HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TOLVAPTAN TABLETS safely and effectively. See full prescribing information for TOLVAPTAN TABLETS.

TOLVAPTAN tablets, for oral use
Initial U.S. Approval: 2009

WARNING: RISK OF SERIOUS LIVER INJURY
See full prescribing information for complete boxed warning.
- **Tolvaptan can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported (5.1)**
- **Measure transaminases and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months and every 3 months thereafter (5.1)**
- **Tolvaptan tablets are available only through a restricted distribution program called the Tolvaptan for ADPKD Shared System REMS (5.2)**

----------INDICATIONS AND USAGE----------
Tolvaptan tablets are selective vasopressin V_2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD) (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage (2.1)

Initial Dosage		**Titration Step**		**Target Dosage**	
1st Dose	45 mg	1st Dose	60 mg	1st Dose	90 mg
2nd Dose (8 hours later)	15 mg	2nd Dose (8 hours later)	30 mg	2nd Dose (8 hours later)	30 mg
Total Daily Dose	60 mg	**Total Daily Dose**	90 mg	**Total Daily Dose**	120 mg

- Dose adjustment is recommended for patients taking moderate CYP3A inhibitors (2.4, 5.4, 7.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 15 mg, 30 mg, 45 mg, 60 mg and 90 mg (3)

----------CONTRAINDICATIONS----------
- History of signs or symptoms of significant liver impairment or injury, does not include uncomplicated polycystic liver disease (4)
- Concomitant use of strong CYP3A inhibitors is contraindicated (4)
- Uncorrected abnormal blood sodium concentrations (4, 5.3)
- Unable to sense or respond to thirst (4)
- Hypovolemia (4)
- Hypersensitivity to tolvaptan or any of its components (4)
- Uncorrected urinary outflow obstruction (4)
- Anuria (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypernatremia, dehydration and hypovolemia: May require intervention (5.3)

----------ADVERSE REACTIONS----------
Most common observed adverse reactions with tolvaptan tablets (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Avoid concomitant use with:
- Strong CYP3A Inducers (7.1)
- V_2-Receptor Agonists (7.2)

---------- USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm (8.1)
- Lactation: Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2026

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS LIVER INJURY

Tolvaptan can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported *[see Warnings and Precautions (5.1)]*.

Measure ALT, AST and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter *[see Warnings and Precautions (5.1)]*. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.

Because of the risks of serious liver injury, tolvaptan tablets are available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the Tolvaptan for ADPKD Shared System REMS *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Tolvaptan tablets are indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The initial dosage for tolvaptan tablets is 60 mg orally per day as 45 mg taken on waking and 15 mg taken 8 hours later. Titrate to 60 mg plus 30 mg then to 90 mg plus 30 mg per day if tolerated with at least weekly intervals between titrations. Patients may down-titrate based on tolerability. Encourage patients to drink enough water to avoid thirst or dehydration.

2.2 Monitoring

To mitigate the risk of significant or irreversible liver injury, perform blood testing for ALT, AST and bilirubin prior to initiation of tolvaptan tablets, at 2 and 4 weeks after initiation, monthly for 18 months and every 3 months thereafter. Monitor for concurrent symptoms that may indicate liver injury *[see Warnings and Precautions (5.1)]*.

2.3 Missed Doses

If a dose of tolvaptan tablets is not taken at the scheduled time, take the next dose at its scheduled time.

2.4 Co-Administration with CYP3A Inhibitors

CYP3A Inhibitors

Concomitant use of strong CYP3A inhibitors are contraindicated *[see Contraindications (4) and Warnings and Precautions (5.4)]*.

In patients taking concomitant moderate CYP3A inhibitors, reduce the dose of tolvaptan tablets per Table 1. Consider further reductions if patients cannot tolerate the reduced dose *[see Warnings and Precautions (5.4) and Drug Interactions (7.1)]*. Interrupt tolvaptan tablets temporarily for short term therapy with moderate CYP3A inhibitors if the recommended reduced doses are not available.

Table 1: Dose adjustment for patients taking moderate CYP3A inhibitors

Standard Morning and Afternoon Dose (mg)	Dose (mg) with Moderate CYP3A Inhibitors
90 mg and 30 mg	45 mg and 15 mg
60 mg and 30 mg	30 mg and 15 mg
45 mg and 15 mg	15 mg and 15 mg

3 DOSAGE FORMS AND STRENGTHS

Tolvaptan tablets are supplied as:

- 15 mg white to off-white, triangle shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL" over "15" on the other side.
- 30 mg white to off-white, round shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL" over "30" on the other side.
- 45 mg light blue speckled, round shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL" over "45" on the other side.
- 60 mg light blue speckled, oval shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL60" on the other side.
- 90 mg light blue speckled, square shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL" over "90" on the other side.

4 CONTRAINDICATIONS

Tolvaptan tablets are contraindicated in patients:

- With a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease *[see Warnings and Precautions (5.1)]*
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations *[see Warnings and Precautions (5.3)]*
- Unable to sense or respond to thirst *[see Warnings and Precautions (5.3)]*
- Hypovolemia *[see Warnings and Precautions (5.3)]*
- Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product *[see Adverse Reactions (6)]*
- Uncorrected urinary outflow obstruction
- Anuria

5 WARNINGS AND PRECAUTIONS

5.1 Serious Liver Injury

Tolvaptan tablets 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.

