

Tolvaptan

Frequently Asked Questions (for prescribers)

1. What is tolvaptan?

Tolvaptan is a selective V2 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 largest study evaluating tolvaptan is TEMPO 3:4.¹ This was a double-blind 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 **3 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 6.0)

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).
- Slower decrease in GFR (-2.72 vs -3.70 mL/min/1.73 m² per year), with 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 in the tolvaptan arm, versus zero in the placebo arm.

After TEMPO 3:4 was completed, subjects who had an eGFR ≥ 30 mL/min/1.73 m² were offered to participate in a 2-year open-label extension trial called TEMPO 4:4.² In the 871 patients who enrolled, there was a lack of sustained treatment difference on TKV (the primary endpoint). However, this may have been a limitation of the trial design (e.g. patients given placebo in TEMPO 3:4 were now treated with tolvaptan). Nonetheless, the secondary endpoint of slowing renal function decline appeared to be sustained, and the study contributed valuable safety data by confirming that the side effect profile was similar to those reported in TEMPO 3:4.

A second multi-centre placebo-controlled study called REPRISÉ evaluated 1,370 patients with lower levels of kidney function compared to TEMPO 3:4. In this study, 2 groups of patients were enrolled³:

- 18 to 55 years old with an eGFR of 25 to 65 mL/min/1.73 m².
- 56 to 65 years old with an eGFR of 25 to 44 mL/min/1.73 m² that was decreasing by more than 2 mL/min/1.73 m² every year.

The primary outcome was a mean change in eGFR at **1 year**. In the patients treated with tolvaptan, the eGFR declined by 2.34 mL/min/1.73 m², compared to 3.61 mL/min/1.73 m² in the placebo group. This is a mean difference of 1.27 mL/min/1.73 m² (95% CI 0.86 to 1.68, p < 0.001).

One consideration from REPRISÉ is that, in a subgroup analysis, there was no benefit seen in the group of patients 56 to 65 years old. Although the study was not powered to examine this, one possibility is that this group of patients included individuals with slowly progressive disease; their decline in eGFR was much slower than the rate observed in younger patients in the trial with similar stages of chronic kidney disease.

The adverse event rate was lower in REPRISÉ compared to TEMPO 3:4, likely due to its 8-week run-in period and required monthly patient follow up. 9.5% of patients discontinued tolvaptan (compared to 2.2% taking placebo), which was lower than the 15.4% discontinuation rate reported in TEMPO 3:4.

Data from both studies suggest that 30 to 50% of patients will experience thirst, polyuria or nocturia, and approximately 1 to 2% of patients will experience hepatic enzyme abnormalities.

At this time, there is still no data that the use of tolvaptan delays time to ESRD, as studies have not been of sufficient duration to ascertain rates of ESRD as an endpoint. It is expected that a reduction in GFR decline will delay time to onset of ESRD, but as progression of ADPKD is not always a linear or a predictable process,

it is uncertain how much of a delay will occur in individual patients.

3. Are there contraindications or warnings regarding tolvaptan?

Due to the hepatic injury seen in the TEMPO 3:4 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 as evidenced by hepatic biochemical abnormalities. This does not include the simple presence of hepatic cysts, which is not a contraindication.
- 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.
- Concurrent use with a strong CYP3A inhibitor (e.g. clarithromycin).

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

4. Which ADPKD patients may benefit from tolvaptan?

Potential candidates for treatment with tolvaptan are patients with ADPKD who have a more rapidly progressive disease. These criteria are based on evidence from the clinical

trials described above, the BC Renal ADPKD Advisory Group, and the Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease.⁴

There are three groups of patients that may benefit from tolvaptan. They are:

1. Patients 18 to 55 years old with an eGFR > 25 mL/min/1.73 m² and evidence of renal enlargement. Renal enlargement can be defined as a TKV > 750 mL (or bilateral ultrasound kidney length > 16.5 cm if the absence of TKV) in those with an eGFR > 45 mL/min/1.73 m², or class 1C, 1D or 1E in the Mayo Clinic Classification.
2. Patients 55 to 65 years old with an eGFR of 25 to 44 mL/min/1.73 m² and historical evidence of a decline in eGFR > 2 mL/min/1.73 m²/year, and a TKV demonstrating Mayo Class 1D or 1E.
3. Consideration may be given to patients 18-65 years old who do not fall into the first two categories but have a marker or combination of markers that indicates that they are at risk of reaching ESRD within their lifetimes. Markers include:
 - Observed annual decrease in eGFR of > 2.5 mL/min/1.73 m²
 - Observed increase in TKV of > 5% per year
 - Mayo Clinic Classification groups 1D or 1E
 - PKD 1 protein truncating mutation
 - Classified as high risk via the PROPKD risk score
 - Consideration can be given to patients with high symptom burden related to renal expansion, but this alone is not generally an indication for treatment.

These recommendations are based on the current best evidence and expert opinion. They are not 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. Which patients do not benefit from tolvaptan?

Patients who are not likely to benefit from tolvaptan are those with slowly progressive disease and who are therefore unlikely to reach ESRD. In addition, patients with eGFR less than 25 mL/min/1.73 m² 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.

