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Prescriber Guide
For Healthcare Professionals Only

TOLVAPTAN LUPIN

(tolvaptan tablets)

Contents

About This Guide

This guide offers crucial information for healthcare professionals (HCPs) prescribing Tolvaptan Lupin (tolvaptan tablets) and keeping track of patients being treated with Tolvaptan Lupin.

It will help you to:

- identify patients suitable for treatment with Tolvaptan Lupin.
- recognise the potential risks and benefits of treatment with Tolvaptan Lupin.
- titrate and adjust the dose of Tolvaptan Lupin as required.
- monitor and manage hepatic safety.

This manual is not meant to be used in place of the complete Product Information (PI) – rather, it is meant to be utilised in conjunction with it. It is not intended to replace professional or clinical judgement.

Prescriber education and certification on the risk of liver injury and the importance of regular liver function monitoring is compulsory. Prescribers must confirm review of educational materials by signing the Prescriber Certification Form and returning it to Generic Health. Pharmacists should only dispense Tolvaptan Lupin prescribed by certified nephrologists.

This guide is only intended for Healthcare Professionals only when prescribing Tolvaptan Lupin for autosomal dominant polycystic kidney disease (ADPKD).

This guide is also available from Generic Health's website:
www.generichealth.com.au/tolvaptan/prescribers

Introducing Tolvaptan Lupin

WARNING: Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations in bilirubin-total (BT). To help mitigate the risk of liver injury, blood testing for hepatic transaminases is required prior to initiation of Tolvaptan Lupin, then continually monthly for 18 months, then every 3 months thereafter during treatment with Tolvaptan Lupin (see Section 4.4 Special Warnings and Precautions for Use in the full Product Information). Prescriber education and certification on the risk of liver injury and the importance of regular liver function monitoring is mandatory. These are available through the Tolvaptan portal on the Generic Health website.

