADPKD should be directed to the RaDaR website.

- **UKKA » RaDaR Registry**

DRAFT

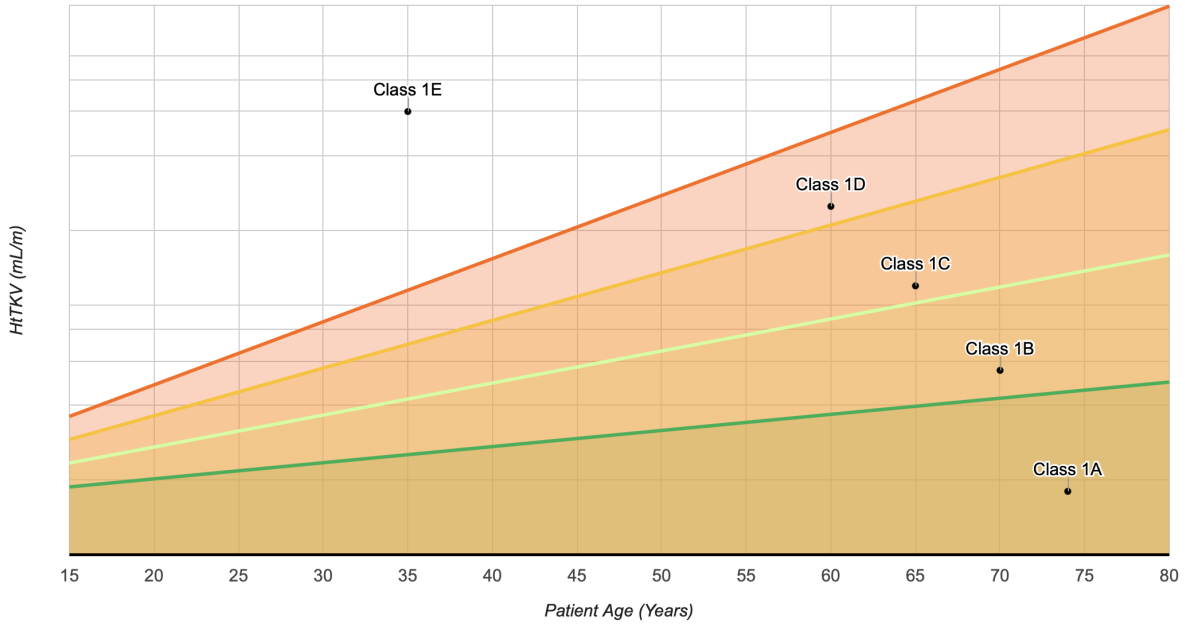
Appendices

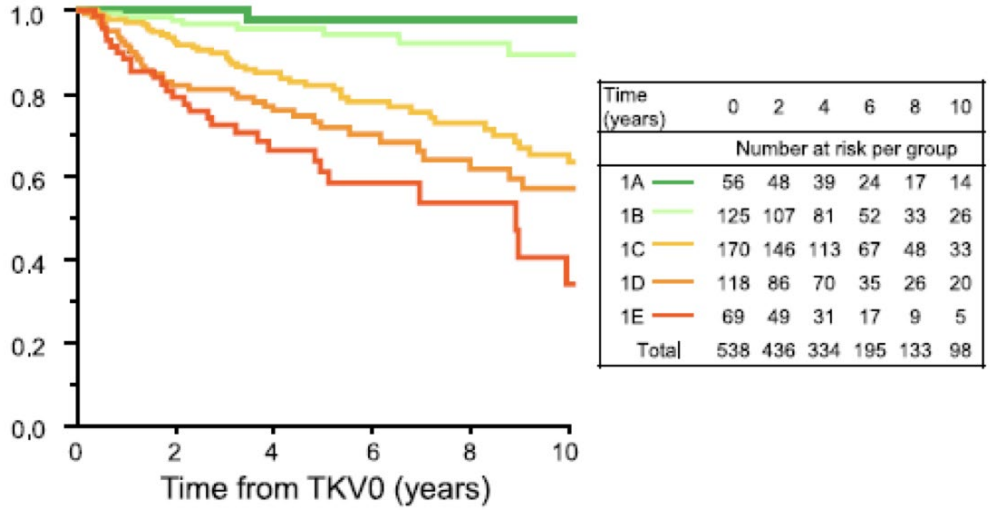
Appendix 1: Unified criteria for ultrasonographic diagnosis of ADPKD[1]

These diagnostic criteria are only valid in patients with positive family history and are specific to ultrasound imaging only.

Age (years)	Imaging criteria	PPV	Sensitivity
15-29	≥3 cysts (total)	100%	81.7%
30-39	≥3 cysts (total)	100%	95.5%
40-59	≥2 cysts (each kidney)	100%	90%
>60	≥4 cysts (each kidney)	100%	100%

Appendix 2: Mayo Imaging Classification of risk of disease progression[25]





Imaging classification of patients with typical (Class 1) ADPKD based on height-adjusted TKV measured on MRI. The Kaplan-Meier survival plot of renal survival at follow-up following the MRI measurement of TKV in the Mayo patients shows the increased risk of ESKD in patients with Class 1C-E. Please note the arbitrary nature of the linear divisions in this classification scheme (lower panel).