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

Due to the potential for idiosyncratic hepatotoxicity, Health Canada has mandated two precautions to 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 BC Renal website. Although

the manufacturer will help ensure the required blood tests have been completed prior to dispensing tolvaptan, it is the responsibility of the prescriber or delegated team member (pharmacist or nurse) 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.

7. 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 the lower dose in the afternoon. In the TEMPO 3:4 trial, tolvaptan 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 qAM and 30 mg 8 hours later (120 mg total daily dose)

Dose titration should be performed judiciously (no more than once weekly) to ensure that high doses are not poorly tolerated through overly rapid up-titration. Physicians may down-titrate to lower doses based on patient tolerability, and up-titrate again when appropriate. Patients should normally be maintained on the highest tolerated dose of tolvaptan.

The aim of dose titration is to block activity of vasopressin at the renal V2 receptor as completely and constantly as possible, while maintaining acceptable fluid balance.

In general, the goal should be to titrate tolvaptan up to the maximum tolerated dose, which is in keeping with clinical trials.

When titrating the dose, the adequacy of vasopressin suppression can be monitored by measuring urine osmolality prior to the morning dose. A subanalysis from the TEMPO 3:4 trial showed that patients who experienced a greater mean change from baseline urine osmolality were also more likely to achieve a better clinical response. Based on this, it has been suggested that a target decrease of at least 300 mOsm/kg from baseline may be considered a marker of ideal response in most cases. However, this decrease is in part dependent on the baseline urine osmolality, which changes throughout the course of the disease. The achieved urine osmolality can also be used as an indicator of drug effect. If possible, the goal should be to maintain a dilute urine at all times, which approximates an absolute first morning urine osmolality of less than 250-300 mOsm/kg.

In patients who have not met these urine osmolality targets, consideration should be made to increase the dose of tolvaptan. However, in all cases, urine osmolality targets should be individualized to the patient, recognizing that the severity of aquaretic effects may increase with lower targets.

As of 2020, two lower dose regimens are available: 30mg qAM and 15 mg 8 hours later, and 15 mg qAM and 15 mg 8 hours later. It should be noted that these medications are **NOT** intended as the starting doses, but rather are reserved for patients who experience excessive/intolerable aquaretic symptoms on the conventional doses, or are concurrently taking other medications that affect tolvaptan pharmacokinetics.

8. How long should tolvaptan therapy be continued?

Tolvaptan is considered lifelong therapy, as it is not curative and will not stop the progression of ADPKD. Patients may still develop cysts and eventually develop kidney failure; the aim of treatment is to slow the rate at which this happens. It is uncertain how much of a delay will occur in individual patients, and when therapy should be discontinued.

9. Are there strategies to manage or minimize aquaretic effects?

Once tolvaptan is initiated, all patients should have access to water and be encouraged to drink water liberally on an ongoing basis to match increased urine output. If dehydration becomes evident, take appropriate action, such as interrupting or reducing the dose of tolvaptan and having the patient increase fluid intake.

With vasopressin blockade resulting in a relatively fixed urine osmolality, urine output is strongly related to the urinary osmolar load. Minimizing salt and protein intake can be helpful dietary strategies to reduce osmolar load and consequently reduce urine output.

It is acceptable for patients to skip a dose if they wish to avoid aquaretic effects for a short time when frequent voiding would be intolerable - they should be advised to start tolvaptan again at the next scheduled dose.

10. How do I obtain approval for tolvaptan and prescribe it to my patient?

Once you have made the decision to prescribe tolvaptan, there are two documents to complete: the Application for tolvaptan use in ADPKD and the Patient Prescriber Agreement Form (PPAF). Both forms are available on the BC Renal website. Once completed, send these forms as well as the supporting documentation specified in the Application for

tolvaptan use in BC to the BC Renal tolvaptan adjudication committee at Fax 604-875-7366. The adjudication committee will then determine if your patient meets criteria for usage of tolvaptan based on the criteria listed above, and will send you a decision letter.

If tolvaptan is approved by the adjudication committee, send both the decision letter and the tolvaptan prescription to Macdonald's Prescriptions by fax to: 604-872-4255.

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

If your patient meets criteria for treatment with tolvaptan as listed above, there are two ways that this drug is funded. If your patient has a private drug coverage plan that includes use of tolvaptan in ADPKD, the drug will be funded under that plan. For patients with no such plan, BC Renal will fund the cost of tolvaptan for patients who meet the approval criteria.

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

References:

1. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367(25):2407-2418.
2. Torres VE, Chapman AB, Devuyst O, et al. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2017;32(7):1262.
3. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in Later-Stage Autosomal

Dominant Polycystic Kidney Disease. *N Engl J Med.* 2017;377(20):1930-1942.

4. Soroka S, Alam A, Bevilacqua M, et al. Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease. *Can J Kidney Health Dis.* 2018;5.
5. Devuyst O, Chapman AB, Gansevoort RT, Higashihara E, Perrone RD, Torres VE, et al. Urine Osmolality, Response to Tolvaptan, and Outcome in Autosomal Dominant Polycystic Kidney Disease: Results from the TEMPO 3:4 Trial. *J Am Soc Nephrol.* 2017;(5):1592-1602.