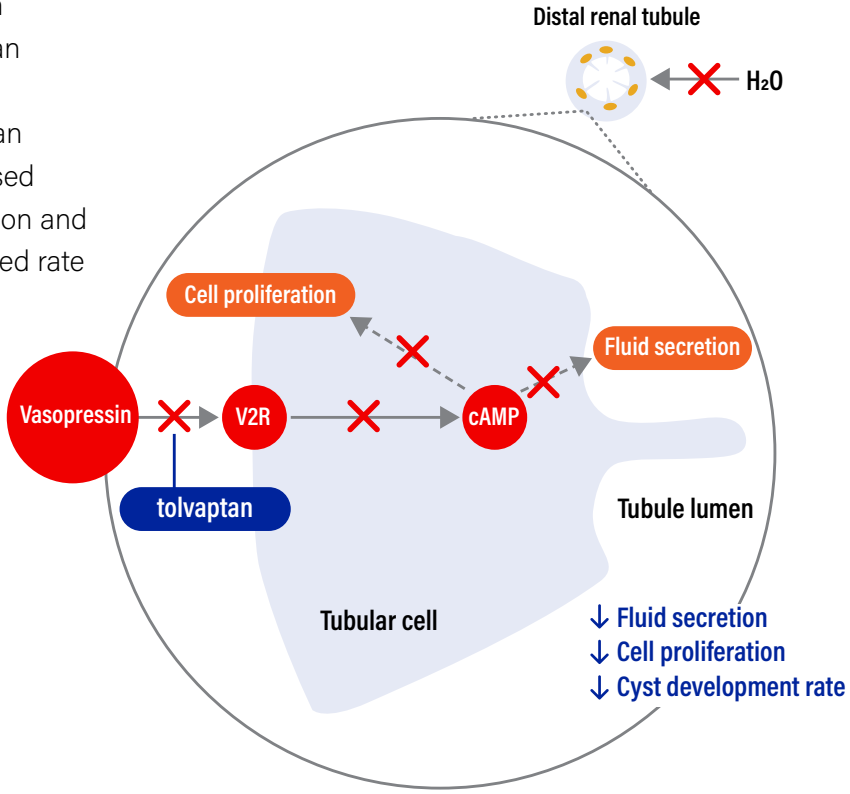
Mechanism of Action

Tolvaptan is a vasopressin antagonist that specifically blocks the binding of arginine vasopressin (AVP) at the V2 receptors of the distal portions of the nephron[1]. In autosomal dominant polycystic kidney disease (ADPKD), elevated renal levels of cyclic Adenosine Monophosphate (cAMP) are responsible for promoting cystic cell proliferation and secretion of fluid into the cysts. AVP stimulates cAMP production in collecting ducts and the distal nephron, which are believed to be the major sites of cyst development in ADPKD[2,3]. By blocking vasopressin, tolvaptan decreases adenylate cyclase activity and intracellular cAMP concentrations, which can result in increased water clearance, decreased urine osmolality, a decreased rate of formation and enlargement of kidney cysts, and a decreased rate of growth of total kidney volume[1,3].

Indication

Tolvaptan Lupin is indicated to slow the progression of cyst development and renal insufficiency of AKPKD in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease[1].

Tolvaptan Mechanism of Action



Adapted from Torres VE. *Adv Chronic Kidney Dis* 2010; 17:190-204.
Reif GA et al. (2011). *AM J Physial Renal Physiol.* 301(5): F1005-13

Identifying Patients With Disease Progression

In ADPKD, kidney enlargement reflects renal cyst burden. Increased kidney size and renal cyst burden are indicative of disease progression as well as declining kidney function[5]. The KHA-CARI (see Glossary) guidelines recommend measuring kidney function decline in patients with ADPKD by eGFR CKD-EPI (see Glossary) and albuminuria to monitor disease progression[6]. ADPKD patients most likely to benefit from Tolvaptan Lupin appear to be those with rapidly-progressing ADPKD[1,7].

Predictors of Rapid Progression

Factors associated with rapid progression may include any of the following[8]:

- hypertension (early onset).
- high kidney volume compared to the age-corrected mean for ADPKD patients.
- rapid deterioration of renal function.
- gross haematuria.
- PKD1 mutations or family history of ADPKD with early end-stage renal disease (especially truncating mutations).

Prescribing Tolvaptan Lupin

The Therapeutic Goods Administration has stipulated that prescriber education and certification on the risk of liver injury and the importance of liver function monitoring must be done monthly for the first 18 months of therapy and every 3 months thereafter.

Tolvaptan Lupin treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD, who have a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements[1].

Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in bilirubin-total (BT). While these concomitant elevations were reversible with prompt discontinuation of tolvaptan, they represent a potential for significant liver injury[1].

Tolvaptan Lupin can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine, or jaundice) can reduce the risk of severe hepatotoxicity.

To mitigate the risk of significant and/or irreversible liver injury, blood testing for hepatic transaminases and bilirubin is required prior to initiation of Tolvaptan Lupin, continuing monthly for 18 months and at regular 3-month intervals thereafter[1].

Precautions[1]

Idiosyncratic Hepatic Toxicity

Tolvaptan has been associated with idiosyncratic elevations of blood ALT and AST with infrequent cases of concomitant elevations in BT[1]. Prescribing physicians must comply fully with the safety measures outlined in this section and in the PI.

Monitoring

Tolvaptan Lupin should only be supplied to patients whose physician has determined that liver function supports continued therapy.

Criteria for Permanent Discontinuation[1]

Recommended guidelines for permanent discontinuation include:

- ALT or AST >8-times ULN;
- ALT or AST >5-times ULN for more than 2 weeks;
- ALT or AST >3-times ULN and (BT >2-times ULN or international normalised ratio >1.5);
- ALT or AST >3-times ULN with persistent symptoms of hepatic injury noted above.

Differential Diagnosis for Liver Function

While tolvaptan may cause liver abnormalities in some patients, it is important to investigate and treat any other potential causes of abnormal liver function.

Monitoring to Mitigate the Risk of Significant and/or Irreversible Liver Injury

When Liver Function is Normal

- Monitor ALT, AST and BT:
  - prior to initiation;
  - monthly for 18 months; then
  - every 3 months from 18 months onwards.
- Concurrent monitoring for symptoms that may indicate liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice) is recommended[1].