Appendix 3: PROPKD score[38]

Variable	Points
Sex	
Female	0
Male	1
Hypertension <35 years	
No	0
Yes	2
First urological event <35 years*	
No	0
Yes	2
Variant type	
PKD2	0
PKD1 non-truncating	2
PKD1 truncating	4

* A urological event is defined by frank haematuria, cyst infection or flank pain related to cysts

Score 0-3 = LOW RISK

- 70.6 years median age for ESKD onset
- Eliminates evolution to ESKD before the age of 60 (negative predictive value of 81.4%)

Score 4-6 = INTERMEDIATE RISK

- 56.9 years median age for ESKD onset

Score 7-9 = HIGH RISK

- 49 years median age for ESKD onset
- Risk of rapid progression and 92% chance of reaching kidney failure before the age of 60

DRAFT

Appendix 4: Tolvaptan prescribing checklist for treatment initiation[39]

JINARC® ▼ (tolvaptan) prescribing checklist for treatment initiation

Patient name		Patient hospital number	

JINARC (tolvaptan) is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease. The following checklists are provided as items that can help you before you initiate patients on JINARC (Section A) and to assist you with assessing patients for ongoing treatment with JINARC (Section B). It may be useful to use these checklists in patient records or notes to assist in the documentation of prescribing decisions. For full information on JINARC please consult the Summary of Product Characteristics. If you require further information on JINARC please contact Otsuka UK Medical Information via medinfo@otsuka.co.uk or call **0808 168 6726**.

Section A: Checklist for patient assessment prior to initiation of JINARC treatment

CONTRAINDICATIONS – if any of the following apply to the patient then they should **not** be treated with JINARC	Yes	No
Elevated liver enzymes as follows: • ALT or AST >8 x upper limit of normal (ULN) • ALT or AST >5 x ULN for more than 2 weeks • ALT or AST >3 x ULN and BT >2 x ULN or international normalized ratio (INR) >1.5 and/or signs or symptoms of liver injury (fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice)		
Hypersensitivity to the active substance or any of its excipients (e.g. lactose or galactose intolerance)		
Volume depletion		
Hypernatraemia		
Inability to perceive or respond to thirst		
Pregnancy or breastfeeding		
PRECAUTIONARY CONDITIONS – if any of the following apply to the patient, JINARC may be prescribed with caution along with appropriate monitoring	Yes	No
Raised liver enzymes, AST and/or ALT stabilised at no greater than 3 x ULN **In case of abnormal baseline levels below the limits for permanent discontinuation, treatment can only be initiated if the potential benefits of treatment outweigh the potential risks, and liver function testing must continue at increased time frequency. The advice of a hepatologist is recommended.**		
Severe hepatic impairment (Child-Pugh class C)		
Cirrhosis (if benefits outweigh the risks)		
Limited access to water		
Dehydration		
Partial obstruction of urinary outflow (e.g. prostatic hypertrophy)		
Fluid and electrolyte imbalance		
Serum sodium abnormalities		
Anaphylaxis		
Lactose and galactose intolerance		
Diabetes mellitus		
Elevated uric acid concentration		
Use of medicines likely to interact with JINARC such as CYP3A inhibitors (e.g. ketoconazole), CYP3A inducers (e.g. rifampicin), CYP3A substrates (warfarin/amiodarone), digoxin, drugs increasing serum sodium concentration and vasopressin analogues. JINARC is to be administered in daily doses of 15 mg or 30 mg in patients taking drugs that are moderate or strong CYP3A inhibitors, as concomitant use of these drugs increases JINARC exposure.		

PRESCRIBING DECISION (initiation)

I intend to initiate treatment with JINARC at the following dose (enter dosing):

Clinician name		Date	

If you have decided to prescribe JINARC the patient should be informed of the following points:
• There is a need for monthly blood tests for liver function during the first 18 months of therapy
• The patient needs to be vigilant for signs and symptoms of hepatic injury
• The patient needs to drink adequate fluids ahead of thirst and to drink 1-2 glasses of fluid before bedtime
• If the patient is a female of childbearing potential, she will need to use adequate contraception and to report pregnancy if it occurs
• You will provide them with a patient/carer education brochure and patient alert card

JINARC® ▼ (tolvaptan) prescribing checklist for patient monitoring

Patient name		Patient hospital number	

Section B: Checklist for patient assessment for ongoing eligibility for JINARC treatment
It is suggested that the following checklist is completed monthly for JINARC patients who are being treated for ADPKD for the first 18 months, and then every 3 months thereafter.

All adverse events should be reported to the MHRA and Otsuka UK as described in the box below.

