NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation statement (STA)

ID 652 – Tolvaptan for treating autosomal dominant polycystic kidney disease

Your name: [redacted]
Name of your organisation: PKD Charity
Your position in the organisation: [redacted]
Brief description of the organisation: The PKD Charity was established in December 2000 by patients, professionals and members of families affected by all forms of polycystic kidney disease (PKD). The charity provides information, advice and support for patients and their families, raises awareness and funds research into the causes, impact and management of the condition. Around 90% of our funding is from those affected by ADPKD, including donations from family fundraising and funerals. We are not a 'membership' organisation but estimate we reach over 4,000 affected people with our communications and support. We are therefore in a prime position to contribute to the current assessment of Tolvaptan in autosomal dominant polycystic kidney disease (ADPKD).

This submission: Our submission has been compiled on the basis of 14 years supporting ADPKD patients, their families and carers. Currently, seven (of 8) PKD Charity trustees have ADPKD (3 transplanted); the other trustee is affected by ARPKD, the recessive form of PKD. The chief executive also has ADPKD. Our charity experiences have been reinforced by the results of a specifically-designed survey conducted in November/ December 2014. This survey involved a questionnaire sent out to people on the PKD Charity's database, 2,000 by e-mail and 700 by mail; it was also promoted via various social networks. The questionnaire contained both structured multiple choice and free text questions, to allow respondents to describe their experiences and opinions verbatim. 635 individuals responded of whom 504 were ADPKD patients, including 18 who had taken Tolvaptan, and 131 relatives/carers. Of the patients, 65% of respondents were female and 35% male, with ages ranging from 20-24 years to 65 years or older.

Living with the condition

ADPKD is a dominantly inherited systemic condition, first clinically described in 1888, and incurable. In our survey, 73% of the responding patients reported that either their mother or father had been affected, whilst 51% had brothers or sisters affected and over 31% already knew they had children affected.

The survey probed a number of different symptoms and problems experienced by ADPKD patients and the impact that these had on their daily lives and that of their relatives and carers. Overall, 35% reported their general health as being 'poor' or 'fair' and reported suffering a wide range of ongoing symptoms. The following table lists the most common of the different disease effects, many corresponding with the published literature on symptom burden:

Symptom	% patients reporting
Hypertension	85
Tiredness	72
Fatigue	56
Acute pain	51
Leg cramps	48
Haematuria	47
Urinary tract infections	44
Polycystic liver	44
Enlarged abdomen/ fullness	42
Restless legs	40
Kidney cyst infections	39
Chronic pain	35

In terms of severity and impact:

- 47% reported suffering acute severe pain at least once a month, 11% on a daily basis
- 30% reported suffering 'extreme', 'severe 'or 'moderate' chronic pain, with an additional 18% reporting 'slight' such pain
- 41% said that pain interferes with their normal daily life 'extremely', 'a lot' or 'moderately', with an additional 28% reporting a slight influence
- 42% reported receiving inadequate pain relief
- 77% were taking prescription medicines as a result of their ADPKD (mostly for hypertension and pain relief)
- 66% reported that they were 'extremely', 'very much' or 'moderately' bothered by tiredness, with 62% reporting the same for fatigue
- 35% had experienced surgical interventions, the most common being kidney and liver cyst aspirations. 5% had had both kidneys removed.

Turning to lifestyle, work and family:

- 70% were ‘extremely’ or ‘moderately’ limited in their ability to do activities such as running sports and lifting, whilst 47% were similarly limited in climbing stairs
- 68% reported concern as to the impact on overall family life, with 54% reporting limitations on normal social activities with family, friends and neighbours
- 44% also reported an impact on their sex life
- Over 90% admitted to having feelings of anxiety, sadness, guilt, inability to make decisions, lack of concentration, loss of self-confidence and hopelessness
- 44% reported that ADPKD affected their ability to travel
- 25% were concerned about the impact on their career, with 35% saying they had already had to make career sacrifices
- When asked to estimate the financial impact of having ADPKD, the direct costs of hospital visits, prescription charges and loss of earnings of between £10,000 and £100,000 were frequently cited, not only for the person with ADPKD but also for the carer - 19% of responding carers had had to leave their employment and 21% had had to make career sacrifices
- 73% of patients were ‘extremely’,’ very much’ or ‘moderately’ bothered by the future of children who inherit ADPKD. Indeed, 35% of the carers responding reported having both a spouse/ partner *and* a child with ADPKD
- Over 60% reported difficulties getting life, mortgage protection and travel insurance

The impact on all aspects of life was vividly described by responding patients, as these few indicative examples demonstrate:

“I don't think my drugs deal adequately with the type of pain that I have, for example they don't work well in dealing with the chronic pain that interferes with my sleep”.