When Liver Function is Abnormal[1]

(Liver function tests (LFTs) do not meet criteria for permanent discontinuation)

Prior to initiating Tolvaptan Lupin:

Treatment can start only if the potential benefit of treatment outweighs the potential risks. The advice of a hepatologist is recommended.

During treatment with Tolvaptan Lupin:

- At the onset of symptoms or signs consistent with hepatic injury or if clinically significant abnormal ALT or AST increases are detected during treatment, Tolvaptan Lupin administration must be immediately interrupted.
- Repeat tests, including ALT, AST, BT and alkaline phosphatase (AP), must be obtained as soon as possible (ideally within 48-72 hours)
- Testing must continue at increased time frequency until symptoms/signs/laboratory abnormalities stabilise or resolve, at which point Tolvaptan Lupin may be cautiously reinitiated.
- If the abnormal liver tests results are determined to be definitely related to Tolvaptan Lupin therapy, restarting therapy is not recommended.
- If ALT, AST, BT levels remained below the permanent discontinuation threshold, and if it is determined that Tolvaptan Lupin would still benefit the patient, Tolvaptan Lupin may be cautiously reinitiated with more frequent monitoring at the same or a lower dose.
- In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times ULN, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.

When Liver Function is Abnormal[1]

(LFTs meet criteria for permanent discontinuation)

- The use of Tolvaptan Lupin is contraindicated.

Access to Water

- Tolvaptan Lupin may cause adverse reactions related to water loss, such as thirst, polyuria, nocturia, and pollakiuria. Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amount of these fluids.
- Patients must be instructed to drink water or other aqueous fluids at the first sign of thirst in order to avoid excessive thirst or dehydration. In addition, regardless of whether they are thirsty, patients must consume 1 to 2 glasses of fluid before going to bed and must rehydrate overnight with each episode of nocturia.
- Volume status must be monitored because treatment with Tolvaptan Lupin may result in severe dehydration.

Use in Pregnancy (Category D)

- Tolvaptan Lupin must not be used during pregnancy.
- Women of childbearing potential must use adequate contraceptive measures during treatment with Tolvaptan Lupin.
- Women should continue using contraceptives for at least 1 month after stopping treatment[9].

Use in Lactation[1]

- Tolvaptan Lupin is contraindicated during lactation.
- It is unknown whether tolvaptan is excreted in human breast milk. Studies in rats have shown excretion of tolvaptan in milk.
- The potential risk for humans is unknown.

Other Precautions

Review the PI for a full list and explanation of precautions.

Contraindications[1]

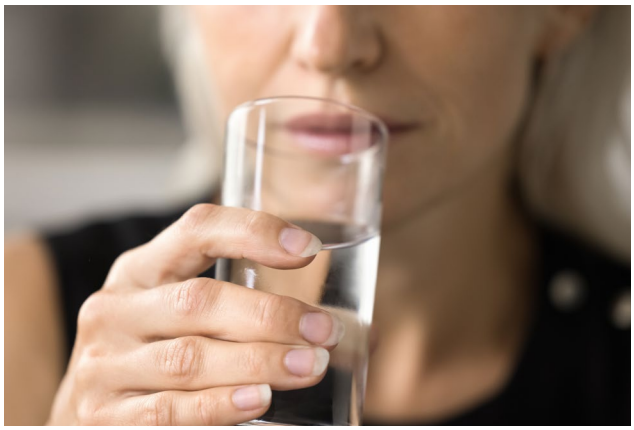
Tolvaptan Lupin is contraindicated in patients with any of the following:

- hypersensitivity to the active substance (tolvaptan), benzazepine derivatives or to any of the excipients listed in the PI.
- elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan.
- volume depletion (hypovolaemia).
- anuria.
- hypernatraemia.
- patients who cannot perceive or respond to thirst.
- pregnancy.
- lactation.

Dosing and Titration[1]

Split Dose Regimen

Tolvaptan Lupin is taken twice a day. The total daily dose is given as a split dose regimen, with a higher dose taken in the morning (at least 30 minutes before the morning meal) and a second, lower dose taken 8 hours later (with or without food). Tolvaptan Lupin should not be taken with grapefruit juice as it may increase the peak tolvaptan concentration.



