PRESCRIBER & HEALTHCARE PROFESSIONAL TRAINING MODULE

TREATMENT OPTION FOR PATIENTS WITH ADPKD



PrLUPIN-TOLVAPTAN – Indication

LUPIN-TOLVAPTAN is indicated to slow the progression of kidney enlargement and kidney function decline in adult patients with autosomal dominant polycystic kidney disease (ADPKD).
In ADPKD, kidney enlargement reflects renal cyst burden.[1]

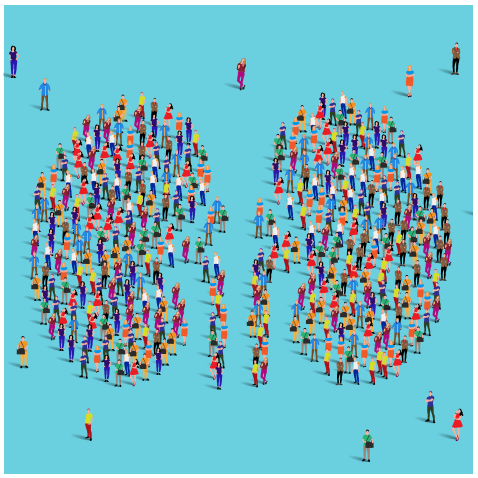
LUPIN GENESIS
PATIENT SUPPORT PROGRAM

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

AUTOSOMAL DOMINANT POLYCYSTIC DISEASE: SYNOPSIS

Introduction to ADPKD:

- ADPKD is an inherited disease, that is autosomal dominant[1]
- It is a form of nephropathy that is characterized by formation of numerous kidney cysts, which lead to slow, gradual, and massive bilateral kidney enlargement[1,2]



Impact of ADPKD on Public Health:

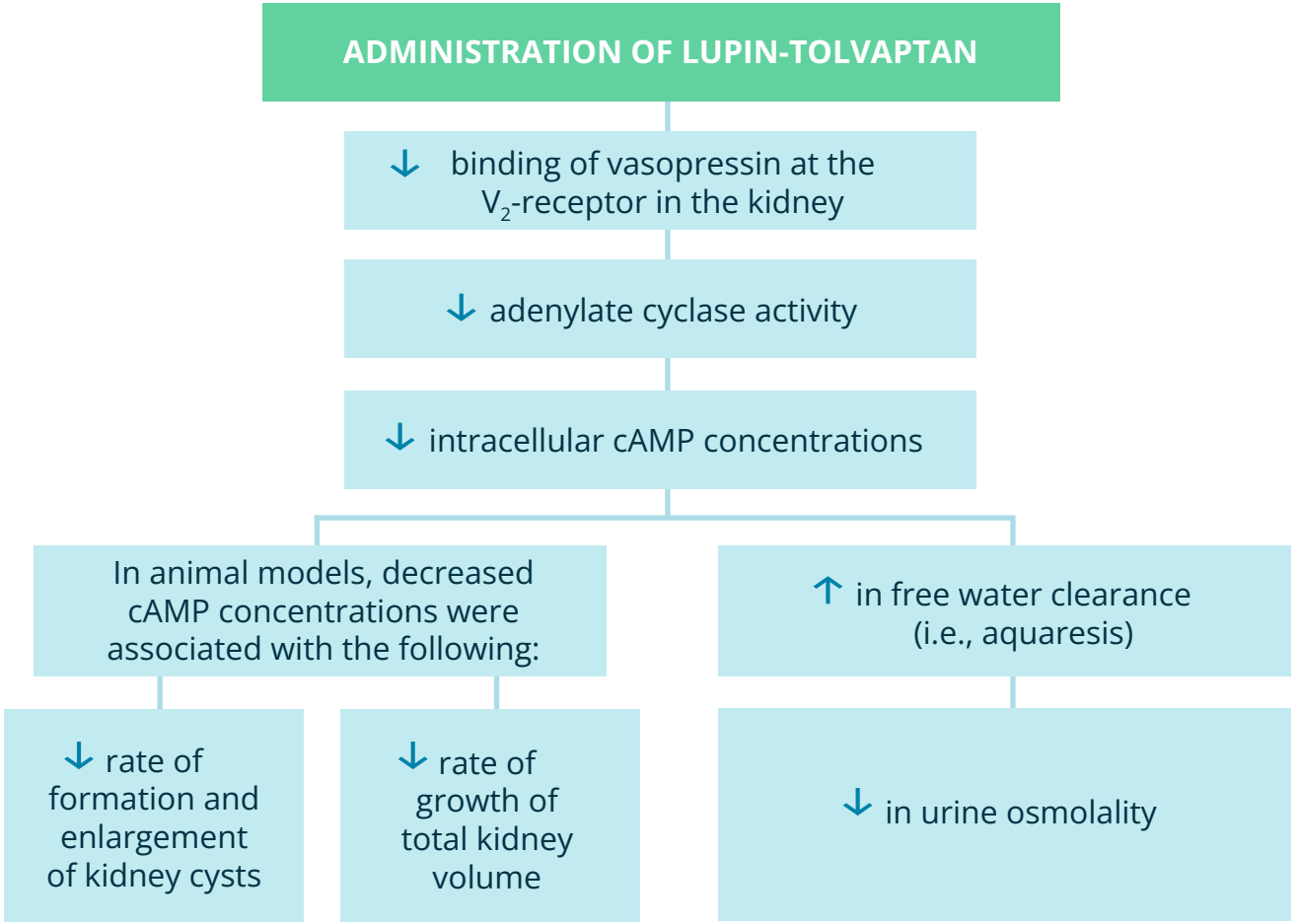
- ADPKD affects around 35,000 people in Canada[1]
- Frequency of occurrence is around 1:400–1:1000 live births[1]