HEPATIC INJURY	Yes	No
Is the patient showing any signs or symptoms of liver injury? (fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) **If the answer is Yes, treatment with JINARC should be interrupted, the cause investigated and the occurrence reported using the reporting mechanism below**		

Liver function test results	Recommended action
ALT or AST abnormal	**Interrupt JINARC treatment and investigate the cause of the raised liver enzyme(s) including repeat tests as soon as possible (ideally within 48–72 hours). Report decision to Otsuka UK using the reporting mechanism below. Continue monitoring.**
Liver function results stabilise If ALT and AST levels remain below 3 x ULN	**Restart JINARC treatment at same or lower dose with frequent monitoring and report decision to Otsuka UK using the reporting mechanism below.**
ALT or AST >8 x ULN	**Permanently discontinue and report decision to Otsuka UK using the reporting mechanism below.**
ALT or AST >5 x ULN for more than 2 weeks	
ALT or AST >3 x ULN and (BT >2 x ULN or International Normalized Ratio (INR) >1.5)	

PRESCRIBING DECISION (ongoing treatment) Titrate dose upward, if tolerated, with at least weekly intervals between up-titrations.	Tick box
Based on tolerability and other tests performed on this patient (select one option below)	
• **I intend to continue JINARC at the following dose (enter dosing)**	
• **I have decided to interrupt treatment with JINARC**	
• **I have decided to permanently discontinue treatment with JINARC**	

Clinician name		Date	

Appendix 5: Drug interactions[43]

At the time of publication of the commentary, the following medications are listed on the BNF as interacting with Tolvaptan.

Medication	Interaction	Severity
Aceclofenac	Risk of hyperkalaemia	
Aliskiren	Risk of hyperkalaemia	
Amiloride	Risk of hyperkalaemia	
Apalutamide	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Severe
Aprepitant	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Atazanavir	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Azilsartan	Risk of hyperkalaemia	
Bemiparin	Risk of hyperkalaemia	
Berotralstat	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Candesartan	Risk of hyperkalaemia	
Captopril	Risk of hyperkalaemia	
Carbamazepine	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Severe
Celecoxib	Risk of hyperkalaemia	
Cenobamate	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Moderate
Ciclosporin	Risk of hyperkalaemia	
Ciprofloxacin	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Clarithyromycin	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Cobicstat	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Crizotinib	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Darbepoetin alfa	Risk of hyperkalaemia	
Darunavir	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Dexketoprofen	Risk of hyperkalaemia	
Diclofenac	Risk of hyperkalaemia	

Digoxin	Tolvaptan increases exposure to drug	Mild
Diltiazem	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Dronedarone	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Drospirenone	Risk of hyperkalaemia	
Enalapril	Risk of hyperkalaemia	
Enoxaparin	Risk of hyperkalaemia	
Enzalutamide	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Severe
Eplerenone	Risk of hyperkalaemia	
Epoetin alfa	Risk of hyperkalaemia	
Epoetin beta	Risk of hyperkalaemia	
Epoetin zeta	Risk of hyperkalaemia	
Eprosartan	Risk of hyperkalaemia	
Erythromycin	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Etodolac	Risk of hyperkalaemia	
Etoricoxib	Risk of hyperkalaemia	
Finerenone	Risk of hyperkalaemia	
Fluconazole	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Flurbiprofen	Risk of hyperkalaemia	
Fosamprenavir	Increase exposure to Tolvaptan	Severe
Fosphenytoin	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Severe
Grapefruit/Pomelo/Seville Oranges	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Heparin	Risk of hyperkalaemia	
Ibuprofen	Risk of hyperkalaemia	
Idelalisib	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Imatinib	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Imidrapril	Risk of hyperkalaemia	
Indomethacin	Risk of hyperkalaemia	
Irbesartan	Risk of hyperkalaemia	
Isavuconazole	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate

Itraconazole	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Ketoconazole	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Ketoprofen	Risk of hyperkalaemia	
Ketorolac	Risk of hyperkalaemia	
Letermovir	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Lisinopril	Risk of hyperkalaemia	
Lomitapide	Tolvaptan increases exposure to drug	
Lopinavir	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Losartan	Risk of hyperkalaemia	
Mefenamic acid	Risk of hyperkalaemia	
Meloxicam	Risk of hyperkalaemia	
Mitotane	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Severe
Nabumetone	Risk of hyperkalaemia	
Naproxen	Risk of hyperkalaemia	
Netupitant	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Nilotinib	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Olmesartan	Risk of hyperkalaemia	
Parecoxib	Risk of hyperkalaemia	
Perindopril	Risk of hyperkalaemia	
Phenazone	Risk of hyperkalaemia	
Phenobarbital	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Severe
Phenytoin	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Severe
Piroxicam	Risk of hyperkalaemia	
Posaconazole	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Potassium aminobenzoate	Risk of hyperkalaemia	
Potassium canrenoate	Risk of hyperkalaemia	
Potassium chloride	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Severe
Primidone	Risk of hyperkalaemia	
Quinapril	Risk of hyperkalaemia	
Ramipril	Risk of hyperkalaemia	

Rifampicin	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Severe
Ritonavir	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Selpercatinib	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Spironolactone	Risk of hyperkalaemia	
St John's wort	Decrease exposure to Tolvaptan (CYP3A4 inducer)	Moderate
Sulindac	Risk of hyperkalaemia	
Tacrolimus	Risk of hyperkalaemia	
Telmisartan	Risk of hyperkalaemia	
Tenoxicam	Risk of hyperkalaemia	
Tiaprofenaic acid	Risk of hyperkalaemia	
Tinzaparin	Risk of hyperkalaemia	
Tolfenamic acid	Risk of hyperkalaemia	
Trandolapril	Risk of hyperkalaemia	
Triamterene	Risk of hyperkalaemia	
Trimethoprim	Risk of hyperkalaemia	
Valsartan	Risk of hyperkalaemia	
Verapamil	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate
Voclosporin	Risk of hyperkalaemia	
Voriconazole	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Severe
Voxelotor	Increase exposure to Tolvaptan (CYP3A4 inhibitor)	Moderate

Appendix 6: Example patient information letter

Getting the most from Tolvaptan

Information for patients, relatives and carers

Introduction

This leaflet has been designed to give you information about Tolvaptan and answers some of the questions that you or those who care for you may have about these medicines. It is not meant to replace the discussion between you and your medical team but aims to help you understand more about what is discussed. If you have any questions about the information below, please contact the person who provided you with this leaflet.