Dose Titration Process

The aim of dose titration is to block the activity of vasopressin at the renal V2 receptor as completely and constantly as possible, while maintaining acceptable fluid balance, in order to achieve optimal effects on kidney volume progression or diminution of renal function decline. To maximise the potential benefit of Tolvaptan Lupin therapy, patients should be maintained on the highest tolerable dose.

Titration should be done cautiously to ensure that high doses are not poorly tolerated through overly rapid up-titration. In addition, dosing may be down-titrated and up-titrated again as appropriate. Titration intervals should be of at least 1 week.

The dose should be up-titrated as below:

	Initial Dose		First Titration		Second Titration
Morning Dose (at least 30 minutes before meal)	45 mg	At least 1 week after initial dose (if tolerated) →	60 mg	At least 1 week after first titration (if tolerated) →	90 mg
Second Dose (8 hours later with or without food)	15 mg		30 mg		30 mg
Total Daily Dose	**60 mg**		**90 mg**		**120 mg**

Importance of Adherence

Patients should be told that unnecessary treatment interruption should be avoided and that daily adherence to Tolvaptan Lupin is important to achieve the best possible outcomes in terms of diminution of renal cyst progression and preservation of renal function.

Missed Doses

If a dose is missed, patients should take the dose as soon as they remember on the same day. If patients do not take their tablets on one day, they should take their normal dose on the next day. Patients MUST NOT take a double dose to make up for forgotten individual doses.

Dose Adjustments and Interactions With Other Medicines[1]

Tolvaptan Lupin is a substrate of CYP3A and co-administration with CYP3A inhibitors or inducers may lead to changes in tolvaptan exposure. Concomitant use of strong CYP3A inducers should be avoided.

Dose adjustment is not required in patients with renal impairment or mild to moderate hepatic impairment (Child-Pugh classes A and B).

Table of Interactions and Dose Adjustments

Interactions	Dose Adjustments
Strong CYP3A Inhibitors (eg. itraconazole, ketoconazole, ritonavir, clarithromycin, saquinavir)	• Substantial dose reduction is required: – Split dose regimens of 120 mg/day (90+30) and 90 mg/day (60+30): down-adjust to 30 mg once-daily upon waking. – Split dose regimens of 60 mg/day (45+15): down-adjust to 15 mg once a day upon waking. – Treatment should proceed with caution. If these doses are not well tolerated, further down-titration should be considered or co-administration discontinued.
Moderate CYP3A Inhibitors (eg. amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil)	• Dose reduction is required: – Split dose regimen of 120 mg/day (90+30): down-adjust to 60 mg/day (45+15). – Split dose regimen of 90 mg/day (60+30): down-adjust to 45 mg/day (30+15). – Split dose regimen of 60 mg/day (45+15): down-adjust to 30 mg/day (15+15).
CYP3A Inducers (eg. rifampicin, rifabutin, rifapentin, phenytoin, carbamazepine, and St. John's Wort)	• Avoid concomitant use. • CYP3A inducers decrease tolvaptan exposure and efficacy.
P-gp Inhibitors (eg. cyclosporine, quinidine)	• Reduction in the dose of tolvaptan may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors. • If P-gp inhibitor also acts as a strong CYP3A inhibitor, substantial dose reduction of Tolvaptan Lupin is required as mentioned above.

Table of Interactions and Dose Adjustments (continued)

Interactions	Dose Adjustments
Products That Increase Serum Sodium Concentration	• Concomitant use may result in a higher risk for developing hypernatraemia and is not recommended.
Diuretics	• May require interruption or dose reduction of tolvaptan and/or diuretics if dehydration or renal dysfunction occur.
CYP3A Substrates	• In healthy subjects, tolvaptan had no effect on the plasma concentrations of some other CYP3A substrates (eg. warfarin or amiodarone). • Tolvaptan increased plasma levels of lovastatin by 1.3- to 1.5-fold, which, despite absence of clinical relevance, indicates tolvaptan can potentially increase exposure to CYP3A4 substrates.
Digoxin	• Steady state digoxin concentrations were increased (1.3-fold in maximum observed plasma concentration [C_{max}] and 1.2-fold in area under the plasma concentration-time curve over the dosing interval [AUCT]) when co-administered with multiple once-daily 60 mg doses of tolvaptan. • Patients receiving digoxin or other narrow therapeutic P-gp substrates (eg. dabigatran) must be managed cautiously and evaluated for excessive effects.
Diuretics or Non-diuretic Anti-hypertensive Drugs	• Standing blood pressure was not routinely measured in ADPKD trials; therefore, a risk of orthostatic/postural hypotension cannot be excluded.
Vasopressin Analogues (eg. desmopressin)	• Effect of vasopressin analogues may be attenuated when co-administered with tolvaptan. • Co-administration of tolvaptan with vasopressin analogues is not recommended.
Smoking and Alcohol	• Data too limited to determine possible interactions.