“I find that my renal consultant has a hard time understanding the chronic and acute pain I get due to ADPKD. It is often brushed aside”.

“Have to wait a long time to get treatment for pain. Ended up in casualty for pain relief”.

"I have noticed recently I get tired very easily and find it difficult to get up in the morning. When I am in a lot of pain I have to lie in bed and basically not move. Therefore I have to take time off work. I feel like I let my work colleagues down. I now know my limitations and it can be very frustrating. My daughter has PKD and I feel guilty about it".

"I had seizures due to peritonitis and stress, then a brain haemorrhage. Haemodialysis does not agree with me".

"Been in hospital 4 times in the last 28 months".
"I worry that I may someday have to give up work due to the pain in my kidneys".

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

"Having to give up my job that I loved because I could not continue to do the job and now the loss of earnings which is now putting me into debt that I will never be able to pay off till I die and my house is sold".

"Had to retire early from a senior position I loved. As the disease progressed it limited my ability to apply for further promotion. It really ended my career".

"Unsuccessful in joining police force on medical grounds".

"I was made redundant and felt attending job interviews that my large abdomen from ADPKD and PLD was viewed as a pregnancy and I was not offered jobs, or perhaps my self-esteem was so low that I came across negatively".

"I am a nurse and can no longer work on the wards due to heavy loads as I have ruptured cysts when helping others".

"Dismissed from job".

"I had a physical job which I could no longer carry out".

"ADPKD has had an enormous impact on relationships. I can't ever think of starting a relationship because of the enlarged kidneys. My life's finished in that respect".

"My appearance was a huge issue plus not being able to have more children".

"I lost my marriage because of suffering from ADPKD".

"My husband has probably noticed the biggest impact as we have no sex life anymore and I am tired all the time."

"It has given me huge sense of guilt about my young family. The main impact is uncertainty caused by being currently unable to slow / treat the disease. Basically it is simply now a waiting game".

"Feeling a burden, being ill all the time, not wanting to share how you feel because you will seem like you are moaning, impossible to describe how you feel unless you have had this disease".

"My son thinks he will have kidney failure no matter what I say. He copies me and is cautious about sport when he does not need to be. My wife has shouldered the burden many times over the last 30 years when I have been hospitalised or simply out of action for a while".

"I have not been able to accumulate the level of savings I had planned for a comfortable retirement. Further, my pension is significantly reduced because of my truncated working life".

Carers were vocal about the impact of ADPKD.

One carer listed the symptoms experienced by three affected children: *"Eldest son has kidney cysts, cerebral cyst, tiredness, fatigue; daughter has chronic & acute pain, liver cysts, cysts on head, kidney stones, nausea, iron deficiency, anaemia, cold feet and hands, tiredness, UTIs, enlarged abdomen, fatigue; younger son has only one kidney, kidney cysts, cerebral cyst, high BP".*

"For years GPs thought my son was a school refuser due to chronic back pain only since he transferred to adult services that chronic back pain was confirmed as ADPKD".

"When my child was diagnosed with further symptoms of ADPKD, there were many tests and hospital visits. I could not want to work full-time and lost my job because of this. I now take work that provides me with flexibility instead in order to take my child for appointments".

"Unable to accept a career move which would involve working further away from home as frequently required to drive husband to dialysis. Ended up taking redundancy about 5 years earlier than I would have normally".

"Had to put my career on hold as at one point they thought my spouse would live a few months".

