NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tolvaptan for treating autosomal dominant polycystic kidney disease [ID652]

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: John Andrew SAYER

Name of your organisation Newcastle Univeristy/ Newcastle upon Tyne NHS Foundation Trust

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.)?
- other? (please specify)

Clinical lead for Renal Genetics Service, Newcastle upon Tyne NHS Foundation Trust

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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.

ADPKD is currently treated with blood pressure control and management of secondary risk factors (cholesterol control, lifestyle etc) in a similar manner to many patients with chronic kidney disease. Care is shared between primary and secondary care, depending on stage of CKD.
I am not aware of any geographical variations in current practise.
There are no current pharmacological alternatives to tolvaptan.

Regarding subgroups, the TEMPO 3:4 study included ADPKD patients with an estimated creatinine clearance of ⩾60 ml/min and a TKV of⩾750 ml. Both genotypes (PKD1 and PKD2) were included.
A stratified analysis in TEMPO 3:4 showed that tolvaptan is more likely to be beneficial in patients older than 35 years, those with hypertension, and those with TKV 1500 ml or higher.

Tolvaptan should be used within secondary care, preferably in dedicated clinics with specialist nurse support. The widespread use of tolvaptan would necessitate an expansion of renal specialist nurses to ensure that close monitoring of patients was performed (in a similar manner to renal anaemia for example).

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Tolvaptan is not available for use in ADPKD patients in the UK at the moment.

There are no current clinical guidelines for tolvaptan use in this country but clearly these are required to allow appropriate use of this drug in the ADPKD population.

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?

There are no current treatments for ADPKD, so tolvaptan represents a considerable advance. The practical implications include close monitoring of liver enzymes ans serum sodium (risk of hypernatraemia) during the treatment. The scientific community is still debating the sort of imaging that patients need to quantify total kidney volume and the followup imaging that is required once treatment is initiated (to document response in cyst volume to treatment).
Concomitant use of diuretics (as antihypertensive medications) will need to be reviewed before commencing tolvaptan. It is my opinion that a trial of tolvpatan to see if the diuresis can be tolerated should be offered to patients before long term treatment is considered. (The current "reprise" study offers this as part of the run in before randomisation).

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Monitoring of blood tests will be required throughout treatment and probably "sick day rules" apply to this medication in a similar manner to ACE inhibitors (ie stop if intercurrent illness, volume depletion etc).

The TEMPO3:4 study reflects UK clinical practise and I do not see a problem with extending the use from clinical trial to clinical practise in the UK. 73 patients in TEMPO 3:4 came from the UK.

The most important outcome is change in eGFR. The aim is to slow progression of disease to prevent ESRD. The results of the TEMPO3:4 study could be extrapolated in a linear fashion to show delay in ESRD. The rate of change in eGFR remains a surrogate endpoint until long term data is established with this drug.

Adverse events include hypernatraemia and abnormal liver enzymes. Also female patients should NOT conceive whilst taking this drug (so adequate contraception needs to be ensured).

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

I do not believe there are any equality and diversity issues with this treatment.

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

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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.

No other sources to declare.

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.

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)?

ADPKD is a relatively common inherited disease. The use of this drug in a clinical setting has the potential to increase the burden of care for secondary care facilities. I would anticipate that dedicated ADPKD clinics would need to be established within renal units to allow the safe and proper long term management of these patients. The model of care delivery is best suited to specialist nurses would could monitor and keep track of all patients, ensure compliance and arrange imaging and other tests to assess response to tolavaptan. Depending on the imaging modality, access to MRI scans may be an issue.