In a 3-year placebo-controlled trial and its open-label extension (in which patients' liver tests were monitored every 4 months), evidence of serious hepatocellular injury (elevations of hepatic transaminases of at least 3 times the upper limit of normal [ULN] combined with elevated bilirubin at least 2 times the ULN) occurred in 0.2% (3/1487) of tolvaptan-treated patients compared to none of the placebo-treated patients.

To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiation of tolvaptan tablets, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

At the onset of signs or symptoms consistent with hepatic injury or if ALT, AST, or bilirubin increase to >2 times ULN, immediately discontinue tolvaptan tablets, obtain repeat tests as soon as possible (within 48 to 72 hours), and continue testing as appropriate. If laboratory abnormalities stabilize or resolve, tolvaptan tablets may be reinitiated with increased frequency of monitoring as long as ALT and AST remain below 3 times the ULN.

Do not restart tolvaptan tablets in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3 times the ULN during treatment with tolvaptan, unless there is another explanation for liver injury and the injury has resolved.

In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times the ULN, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48 to 72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.

5.2 Tolvaptan for ADPKD Shared System REMS

Tolvaptan tablets are available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the Tolvaptan for ADPKD Shared System REMS, because of the risks of liver injury *[see Warnings and Precautions (5.1)]*.

Notable requirements of the Tolvaptan for ADPKD Shared System REMS include the following:

- Prescribers must be certified by enrolling in the REMS program.
- Prescribers must inform patients receiving tolvaptan tablets about the risk of hepatotoxicity associated with its use and how to recognize the signs and symptoms of hepatotoxicity and the appropriate actions to take if it occurs.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements.
- Pharmacies must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive tolvaptan tablets.

Further information, including a list of qualified pharmacies/distributors, is available at www.TolvaptanADPKDSharedREMS.com or by telephone at 1-866-244-9446.

5.3 Hypernatremia, Dehydration and Hypovolemia

Tolvaptan tablets increases free water clearance and, as a result, may cause dehydration, hypovolemia and hypernatremia. Therefore, ensure abnormalities in sodium concentrations are corrected prior to initiation of therapy.

Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration.

In the two double-blind, placebo-controlled trials of patients with ADPKD, hypernatremia (defined as any serum sodium concentration >150 mEq/L) was observed in 4% versus 0.6% and 1.4% versus 0% of tolvaptan-treated versus placebo-treated patients, respectively. The rate of dehydration and hypovolemia in the two studies was 2.1% versus 0.7% and 2.3% versus 0.4% for tolvaptan-treated versus placebo-treated patients, respectively.

During tolvaptan therapy, if serum sodium increases above normal range or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, then suspend tolvaptan until serum sodium, hydration status and volume status is within the normal range.

5.4 Co-Administration with Inhibitors of CYP3A

Concomitant use of tolvaptan with drugs that are moderate or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*. Use with strong CYP3A inhibitors is contraindicated; dose reduction of tolvaptan tablets are recommended for patients while taking moderate CYP3A inhibitors *[see Dosage and Administration (2.4) and Contraindications (4)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Serious Liver Injury *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hypernatremia, Dehydration and Hypovolemia *[see Warnings and Precautions (5.3)]*

- Drug Interactions with Inhibitors of CYP3A *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Tolvaptan has been studied in over 3,000 patients with ADPKD. Long-term, placebo-controlled safety information of tolvaptan in ADPKD is principally derived from two trials where 1,413 subjects received tolvaptan and 1,098 received placebo for at least 12 months across both studies.

TEMPO 3:4: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD

The TEMPO 3:4 (NCT00428948) trial employed a two-arm, 2:1 randomization to tolvaptan or placebo, titrated to a maximally-tolerated total daily dose of 60 to 120 mg. A total of 961 subjects with rapidly progressing ADPKD were randomized to tolvaptan. Of these, 742 (77%) subjects who were treated with tolvaptan remained on treatment for at least 3 years. The average daily dose in these subjects was 96 mg daily.

Adverse events that led to discontinuation were reported for 15.4% (148/961) of subjects in the tolvaptan group and 5% (24/483) of subjects in the placebo group. Aquaretic effects were the most common reasons for discontinuation of tolvaptan. These included pollakiuria, polyuria, or nocturia in 63 (6.6%) subjects treated with tolvaptan compared to 1 subject (0.2%) treated with placebo.

Table 2 lists the adverse reactions that occurred in at least 3% of ADPKD subjects treated with tolvaptan and at least 1.5% more than on placebo.

Table 2: TEMPO 3:4, Treatment Emergent Adverse Reactions in ≥3% of Tolvaptan Treated Subjects with Risk Difference ≥ 1.5%, Randomized Period

Adverse Reaction	Tolvaptan (N=961)			Placebo (N=483)		
	Number of Subjects	Proportion (%)*	Annualized Rate†	Number of Subjects	Proportion (%)*	Annualized Rate†
Increased urination‡	668	69.5	28.6	135	28.0	10.3
Thirst§	612	63.7	26.2	113	23.4	8.7
Dry mouth	154	16.0	6.6	60	12.4	4.6
Fatigue	131	13.6	5.6	47	9.7	3.6
Diarrhea	128	13.3	5.5	53	11.0	4.1
Dizziness	109	11.3	4.7	42	8.7	3.2
Dyspepsia	76	7.9	3.3	16	3.3	1.2
Decreased appetite	69	7.2	3.0	5	1.0	0.4
Abdominal distension	47	4.9	2.0	16	3.3	1.2
Dry skin	47	4.9	2.0	8	1.7	0.6
Rash	40	4.2	1.7	9	1.9	0.7
Hyperuricemia	37	3.9	1.6	9	1.9	0.7
Palpitations	34	3.5	1.5	6	1.2	0.5