1. Cabellon M. Cystic Disease of the Kidney. In: Windus, David, editor. *Nephrology subspecialty consult.* 2nd edition. New York: Lippincott, Williams & Wilkins, 2008.
2. National Kidney Foundation. Primer on Kidney Diseases. New York: Saunders, 2005.

Treatment Option for Patients with ADPKD

LUPIN-TOLVAPTAN is indicated to slow the progression of kidney enlargement and kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, kidney enlargement reflects renal cyst burden.[1]

Mechanism of Action of Tolvaptan



cAMP: adenosine 3',5'-cyclic monophosphate

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

TOLVAPTAN DATA FROM 2 PIVOTAL TRIALS

DONE BY INNOVATOR (OTSUKA) IN PATIENTS WITH EARLIER TO LATER STAGES OF ADPKD

Design of the TEMPO 3:4 Trial[1,2]

36-month, placebo-controlled trial

Interventions: Randomized 2:1 ratio

- Tolvaptan + standard of care vs. placebo + standard of care
- Patients were titrated to receive the highest tolerable dose starting with morning and afternoon doses of 45 mg and 15 mg, respectively, with weekly increases to 60 mg and 30 mg, and then to 90 mg and 30 mg
- All patients remained on standard concomitant medications

Subjects: 1445 patients with ADPKD

- TKV ≥ 750 mL by MRI (mean baseline 1705 mL in tolvaptan group; 1668 mL in placebo group). Baseline estimated creatinine clearance ≥ 60 mL/min (mean baseline 104 mL/min in both groups)

Baseline characteristics:

- Patient distribution by CKD Stage: CKD Stage 1 (35%), CKD Stage 2 (48%) and CKD Stage 3 (17%)

Primary outcome:

Annual rate of TKV change (normalized as a percentage) for tolvaptan relative to placebo

Composite secondary outcome reflecting clinical progression:

- Worsening kidney function, defined as a persistent 25% reduction, i.e., reproduced over at least two weeks, in reciprocal serum creatinine during treatment (equivalent to a 33% increase in serum creatinine), from end of titration to last on-drug visit;
- Medically significant kidney pain, defined as requiring prescribed leave, last-resort analgesics, narcotic or anti-nociceptive, radiologic or surgical interventions;
- Worsening hypertension, defined as a persistent increase in blood pressure category, or an increase in anti-hypertensive medication(s); or
- Worsening albuminuria, defined as a persistent increase in albumin/creatinine ratio category (seen at 2 of 3 successive assessments).

Additional secondary outcome:

Rate of kidney function change, measured by the reciprocal of the serum creatinine level and calculated as estimated glomerular filtration rate ($eGFR_{CKD\text{-}EPI}$)

TKV: total kidney volume

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.
2. Torres VE et al. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2012; 367:2407-2418.

TOLVAPTAN DATA FROM 2 PIVOTAL TRIALS

DONE BY INNOVATOR (OTSUKA) IN PATIENTS WITH EARLIER TO LATER STAGES OF ADPKD

Design of the REPRISE Trial[1,2]

12-month, placebo-controlled trial

Interventions: Randomized trial with a 1:1 ratio

- Tolvaptan + standard of care vs. placebo + standard of care
- Patients were maintained on their highest tolerated dose for a period of 12 months but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses
- All patients remained on standard concomitant medications

Subjects: 1370 patients with ADPKD

- Randomization was stratified according to the baseline estimated GFR (≤ 45 or > 45 mL/min/1.73 m^2), patient age (≤ 55 or > 55 years) and TKV (≤ 2000 mL, > 2000 mL or unknown)

Baseline characteristics:

- Patient distribution by CKD Stage: CKD Stage 2 (5.2%), CKD Stage 3a (30%), CKD Stage 3b (45.1%) and CKD Stage 4 (19.5%)

Primary outcome:

Annualized change in eGFR from pre-treatment baseline to post-treatment follow-up for tolvaptan relative to placebo

Key secondary endpoint:

- Slope of the change in the eGFR that was derived from individual slopes for each patient, with adjustment for the duration of the observation and with interpolation to 1 year

TKV: total kidney volume

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.
2. Torres VE et al. Tolvaptan in Later-stage Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2017; 377(20):1930-1942.