What is Tolvaptan and what are the benefits of taking it?

Tolvaptan is a medicine used to treat autosomal dominant polycystic kidney disease (ADPKD). ADPKD cannot be cured but it is possible to slow the onset of kidney failure and through medication.

Tolvaptan blocks the effects of the hormone vasopressin. When thirsty, the brain uses vasopressin to tell the kidneys to hold on to water. Unfortunately, vasopressin also tells the cysts to grow. Hence Tolvaptan tells the kidneys to slow the growth of cysts but also to release water increasing urination.

Tolvaptan has also been shown to reduce kidney pain.

How to take Tolvaptan

Tolvaptan comes as a tablet and is taken twice a day in two different doses. Swallow the tablets without chewing, with a glass of water. The higher dose is taken in the morning when you wake up. The lower dose is taken eight hours later with or without food. You will start on a low overall dose which will be increased usually on a monthly basis.

How long does Tolvaptan take to work?

You will notice the effects of taking Tolvaptan immediately. This includes an increased thirst and urine production. The effects on cyst growth and kidney failure are much slower occurring with long-term treatment (over years).

It is important to understand that Tolvaptan does not stop the progression of your ADPKD. You may still develop cysts and eventually develop kidney failure. However, the aim of treatment with Tolvaptan is to slow the speed at which this happens. Studies have shown that for each four years of taking Tolvaptan, dialysis can be delayed by one year.

Are there any side effects?

More common:

- Passing urine more frequently
- Passing more urine volume
- Passing urine in the night
- Increased thirst
- Dehydration presenting as dizziness and light-headedness

Less common:

- Liver damage - skin and eyes that appear yellow (jaundice), loss of appetite, tiredness, itching, nausea and pain under your ribs on the right side
- Gout

DRAFT

How can I manage the side effects?

1) Drink plenty

- Always carry a bottle of water with you
- Drink plenty throughout the day
- Drink before going to bed and whenever you wake up during the night

2) Cut down on salt

- Avoid adding extra salt at the table and in cooking
- Use salt-free seasonings (excluding NoSalt and other salt alternatives as they contain potassium instead which can be an issue for people with kidney disease)
- Chose fresh food over heavily processed foods
- Aim for no more than 140mg of sodium per portion or no more than 600mg of sodium per meal
- Limit restaurant meals or takeaways to special treats

3) Eat moderate amounts of protein

- Choose meat substitutes with less protein (including lentils, nuts, tofu, edamame, eggs and cheese)
- Some people taking Tolvaptan try to avoid eating lots of protein in the evening especially red meat or eat earlier in the day to avoid passing lots of urine over night
- Remember that protein is important for your body so don't eat too little

Hand location	Approximately equals	Types of food
Your fist	1 cup	Cooked pasta, cooked rice, fruit and vegetables
Your palm	85 grams	Meat, fish and poultry
A handful (small of your hand)	28 grams	Nuts and raisins
2 handfuls (small of your hand)	28 grams	Popcorn and potato crisps
Your thumb	28 grams	Hard cheese
Your tip of your thumb	5 grams	Butter, cooking oil and mayonnaise

Does Tolvaptan interact with any foods or medications?

Before you start Tolvaptan, your doctor or pharmacist will check what other medications you are taking to make sure they are safe with Tolvaptan. Not all doctors, nurses or pharmacists will be familiar with Tolvaptan so it is important that you remind them that you are taking Tolvaptan. If you are worried that there might be an interaction the safest option

DRAFT

would be to delay taking the new medication or temporarily stop taking Tolvaptan then contact your doctor, nurse or pharmacist at your kidney unit. A list of the things that might interact with Tolvaptan is included at the end of this document.

Should I stop taking these tablets if I become unwell?

If you have more than two episodes of vomiting or diarrhoea, we would recommend that you stop taking your Tolvaptan tablets. You can restart Tolvaptan once you have had no more vomiting or diarrhoea for 24 hours.

What should I do if I forget to take Tolvaptan?

Take the next dose as normal. You should not take a double dose to make up for forgetting. Occasionally, you may need to take a drug "holiday" or "break" from Tolvaptan. For example, if you are going on a long car journey or access to toilet facilities may be limited you may not want to take your Tolvaptan that day.

If you find you are taking frequent drug "holidays" or missing doses each week, Tolvaptan might not be right for you are you won't be getting the full benefit from taking it. In this case, you should think about whether you want to continue taking Tolvaptan and discuss this with your doctor, nurse or pharmacist at the kidney unit.

Pregnancy and breastfeeding

You should not take Tolvaptan if you are trying to become pregnant or during pregnancy as it may damage your unborn baby. Tolvaptan should also not be used while breastfeeding.