*100x (Number of subjects with an adverse event/N)
†100x (Number of subjects with an adverse event/Total subject years of drug exposure)
‡ Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria
§ Thirst includes polydipsia and thirst

REPRISE: A Phase 3, Randomized-Withdrawal, Placebo-Controlled, Double-Blind, Trial in Late Stage 2 to Early Stage 4 ADPKD

The REPRISE (NCT02160145) trial employed a 5-week single-blind titration and run-in period for tolvaptan prior to the randomized double-blind period. During the tolvaptan titration and run-in period, 126 (8.4%) of the 1,496 subjects discontinued the study, 52 (3.5%) were due to aquaretic effects and 10 (0.7%) were due to liver test findings. Because of this run-in design, the adverse reaction rates observed during the randomized period are not described.

Liver Injury
In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with tolvaptan compared with placebo (4.9% [80/1,637] versus 1.1% [13/1,166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of tolvaptan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary Disorders: Liver failure requiring transplant
Immune System Disorders: Anaphylaxis
Investigations: Blood creatine phosphokinase increased

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors and Inducers

CYP3A Inhibitors

Tolvaptan's AUC was 5.4 times as large and C_{max} was 3.5 times as large after co-administration of tolvaptan and 200 mg ketoconazole *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*. Larger doses of the strong CYP3A inhibitor would be expected to produce larger increases in tolvaptan exposure. Concomitant use of tolvaptan with strong CYP3A inhibitors is contraindicated *[see Contraindications (4)]*.

Dose reduction of tolvaptan tablets is recommended for patients while taking moderate CYP3A inhibitors *[see Dosage and Administration (2.4)]*. Patients should avoid grapefruit juice beverages while taking tolvaptan tablets.

Strong CYP3A Inducers

Co-administration of tolvaptan with strong CYP3A inducers reduces exposure to tolvaptan *[see Clinical Pharmacology (12.3)]*. Avoid concomitant use of tolvaptan with strong CYP3A inducers *[see Dosage and Administration (2.4)]*.

7.2 V_2-Receptor Agonist

As a V_2-receptor antagonist, tolvaptan will interfere with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of tolvaptan with a V_2-agonist.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with tolvaptan use in pregnant women are insufficient to determine if there is a drug associated risk of adverse developmental outcomes. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. At maternally non-toxic doses, tolvaptan did not cause any developmental toxicity in rats or in rabbits at exposures approximately 4- and 1-times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 90/30 mg. However, effects on embryo-fetal development occurred in both species at maternally toxic doses. In rats, reduced fetal weights and delayed fetal ossification occurred at 17 times the human exposure. In rabbits, increased abortions, embryo-fetal death, fetal microphthalmia, open eyelids, cleft

palate, brachymelia and skeletal malformations occurred at approximately 3 times the human exposure *(see Data).* Advise pregnant women of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2 to 4% and 15 to 20% of clinically recognized pregnancies, respectively.

Data

Animal Data
Oral administration of tolvaptan during the period of organogenesis in Sprague-Dawley rats produced no evidence of teratogenesis at doses up to 100 mg/kg/day. Lower body weights and delayed ossification were seen at 1,000 mg/kg, which is approximately 17 times the human exposure at the 90/30 mg dose (AUC_{24h} 6,570 h·ng/mL). The fetal effects are likely secondary to maternal toxicity (decreased food intake and low body weights). In a prenatal and postnatal study in rats, tolvaptan had no effect on physical development, reflex function, learning ability or reproductive performance at doses up to 1,000 mg/kg/day.

In New Zealand White rabbits, placental transfer was demonstrated with C_{max} values in the yolk sac fluid approximating 22.7% of the value in maternal rabbit serum. In embryo-fetal studies, teratogenicity (microphthalmia, embryo-fetal mortality, cleft palate, brachymelia and fused phalanx) was evident in rabbits at 1,000 mg/kg (approximately 3 times the exposure at the 90/30 mg dose). Body weights and food consumption were lower in dams at all doses, equivalent to 0.6 to 3 times the human exposure at the 90/30 mg dose.

8.2 Lactation

Risk Summary

There are no data on the presence of tolvaptan in human milk, the effects on the breastfed infant, or the effects on milk production. Tolvaptan is present in rat milk. When a drug is present in animal milk, it is possible that the drug will be present in human milk, but relative levels may vary *(see Data)*. Because of the potential for serious adverse reactions, including liver toxicity, electrolyte abnormalities (e.g., hypernatremia), hypotension, and volume depletion in breastfed infants, advise women not to breastfeed during treatment with tolvaptan tablets.

Data

In lactating rats administration of radiolabeled tolvaptan, lacteal radioactivity concentrations reached the highest level at 8 hours after administration and then decreased gradually with time with a half-life of 27.3 hours. The level of activity in milk ranged from 1.5- to 15.8-fold those in blood over the period of 72 hours post-dose. In a prenatal and postnatal study in rats, maternal toxicity was noted at 100 mg/kg/day or higher (≥4.4 times the human exposure at the 90/30 mg dose). Increased perinatal death and decreased body weight of the offspring were observed during the lactation period and after weaning at approximately 17.3 times the human exposure at the 90/30 mg dose.

