

1. What is tolvaptan?

Tolvaptan is a selective V_2 vasopressin receptor antagonist. It was originally approved as an aquaretic for use in hypervolemic hyponatremia. In February, 2015, it was approved for use in Canada as a treatment for Autosomal Dominant Polycystic Kidney Disease (ADPKD).

2. What is the evidence supporting the use of tolvaptan in ADPKD?

The TEMPO 3:4 trial was a double-blinded study that randomized patients with ADPKD aged 18 to 50 years, total kidney volume (TKV) > 750 mL and CrCl > 60 mL/min (approximately eGFR > 45 mL/min) to tolvaptan or placebo.

In **three years** of follow-up, the use of tolvaptan was associated with the following:

Primary outcome:

- A slower annual rate of kidney enlargement, 2.8% (95% CI, 2.5 to 3.5) vs 5.5% (95% CI, 5.1 to 6)

Secondary outcomes:

- Fewer events of renal decline, defined by a 25% decrement in reciprocal of serum creatinine (2 vs. 5 events per 100 patient years; HR 0.39; 95% CI, 0.26 to 0.57; $p < 0.001$) after at least 2 weeks
- Slower decrease in GFR (-2.72 vs -3.70 mL/min/1.73 m² per year), an annual difference of 0.98 mL/min/1.73 m²; 95% CI, 0.6 to 1.36; $p < 0.001$.
- Fewer severe pain events (5 vs. 7 events per 100 patient years; HR 0.64; 95% CI, 0.47 to 0.89; $p = 0.007$).

A large proportion of patients had aquaretic symptoms of thirst, polyuria and nocturia

necessitating discontinuation (8.3 vs. 1.2%). 4.9 vs 1.2% of patients had elevations of transaminases > 2.5x ULN. Serious changes in liver enzymes (transaminases > 3x ULN *and* elevated bilirubin and elevated bilirubin > 2x ULN) occurred in 2 patients (zero in the placebo arm).

At present, there is no data that use of tolvaptan delays time to ESRD, as studies have not been of sufficient duration to ascertain rates of ESRD as an endpoint.

Results from a longer-term follow-up of the original TEMPO patients is pending and an additional study of tolvaptan in patients with a lower eGFR of 25 to 65 mL/min is currently underway.

3. Are there contraindications or warnings regarding tolvaptan?

Due to the hepatic injury seen in the TEMPO trial, there is a warning for idiosyncratic hepatotoxicity with tolvaptan. Health Canada has mandated hepatic monitoring as a condition of prescribing the drug (see question 5).

Current contraindications include:

- Underlying hepatic dysfunction
- Hyponatremia, hypovolemia or inability to respond to thirst
- Pregnant or breastfeeding women (women of reproductive age should be maintained on contraception)
- Patients < 18 years old

Other potential side effects include hyperkalemia, hyperuricemia and gout. There are multiple potential drug interactions with tolvaptan as it is a substrate of cytochrome P3A and P-glycoprotein, so medications must be reviewed prior to prescribing and when initiating a new drug in a patient on tolvaptan.

4. Which ADPKD patients may benefit from tolvaptan?

Only a subset of ADPKD patients may benefit from tolvaptan. Based on its mechanism of action and the current studies available, patients most likely to benefit are those who are younger, with preserved eGFR and evidence of enlarged or rapidly enlarging kidneys. These ideal patients are at high risk of rapid progression but still have relatively preserved renal function.

Patients with slowly progressive disease, who are not likely to reach ESRD, are not likely to benefit from tolvaptan. Patients with substantial renal dysfunction have not been evaluated from an efficacy or safety perspective (e.g., impact of aquaresis on rate of renal decline) and tolvaptan is not recommended in these patients at this time.

Canadian Expert Consensus recommendations on the management of ADPKD (Soroka et al., CJKHD 2017) suggest that tolvaptan can be considered in the following patients:

Those similar to the TEMPO 3:4:

- Age 18 to 50, eGFR > 45 mL/min, and TKV > 750 mL

Other patients deemed to be at risk of rapid renal progression:

- Those who are class 1D or 1E using the [Mayo imaging classification for ADPKD](#) with eGFR > 45 mL/min.
- Those who are class 1C using the Mayo imaging classification for ADPKD and < 50 years old.
- Those with an ultrasound kidney length > 16.5 cm bilaterally (In the setting of 'typical' diffuse cystic morphology of enlargement as described in the Mayo Imaging classification)
- Those with serial imaging that demonstrates an average annual increase in TKV of > 5%

These recommendations are based on the current best evidence and expert opinion; these are not funding or approval criteria, nor are they meant to interfere with individual clinician and patient decision making which should be tailored to individual circumstances. These recommendations may change as more evidence about the efficacy and safety of tolvaptan become available.

5. If I prescribe tolvaptan, what monitoring is necessary?

Due to the potential for idiosyncratic hepatotoxicity, Health Canada has mandated two precautions be taken before tolvaptan is prescribed:

1. Informed consent must be provided and documented in a Patient-Provider Agreement Form (PPAF).
2. There must be evidence that hepatic monitoring has been performed prior to the drug being dispensed. The monitoring frequency is monthly for the first 18 months, every 3 months for the next year and then every 3 to 6 months thereafter

These criteria are satisfied via a monitoring agreement between the manufacturer and Health Canada; the forms necessary to enroll in the monitoring program in BC are available on the BCPRA website. Although the manufacturer will help ensure the required blood tests have been completed prior to dispensing tolvaptan, it is the prescriber's responsibility to ensure the results are within an acceptable range.

All patients on tolvaptan should be registered in PROMIS to allow for complete outcome and safety evaluation of this new treatment.

6. What is the recommended dose of tolvaptan?

To ensure continuous blockade of the V₂ receptor, tolvaptan is recommended to be taken twice a day with the higher dose in the morning and lower dose in the afternoon. If patients wish to skip a dose to avoid the aquaretic symptoms for a short time where frequent voiding would be intolerable, that is acceptable and they are advised to just start again at the next scheduled dose. In the TEMPO 3:4 trial, the drug was titrated on a weekly basis to reach the highest tolerated dose.

The doses used were:

- 45 mg qAM and 15 mg 8 hours later (60 mg total daily dose) ← this is the recommended starting dose
- 60 mg qAM and 30 mg 8 hours later (90 mg total daily dose)
- 90 mg q AM and 30 mg 8 hours later (120 mg total daily dose)

There are no data that establish the optimal dose of tolvaptan for treating ADPKD. Please note that as the dose is increased, aquaretic symptoms also increase.

7. Where do I send all the completed paperwork to prescribe tolvaptan?

Once you have made the decision to prescribe, send the completed Patient Prescriber Agreement Form (PPAF) along with the prescription to Macdonalds pharmacy at 1-855-569-0660.

8. Is the cost of tolvaptan covered for my patient?

At the present time, tolvaptan is not included on either the BC Provincial Renal Agency or BC PharmaCare formulary but is covered by some private insurers. There is a flat price for all tablet sizes, so dose does not impact cost. We suggest

that potential patients discuss coverage, including any potential life-time maximums with their private drug insurance provider prior to initiating treatment with tolvaptan. Once a prescription is completed, the distributor will also ensure that funding is in place before dispensing the drug. This may result in a delay of up to several weeks between prescribing and the first delivery of tolvaptan.

Please ensure that your patient is registered in PROMIS before prescribing tolvaptan. For more information and relevant forms, visit the BCPRA website at www.bcrenalagency.ca.