If you are a woman who is able to become pregnant, we would encourage you to start using contraception for at least four weeks before starting treatment with Tolvaptan, during treatment with Tolvaptan and for at least a further four weeks after stopping Tolvaptan.

If you are or thin you may be pregnant while taking Tolvaptan you should stop taking it immediately and tell your doctor, nurse or pharmacist.

How often do I need to see my medical team about Tolvaptan?

At the start of treatment, appointments will be monthly for the first 18 months. Please speak to your medical team at the kidney unit about ways that the high frequency of appointments can be made easier.

DRAFT

Drugs interacting with tolvaptan*:

- A
  - Aceclofenac
  - Aliskiren
  - Amiloride
  - Apalutamide
  - Aprepitant
  - Atazanavir
  - Azilsartan
- B
  - Bemiparin
  - Berotralstat
- C
  - Candesartan
  - Captopril
  - Carbamazepine
  - Celecoxib
  - Cenobamate
  - Ciclosporin
  - Ciprofloxacin
  - Clarithromycin
  - Cobicstat
  - Crizotinib
- D
  - Darbepoietin alfa
  - Darunavir
  - Dexketoprofen
  - Diclofenac
  - Digoxin
  - Diltiazem
  - Dronedarone
  - Drospirenone
- E
  - Enalapril
  - Enoxaparin
  - Enzalutamide
  - Eplerenone
  - Epoetin alfa
  - Epoetin beta
  - Epoetin zeta
  - Eprosartan
  - Erythrymycin
  - Etodolac
  - Etoricoxib
- F
  - Finerenone
  - Fluconazole
  - Flurbiprofen
  - Fosamprenavir
  - Fosphenytoin
- G
  - Grapefruit
- H
  - Heparin
- I
  - Ibuprofen
  - Idelaslisib
  - Imatinib
  - Imidrapril
  - Indomethacin
  - Irbesartan
  - Isavuconazole
  - Itraconazole
- K
  - Ketoconazole
  - Ketoprofen
  - Ketorolac
- L
  - Letermovir
  - Lisinopril
  - Lomitapide
  - Lopinavir
  - Losartan
- M
  - Mefenamic acid
  - Meloxicam
  - Mitotane
- N
  - Nabumetone
  - Naproxen
  - Netupitant
  - Nilotinib
- O
  - Olmesartan
- P
  - Parecoxib
  - Perindopril
  - Phenazone
  - Phenobarbital
  - Phenytoin
  - Piroxicam
  - Pomelo
  - Posaconazole
  - Potassium aminobenzoate
  - Potassium canrenoate
  - Potassium chloride
  - Primidone
- Q
  - Quinapril
- R
  - Ramipril
  - Rifampicin
  - Ritonavir
- S
  - Selpercatinib
  - Sevile Oranges
  - Spironolactone
  - St John's wort
  - Sulindac
- T
  - Tacrolimus
  - Telmisartan
  - Tenoxicam
  - Tiaprofenaic acid
  - Tinzaparin
  - Tolfenamic acid
  - Trandolapril
  - Triamterene
  - Trimethoprim
- V
  - Valsartan
  - Verapamil
  - Voclosporin
  - Voriconazole
  - Voxeloto

**Correct at time of writing 13th September 2023*

DRAFT

Appendix 7: Example supporting letters for patient use

To be printed on hospital headed paper

To whom it may concern,

Re: [Patient name] [DOB]

This patient is currently taking the drug **TOLVAPTAN** to treat Autosomal Dominant Polycystic Kidney Disease. A major side effect of this medication is significantly increased urination. Therefore this patient needs **UNRESTRICTED ACCESS TO WATER AND TOILET FACILITIES** at all times. This includes but is not limited to the workplace, air travel and entertainment or social venues. Water restriction in patients on Tolvaptan is dangerous and must be avoided at all costs. I would recommend that they be allowed to carry at least 2 litres of water at all times.

Yours faithfully

[Your name]
[Your title]
[Qualifications]
[Kidney unit]

DRAFT

To whom it may concern,

Re: [Patient name] [DOB]

This patient is currently taking the drug **TOLVAPTAN** to treat Autosomal Dominant Polycystic Kidney Disease. A major side effect of this medication is significantly increased urination. Therefore this patient needs **UNRESTRICTED ACCESS TO WATER AND TOILET FACILITIES** at all times. This includes but is not limited to the workplace, air travel and entertainment or social venues. Water restriction in patients on Tolvaptan is dangerous and must be avoided at all costs. I would recommend that they be allowed to carry at least 2 litres of water at all times.

The **EQUALITY ACT 2010** legally protects people from discrimination in the workplace and in wider society. This includes people with ADPKD who are taking Tolvaptan as they fulfil the criteria for having a disability which is a protected characteristic so reasonable adjustments should be made legally. This protection includes at work, in education, as a consumer, when using public services, when buying or renting property and as a member or guest of a private club or association.