8.4 Pediatric Use

Safety and effectiveness of tolvaptan in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of tolvaptan did not include sufficient numbers of subjects aged 65 years old and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Use in Patients with Hepatic Impairment

Because of the risk of serious liver injury, use is contraindicated in patients with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease which was present in 60% and 66% of patients in TEMPO 3:4 and REPRISE, respectively. No specific exclusion for hepatic impairment was implemented in TEMPO 3:4. However, REPRISE excluded patients with ADPKD who had hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease *[see Contraindications (4)].*

8.7 Use in Patients with Renal Impairment

Efficacy studies included patients with normal and reduced renal function *[see Clinical Studies (14)]*. TEMPO 3:4 required patients to have an estimated creatinine clearance ≥60 mL/min, while REPRISE included patients with $eGFR_{CKD\text{-}Epi}$ 25 to 65 mL/min/1.73m^2.

10 OVERDOSAGE

Single oral doses up to 480 mg (4 times the maximum recommended daily dose) and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia.

No mortality was observed in rats or dogs following single oral doses of 2,000 mg/kg (maximum feasible dose). A single oral dose of 2,000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

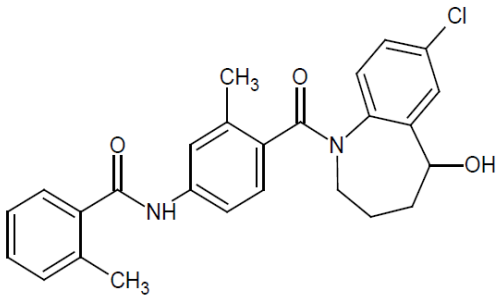
In patients with suspected tolvaptan tablets overdosage, assessment of vital signs, electrolyte concentrations, ECG and fluid status is recommended. Continue replacement of water and electrolytes until aquaresis abates. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (>98%).

11 DESCRIPTION

Tolvaptan tablets contains tolvaptan, a selective vasopressin V_2-receptor antagonist in immediate release tablets for oral administration available in 15 mg, 30 mg, 45 mg, 60 mg and 90 mg strengths. Tolvaptan is 7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine.

The molecular formula is $C_{26}H_{25}ClN_2O_3$. Molecular weight is 448.94 g/mol.

The chemical structure is:



Tolvaptan is a white to off-white powder. It is practically insoluble in water, slightly soluble in ethyl acetate, sparingly soluble in ethanol, soluble in methanol and freely soluble in benzyl alcohol.

Inactive ingredients include anhydrous lactose, colloidal silicon dioxide, copovidone, croscarmellose sodium, magnesium stearate, polysorbate, and indigotine aluminum lake 12 to 14% as colorant (45 mg, 60 mg and 90mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tolvaptan is a selective vasopressin V_2-receptor antagonist with an affinity for the V_2-receptor that is 1.8 times that of native arginine vasopressin (AVP). Tolvaptan affinity for the V_2-receptor is 29 times that for the V_{1a}- receptor. Decreased binding of vasopressin to the V_2-receptor in the kidney lowers adenylate cyclase activity resulting in a decrease in intracellular adenosine 3′, 5′-cyclic monophosphate (cAMP) concentrations. Decreased cAMP concentrations prevent aquaporin 2 containing vesicles from fusing with the plasma membrane, which in turn causes an increase in urine water excretion, an increase in free water clearance (aquaresis) and a decrease in urine osmolality. In human ADPKD cyst epithelial cells, tolvaptan inhibited AVP- stimulated *in vitro* cyst growth and chloride-dependent fluid secretion into cysts. In animal models, decreased cAMP concentrations were associated with decreases in the rate of growth of total kidney volume and the rate of formation and enlargement of kidney cysts. Tolvaptan metabolites have no or weak antagonist activity for human V_2-receptors compared with tolvaptan.

12.2 Pharmacodynamics

In healthy subjects or patients with eGFRs as low as 10 mL/min/1.73 m^2 receiving a single dose of tolvaptan, the onset of the aquaretic effects occurs within 1 to 2 hours post-dose. In healthy subjects, single doses of 60 mg and 90 mg produce a peak effect of about a 9 mL/min increase in urine excretion rate is observed between 4 and 8 hours post-dose. Higher doses of tolvaptan do not increase the peak effect in urine excretion rate but sustain the effect for a longer period of time.

Urine excretion rate returns to baseline within 24 hours following the maximum recommended 90 mg dose of tolvaptan.

Changes in free water clearance mirror the changes in urine excretion rate. Increased free water clearance causes an increase in serum sodium concentration unless fluid intake is increased to match urine output.

Increases in urine excretion rate and free water clearance are positively correlated with baseline glomerular filtration rate with increases in both values observed in patients with creatinine clearance as low as 15 mL/min.

With the recommended split-dose regimens, tolvaptan inhibits vasopressin from binding to the V_2-receptor in the kidney for the entire day, as indicated by increased urine output and decreased urine osmolality. Following a 90/30 mg split-dose regimen in patients with eGFR >60 mL/min/1.73 m^2, the change in mean daily urine volume was about 4 L for a mean total daily volume of about 7 L. In patients with eGFR <30 mL/min/1.73 m^2, the mean change in daily urine volume was about 2 L for a total daily urine volume of about 5 L.

Plasma concentrations of native AVP may increase (avg. 2 to 9 pg/mL) with tolvaptan treatment and return to baseline levels when treatment is stopped.