For a full list of known interactions, please review the Product Information or check the Australian Medicines Handbook at **amhonline.amh.net.au**

Pharmaceutical Benefits Scheme (PBS) Patient Eligibility Criteria

Check Patient Eligibility 1

PBS Treatment Initiation Criteria

- Must be treated by a nephrologist.

PBS Clinical Criteria

- Adult ADPKD patient.
- Patient must have an eGFR between 30 mL/min/1.73 m^2 and 89 mL/min/1.73 m^2 at the initiation of treatment.

AND

- Patient must have or have had rapidly progressing disease at the time of initiation.

Rapid progressing disease is defined by either of the following:

- a decline in eGFR ≥5 mL/min/1.73 m^2 within one year; or
- an average decline in eGFR of ≥2.5 mL/min/1.73 m^2 per year over a period of 5 years.

Apply for PBS Authority 2

PBS Authority

- For initial treatment TELEPHONE Authority Required: call 1800 888 333 or apply via the Services Australia PBS authority's website: www.servicesaustralia.gov.au/hpos.

PBS Listing – Strength and Pack Size

- For initiating treatment Tolvaptan 15 mg tablet [28] & Tolvaptan 45 mg tablet [28], (56) Item code: **11602P**.
- For continuing treatment STREAMLINED Authority Required via code: **8288**.
  - Tolvaptan 15 mg tablet [28] & Tolvaptan 45 mg tablet [28], (56).
  - Tolvaptan 30 mg tablet [28] & Tolvaptan 60 mg tablet [28], (56).
  - Tolvaptan 30 mg tablet [28] & Tolvaptan 90 mg tablet [28], (56).

Ongoing Management

Review Patient LFTs

- Review the patient's ALT, AST and total bilirubin monthly for the first 18 months and at 3-monthly intervals thereafter.
- Provide the patient with a new script if changing dose or if the patient has run out of repeats.
- Ongoing PBS Authority STREAMLINED (code 8288).
- Patients may continue on Tolvaptan Lupin until CKD stage 5 or until they receive a kidney transplant.
- Advise patient to use the same pharmacy each time Tolvaptan Lupin is dispensed to ensure that there are no issues with continuity of supply.

Things to Remember

- Provide the patient with a copy of the "Patient's Guide" for Tolvaptan Lupin, the CMI for Tolvaptan Lupin and the Wallet Card (which is also provided in each pack of Tolvaptan Lupin). All documents are available from **www.generichealth.com.au/tolvaptan/prescribers**
- Give the patient a recurring pathology slip for liver function tests (LFTs). Ensure you request ALT, AST and total bilirubin.

Glossary

ADPKD	Autosomal Dominant Polycystic Kidney Disease
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AVP	Arginine Vasopressin
BT	Bilirubin-Total
cAMP	cyclic Adenosine Monophosphate
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	estimated Glomerular Filtration Rate
KHA-CARI	Kidney Health Australia – Caring for Australasians with Renal Impairment
LFT	Liver Function Test
PBS	Pharmaceutical Benefits Scheme
PKD	Polycystic Kidney Disease
PKD1	gene, Polycystic Kidney Disease-1 gene
ULN	Upper Limit of Normal