> *"You're disabled under the Equality Act 2010 if you have a physical or mental impairment that has a substantial and long-term negative effect on your ability to do normal daily activities".*
>
> *"Employers must make reasonable adjustments to make sure workers with disabilities, or physical or mental health conditions, are not substantially disadvantaged when doing their jobs".*

Yours faithfully

[Your name]
[Your title]
[Qualifications]
[Kidney unit]

DRAFT

Appendix 8: Working group membership affiliations

Name	Role and affiliations
Albert Ong	Nephrologist, Sheffield Teaching Hospitals NHS Trust (chair)
Matt Gittus	Nephrology trainee, Sheffield Teaching Hospitals NHS Trust

Helen Haley	Advanced specialist pharmacist, University Hospitals of North Midlands
Tess Harris	Patient representative
Sarah Burrows	Nephrology specialist nurse, Queen Elizabeth Hospital Birmingham
Neal Padmanabhan	Nephrologist, NHS Greater Glasgow and Clyde
Danny Gale	Nephrologist, Royal Free London NHS Foundation Trust
Roslyn Simms	Nephrologist, Sheffield Teaching Hospitals NHS Trust
Terri Williams	Patient representative
Aaron Acquaye	Renal pharmacist, Hull and East Yorkshire Hospitals NHS Trust
Alisa Wong	Nephrology specialist nurse, Royal Free London NHS Foundation Trust
Melanie Chan	Nephrologist, Imperial College Healthcare NHS Trust
Eduardo Lee	Nephrology specialist nurse, Guy's and St Thomas' NHS Foundation Trust

DRAFT

References

1. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *New England Journal of Medicine* 2012; 367: 2407-2418.
2. Torres VE, Chapman AB, Devuyst O, et al. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with Tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4: 4 Trial. *Nephrology dialysis transplantation* 2018; 33: 477-489.
3. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *New England Journal of Medicine* 2017; 377: 1930-1942.
4. Müller R-U, Messchendorp AL, Birn H, et al. An update on the use of Tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. *Nephrology Dialysis Transplantation* 2022; 37: 825-839.
5. National Institute for Health and Care Excellence. Tolvaptan for treating autosomal dominant polycystic kidney disease (TA358). 2015.
6. Scottish Medicines Consortium. Tolvaptan (SMC No. 1114/1115). 2016.
7. Ong AC. Tolvaptan slows disease progression in late-stage ADPKD. *Nature Reviews Nephrology* 2018; 14: 146-148.
8. Edwards ME, Chebib FT, Irazabal MV, et al. Long-term administration of Tolvaptan in autosomal dominant polycystic kidney disease. *Clinical journal of the American Society of Nephrology: CJASN* 2018; 13: 1153.
9. Chebib FT, Perrone RD, Chapman AB, et al. A practical guide for treatment of rapidly progressive ADPKD with Tolvaptan. *Journal of the American Society of Nephrology: JASN* 2018; 29: 2458.
10. Pei Y and Watnick T. Diagnosis and screening of autosomal dominant polycystic kidney disease. *Advances in chronic kidney disease* 2010; 17: 140-152.
11. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *Journal of the American Society of Nephrology: JASN* 2009; 20: 205.
12. Pei Y, Hwang Y-H, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *Journal of the American Society of Nephrology: JASN* 2015; 26: 746.
13. Gittus M, Harris T and Ong AC. Patient Perspectives on ADPKD. *Advances in Kidney Disease and Health* 2023; 30: 294-302.
14. NHS England. The structure of the NHS Genomic Medicine Service, https://www.england.nhs.uk/genomics/the-structure-of-the-nhs-genomic-medicine-service/ (2023, accessed 16/14/2023).
15. NHS National Services Scotland. SSNGM Rare and Inherited Disease Test Directory, https://www.nss.nhs.scot/publications/ssngm-rare-and-inherited-disease-test-directory/ (2023, accessed 16/11/2023).

DRAFT

16. All Wales Medical Genomics Service. All Wales Medical Genomic Service, https://medicalgenomicswales.co.uk/index.php/download-services (2023, accessed 16/11/2023).
17. Belfast Health and Social Care Trust. Clinical Genetics Service, https://belfasttrust.hscni.net/service/laboratory-services/clinical-genetics/ (2023, accessed 16/11/2023).
18. Genomics England. National Genomic Test Directory, https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-inherited-disease-eligibility-criteria-version-5.2.pdf (2023, accessed 16/11/2023).
19. National Kidney Foundation. Diagnostic tests & procedures - Estimated glomerular filtration rate, https://www.kidney.org/sites/default/files/01-10-8374_2212_patflyer_egfr.pdf. (2022, accessed 16/11/2023).
20. Mekahli D, Guay-Woodford LM, Cadnapaphornchai MA, et al. Tolvaptan for Children and Adolescents with Autosomal Dominant Polycystic Kidney Disease.
21. Ong AC, Devuyst O, Knebelmann B, et al. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *The Lancet* 2015; 385: 1993-2002.
22. Spithoven EM, Kramer A, Meijer E, et al. Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival—an analysis of data from the ERA-EDTA Registry. *Nephrology Dialysis Transplantation* 2014; 29: iv15-iv25.
23. Messchendorp AL, van Londen M, Taylor JM, et al. Kidney function reserve capacity in early and later stage autosomal dominant polycystic kidney disease. *Clinical Journal of the American Society of Nephrology: CJASN* 2018; 13: 1680.
24. Harris PC and Torres VE. Polycystic kidney disease, autosomal dominant. 2018.
25. Irazabal MV, Rangel LJ, Bergstralh EJ, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *Journal of the American Society of Nephrology: JASN* 2015; 26: 160.
26. Thöni S, Keller F, Denicolò S, et al. Biological variation and reference change value of the estimated glomerular filtration rate in humans: A systematic review and meta-analysis. *Frontiers in Medicine* 2022; 9: 1009358.
27. Alan S, Shen C, Landsittel DP, et al. Long-term trajectory of kidney function in autosomal-dominant polycystic kidney disease. *Kidney international* 2019; 95: 1253-1261.
28. Cheung KL and Lafayette RA. Renal physiology of pregnancy. *Advances in chronic kidney disease* 2013; 20: 209-214.
29. Chapman AB, Devuyst O, Eckardt K-U, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney international* 2015; 88: 17-27.
30. Müller RU, Haas CS and Sayer JA. Practical approaches to the management of autosomal dominant polycystic kidney disease patients in the era of Tolvaptan. *Clin Kidney J* 2018; 11: 62-69. 20170727. DOI: 10.1093/ckj/sfx071.