During tolvaptan treatment, small changes in renal function are expected and the changes are independent of baseline renal function. Glomerular filtration rate is decreased about 6% to 10% and uric acid clearance is decreased about 20% to 25%. Percent changes in renal plasma flow are highly correlated to percent changes in GFR. These changes are reversed upon discontinuation of tolvaptan.

Cardiac Electrophysiology

No prolongation of the QT interval was observed with tolvaptan following multiple doses of 300 mg/day for 5 days.

12.3 Pharmacokinetics

In healthy subjects, the pharmacokinetics of tolvaptan after single doses of up to 480 mg and multiple doses up to 300 mg once daily have been studied. In ADPKD patients, single doses up to 120 mg and multiple split-doses up to 90/30 mg have been studied.

Absorption

In healthy subjects, peak concentrations of tolvaptan are observed between 2 and 4 hours post-dose. Peak concentrations increase less than dose proportionally with doses greater than 240 mg.

The absolute bioavailability of tolvaptan decreases with increasing doses. The absolute bioavailability of tolvaptan following an oral dose of 30 mg is 56% (range 42% to 80%).

Co-administration of 90 mg tolvaptan tablets with a high-fat meal (~1,000 calories, of which 50% are from fat) doubles peak concentrations but has no effect on the AUC of tolvaptan; tolvaptan may be administered with or without food.

Distribution

Tolvaptan binds to both albumin and α1-acid glycoprotein and the overall protein binding is >98%; binding is not affected by disease state. The volume of distribution of tolvaptan is about 3 L/kg. The pharmacokinetic properties of tolvaptan are stereospecific, with a steady-state ratio of the S-(-) to the R-(+) enantiomer of about 3. When administered as multiple once-daily 300 mg doses to healthy subjects or as split-dose regimens to patients with ADPKD, tolvaptan's accumulation factor is <1.2. There is marked inter-subject variation in peak and average exposure to tolvaptan with a percent coefficient of variation ranging between 30% and 60%.

Metabolism and Elimination

Tolvaptan is metabolized almost exclusively by CYP3A. Fourteen metabolites have been identified in plasma, urine and feces; all but one were also metabolized by CYP3A and none are pharmacodynamically active. After oral administration of radiolabeled tolvaptan, tolvaptan was a minor component in plasma representing 3% of total

plasma radioactivity; the oxobutyric acid metabolite was present at 52.5% of total plasma radioactivity with all other metabolites present at lower concentrations than tolvaptan. The oxobutyric acid metabolite shows a plasma half-life of ~180 h. About 40% of radioactivity was recovered in urine (<1% as unchanged tolvaptan) and 59% in feces (19% as unchanged tolvaptan). Following intravenous infusion, tolvaptan half-life is approximately 3 hours. Following single oral doses to healthy subjects, the estimated half-life of tolvaptan increases from 3 hours for a 15 mg dose to approximately 12 hours for 120 mg and higher doses due to more prolonged absorption of tolvaptan at higher doses; apparent clearance is approximately 4 mL/min/kg and does not appear to change with increasing dose.

Specific Populations

Age, Gender and Race

Age, gender and race have no effect on tolvaptan pharmacokinetics.

Hepatic Impairment

In studies involving patients with hepatic impairment (Child-Pugh class A-C), but without ADPKD; moderate (class A, B) or severe (class C) hepatic impairment decreases the clearance and increases the volume of distribution of tolvaptan.

Renal Impairment

In subjects with creatinine clearances ranging from 10 to 124 mL/min administered a single dose of 60 mg tolvaptan, the AUC and C_{max} of plasma tolvaptan was increased 90% and 10%, respectively, for subjects with clearances of <30 mL/min compared to subjects with clearances >60 mL/min *[see Use in Special Populations (8.7)].*

In ADPKD patients with estimated creatinine clearance >60 mL/min, pharmacokinetics were similar to healthy subjects.

Drug Interaction Studies

Impact of Other Drugs on Tolvaptan

Strong CYP3A Inhibitors

Tolvaptan's C_{max} and AUC were, respectively, 3.5 times and 5.4 times as high following ketoconazole 200 mg given one day prior to and concomitantly with 30 mg tolvaptan.

Moderate CYP3A4 Inhibitors

Fluconazole: Fluconazole 400 mg given one day prior and 200 mg given concomitantly, produced an 80% and 200% increase in tolvaptan C_{max} and AUC, respectively.

Grapefruit Juice: When 60 mg tolvaptan was taken with 240 mL regular strength grapefruit juice, tolvaptan C_{max} and AUC increased 90% and 60%, respectively.

CYP3A Inducers

Rifampin: Rifampin 600 mg once daily for 7 days followed by a single 240 mg dose of tolvaptan decreased both tolvaptan C_{max} and AUC about 85%.

Other Drugs

Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with tolvaptan has no clinically relevant impact on the exposure to tolvaptan.

Impact of Tolvaptan on Other Drugs

CYP3A Substrates

Co-administration of lovastatin and tolvaptan increases the AUC of lovastatin and its active metabolite lovastatin-β hydroxy acid by 40% and 30%, respectively. These are non-clinically significant increases in exposure.

P-gp Substrates

Digoxin: Digoxin 0.25 mg was administered once daily for 12 days. Tolvaptan 60 mg, was co-administered once daily on Days 8 to 12. Digoxin C_{max} and AUC were increased 30% and 20%, respectively.

