Polycystic Kidney Disease Charity

OFFICIAL RESPONSE TO NICE APPRAISAL CONSULTATION DOCUMENT

The Polycystic Kidney Disease (PKD) Charity is **deeply disappointed** that the National Institute for Health and Care Excellence (NICE) **has not recommended tolvaptan** within its European marketing authorisation for treating autosomal dominant polycystic kidney disease (ADPKD)[i].

Tolvaptan is acknowledged by NICE as an **'innovative treatment[ii]'** and the '**first shown to specifically impact on ADPKD progression[iii]**', targeting the disease and not just managing the symptoms and complications. The Committee further noted that the '**availability of Tolvaptan gives hope[iv]'** for people with ADPKD, their children and families.

The PKD Charity recognises that the Appraisal Consultation Document or ACD (issued May 2015) is not the final guidance on tolvaptan. We understand the challenges in modelling the economic cost-benefit associated with this long-term incurable disease.

We urge the Committee to re-consider their initial considerations and recommend tolvaptan to address the significant unmet need and continuing disease burden in the cohort of patients who would derive most value from this important new treatment.

Our argument for access

We do not feel that the NICE Committee has taken all relevant evidence into account, for example the direct healthcare costs of treating both kidney and liver cyst ruptures, surgical interventions on the kidneys and other organs, infections and pain throughout a patient's lifetime and especially in the years prior to kidney failure. In addition, we do not feel that the Committee has acknowledged the full impact of living with ADPKD – the psychosocial and emotional effects of a long-term inherited condition, and the indirect cost burden of lost employment, productivity and earnings on individuals and their families.

The current situation for someone with ADPKD

- ADPKD is uniquely different from other chronic kidney diseases. It is a complex, progressive, systemic condition affecting many parts of the body, and the **most commonly inherited kidney disease**. First reported in the 16th century, ADPKD is incurable, with those affected enduring a relentless progression towards end-stage renal disease (ESRD), accompanied by a plethora of renal and extra-renal complications.

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- Global prevalence rates range from 1 in 500 to 1 in 4000[v], with a large number of individuals being undiagnosed during life. ADPKD can, however, be diagnosed at any time, in adulthood or in children (sometimes in utero). Being dominantly inherited, the risk of passing on ADPKD to children is 1 in 2. Many patients with ADPKD will know similarly affected family members; many will have lost loved ones from ADPKD.
- ADPKD is characterised by the formation, growth and multiplication of fluid-filled cysts in the kidney and other organs. The bulging cysts **profoundly enlarge the kidneys** replacing healthy tissue. A normal kidney weighs approximately 150g; an ADPKD kidney can grow 80 to 120 times as big. In one extreme case, two ADPKD kidneys together weighed 22kg or approximately one fifth of the patient's body weight. Individual cysts themselves can expand to 9 or 10cm in length – which is the size of an average, normal human kidney. **The photo below shows the extent of abdominal distention caused by massive kidney growth – this man is 40 years old and has given permission for his photo to be shown**.

- Symptoms such as burst kidney and liver cysts, bleeding and infections are common. These recurring incidents cause both chronic and acute pain. In the PKD Charity's **survey of UK Patients' and Carers' Experiences of ADPKD**[vi], nearly half of all patients (250 individuals) - reported suffering acute severe pain at least once

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a month, 1 in 10 on a daily basis. Most said that pain interfered with normal daily life 'extremely'. Over 4 in 10 reported inadequate pain relief.

"I don't think my drugs deal adequately with the type of pain that I have… the pain that interferes with my sleep."

"Had to wait a long time to get treatment for pain. Ended up in casualty for pain relief."

- Kidney failure occurs in most ADPKD patients, on average before the age of 60 years[vii]. Not all patients will reach ESRD, but when that occurs, dialysis and/or transplantation are the only **life-saving treatments**.
- An epidemiological study of patients on the UK Renal Registry in England and Wales with ADPKD and ESRD was carried out for the period 1 January 2000 and 31 December 2011[viii]. A total of 52,608 individuals started renal replacement therapy (RRT) during the study period, of which 3,598 (6.8%) had ADPKD. **The median age of commencing RRT was 55 years in the ADPKD group** compared with 62 and 66 years in those with diabetes or other kidney disease. This young age of starting RRT had not changed within the ADPKD group over the 10-year period.
- It is common knowledge that treating chronic kidney disease patients consumes a substantial amount (nearly £1.5bn or 3%) of the NHS budget for a relatively small number of the overall population. Half of this sum is on RRT. ADPKD patients, though few in number, are therefore costly to treat. Moreover, many are living longer owing to lower cardiovascular risk through better blood pressure control[ix], which can mean they may need more than one transplant or several periods on dialysis.
- The NICE Committee does not seem to have taken account of other healthcare costs associated with treating ADPKD.
- Some patients may require removal of their native kidneys (by surgical nephrectomy), before and/or after RRT, to enable transplant to go ahead or deal with complications such as pain and infections from massive cystic kidneys. Some patients will need cyst aspiration or de-roofing. These nephrectomies and other interventions carry surgical risk and are costly procedures.