Current practice in treating the condition

There is currently no licensed treatment available that addresses the underlying condition of ADPKD. Management is restricted to symptomatic control, including widespread antihypertensive medication, antibiotics to deal with infections arising, and analgesics to help alleviate the pain. In addition, emergencies arising, especially with kidney and liver cysts and associated

complications, have also to be dealt with on an ad hoc basis, often involving hospitalisation.

As the disease progresses and organ function diminishes, dialysis and ultimately transplantation may be necessary, procedures which are both expensive of resources and time, NHS and human. Kidney failure occurs in most patients, on average before 60 years [Shaw et al. 2013; Spithoven et al. 2014A] and ADPKD accounts for 1 in 10 patients on dialysis, 1 in 8 with a transplant [UKRR data].

Patients certainly need better symptomatic control – 45% of the patients responding to the PKD Charity survey rated current treatments as fair, poor or very poor in managing their ADPKD. However, the real need is for something which actually delays the disease process, with the associated decline in kidney function. As one patient clearly put it:

"In general the only treatments available for PKD [are] pain relief and blood pressure drugs, beyond that very little else is available unless your symptoms become life threatening in some way. There is no proactive treatment available that specifically attempt to hold back the growth of cysts".

Another respondent summarised the views of many patients and carers in venturing that *"Something to slow down the rate of decline would be good".*

There are no ADPKD guidelines or even care plans for patients. Only 30% of patients and 20% of carers reported being offered any form of genetic counselling or family planning advice.

"It's very confused. GP and specialist seem not to communicate".

"My GP doesn't take any notice".

"My doctor does not take much interest".

"Once yearly check-up isn't enough and I don't feel that my partner is really registered on a system of care even though father and grandmother died in their early 50s of heart attack due to ADPKD."

"The local hospital is sub-standard and we lost another family member to their negligence. Therefore we fear the future when PKD really progresses".

"I'd have liked more information about the genetic side of things – counselling etc".

What do patients or carers consider to be the advantages of the treatment being appraised?

Around 60% of responding patients and carers were aware of Tolvaptan, and most of these had heard of its potential ability to slow progression of the disease. To quote responding patients themselves:

" [ ] anything that can help at all. I just want the opportunity to try Tolvaptan. I strongly believe it will change my life".

"Tolvaptan brings hope to people like me who are young and are experiencing slow progression of ADPKD. Knowing that my next stage of help could be Tolvaptan and not dialysis is such a relief".

A number expressed the feeling that the importance may be greater for younger patients and the next generation(s). For example:

"I do not expect to be an appropriate patient for Tolvaptan but have hopes that my children or grandchildren may benefit".

"Would love for my son to have the chance to take Tolvaptan as I have lost both of my kidneys and I don't want him to go through what I've had to - hoping drugs will extend the life of his kidneys one day".

There were a number of specific reports of benefits from responding patients who had first-hand experience of Tolvaptan as part of the trial, 66% of whom were still in the follow-up phase.

"I felt much better/healthier when on Tolvaptan"
"I really think the Tolvaptan has slowed things down".
"The constant and brilliant care I receive. The potential that my cysts are not developing".

It should be noted that during the trial, the patients were regularly monitored and had repeat MRIs to measure total kidney volume (TKV) and cyst growth. MRIs are not current NHS practice and monitoring is determined by current NICE CKD guidelines on eGFR.

What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

The two main side effects quoted spontaneously by patients and carers were effects on the liver and the potential for excessive thirst/ drinking and frequent urination – especially the latter. To quote one patient:

"There is the risk of liver damage and raised liver enzymes although they have found that the levels return to normal once the drug is stopped. Patients on the drug have to consume a large amount of water daily meaning that they urinate more which may have a negative impact on lifestyle and quality of life (hard to travel, disturbed sleep, always needing to be near toilets etc)"

One particular concern came from patients with existing liver cysts who, when asked if they would have any concerns about taking Tolvaptan reasoned:

"My main concern would be the risks associated with the possibility to have adverse effect in the liver (considering I already have cysts in the liver)".

Having said that there was a lot of realism expressed, such as:

"All drugs have side effects; some of these will undoubtedly be intolerable for some people".