DRAFT

31. Schrier RW, Brosnahan G, Cadnapaphornchai MA, et al. Predictors of autosomal dominant polycystic kidney disease progression. *J Am Soc Nephrol* 2014; 25: 2399-2418. 20140612. DOI: 10.1681/asn.2013111184.
32. Bhutani H, Smith V, Rahbari-Oskoui F, et al. A comparison of ultrasound and magnetic resonance imaging shows that kidney length predicts chronic kidney disease in autosomal dominant polycystic kidney disease. *Kidney international* 2015; 88: 146-151.
33. Chebib FT and Torres VE. Assessing risk of rapid progression in autosomal dominant polycystic kidney disease and special considerations for disease-modifying therapy. *American Journal of Kidney Diseases* 2021; 78: 282-292.
34. Chong J, Harris T and Ong AC. Regional variation in Tolvaptan prescribing across England: national data and retrospective evaluation from an expert centre. *Clinical Kidney Journal* 2023; 16: 61-68.
35. Chapman AB, Bost JE, Torres VE, et al. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. *Clinical journal of the American Society of Nephrology: CJASN* 2012; 7: 479.
36. Ministry of Health WaLoJ-PRD. Polycystic kidney disease clinical guideline. 2010.
37. Lavu S, Vaughan LE, Senum SR, et al. The value of genotypic and imaging information to predict functional and structural outcomes in ADPKD. *JCI insight* 2020; 5.
38. Cornec-Le Gall E, Audrézet M-P, Rousseau A, et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *Journal of the American Society of Nephrology: JASN* 2016; 27: 942.
39. Otsuka. Full Prescribing Information JYNARQUE, https://www.otsuka-us.com/sites/g/files/qhldwo7076/files/media/static/JYNARQUE-PI.pdf (2009, accessed 16/11/2023).
40. TEVA UK. Tolvaptan TEVA - patient/carer education brochure, https://www.medicines.org.uk/emc/rmm/2192/Document (2021, accessed 16/11/2023).
41. Devuyst O, Chapman AB, Shoaf SE, et al. Tolerability of aquaretic-related symptoms following Tolvaptan for autosomal dominant polycystic kidney disease: results from TEMPO 3: 4. *Kidney international reports* 2017; 2: 1132-1140.
42. Shoaf SE, Bricmont P and Mallikaarjun S. Effects of CYP3A4 inhibition and induction on the pharmacokinetics and pharmacodynamics of Tolvaptan, a non-peptide AVP antagonist in healthy subjects. *British journal of clinical pharmacology* 2012; 73: 579-587.
43. British National Formulary. Tolvaptan - Medicinal forms, https://bnf.nice.org.uk/drugs/Tolvaptan/medicinal-forms/ (2023, accessed 16/06/2023).
44. UpToDate. Cytochrome P450 3A (including 3A4) inhibitors and inducers, https://www.uptodate.com/contents/image?imageKey=CARD%2F76992 (2023, accessed 16/11/2023).
45. Devuyst O, Chapman AB, Gansevoort RT, et al. Urine osmolality, response to Tolvaptan, and outcome in autosomal dominant polycystic kidney disease: results from the TEMPO 3: 4 trial. *Journal of the American Society of Nephrology: JASN* 2017; 28: 1592.