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- Nearly 8 out of 10 patients in the PKD Charity survey were taking a range of prescription medicines as a result of their ADPKD. As well as painkillers and antibiotics, drugs typical in managing CKD may be needed, eg allopurinol to prevent gout, statins, EPO, vitamin D and phosphate binders.
- Additional complications include: increased risk of brain aneurysms needing major brain surgery (such as coiling) and leading to strokes or death; increased frequency of kidney stones; and highly debilitating polycystic liver disease, which sometimes necessitates costly liver transplantation.
- In addition – also not considered by the NICE Committee – are the non-healthcare costs associated with long-term, debilitating conditions.
- Aside from the clinical manifestations, people with ADPKD are frequently **profoundly affected by the psychological, emotional and social side-effects** of this inherited, long-term condition. The PKD Charity survey found that over 9 in 10 people admitted to feelings of anxiety, sadness, guilt, loss of self-confidence and hopelessness. Over two-thirds reported impact on overall family life, nearly half reported impact on their sex life and 1 in 3 had made career sacrifices due to pain and general debility.

> *"Failure of marriage, lack of earning potential and constant guilt for being a burden when unwell and passing it to children."*

- Patients complain about being viewed as 'obese', having a 'beer belly' or looking perpetually 'pregnant' - resulting in body dysmorphia and sometimes desperate attempts to 'lose weight' with malnutrition consequences.
- The NICE Committee noted the absence of HRQoL assessment in the TEMPO 3:4 trial. However, there are no specific ADPKD patient-reported outcome measures which capture the impact of symptom. Studies employing widely-used measures such as SF-36 QoL have had mixed results; researchers consider them too generic and insensitive to measure the diversity and slowly progressive effects of ADPKD[x].
- In severe cases of ADPKD, people will experience kidney failure at the peak of their earning potential and in the prime of their personal and family lives – resulting in sometimes cataclysmic loss of jobs and future earnings/pensions/tax contributions.

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- In the PKD Charity survey, people reported loss of personal and family earnings of between £10,000 and £100,000. Costs fall on carers as well as patients: 1 in 5 carers in the PKD survey said they had left their employment to take care of affected family members (spouses and children). Most people diagnosed with ADPKD will also experience increased travel insurance premiums and the majority will be denied life and health insurance. Many will need welfare benefits.
- All this can have significant consequences on parenthood decisions. In the PKD Charity survey, some respondents said they had chosen not to have children.
- When many family members are affected or may have died prematurely - whether parents, siblings or children – "**ADPKD can feel like a death sentence"**.

"On the balance of probability you face death in your later 50s early 60s if there is no intervention. I fear for my future and the fact that I could die prematurely and as a single parent not be there for my children."

Hopes were raised by first-ever licensed therapy

- Until recently, there were no licensed therapies available to slow progression of ADPKD. The successful global clinical trial by Otsuka Pharmaceuticals (TEMPO 3:4[xi]) has resulted in the first-ever drug JINARC® to receive marketing authorisation in Europe on 28 May 2015.
- The active ingredient, tolvaptan, was shown to affect the rate of kidney cyst growth and modify the progression in trial participants. JINARC® has been licensed in the EU, Japan and Canada, and represents a significant step forward for thousands of people with ADPKD, their families and carers, and future generations.
- There was a hope among the many thousands of people with ADPKD that tolvaptan could give a "better quality of life". From the PKD Charity survey:

"I hope Tolvaptan to be successful so that my son will never reach end stage renal failure. I hope for him to live his life to the full without ADPKD impacting his life as much as it has mine and my sister."

- Whilst not all respondents in the PKD survey were certain about taking tolvaptan, all welcomed a drug that could potentially delay dialysis and transplantation.

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- Additional benefits, as seen in the trial, include fewer infections and less pain from slower cyst and kidney growth.

Are there other commissioning options?