Turning to patients who had actually been exposed to Tolvaptan, the thirst/ urination effect was the only potential downside spontaneously quoted, for example:

"The impact that the drug has on your day to day life from ability to sleep at night to limiting activities like travel - occasionally I do have to stop taking it when the situation means I have no access to fluid or toilets but generally I have tolerated it very well for 6 years".

"Poor sleep at night, having to change the way I work so I work from home to avoid travel on the tube. Long distance trips have to be planned well with a doctor's note for long flights. The impact on sleep was reduced when I changed the times I took the tablet from 9am to 7am and 6pm to 4pm. Sleep improved significantly as the drugs impact was weaker and I had less trips to the loo".

Indeed, when asked if they had managed to adapt to the side effects, 66% said that they had 'a lot' and the remaining 33% said they had 'a little'.

Patient population

It is difficult to be definitive at this stage as to patients who might particularly benefit from Tolvaptan therapy and guidelines would no doubt need to be drawn up in consultation with various expert parties involved. The clinical trials were conducted on patients with average age of 51 and well-preserved kidney function (eGFR 80+). Their average height-adjusted TKV was nearly 1000ml.

However, there are a few potential indicators at this stage:

- Patients with large kidneys or whose kidneys show rapid enlargement over time - on the presumption that TKV growth is a surrogate marker or possible predictor of kidney function decline. We are aware that TKV is being considered by the EMA and FDA as a prognostic biomarker in ADPKD clinical trials and could be recommended for clinical management.
- Fast progression and/or family history e.g. age of entering end-stage renal failure as a surrogate for genotyping. It is known that PKD1 mutations result in a more severe form of ADPKD but no routine genetic testing is carried out in the UK to distinguish patients.
- Transplanted patients with extremely large native cystic kidneys, who could benefit from decline in TKV and improvement in pain/infection management
- Patients who would be motivated to comply with the treatment. We have already seen from our survey that patients on Tolvaptan do adapt to the side effects.

Research evidence on patient or carer views of the treatment

The PKD Charity is well aware of the published research literature on Tolvaptan and publicises the results of studies to patients and families.

In our view, the TEMPO 3:4 global clinical trial was a well-designed study and its primary outcome of the annual rate of change in TKV was understandable. We were especially encouraged by the composite secondary endpoints of time to clinical progression, in particular slower kidney function decline, fewer infections and less pain.

We understand that follow-up studies (unpublished) show that the effects of Tolvaptan observed in TEMPO 3:4 persist.

We have already discussed that there is currently no other treatment available with the potential for these effects, so the results to date are exciting for the ADPKD population.

Given the nature of ADPKD it would also be helpful to gather more evidence on the impact on overall quality of life but there is currently no agreed QoL score relevant to the condition. Were Tolvaptan to become available and in wider use we would look forward to collaborating on such a programme.

The PKD Charity has also participated in the international KDIGO ADPKD Controversy Conference and we await the published report which will recommend the development of global guidelines for all patients with ADPKD.

Equality

No comments.

Other issues

The treatment is obviously innovative as it is the first treatment for ADPKD which is not aimed simply at relieving symptoms.

The PKD Charity welcomes the chance to participate in the appraisal of this first-ever treatment of an otherwise incurable and sometimes devastating condition.

As one patient commented when asked about expectations for Tolvaptan: *"I am 41 and feel 70, I try and keep positive but the size of my liver and kidneys is getting too much for me, I often sit and think I cannot take this any longer. I do not want to have too high expectations of Tolvaptan but I would accept any improvement, however small, on my quality of life".*

Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- ADPKD is a chronic, progressive, incurable condition with multiple clinical effects and has significant lifestyle and socioeconomic implications for patients, their extended families, friends and the NHS.
- The ultimate goal is to preserve kidney function and delay or prevent progression to dialysis or transplantation, with all the associated health and social burdens and costs for patients, families and the NHS.
- To date management of the condition has been entirely symptomatic and Tolvaptan is the first therapy to offer the potential for slowing disease progression and giving new hope to thousands of affected patients in the UK.
- As with any drug there are side effects, most notably with regard to liver function and excessive thirst with associated polyuria, but the side effect profile appears relatively tolerable.
- There may be some patients for whom Tolvaptan offers greater benefits than others and there are already indicative criteria for these.