

Is there any treatment for ADPKD?

In the early stages of ADPKD, there are ways to maintain kidney health. And there are many things that you are currently doing (or should be doing) that are very helpful for your kidneys and/or your general health. These include good blood pressure control (using medication if necessary, having a healthy diet (in particular minimising salt intake), maintaining a healthy weight and controlling your cholesterol. You should do your best to reach these goals and work with your nephrologist to achieve the best outcomes. As each person's experience is different, you should ask your doctor for more information.

While no cure currently exists for PKD, there is one pharmaceutical treatment known as Tolvaptan (JINARC®), approved in Australia and available on the Pharmaceutical Benefits Scheme (PBS) for eligible patients with ADPKD.

Tolvaptan (JINARC®) is a new treatment available in Australia for adults with ADPKD (autosomal dominant polycystic kidney disease) that can help slow the progression of ADPKD. Clinical trials have shown tolvaptan can slow the rate at which your kidneys become enlarged by cysts and can help to slow the rate at which your kidney function declines.

How does tolvaptan work?

Vasopressin is a naturally occurring hormone which is released by the brain when it senses that the body is dehydrated (i.e. lacks water). When released from the brain, vasopressin enters the blood stream and goes to the kidney where it tells the tubules of the kidney to reabsorb more water. This action then partly helps restore normal water balance to the body during times of mild dehydration, and it is a completely normal process.

However, in adults with ADPKD, research has discovered that vasopressin also partly contributes to the growth of kidney cysts, by making them accumulate fluid.

Tolvaptan is a specific drug that is taken twice daily as a tablet. It blocks the effect of vasopressin in the body. In ADPKD it has been shown to slow cyst growth and reduce the decline in kidney function.

Who is eligible to receive tolvaptan in Australia?

Tolvaptan may be of benefit to people with ADPKD who are at high-risk of developing kidney failure, some people with ADPKD may not need tolvaptan because they are low-risk. Kidney function is measured with a blood test called estimated glomerular filtration rate (eGFR). The normal eGFR is 90 ml/min or greater and indicates normal kidney

function. In ADPKD, kidney function tends to stay normal for many years and in about 50% of patients does not change much at all.

To qualify for tolvaptan (JINARC®), a person with ADPKD must:

- be older than 18 years old (not pregnant or breast-feeding) *and*
- have reduced kidney function (i.e. Stage 2 or Stage 3 chronic kidney disease (CKD) defined as an eGFR between 30-89 ml/min/1.73 m²) *and*
- have evidence that the kidney function (or eGFR) is declining (This is defined as a decline in eGFR of either 5ml/min/1.73 m² in 1 year or 2.5ml/min/1.73 m² per year over 5 years) *and*
- Measure liver function tests on a blood test before starting the drug (see below for reasons)

It is important to note that eGFR can fluctuate slightly from day-to-day and there can also be other reasons why someone's eGFR is declining. Your nephrologist (kidney specialist) will be able to discuss this in more detail with you and advise you if tolvaptan is suitable for you.

What are the benefits of tolvaptan?

Two large international clinical trials each with more than 1000 patients (called TEMPO and REPRISE trials), showed that treatment of patients with ADPKD with tolvaptan slowed the decline in eGFR (kidney function) on average by about 1ml/min/1.73 m² per year compared to those receiving placebo.

In the TEMPO trial, tolvaptan also slowed the growth of kidney cysts (as measured by total kidney volume in MRI scans), but follow-up studies showed that the benefit might only occur in the first 1-2 years of taking the medication. The effect of tolvaptan on the growth of kidney cysts was not investigated in the REPRISE trial.

Who would most benefit from treatment with tolvaptan?

Tolvaptan is recommended for some patients with ADPKD who are at high-risk of developing kidney failure. Not all patients require treatment with tolvaptan and this is a clinical decision that you should discuss with your nephrologist. In the REPRISE trial the impact was greatest in CKD Stage 3a, where the rate of decline in the untreated patients was 4.4ml/min/1.73 m² per year, and in the group taking tolvaptan it slowed to 2.1ml/min/1.73 m² per year. There was a similar impact in CKD Stage 2. The benefit of tolvaptan is less with very advanced levels of kidney function and not recommended in these situations (i.e. Stage 4 or 5).