DRAFT

46. Gansevoort RT, van Gastel MD, Chapman AB, et al. Plasma copeptin levels predict disease progression and Tolvaptan efficacy in autosomal dominant polycystic kidney disease. *Kidney international* 2019; 96: 159-169.
47. Raina R, Houry A, Rath P, et al. Clinical utility and tolerability of Tolvaptan in the treatment of autosomal dominant polycystic kidney disease (ADPKD). *Drug, Healthcare and Patient Safety* 2022: 147-159.
48. Higashihara E, Torres VE, Chapman AB, et al. Tolvaptan in autosomal dominant polycystic kidney disease: three years' experience. *Clinical journal of the American Society of Nephrology: CJASN* 2011; 6: 2499.
49. Capelli I, Iacovella F, Ghedini L, et al. A Case Report of Tolvaptan Therapy for ADPKD Patients With COVID-19. The Need for Appropriate Counselling for Temporary Drug Discontinuation. *in vivo* 2022; 36: 1994-1997.
50. Ali Y, Dohi K, Okamoto R, et al. Novel molecular mechanisms in the inhibition of adrenal aldosterone synthesis: Action of Tolvaptan via vasopressin V2 receptor-independent pathway. *British Journal of Pharmacology* 2019; 176: 1315-1327.
51. Blair HA. Tolvaptan: A Review in Autosomal Dominant Polycystic Kidney Disease. *Drugs* 2019; 79: 303-313. DOI: 10.1007/s40265-019-1056-1.
52. Kramers BJ, van Gastel MD, Boertien WE, et al. Determinants of urine volume in ADPKD patients using the vasopressin V2 receptor antagonist Tolvaptan. *American Journal of Kidney Diseases* 2019; 73: 354-362.
53. Amro OW, Paulus JK, Noubary F, et al. Low-osmolar diet and adjusted water intake for vasopressin reduction in autosomal dominant polycystic kidney disease: a pilot randomized controlled trial. *American Journal of Kidney Diseases* 2016; 68: 882-891.
54. Lambert K, Gardos R, Coolican H, et al. Diet and Polycystic Kidney Disease: Nutrients, Foods, Dietary Patterns, and Implications for Practice. *Semin Nephrol* 2023; 43: 151405. 20230804. DOI: 10.1016/j.semnephrol.2023.151405.
55. Tarabzuni O and TARABZUNI O. The Effect of Dietary Intervention on Autosomal-Dominant Polycystic Kidney Disease (ADPKD) Patients on Tolvaptan and Their Quality of Life. *Cureus* 2022; 14.
56. Kramers BJ, Koorevaar IW, Drenth JPH, et al. Salt, but not protein intake, is associated with accelerated disease progression in autosomal dominant polycystic kidney disease. *Kidney International* 2020; 98: 989-998. DOI: https://doi.org/10.1016/j.kint.2020.04.053.
57. Levin A and Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney International* 2014; 85: 49-61. DOI: 10.1038/ki.2013.444.
58. Obeid W, Hiremath S and Topf JM. Protein restriction for CKD: time to move on. *Kidney360* 2022; 3: 1611.
59. Rangan GK, Alexander SI, Campbell KL, et al. KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease. *Nephrology* 2016; 21: 705-716.

60. Kramers BJ, van Gastel MDA, Meijer E, et al. Case report: a thiazide diuretic to treat polyuria induced by Tolvaptan. *BMC Nephrology* 2018; 19: 157. DOI: 10.1186/s12882-018-0957-7.
61. Kramers BJ, Koorevaar IW, van Gastel MD, et al. Effects of hydrochlorothiazide and metformin on aquaresis and nephroprotection by a vasopressin V2 receptor antagonist in ADPKD: a randomized crossover trial. *Clinical Journal of the American Society of Nephrology* 2022; 17: 507-517.
62. Katarey D and Verma S. Drug-induced liver injury. *Clinical Medicine* 2016; 16: s104.
63. Attalah E. A, G.P. Drug-induced liver injury, https://www.bsg.org.uk/web-education-articles-list/drug-induced-liver-injury/ (2023, accessed 16/11/2023).
64. Watkins PB, Lewis JH, Kaplowitz N, et al. Clinical pattern of Tolvaptan-associated liver injury in subjects with autosomal dominant polycystic kidney disease: analysis of clinical trials database. *Drug safety* 2015; 38: 1103-1113.
65. Alpers DH, Lewis JH, Hunt CM, et al. Clinical pattern of Tolvaptan-associated liver injury in trial participants with autosomal dominant polycystic kidney disease (ADPKD): an analysis of pivotal clinical trials. *American Journal of Kidney Diseases* 2023; 81: 281-293. e281.
66. Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. *Gut* 2018; 67: 6-19.
67. Giannini EG, Testa R and Savarino V. Liver enzyme alteration: a guide for clinicians. *Cmaj* 2005; 172: 367-379.
68. European Medicines Agency. Assessment Report - Jinarc, https://www.ema.europa.eu/en/documents/assessment-report/jinarc-epar-public-assessment-report_en.pdf (2015, accessed 16/11/2023).
69. National Health Service. Visiting an opticians, https://www.nhs.uk/nhs-services/opticians/visiting-an-optician/#:~:text=The%20NHS%20recommends%20that%20you,test%20is%20considered%20clinically%20necessary (2023, accessed 16/11/2023).
70. Popovich I, Szecket N and Nahill A. Framing of clinical information affects physicians' diagnostic accuracy. *Emergency Medicine Journal* 2019; 36: 589-594. DOI: 10.1136/emermed-2019-208409.
71. Almashat S, Ayotte B, Edelstein B, et al. Framing effect debiasing in medical decision making. *Patient Educ Couns* 2008; 71: 102-107. 20071227. DOI: 10.1016/j.pec.2007.11.004.
72. Gong J, Zhang Y, Feng J, et al. Influence of framing on medical decision making. *Excli j* 2013; 12: 20-29. 20130118.
73. UK Government. Reasonable adjustments for workers with disabilities or health conditions, https://www.gov.uk/reasonable-adjustments-for-disabled-workers (2023, accessed 16/11/2023).

DRAFT