EFFICACY ENDPOINTS OF TOLVAPTAN IN PATIENTS WITH ADPKD

Key Results of the TEMPO Trial[1,2]

EFFICACY ENDPOINT	RESULTS			
	Tolvaptan	Placebo	*p* value	Relative reduction
Annual increase in total kidney volume (TKV), % per year • TKV results were due to a combination of the secretory and anti-proliferative effects of tolvaptan. The secretory effect is largely reversible upon discontinuation: see Product Monograph for more information.	2.8%	5.5%	< 0.0001	49.2%
Clinical progression†; events/100 person-years	44	50	0.01	13.5%
Worsening hypertension	31	32	NS	-
Worsening albuminuria	8	8	NS	-
Clinically significant kidney pain	5	7	0.007	35.8%
Worsening kidney function	2	5	< 0.001	61.4%
Annual decrease in renal function, reciprocal of the sCr level	-2.6	-3.8	< 0.001	31.6%
Annual decrease in renal function, eGFR	-2.7	-3.6	< 0.0001	26.4%

NS: non-significant
† Composite of worsening kidney function, kidney pain, hypertension or albuminuria.
1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.
2. Torres VE et al. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2012; 367:2407-2418.

EFFICACY ENDPOINTS OF TOLVAPTAN IN PATIENTS WITH ADPKD



Key Results of the REPRISE Trial[1,2]

- 35% relative reduction in the rate of decline of kidney function was observed in tolvaptan patients (-2.34 vs. -3.61 with placebo, treatment effect of 1.27 mL/min/1.73 m^2/year, primary endpoint, $p < 0.0001$)
- Key secondary endpoint (eGFR slope) and all sensitivity analyses were significant ($p \leq 0.0005$)
- Subgroup analysis for the primary and key secondary endpoints demonstrated consistent treatment effects of tolvaptan for subjects in CKD Stages 2, 3a, 3b and 4

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.
2. Torres VE et al. Tolvaptan in Later-stage Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2017; 377(20):1930-1942.

TOLVAPTAN WARNING FROM PIVOTAL TRIALS

Potential for Idiosyncratic Hepatic Toxicity[1]

1. In the TEMPO 3:4 trial, 3 individuals taking tolvaptan experienced ALT > 3 x ULN with bilirubin > 2 x ULN
   - All 3 returned to normal liver function after stopping tolvaptan.

2. In the REPRISE trial, all patients were monitored monthly for liver enzymes elevation. In the single-blind tolvaptan run-in phase, elevations were observed in patients on tolvaptan. Overall, all patients recovered and no subject met Hy's laboratory criteria relative to laboratory values of potential clinical relevance, i.e., increases in hepatic enzymes (> 3 x ULN) with concomitant elevations in total bilirubin (> 2 x ULN).

3. In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported.

4. Data suggests that monthly liver function monitoring during treatment helps detect liver enzyme elevation early on.

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

PATIENT SELECTION CONSIDERATIONS FOR LUPIN-TOLVAPTAN[1]

- From TEMPO 3:4, patients most likely to benefit from LUPIN-TOLVAPTAN appear to be those who have rapidly-progressing ADPKD (meeting modified Ravine criteria), are at early stage of CKD, TKV ≥ 750 mL, and estimated creatinine clearance ≥ 60 mL/min.
- From REPRISE, patients most likely to benefit from LUPIN-TOLVAPTAN appear to be those at high risk of progressive eGFR decline based on renal function for age (18 to 65 years of age with baseline eGFR between 25 and 65 mL/min/1.73 m^2).



1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

LUPIN-TOLVAPTAN CONTRAINDICATIONS[1]

- Patients who have been asked to permanently discontinue tolvaptan in the past
- Patients with known or suspected hypersensitivity to tolvaptan, benzazepine or benzazepine derivatives (e.g., mirtazapine) or any of the excipients
- Patients with hypovolemia
- Patients with hypernatremia
- Patients with anuria
- Patients who do not have access to fluids or who cannot respond to the physiologic sensation of thirst
- Patients with a history, signs or symptoms of significant liver impairment or injury, excluding uncomplicated polycystic liver disease
- Concomitant use of strong CYP3A inhibitors, e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone
- Pregnancy
- Nursing women
- Patients with one of the following rare hereditary diseases: Galactose intolerance, Lapp lactase deficiency or Glucose-galactose malabsorption, because lactose is a non-medicinal ingredient in LUPIN-TOLVAPTAN

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

PURPOSE AND FEATURES OF THE LUPIN GENESIS PROGRAM FOR LUPIN-TOLVAPTAN

Goals of the Lupin Genesis program are as follows:

- Reduce the risk of liver injury that may occur with LUPIN-TOLVAPTAN
- Ensure appropriate patient selection for the treatment with LUPIN-TOLVAPTAN
- Document and ensure appropriate monitoring of hepatic function while on treatment with LUPIN-TOLVAPTAN
- Educate prescribers, healthcare professionals and patients about risk of adverse events and steps that should be taken to prevent or minimize them

Basic Features of the Lupin Genesis program are as follows:

- Available to be prescribed by nephrologists or specialists with expertise in the management of patients with ADPKD and a full understanding of the benefits and risks of tolvaptan therapy, including hepatic toxicity and monitoring requirements
- Provide education on LUPIN-TOLVAPTAN and the Lupin Genesis program to patients, prescribers and other healthcare professionals
- Provide access to consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form prior to initiation of treatment with LUPIN-TOLVAPTAN
- Distribution of LUPIN-TOLVAPTAN through patient's designated pharmacy, which will distribute LUPIN-TOLVAPTAN only after verifying consolidated PPAF enrollment form is documented with the Lupin Genesis program
- System to track liver function test of patients on LUPIN-TOLVAPTAN
- Patient permanent discontinuation list (non-rechallengeable patient status) for tolvaptan in ADPKD

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

THE CONSOLIDATED PATIENT-PRESCRIBER AGREEMENT FORM (PPAF)

ENROLLMENT FORM FOR LUPIN-TOLVAPTAN

Once the patient and the prescriber both decide to initiate treatment with LUPIN-TOLVAPTAN, it is required that they both co-sign a duly-documented, manufacturer- and product-specific, consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form.