References

1. Tolvaptan Lupin Product Information.

2. Wallace DP. *Biochim Biophys Acta*. 2011; 1812(10):1291–1300.

3. Reif GA et al.*Am J Physiol Renal Physiol* 2011; 301(5):F1005–13.

4. Torres VE. *Adv Chronic Kidney Dis.* 2010;17(2):190-204.

5. Grantham JJ, Torres VE, Chapman AB et al. *N Engl J Med* 2006; 354:2122–30.

6. Rangan GK, Alexander SI, Campbell KL et al. *Nephrology* 2016; 21:705–15.

7. Torres VE, Chapman AB, Devuyst O et al. *N Engl J Med* 2012; 367(25):240718.

8. Schrier RW, Brosnahan G, Cadnapaphornchai MA et al. *J Am Soc Nephrol* 2014; 25:2399–2418.

9. Tolvaptan Lupin Consumer Medicine Information.

More Information

Tolvaptan Lupin is distributed in Australia by Generic Health Pty Ltd.

For more information on Tolvaptan Lupin, please contact:

Email: **customer.service@generichealth.com.au**

Phone: **03 9809 7900**, Option 1

Website: **www.generichealth.com.au**

For adverse event reporting or medical information, please contact:

Email: **ghinfo@generichealth.com.au**

Phone: **03 9809 7900**, Option 2

Website: **www.generichealth.com.au**

Adverse events should be reported within 24 hours of awareness or on the next working day.

PBS Information: Authority required

Refer to full PBS schedule for full authority information.

PLEASE REVIEW THE FULL PRODUCT INFORMATION (PI) BEFORE PRESCRIBING.

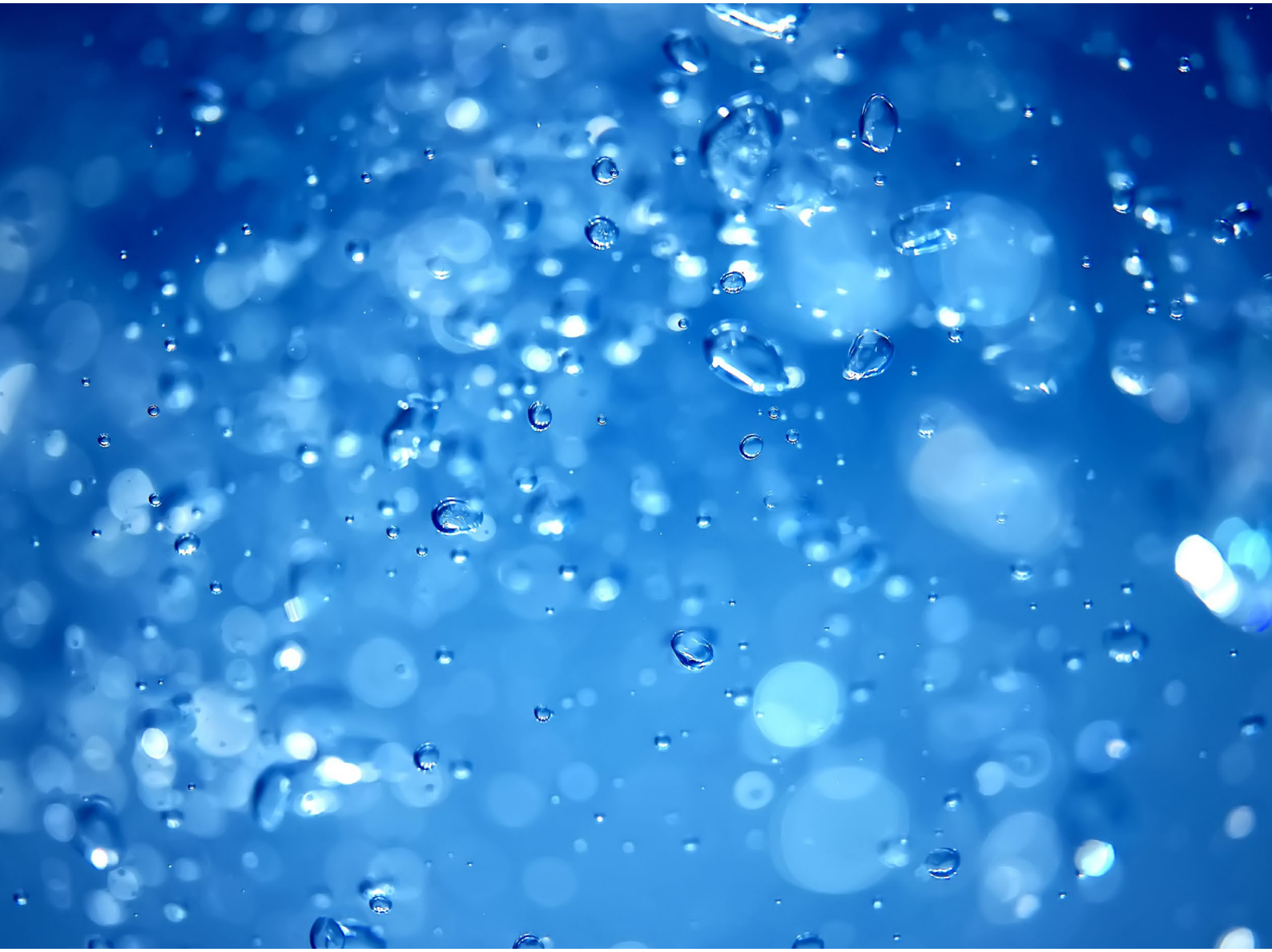
The approved PI is available from Generic Health Pty Ltd by calling 03 9809 7900 or on the website at www.generichealth.com.au/tolvaptan/prescribers