Transporter Substrates

Tolvaptan is a substrate of P-gp and an inhibitor of P-gp and BCRP. The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1 and OAT3. Co-administration of tolvaptan with rosuvastatin (BCRP substrate) did not have a clinically significant effect on rosuvastatin exposure. Rosuvastatin C_{max} and AUC_t increased 54% and 69%, respectively.

Administration of rosuvastatin (OATP1B1 substrate) or furosemide (OAT3 substrate) to healthy subjects with elevated oxobutyric acid metabolite plasma concentrations did not meaningfully alter the pharmacokinetics of rosuvastatin or furosemide.

Other Drugs

Co-administration of tolvaptan did not meaningfully alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of tolvaptan was assessed in 2-year carcinogenicity studies in mice and rats. Tolvaptan was not tumorigenic in male or female rats at doses up to 1,000 mg/kg/day (1.9 to 5.1 times the human exposure at the 90/30 mg dose), in male mice at doses up to 60 mg/kg/day (0.4 times the human exposure at the 90/30 mg dose) and to female mice at doses up to 100 mg/kg/day (0.7 times the human exposure at the 90/30 mg dose).

Mutagenesis

Tolvaptan was not clastogenic in the *in vitro* chromosomal aberration test in Chinese hamster lung fibroblast cells or the *in vivo* rat micronucleus assay and was not mutagenic in the *in vitro* bacterial reverse mutation assay.

Impairment of fertility

In a fertility study in which male and female rats were administered tolvaptan orally at 100, 300 or 1,000 mg/kg/day, altered estrous cycles due to prolongation of diestrus were observed in dams given 300 and 1,000 mg/kg/day (9.7- and 17.3 times the human exposure at the 90/30 mg dose). Tolvaptan had no effect on copulation or fertility indices. There were also no effects on the incidences of early or late resorption, dead fetuses, pre- or post-implantation loss, external anomalies, or fetal body weights.

14 CLINICAL STUDIES

Tolvaptan was shown to slow the rate of decline in renal function in adult patients at risk of rapidly progressing ADPKD in two trials: TEMPO 3:4 in patients at earlier stages of disease and REPRISE in patients at later stages. The findings from these trials, when taken together, suggest that tolvaptan slows the loss of renal function progressively through the course of the disease.

TEMPO 3:4: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD

In TEMPO 3:4 (NCT00428948), 1,445 adult patients (age >18 years) with early (estimated creatinine clearance [eCrCl] ≥60 mL/min), rapidly-progressing (total kidney volume [TKV] ≥750 mL and age <51 years) ADPKD (diagnosed by modified Ravine criteria) were randomized 2:1 to treatment with tolvaptan or placebo. Patients were treated for up to 3 years; patients who discontinued medication prematurely were only required to attend clinic visits to assess renal function for up to 42 days after treatment withdrawal and to attend telephone visits at all scheduled visits for up to 36 months. Patients who completed treatment at the 3-year visit had treatment interrupted for 2 to 6 weeks to assess renal function post treatment. Patients received treatment twice a day (first dose on waking, second dose approximately 9 hours later). Patients were initiated on 45 mg/15 mg, and up-titrated weekly to 60 mg/30 mg and then to 90 mg/30 mg as tolerated. Patients were to maintain the highest tolerated dose for 3 years, but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to drink adequate water to avoid thirst or dehydration and before bedtime.

The primary endpoint was the intergroup difference for rate of change of TKV normalized as a percentage. The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of: 1) worsening kidney function (defined as a persistent 25% reduction in reciprocal serum creatinine during treatment from end of titration to last on-drug visit); 2) medically significant kidney pain (defined as requiring prescribed leave,

last-resort analgesics, narcotic and anti-nociceptive, radiologic or surgical interventions); 3) worsening hypertension (defined as a persistent increase in blood pressure category or an increased anti-hypertensive prescription); 4) worsening albuminuria (defined as a persistent increase in albumin/creatinine ratio category).

At baseline, average estimated glomerular filtration rate (eGFR) was 82 mL/min/1.73 m^2 (CKD- Epidemiology formula) and mean TKV was 1692 mL (height adjusted 972 mL/m). Approximately 35% had an eGFR of 90 mL/min/1.73 m^2 or greater, 48% had an eGFR between 60 to 89 mL/min/1.73 m^2, 14% had an eGFR of 45 to 60 mL/min/1.73 m^2, and 3% had an eGFR of <45 mL/min/1.73 m^2. The subjects' mean age was 39 years, 48% were female, 84% were Caucasian, 13% were Asian, and 1.7% were Black or African-American. Approximately 80% had hypertension and approximately 71% were taking an agent that acts on the renin-angiotensin system. Of the 770 subjects who submitted to genetic analysis in TEMPO 3:4's open-label extension, 749 (97%) had an identifiable mutation in the PKD1 (656 or 88%), or PKD2 (93 or 12%) gene.

The trial met its prespecified primary endpoint of 3-year change in TKV ($p<0.0001$). The difference in TKV between treatment groups mostly developed within the first year, the earliest assessment, with little further difference in years two and three. In years 4 and 5 during the TEMPO 3:4 extension trial, both groups received tolvaptan and the difference between the groups in TKV was not maintained. Tolvaptan has little effect on kidney size beyond what accrues during the first year of treatment.

The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (44 vs. 50 events per 100 person-years; hazard ratio, 0.87; 95% CI, 0.78 to 0.97; $p=0.0095$). As shown in the table below, the result of the key secondary composite endpoint was driven by effects on worsening kidney function and kidney pain events. In contrast, there was no effect of tolvaptan on either progression of hypertension or albuminuria. Few subjects in either arm required a radiologic or surgical intervention for kidney pain. Most kidney pain events reflected use of a medication to treat pain such as use of paracetamol, tricyclic antidepressants, narcotics and other non-narcotic agents.