For treatment-naive patients only, the patient and prescriber must co-sign the PPAF at the same time, in person.

Patient-Prescriber Agreement Form includes:

- Patient selection criteria for LUPIN-TOLVAPTAN
- Expected risks and benefits of treatment
- Need for mandatory hepatic function monitoring
- Statement that the patient understands the benefits and risks of treatment and that they agree to take blood tests



1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

STEPS TO BE TAKEN IN CASE HEPATIC TOXICITY OCCURS WITH LUPIN-TOLVAPTAN

As soon as you notice the onset of symptoms or signs that are consistent with hepatic injury, or if abnormal ALT or AST elevations are detected:

- **Immediately STOP** LUPIN-TOLVAPTAN's administration
- **Must ORDER** repeat liver tests, i.e., ALT, AST, total bilirubin, alkaline phosphatase, as soon as possible, ideally within 48–72 hours
- Liver function tests should be ordered at an increased frequency until symptoms/signs/laboratory abnormalities stabilize or resolve, after which re-initiation of LUPIN-TOLVAPTAN may be considered with great caution
- Report any adverse event to Lupin Pharma Canada at Phone: **1-866-488-6017** or Fax: **1-866-488-1457** or Email: **support@genesispsp.com**

ALT: alanine aminotransferase; AST: aspartate aminotransferase

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

WHEN TO PERMANENTLY DISCONTINUE LUPIN-TOLVAPTAN FOR HEPATIC TOXICITY[1]



LUPIN-TOLVAPTAN treatment should be stopped at once immediately upon confirmation of abnormal or elevated transaminase levels, and permanently discontinued if significant increases and/or clinical symptoms of hepatic injury persist.

Recommended guidelines for permanent discontinuation include:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN, for more than 2 weeks
- ALT or AST > 3 x ULN, **and** total bilirubin > 2 x ULN or INR > 1.5
- ALT or AST > 3 x ULN, with persistent symptoms of hepatic injury as noted above

Permanent discontinuation from receiving tolvaptan is a contraindication, and so once a patient has been permanently discontinued from receiving tolvaptan, treatment **must never be** restarted. The permanent discontinuation status of patients should be verified prior to initiation with LUPIN-TOLVAPTAN.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; INR: international normalized ratio

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

SUMMARY OF MAJOR DRUG INTERACTIONS WITH LUPIN-TOLVAPTAN[1]

- LUPIN-TOLVAPTAN is a substrate of CYP3A and co-administration with CYP3A inhibitors or CYP3A inducers may lead to a change in exposure. Patient response should be monitored and the dose should be adjusted as appropriate.
- Tolvaptan should not be taken with grapefruit juice. Please consult Product Monograph for detailed information.

RECOMMENDATION(S)	EXAMPLES
Concomitant use with strong CYP3A4 inhibitors is contraindicated as it may lead to significant increase in tolvaptan exposure	Ketoconazole, clarithromycin, ritonavir, saquinavir
Concomitant use with moderate CYP3A inhibitors also requires lowered dosing of LUPIN-TOLVAPTAN	Verapamil, fluconazole, erythromycin
Concomitant use of LUPIN-TOLVAPTAN with strong CYP3A inducers should be avoided	Rifampin, phenytoin, carbamazepine, St. John's Wort
Reduction in the dose of LUPIN-TOLVAPTAN may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors **Please note, however, concomitant use with those P-gp inhibitors that also act as strong CYP3A inhibitors (examples above) is contraindicated**	Cyclosporine, quinidine

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

SUMMARY OF OTHER WARNINGS AND PRECAUTIONS WITH LUPIN-TOLVAPTAN[1]

Dehydration	• Due to a prominent aquaretic effect, treatment with tolvaptan may result in dehydration, which constitutes a risk factor for renal dysfunction. Therefore, patients should be encouraged to drink water while taking LUPIN-TOLVAPTAN to avoid development of dehydration or hypernatremia, and to improve tolerability of tolvaptan
Anaphylaxis	• Patients have to be carefully monitored during treatment. If an anaphylactic reaction or other serious allergic reactions occur, administration of tolvaptan must be discontinued immediately and appropriate therapy initiated. Since hypersensitivity is a contraindication, treatment **must never be** restarted after an anaphylactic reaction or other serious allergic reactions • Patients with known hypersensitivity reactions to benzazepines or benzazepine derivatives (e.g., benazepril, conivaptan, fenoldopam mesylate or mirtazapine) may be at risk for hypersensitivity reaction to tolvaptan. If a hypersensitivity reaction is suspected, tolvaptan should be discontinued
Hypernatremia	• During treatment initiation, patients must be frequently monitored for serum sodium and volume status • If serum sodium increases above the normal range, treatment must be down-titrated or discontinued promptly
Hyperkalemia	• Treatment with tolvaptan could result in increased serum potassium • Serum potassium levels should be monitored carefully after starting tolvaptan
Hyperuricemia	• Treatment with tolvaptan may lead to increases in serum uric acid and clinical gout • Uric acid concentrations should be evaluated prior to initiation of LUPIN-TOLVAPTAN treatment, and as indicated during treatment
Hypotension	• Increased incidence of hypotension-related adverse events including dizziness and syncope in patients taking concomitant anti-hypertensives
Serum sodium abnormalities	• Must be corrected prior to initiation of LUPIN-TOLVAPTAN treatment