Will tolvaptan delay the need for dialysis or renal transplant?

Although the trials showed benefit on kidney function decline, they were short in duration. It is not known whether long-term treatment with tolvaptan continues to slow the rate of renal function decline over many years, or if it will delay the need for dialysis or transplantation. The investigators have extrapolated from the data obtained in the REPRISE and TEMPO trials to suggest that tolvaptan may delay dialysis or transplantation for between 6 to 9 years. This is likely to be restricted to patients starting at the time of CKD Stage 2 or early Stage 3a.

What are the side effects of taking tolvaptan?

Tolvaptan increases urine output in all patients because it blocks the action of vasopressin on healthy tubules of the kidney. This is not so much a side effect but arises directly from the way the drug works. On average, someone taking tolvaptan passes about 5-7 litres of urine per day. As a result, the frequency of urination increases, and on average this may be up to 20 x during day and 2-4 x during the night. Only about half of the people prescribed tolvaptan will tolerate this side effect in the first few weeks of starting the drug, and your doctor will monitor you closely and discuss ways to increase your chances of staying on the drug.

About 5% (one in twenty) of patients on tolvaptan develop abnormalities in the blood tests to assess liver function. These are typically mild and reversible when tolvaptan is stopped, but 1 in every thousand patients can develop more serious liver injury. For this reason, patients treated with tolvaptan must have their liver function tested every month for the first 18 months after starting the medication and then every 3 months while continuing on it.

Three people in hundred treated with tolvaptan may also experience mild gout due an elevation in blood levels of uric acid.

It is important to note a significant proportion of people cannot tolerate tolvaptan due to side effects.

What can I expect when I am taking tolvaptan?

- Passing lots of urine and drinking lots of fluid to keep up with the lost urine
- Need to see your kidney specialist regularly when you start treatment
- Having monthly blood test for the first 18 months, and then 3-monthly while taking tolvaptan

How do I obtain treatment?

You should talk with your nephrologist as to whether tolvaptan is suitable for you. If eligible, your nephrologist will know how to prescribe it for you.

Are clinical trials for other treatment therapies currently underway?

Yes, several clinical trials using other treatments are in progress.

Would increased water intake serve as a substitute for taking tolvaptan?

This is a very important question that everyone has been asking. Unfortunately, the clinical trials (REPRISE and TEMPO) using tolvaptan did not determine whether maintaining adequate water intake has the same effect as tolvaptan. Studies from the laboratory suggest that maintaining adequate hydration is beneficial for ADPKD and could do the same thing as tolvaptan. However, we don't know this for sure, and especially what amount of water is needed, and this is why a clinical trial in Australia (the PREVENT-ADPKD study) is evaluating this. Some individuals drinking excessive amounts of water or other liquids can develop low blood sodium, which can be dangerous. If you are thinking of drinking large volumes of liquid this should only be done after discussion with a doctor and with ongoing supervision.

If I am currently enrolled in a clinical trial will I be able to take tolvaptan?

Your enrolment in a clinical will not affect your medical treatment. It's important that you talk with your nephrologist and also notify the Investigators of your trial.

What do I do if am not suitable or do not tolerate tolvaptan?

A significant proportion of people cannot tolerate tolvaptan. It is important to remember that many things that you are currently doing (or should be doing) are very helpful for your kidneys and/or your general health. These include good blood pressure control, having a healthy diet (in particular minimising salt intake), maintaining a healthy weight and controlling your cholesterol. You should do your best to reach these goals and work with your nephrologist to achieve the best outcomes.

Disclaimer:

The information provided here is an overview of Tolvaptan/JINARC® and does not contain all the available information nor does it take the place of talking to your doctor or pharmacist. All medicines have risks and benefits and your doctor will weigh the risks of you taking this medicine against the benefits they expect it will have for you.