Event	**Tolvaptan**		**Placebo**		**Hazard Ratio, 95% CI**
	Total Number of Events (Events per 100 person- years)	**Number of Subjects with an Event (percentage)**	**Total Number of Events (Events per 100 person- years)**	**Number of Subjects with an Event (percentage)**	
Composite	1,049 (43.9)	572 (59.5)	665 (50.0)	341 (70.6)	0.87 (0.78,0.97)
Worsening Kidney Function	44 (1.9)	42 (4.6)	64 (4.8)	61 (12.8)	0.39 (0.26,0.57)
Kidney Pain	113 (4.7)	95 (9.9)	97 (7.3)	78 (16.2)	0.64 (0.47,0.89)
Onset or Progression of Hypertension	734 (30.7)	426 (44.3)	426 (32.1)	244 (50.5)	0.94 (0.81,1.09)
Worsening Albuminuria	195 (8.2)	195 (20.3)	103 (7.8)	101 (20.9)	1.04 (0.84,1.28)

The third endpoint (kidney function slope) was assessed as slope of eGFR during treatment (from end of titration to last on-drug visit). The estimated difference in the annual rate of change in those who contributed to the analysis was 1 mL/min/1.73 m^2/year with a 95% confidence interval of (0.6, 1.4). Of the subjects enrolled in the trial, 5% of subjects in the tolvaptan arm and 2% in the placebo arm either had missing baseline data or discontinued from treatment prior to the end of the titration visit and hence were excluded from the analysis. In the extension trial, eGFR differences produced by the third year of the TEMPO 3:4 trial were maintained over the next 2 years of tolvaptan treatment.

The efficacy profile was generally consistent across subgroups of interest for this indication; few Black or African-American patients were enrolled in the trial.

<u>REPRISE: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Withdrawal Trial in Later-Stage ADPKD</u>
REPRISE (NCT02160145) was a double-blind, placebo-controlled randomized withdrawal trial in adult patients (age 18 to 65 years) with chronic kidney disease (CKD) with an eGFR between 25 and 65 mL/min/1.73 m^2 if younger than age 56 years, or eGFR between 25 and 44 mL/min/1.73 m^2, plus eGFR decline >2 mL/min/1.73 m^2/year if between age 56 to 65 years. Subjects were to be treated for 12 months; after completion of treatment, patients

entered a 3-week follow-up period to assess renal function. The primary endpoint was the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized by dividing by each subject's treatment duration.

Prior to randomization, patients were required to complete sequential single-blind run-in periods during which they received placebo for 1 week, followed by tolvaptan titration for 2 weeks, and then treatment with tolvaptan at the highest tolerated dose achieved during titration for 3 weeks. During the titration period, tolvaptan was up-titrated every 3 to 4 days from a daily oral dose of 30 mg/15 mg to 45 mg/15 mg, 60 mg/30 mg and up to a maximum dose of 90 mg/30 mg. Only patients who could tolerate the two highest doses of tolvaptan (60 mg/30 mg or 90 mg/30 mg) for the subsequent 3 weeks were randomized 1:1 to treatment with tolvaptan or placebo.

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 were encouraged to start drinking an adequate amount of water at screening and continuing through the end of the trial to avoid thirst or dehydration.

A total of 1,519 subjects were enrolled in the study. Of these, 1,370 subjects successfully completed the pre-randomization period and were randomized and treated during the 12-month double-blind period. Because 57 subjects did not complete the off-treatment follow-up period, 1,313 subjects were included in the primary efficacy analysis.

For subjects randomized, the baseline, average estimated glomerular filtration rate (eGFR) was 41 mL/min/1.73 m^2 (CKD-Epidemiology formula) and historical TKV, available in 318 (23%) of subjects, averaged 2026 mL. Approximately 5%, 75% and 20% had an eGFR 60 mL/min/1.73 m^2 or greater, between 30 to 59 mL/min/1.73 m^2, and between 25 and 29 mL/min/1.73 m^2, respectively. The subjects' mean age was 47 years, 50% were female, 92% were Caucasian, 4% Black or African-American and 3% were Asian, 93% had hypertension, and 87% of subjects were taking antihypertensive agents affecting the angiotensin converting enzyme or receptor. Of the 115 (8%) of subjects who had prior genetic tests, only 54 (47%) knew their results with 48 (89%) of these having PKD1 and 6 (11%) having PKD2 mutations.

In the randomized period, the change of eGFR from pretreatment baseline to post-treatment follow-up was − 2.3 mL/min/1.73 m^2/year with tolvaptan as compared with −3.6 mL/min/1.73 m^2/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m^2/year ($p < 0.0001$). The key secondary endpoint (eGFR slope in ml/min/1.73 m^2/year assessed using a linear mixed effect model of annualized eGFR (CKD- EPI)) showed a difference between treatment groups of 1 ml/min/ m^2/year that was also statistically significant ($p < 0.0001$).

The efficacy profile was generally consistent across subgroups of interest for this indication; few Black or African-American patients were enrolled in the trial.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Tolvaptan tablets are supplied as.