- We recognise that tolvaptan is not suited to every ADPKD patient at CKD stages 1 to 3 (the indicated use). This is a very broad group but within this cohort are the faster progressing, typically younger patients, with young families, struggling to cope with their jobs and daily lives, who are living with the fear of early ESRD and premature death. Could NICE consider some form of restricted commissioning for such patients?
- Could 'Commissioning through Evaluation' for these fast-progressing patients be an option to enable new data to be collected within a formal evaluation programme?
- These fast-progressing patients, historically, were challenging to identify owing to genotype and phenotype variability but this will change with the availability of new academic-led models, eg from Irazabal et al[xii], which promise more accurate stratification of ADPKD patients by total kidney volume (TKV).
- With the support of the UK Renal Registry, an ADPKD Registry is feasible within 6 to 9 months. This will capture more data on ADPKD patients at earlier CKD stages, in particular biomarkers such as TKV, to aid patient identification.

The future without access to tolvaptan

- We asked patients how they rated current healthcare approaches and one in 2 described them as fair, poor or very poor in managing their ADPKD.
- Without a recommended therapy, 'standard care' based on symptom management until ESRD is the only option. There is therefore no motivation to change this unstructured approach to managing ADPKD patients.
- At present, standard care can vary considerably as there are no agreed best practice guidelines. There are no dedicated NHS specialised services (aside from standard CKD and RRT care). Very few hospitals have specialist clinics for ADPKD patients.
- Many patients still report that their doctors have little understanding of what it's like to live with ADPKD and have an attitude of 'sit back and wait for inevitable kidney failure'.

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- Regrettably, the NICE Committee commented that '**aggressive blood pressure management and increased fluid intake may have an impact on decline**[xiii]'. There is no evidence to support these comments. Whilst patients with other forms of chronic kidney disease (CKD) such as diabetes have benefited from approaches to slow the decline of kidney function, these have not worked in ADPKD[xiv].
- In conclusion, the PKD Charity reiterates its deep disappointment that people living with incurable, inherited, life-threatening and debilitating ADPKD are denied access to a licensed therapy which has the potential to improve the quality of their lives, and the lives of their family members and future generations.
- We ask NICE and the manufacturer to work together to develop an economic model that takes account of the latest clinical developments and is scientifically robust to identify the patients that will benefit most from this treatment.

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[i] NICE Appraisal Consultation Document or ACD (issued 5 June 2015) http://www.nice.org.uk/guidance/indevelopment/GID-TAG447/consultation
[ii] NICE Appraisal Consultation Document or ACD (issued 5 June 2015), item 4.17
[iii] NICE Appraisal Consultation Document or ACD (issued 5 June 2015), item 4.17
[iv] NICE Appraisal Consultation Document or ACD (issued 5 June 2015), item 4.3
[v] Ong et al. Lancet 2015; 385: 1993-2002
[vi] During November and December 2014, the PKD Charity ran a specially-designed survey amongst UK adults with ADPKD, plus their relatives and carers, on the impact of the condition on overall health, wellbeing and quality of life. A total of 651 individuals responded, of whom 513 were ADPKD patients, and 138 relatives/carers. Whilst recognising the limitation of patient-led research, we believe this survey highlighted and reinforced what we know from years of listening to patients and family experience stories.
[vii] Spithoven EM, 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. Nephrol Dial Transplant 2014;29 (Suppl 4):iv15-iv25
[viii] Shaw C, et al. Nephrol Dial Transplant 2014;29:1910–8
[ix] Patch C, et al. Use of antihypertensive medications and mortality of patients with autosomal dominant polycystic kidney disease: a population-based study. Am J Kidney Dis 2011;57:856–62
[x] Chapman AB, et al. Autosomal dominant polycystic kidney disease (ADPKD): Executive Summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference (with Online Appendix). Kidney Int Mar 18. doi: 10.1038/ki.2015.59
[xi] Torres VE, Harris PC et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. The New England Journal of Medicine. 2012;367 (25): 2407-2418
[xii] Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials. Irazabal et al. J Am Soc Nephrol. 2015 January; 26(1): 160–172. Published online 2014 June 5. doi: 10.1681/ASN.2013101138
[xiii] NICE Appraisal Consultation Document or ACD (issued 5 June 2015), item 3.20
[xiv] Spithoven EM, et al. Analysis of data from the ERA-EDTA Registry indicates that conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in autosomal dominant polycystic kidney disease. Kidney Int 2014; 86:1244–52

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