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

SUMMARY OF OTHER WARNINGS AND PRECAUTIONS WITH LUPIN-TOLVAPTAN[1]

Vasopressin analogues	• It is not recommended to administer tolvaptan with vasopressin analogues
Special populations	• Women of childbearing potential must have effective contraceptive measures prior to and during tolvaptan use • Tolvaptan has not been studied in pediatric patients (< 18 years) with ADPKD. Its use is not recommended in this patient population • Safety and effectiveness in geriatric patients have not been studied • Tolvaptan is contraindicated in patients with clinically relevant impairment of hepatic function • Tolvaptan is contraindicated in anuric patients
Cognitive & motor impairment	• No controlled trials of the effects of tolvaptan on driving performance. While driving vehicles or operating machines, dizziness, asthenia and syncope may occur occasionally

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

DOSING RECOMMENDATIONS FOR LUPIN-TOLVAPTAN IN PATIENTS WITH ADPKD[1]

Dosing Details	
Regimen overview	2 doses daily: One (larger dose) upon waking each morning and one (smaller dose) 8 hours later each evening
Available dosages	45 + 15 mg, 60 + 30 mg, 90 + 30 mg
Initial dosage	45 + 15 mg (60 mg)
Titration	Maintain at least weekly intervals between titrations
Target split dose regimen	Up to 120 mg (90 + 30 mg) per day if tolerated

Name of Practice/Prescriber
Address and Phone Number

Date: _____

Patient Name: _____ Date of Birth: _____

Address: _____

Rx

LUPIN-TOLVAPTAN 60 mg (45 + 15 mg)

Take 45 mg tablet upon waking in AM
and 15 mg taken 8 hours later in evening

Dispense 4 blister packs (56 tablets) of
45 + 15mg

MD: _____ Signature: _____

The aim of dose titration is to block the activity of vasopressin at the renal V_2-receptor as completely and constantly as possible, while maintaining acceptable fluid balance, in order to achieve optimal effects on TKV progression or diminution of renal function decline.

The adequacy of vasopressin suppression at a given dose of LUPIN-TOLVAPTAN can be monitored through measurement of urine osmolality and may be used to optimize the clinical benefit of LUPIN-TOLVAPTAN in ADPKD patients.

TKV: total kidney volume
Consult the Product Monograph for complete dosing, titration, and patient management information.
1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

DOSING RECOMMENDATIONS FOR LUPIN-TOLVAPTAN IN PATIENTS WITH ADPKD[1]



- Prior to initiation of treatment with LUPIN-TOLVAPTAN, it is important to determine whether expected benefit-risk is deemed to be favourable for the individual patient to be treated.
- Based on TEMPO 3:4 and REPRISE, patients most likely to benefit from LUPIN-TOLVAPTAN appear to be those with rapidly progressing ADPKD, early stage of CKD, TKV ≥ 750 mL, estimated creatinine clearance ≥ 60 mL/min and/or those at high risk of progressive eGFR decline based on renal function for age (18 to 65 years of age with baseline eGFR between 25 and 65 mL/min/1.73 m^2).
- All patients need to be apprised of the risk of idiosyncratic drug-induced liver injury associated with tolvaptan use in ADPKD, and the need for ongoing monitoring of hepatic function during LUPIN-TOLVAPTAN treatment. Consult the Product Monograph for complete dosing, titration, and patient management information.

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

TRANSITIONING PATIENTS TO LUPIN-TOLVAPTAN: DISCUSSING GENERIC ALTERNATIVES WITH PATIENTS

Patients transitioning from a brand name tolvaptan product may have questions about generic alternatives.

LUPIN-TOLVAPTAN meets all the same safety and efficacy criteria as the brand name drug and Health Canada has approved it as interchangeable. An overview of generic alternatives and interchangeability is also included in the Patient Information Guide.

For more information about generic alternatives, patients can visit “Access to Generic Drugs in Canada” at https://bit.ly/genericscanada or scan the QR code.



LUPIN-TOLVAPTAN IN PATIENTS WITH ADPKD: SUMMARY[1]



- LUPIN-TOLVAPTAN is indicated to slow the progression of kidney enlargement and kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD)
- Hepatic safety has been shown to be a major concern with tolvaptan
    - Therefore, participation in the Lupin Genesis program is a REQUIREMENT for both prescribers and patients

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

1 **What is the indication for LUPIN-TOLVAPTAN in patients with autosomal dominant polycystic kidney disease (ADPKD)?**

a) Improve kidney function in patients with ADPKD

b) Slow the progression of kidney function decline in patients with ADPKD

c) Slow the progression of kidney enlargement and kidney function decline in patients with ADPKD

d) Stop the progression of kidney enlargement in patients with ADPKD

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

1 **What is the indication for LUPIN-TOLVAPTAN in patients with autosomal dominant polycystic kidney disease (ADPKD)?**

Option c) is the right answer, as explained below.