Tolvaptan Lupin (tolvaptan tablets) minimum Product Information (PI).

Tolvaptan has been associated with idiosyncratic elevation of blood alanine and aspartate aminotransferases, rarely associated with concomitant elevations in total bilirubin. To help mitigate the risk of liver injury, blood testing for hepatic transaminases is required prior to initiation of Tolvaptan Lupin, then continually for 18 months, then every 3 months thereafter during treatment with Tolvaptan Lupin. Prescriber education and certification on the risk of liver injury and the importance of regular liver function monitoring is mandatory. (see PI for full details).

INDICATION: Tolvaptan Lupin are indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease. **CONTRAINDICATIONS:** Hypersensitivity to the active substance, benzazepine derivatives or to any of the excipients; elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan; volume depletion; anuria; hypernatremia; inability to perceive or respond to thirst. ***Pregnancy:*** Tolvaptan Lupin must not be used during pregnancy (Category D). ***Lactation:*** Tolvaptan Lupin are contraindicated during breastfeeding. **PRECAUTIONS:** Liver injury or disease: tolvaptan can cause irreversible and potentially fatal liver injury; the prescribing physicians must comply fully with the safety measures outlined in the PI. Potent aquaresis may induce hypernatremia, hyperkalemia or other electrolyte imbalances. Dehydration and hypovolaemia: patients receiving Tolvaptan Lupin should have access to water and should continue ingestion of fluid in response to thirst. ***Diabetes:*** Tolvaptan may cause hyperglycaemia, lactose and galactose intolerance, urinary outflow obstruction. Ability to drive and use machines may be impaired. Paediatric use is not recommended. **INTERACTIONS:** CYP3A inhibitors, CYP3A inducers, digoxin, P-glycoprotein inhibitors (eg. ciclosporin, quinidine), vasopressin analogues (eg. desmopressin), diuretics and medicinal products that increase serum sodium concentration. Co-administration with grapefruit juice should be avoided. **ADVERSE EFFECTS:** Very common adverse effects include thirst, polyuria, nocturia, pollakiuria and polydipsia. Common adverse effects include palpitations, constipation, dyspepsia, blood uric acid increased, decreased appetite, gout, hypernatraemia, hyperuricaemia, dry skin, eczema, rash, diarrhoea, alanine aminotransferase increased and hepatic enzyme increased. For further information about very common and common adverse effects, please see the full PI. **DOSAGE AND ADMINISTRATION:** Tolvaptan Lupin is to be administered twice daily in split dose regimens, initiated at 45 mg (morning dose) + 15 mg (evening dose). The morning dose is to be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food. The dose is to be titrated upward to a split-dose regimen of 90 mg tolvaptan (60 mg + 30 mg) per day and then to a target split-dose regimen of 120 mg tolvaptan (90 mg + 30 mg) per day, with at least weekly intervals between titrations. The maximum tolerated dose should be maintained. For oral use, tablets must be swallowed without chewing and with a glass of water.

Date of preparation of minimum PI: December 2024



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