NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tolvaptan for treating autosomal dominant polycystic kidney disease

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: PROFESSOR BRUCE HENDRY

Name of your organisations

King's College London

The Renal Association

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? NO. I am President of the Renal Association (RA) but not an employee. The RA does represent clinicians who treat the condition.
- other? (please specify): I lead preclinical research studies of new potential treatments in ADPKD; these are unrelated to Tolvaptan.

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) currently receive essentially supportive therapy including treatment of hypertension and monitoring and reactive treatment for intercurrent problems such as renal pain and urinary tract infections (UTI). These patients are typically followed up in the secondary or tertiary care setting with co-ordination of on-going primary care.

There is currently no specific treatment for ADPKD either to reduce the progression of renal failure or to prevent the complications of expanding cyst burden including UTI and renal tract pain.

There are no approved dedicated guidelines for the management of ADPKD. However the guidelines for management of chronic kidney disease in general (CKD) and of hypertension would be relevant and used in their care.

Patients with ADPKD can be stratified into different prognostic groups. Genotyping into PKD1 (truncating mutations), PKD1 (other mutations) and PKD2 groups does give clear prognostic guidance, predicting progression rate of renal failure. This genotyping is not routinely performed in ADPKD in the UK at present but may be performed in the future.

Measurement of renal size also gives prognostic information and those with high Total Kidney Volume (TKV) are at highest risk of progression. MRI is the gold standard for this TKV measurement but renal ultrasound can be used to give a result

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with sufficient accuracy to be of value in assessing prognosis. It can be argued that the assessment of kidney volume provides sufficient information about prognosis as to render the precise genotype of limited importance (where the diagnosis of ADPKD is clinically secure). For example a young ADPKD patient with high TKV is unlikely to have PKD2 mutation.

Further prognostic information can be obtained from the degree of renal failure at assessment, the presence of uncontrolled hypertension and the presence of high levels of proteinuria.

Taken together I believe that stratification of ADPKD patients for risk of progression to severe renal failure (CKD stages 4 and 5) can be achieved. Progression to end-stage renal failure (ESRF) is a very significant problem in ADPKD and 5-10% of patients with ESRF on dialysis have this condition due to ADPKD. This creates a heavy burden of mortality and morbidity.

However it is important to point out that the risk of progressive CKD is not the whole story. Many patients experience very significant ill health due to other complications such as renal pain, liver pain, severe urinary tract sepsis, haematuria and cyst rupture. These problems may not coincide with progressive CKD and are hard to manage. Management of the patient requires individual review of all these potential problems and not simply a concern about CKD.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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Tolvaptan is a novel agent for specific treatment of ADPKD and would be the first in a new class of therapies. There is no comparable current treatment and indeed no specific treatment available.

I believe the evidence base on Tolvaptan is secure in demonstrating a reduction in the progression rate of renal failure and in the progression of renal enlargement. These rates are cut to about 50% of those in patients given current standard of care with rigorous advice about high water intake, on an intention to treat basis. The data also show benefits in renal pain and in UTI.

The main side affect of the therapy is excessive frequency of urination and thirst, and this does limit concordance with therapy.

In my view Tolvaptan has value to patients and should be considered favourably for approval. The key issue is deciding which patients will benefit most from treatment. To determine this a stratification by prognosis is required. This can be achieved by baseline assessment of TKV and this is possible using MRI or renal ultrasound. TKV then needs to be considered along with patient age and the other clinical parameters available including baseline renal function.

An analysis of the risk of developing ESRF over time can then be performed to focus use of Tolvaptan on the higher risk group. Models that examine this risk over very long periods (up to 30 years) are not in my view of value as it is unrealistic to imagine that the assumptions used will hold for such long periods (e.g. with the emergence of new understanding and therapies). I therefore favour an approach looking at risk over 0-10 years and determining the value of Tolvaptan in reducing patient related outcomes over this time horizon.

The clinical studies of Tolvaptan have found a statistically significant benefit in the occurrence of non-CKD complications such as renal pain and UTI. These are important to patients and should be considered in the decisions about Tolvaptan use. This has been somewhat neglected in my view in the debate thus far. In certain patients I suggest that use of Tolvaptan to address these complications should be considered without the need for any progressive CKD criteria to have been met.

An alternative view is that we have analgesics for pain and antibiotics for infections. However it is important to recognise that by reducing the rate of cyst enlargement Tolvaptan is preventing the process leading to pain and infections, a far better strategy than treating these episodes as they arise. I think it likely therefore that Tolvaptan will reduce the use of analgesics and antibiotics in ADPKD patients; a good result as both classes of agents carry risks.

The setting for the use of Tolvaptan should be secondary care with good communication with primary care physicians who would see the patients for intercurrent conditions. Careful monitoring of liver function tests will be needed. It will be helpful to have good assessment of concordance with therapy.

Protocols for cessation of therapy will be useful. Reasons for cessation may include:
Severe or unacceptable side effects
LFT abnormality above defined limits

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Limited concordance
Failure to influence symptoms where these were the reason for initiation.

Follow up with serial serum creatinine and eGFR will be helpful but I would not advise treatment cessation based on these data as the evolution of renal function changes is variable. Baseline TKV will be very useful for stratification but I would not mandate routine follow up TKV as variability of the measurement is too great in an individual patient to guide subsequent decisions on therapy.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

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If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?