The indication of LUPIN-TOLVAPTAN as per the Product Monograph is "to slow the progression of kidney enlargement and kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD)." This information can be found on slide #3 of this Prescriber & Healthcare Professional Training Module.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

2 **What was the approximate mean total kidney volume (TKV) at baseline among subjects in the TEMPO 3:4 trial comparing tolvaptan to placebo in ADPKD?**

a) 780 mL

b) 1250 mL

c) 1700 mL

d) 2100 mL

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

2 **What was the approximate mean total kidney volume (TKV) at baseline among subjects in the TEMPO 3:4 trial comparing tolvaptan to placebo in ADPKD?**

Option c) is the right answer; approximate mean TKV was 1700 mL, as explained below.

- The entry criterion to be included in the TEMPO 3:4 study was a TKV of 750 mL or greater. The mean TKV at baseline was 1705 mL in the tolvaptan group and 1668 mL in the placebo group.
- Please refer to slide #4 of this Prescriber & Healthcare Professional Training Module for more information.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

3 **In the TEMPO 3:4 trial, what were the percent annual increases in TKV for tolvaptan and placebo groups?**

a) Placebo at 5.5 %; Tolvaptan at 2.8%

b) Placebo at 0.2%; Tolvaptan at 4.2%

c) Placebo at 4.2%; Tolvaptan at 0.2%

d) Placebo at 2.8%; Tolvaptan at 5.5%

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

3 **In the TEMPO 3:4 trial, what were the percent annual increases in TKV for tolvaptan and placebo groups?**

Option a) is the right answer with placebo at 5.5% and tolvaptan at 2.8%, as explained below.

This is considered a statistically significant difference ($p < 0.0001$).
This represents a 49.2% reduction in growth rate averaged over 3 years ($p < 0.0001$).

- TKV results were due to a combination of the secretory and anti-proliferative effects of tolvaptan. The secretory effect is largely reversible upon discontinuation; please see Product Monograph for more information.
- Please refer to slide #6 of this Prescriber & Healthcare Professional Training Module for more information.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

4 **In clinical trials, how many patients in the tolvaptan group experienced an increase in alanine aminotransferase (ALT) that was 3 times the upper limit of normal, and with a bilirubin increase that was twice the upper limit of normal?**

a) 1

b) 5

c) 3

d) 0

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

4 **In clinical trials, how many patients in the tolvaptan group experienced an increase in alanine aminotransferase (ALT) that was 3 times the upper limit of normal, and with a bilirubin increase that was twice the upper limit of normal?**

Option c) is the right answer, with explanation below.

- In clinical trials, 3 individuals taking tolvaptan experienced ALT greater than 3 times the upper limit of normal concomitantly with total bilirubin greater than twice the upper limit of normal. This includes 2 of 957 patients in the TEMPO study and 1 in an open-label study. All 3 of these individuals returned to normal liver function after stopping tolvaptan within 1 to 4 months.
- Please see slide #8 of this Prescriber & Healthcare Professional Training Module for more information.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

5 **Post initiation of LUPIN-TOLVAPTAN, after the first 18 months, what are the requirements on blood testing for hepatic transaminases?**

a) Blood testing is not required for LUPIN-TOLVAPTAN as it is generic

b) Every month

c) Every 3 months

d) Every 3–6 months

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

5 **Post initiation of LUPIN-TOLVAPTAN, after the first 18 months, what are the requirements on blood testing for hepatic transaminases?**

Option c) is the right answer, with explanation below.

- Under the warning and precautions section in the LUPIN-TOLVAPTAN Product Monograph, it is mentioned that tolvaptan use has led to idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations of total bilirubin.
- To help mitigate the risk of liver injury that has been seen, blood testing for hepatic transaminases and for total bilirubin is required prior to initiation of LUPIN-TOLVAPTAN, then hepatic transaminases continuing monthly for 18 months, every 3 months for the next 12 months, and then every 3–6 months thereafter during treatment with LUPIN-TOLVAPTAN. Please refer to the Product Monograph and slide #45 of this Prescriber & Healthcare Professional Training Module for more information.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

6 **What liver function test results warrant permanent discontinuation of LUPIN-TOLVAPTAN?**

a) ALT or AST > 3 times ULN, with persistent symptoms of hepatic injury

b) ALT or AST > 3 times ULN, **and** total bilirubin > 2 times ULN or INR > 1.5

c) ALT or AST > 5 times ULN, for more than 2 weeks

d) ALT or AST > 8 times ULN

e) All of the above

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

6 **What liver function test results warrant permanent discontinuation of LUPIN-TOLVAPTAN?**

Option e) is the right answer. All of the above warrant permanent discontinuation of LUPIN-TOLVAPTAN.

- The LUPIN-TOLVAPTAN Product Monograph states that permanent discontinuation is recommended for:
  - ALT or AST > 8 x ULN;
  - ALT or AST > 5 x ULN, for more than 2 weeks;
  - ALT or AST > 3 x times ULN, **and** total bilirubin > 2 x ULN or INR > 1.5; or
  - ALT or AST > 3 x times ULN, with persistent symptoms of hepatic injury.
- Please refer to the Product Monograph and slide #14 of this Prescriber & Healthcare Professional Training Module for this information.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

7 **As per the TEMPO 3:4 trial, patients who are most likely to benefit from tolvaptan are patients who have rapidly-progressing ADPKD, or those at a stage of incipient rapid progression. Based on this, which factor or factors are associated with rapid progression of ADPKD?**

a) CKD Stage 2–3

b) Presence of systemic hypertension or albuminuria

c) Large total renal cyst mass for a given age, as measured by TKV

d) Rapid deterioration of renal function

e) All of the above

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

7 **As per the TEMPO 3:4 trial, patients who are most likely to benefit from tolvaptan are patients who have rapidly-progressing ADPKD, or those at a stage of incipient rapid progression. Based on this, which factor or factors are associated with rapid progression of ADPKD?**

Option e) is the right answer. Stating all of the above is correct, with explanation below.

- As per TEMPO 3:4, patients who are most likely to benefit from tolvaptan appear to be those with rapidly-progressing ADPKD, or at a stage of incipient rapid progression, but before widespread destruction of renal architecture.
- The factors associated with rapid progression of ADPKD include: large total renal cyst mass for a given age, as measured by TKV; CKD Stage 2–3; rapid deterioration of renal function; and presence of systemic hypertension or albuminuria.
- Please refer to the Product Monograph and slide #14 of this Prescriber & Healthcare Professional Training Module for this information.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

8 **Is the statement true or false?**

"For prescription of LUPIN-TOLVAPTAN, the consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form MUST be completed."

a) This statement is true

b) This statement is false

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

8

Is the statement true or false?

"For prescription of LUPIN-TOLVAPTAN, the consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form MUST be completed."

Option a) is the right answer.

For prescription of LUPIN-TOLVAPTAN, the consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form must be completed.

- When the patient and provider decide to undertake treatment with LUPIN-TOLVAPTAN, a signed, duly-documented, manufacturer- and product-specific, consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form is required.
- The consolidated PPAF enrollment form includes relevant patient selection criteria, expected risks and benefits of treatment, need for mandatory hepatic function monitoring, and a statement that the patient understands the benefits and risks of treatment and that they agree to take blood tests as prescribed by the doctor to start and remain on treatment.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

9 **Tolvaptan is a substrate of which hepatic isoenzyme(s)?**

a) CYP3A

b) CYP2A

c) CYP2C

d) CYP1A

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

9 **Tolvaptan is a substrate of which hepatic isoenzyme(s)?**

Option a) is the right answer, with explanation below.

- Tolvaptan is a substrate of CYP3A.
- The recommendations based on this are the following:
  - Concomitant use of LUPIN-TOLVAPTAN with strong CYP3A inhibitors is contraindicated as it may lead to a significant increase in tolvaptan exposure.
  - Concomitant use of LUPIN-TOLVAPTAN with moderate CYP3A inhibitors also requires lowered dosing of tolvaptan.
  - Tolvaptan should not be taken with grapefruit juice.
  - Concomitant use of LUPIN-TOLVAPTAN with strong CYP3A inducers should be avoided, and reduction in the dose may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors. However, concomitant use with those P-gp inhibitors that also act as strong CYP3A inhibitors is contraindicated.
  - Please refer to the Product Monograph and slide #15 of this Prescriber & Healthcare Professional Training Module for more information.

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

10 **What is the recommended initial dose of LUPIN-TOLVAPTAN?**

a) 90 mg upon waking, 15 mg approx. 8 hours later

b) 45 mg upon waking, 15 mg approx. 8 hours later

c) 60 mg upon waking, 30 mg approx. 8 hours later

d) None of the above

KNOWLEDGE CHECK QUESTIONS FOR PRESCRIBERS & HEALTHCARE PROFESSIONALS

10 **What is the recommended initial dose of LUPIN-TOLVAPTAN?**

Option b) is the right answer, with explanation below.

- The initial dosage for LUPIN-TOLVAPTAN is generally 60 mg tolvaptan per day, as a split-dose regimen of 45 + 15 mg, with 45 mg taken upon waking and 15 mg taken approximately 8 hours later.
- The initial dose should be titrated upward to a split-dose regimen of 90 mg tolvaptan (60 + 30 mg) per day, and then to a target split-dose regimen of 120 mg tolvaptan (90 + 30 mg) per day, if tolerated, with at least weekly intervals between titrations.
- Dose titration should be performed judiciously to ensure that high doses are not poorly tolerated through overly rapid up-titration.

Safety Information (1/4)[1]

Indications and clinical use:

LUPIN-TOLVAPTAN is indicated to slow the progression of kidney enlargement and kidney function decline in adult patients with autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, kidney enlargement reflects renal cyst burden.

- In order to select patients who might best benefit from the effects of LUPIN-TOLVAPTAN, clinical trials evaluated ADPKD patients having a total kidney volume (TKV) ≥ 750 mL, and/or renal function corresponding to a CKD-EPI eGFR ≥ 25mL/min/1.73 m^2, at the time of initiation of treatment.
- LUPIN-TOLVAPTAN treatment should be initiated and monitored under the supervision of a nephrologist or specialist with expertise in the management of patients with ADPKD and a full understanding of the benefits and risks of tolvaptan therapy, including hepatic toxicity and monitoring requirements.
- Careful consideration and discussion of the appropriateness of LUPIN-TOLVAPTAN treatment should be undertaken between the prescriber and patient before initiation of therapy, taking into account the potential benefits and risks of treatment. Upon mutual agreement to undertake treatment with LUPIN-TOLVAPTAN, a signed, duly-documented, manufacturer- and product-specific, consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form is required outlining the relevant patient selection criteria to be considered, expected benefits and risks of treatment, and the need for mandatory hepatic function monitoring.
- **Lupin Genesis program:** LUPIN-TOLVAPTAN is available for treatment of patients with ADPKD only through a manufacturer- and Lupin Genesis program conducted and maintained by, or for, the market authorization holder of LUPIN-TOLVAPTAN. A duly signed manufacturer- and product-specific consolidated PPAF enrollment form is required for enrollment in the Lupin Genesis program. For more information on the Lupin Genesis program, please call 1-866-488-6017.

Safety and effectiveness have not been established in geriatrics (> 65).

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

Safety Information (2/4)[1]

Contraindications:

LUPIN-TOLVAPTAN is contraindicated in:

- Patients who have been asked to permanently discontinue tolvaptan in the past
- Patients with known or suspected hypersensitivity to tolvaptan, benzazepine or benzazepine derivatives (e.g., mirtazapine) or any of the excipients
- Patients with hypovolemia
- Patients with hypernatremia
- Patients with anuria
- Patients who do not have access to fluids or who cannot respond to the physiologic sensation of thirst
- Patients with a history, signs or symptoms of significant liver impairment or injury, excluding uncomplicated polycystic liver disease
- Concomitant use of strong CYP3A inhibitors, e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone
- Pregnancy
- Nursing women
- Patients with one of the following rare hereditary diseases: Galactose intolerance, Lapp lactase deficiency or Glucose-galactose malabsorption, because lactose is a non-medicinal ingredient in LUPIN-TOLVAPTAN

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

Safety Information (3/4)[1]

Warnings and precautions:

Idiosyncratic hepatic toxicity: LUPIN-TOLVAPTAN has been associated with drug-induced hepatocellular injury, as seen by elevations of serum alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations of total bilirubin (BT). To help mitigate the risk of liver injury, blood testing for hepatic transaminases and for total bilirubin is required prior to initiation of LUPIN-TOLVAPTAN, then blood testing for hepatic transaminases is required:

- monthly for 18 months
- every 3 months for the next 12 months
- Then, at 3–6 month intervals thereafter during treatment with LUPIN-TOLVAPTAN

Therefore, LUPIN-TOLVAPTAN is available for treatment of patients with ADPKD only through a Lupin Genesis program conducted and maintained by, or for, the market authorization holder of LUPIN-TOLVAPTAN.

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

Safety Information (4/4)[1]

Warnings and precautions:

- Dehydration
- Drug Interactions with moderate CYP3A inhibitors, CYP3A inducers or P-glycoprotein inhibitors
- Hepatotoxicity
- Anaphylaxis
- Hypernatremia: Concomitant use with hypertonic saline solutions or drugs that may increase serum sodium should be avoided
- Hyperkalemia
- Hyperuricemia
- Hypotension related adverse events: In patients taking anti-hypertensive agents concomitantly with tolvaptan, an increased incidence of hypotension-related adverse events was observed, including dizziness and syncope
- Serum sodium abnormalities must be corrected prior to initiation of tolvaptan therapy
- Women of childbearing potential must have effective contraceptive measures in place prior to and during tolvaptan use
- Vasopressin analogues: It is not recommended to administer tolvaptan together with vasopressin analogues.
- Potential for cognitive and motor impairment: When driving vehicles or using machines, it should be taken into account that occasionally dizziness, asthenia and syncope may occur.

For more information:

Consult the Product Monograph at www.LupinGenesis.com for adverse reactions, drug interactions, dosing, monitoring tests, and conditions of clinical use. The Product Monograph is also available by calling 1-866-488-6017.

1. LUPIN-TOLVAPTAN Product Monograph. Lupin Pharma Canada Ltd. April 25th, 2025.

Resources

Explore the resources available to support you, your staff, and your patients:

- Consolidated Patient-Prescriber Agreement Form (PPAF) enrollment form
- Prescriber Guide
- Nurse Checklist
- Liver Function Test Fax-Back Form
- Patient Information Brochure (including patient wallet card)
- Patient Welcome Kit

These resources are available at www.LupinGenesis.com or by calling 1-866-488-6017.

Contact the Lupin Genesis team:

1-866-488-6017

support@genesispsp.com

Hours of operation:
Mon - Fri 9:00 am - 5:00 pm EST



LUPIN PHARMA CANADA

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LUPIN GENESIS PATIENT SUPPORT PROGRAM