- 15 mg white to off-white, triangle shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL" over "15" on the other side.
- 30 mg white to off-white, round shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL" over "30" on the other side.
- 45 mg light blue speckled, round shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL" over "45" on the other side.
- 60 mg light blue speckled, oval shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL60" on the other side.

- 90 mg light blue speckled, square shape, beveled edge, biconvex tablet. Engraved "APO" on one side and "TL" over "90" on the other side.

Morning and Afternoon Doses	NDC	
	7-Day Blister Card (Containing 14 Tablets)	28-Day Carton (4 Blister Cards Containing a Total of 56 Tablets)
15 mg and 15 mg	60505-4800-1	60505-4800-0
30 mg and 15 mg	60505-4801-1	60505-4801-0
45 mg and 15 mg	60505-4802-1	60505-4802-0
60 mg and 30 mg	60505-4803-1	60505-4803-0
90 mg and 30 mg	60505-4804-1	60505-4804-0

30 Count Bottles	NDC
15 mg	60505-4781-3
30 mg	60505-4782-3

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

As part of patient counseling, healthcare providers must review the tolvaptan tablets Medication Guide with every patient *[see Medication Guide].*

Serious Liver Injury

Advise patients that blood testing is required before starting tolvaptan tablets, at 2 weeks and 4 weeks after initiation, then monthly during the first 18 months of therapy and every 3 months thereafter as a requirement to reduce the risk of serious liver injury *[see Boxed Warning and Warnings and Precautions (5.1)].*

Advise patients to immediately stop taking tolvaptan tablets and notify their healthcare provider if they have symptoms or signs (e.g., abnormal transaminase elevations) of hepatic injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort or tenderness, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) *[see Warnings and Precautions (5.1)*].

Tolvaptan for ADPKD Shared System REMS

Advise patients that tolvaptan tablets are only available through a restricted program called the Tolvaptan for ADPKD Shared System REMS *[see Warnings and Precautions (5.2)].* Inform the patient of the following notable requirement:

- Patients must enroll in the program and comply with ongoing monitoring requirements *[see Warnings and Precautions (5.2)]*

Advise patients that tolvaptan tablets are only available only through restricted distribution from certified specialty pharmacies participating in the Tolvaptan for ADPKD Shared System REMS. Therefore, provide patients with the telephone number and web site for information on how to obtain the product *[see Warnings and Precautions (5.2)].*

Hypernatremia, Dehydration and Hypovolemia

Advise patients to drink water to avoid thirst, throughout the day and night. Patients should stop taking tolvaptan tablets and notify their healthcare provider if they have symptoms or signs of sodium imbalance or dehydration (e.g., dizziness, fainting, weight loss, palpitations, confusion, weakness, gait instability) *[see Warnings and Precautions*

(5.3)]. Advise the patient that if they cannot drink enough water for any reason (no access to water, cannot sense thirst, unable to maintain hydration due to vomiting, diarrhea) they should stop taking tolvaptan tablets and inform their health care provider right away *[see Warnings and Precautions (5.3)]*.

Pregnancy

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise women not to breastfeed during treatment with tolvaptan tablets *[see Use in Specific Populations (8.2)]*.

Rx Only

APOTEX INC.

TOLVAPTAN TABLETS

15 mg, 30 mg, 45 mg, 60 mg and 90 mg

Manufactured by:	**Manufactured for:**
Apotex Inc.	Apotex Corp.
Toronto, Ontario	Weston, Florida
Canada M9L 1T9	33326

Rev. 5

MEDICATION GUIDE

Tolvaptan (tol vap′ tan) **Tablets**

What is the most important information I should know about tolvaptan tablets?
Tolvaptan tablets can cause serious side effects, including:

- **Serious liver problems.** Tolvaptan tablets can cause serious liver problems that can lead to the need for a liver transplant or can lead to death. Stop taking tolvaptan tablets and call your healthcare provider right away if you get any of the following symptoms:
  - feeling tired
  - loss of appetite
  - nausea
  - right upper stomach (abdomen) pain or tenderness
  - vomiting
  - fever
  - rash
  - itching
  - yellowing of the skin and white part of the eye (jaundice)
  - dark urine

To help reduce your risk of liver problems, your healthcare provider will do a blood test to check your liver:

- **before you start taking tolvaptan tablets**
- **at 2 weeks and 4 weeks after you start treatment with tolvaptan tablets**
- **then monthly for 18 months during treatment with tolvaptan tablets**
- **and every 3 months from then on**

It is important to stay under the care of your healthcare provider during treatment with tolvaptan tablets.

Because of the risk of serious liver problems tolvaptan tablets are only available through a restricted distribution program called the Tolvaptan for ADPKD Shared System REMS.

- Before you start treatment with tolvaptan tablets, you must enroll in the Tolvaptan for ADPKD Shared System REMS. Talk to your healthcare provider about how to enroll in the program.
- Tolvaptan tablets can only be dispensed by a certified pharmacy that participates in the Tolvaptan for ADPKD Shared System REMS. Your healthcare provider can give you information on how to find a certified pharmacy.

What are tolvaptan tablets?

Tolvaptan tablets are prescription medicine used to slow kidney function decline in adults who are at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

It is not known if tolvaptan tablets are safe and effective in children.

Do not take tolvaptan tablets if you:

- have a history of liver problems or have signs or symptoms of liver problems, excluding polycystic liver disease.
- cannot feel if you are thirsty or cannot replace fluids by drinking.
- have been told that the amount of sodium (salt) in your blood is too high or too low.
- are dehydrated.
- are allergic to tolvaptan or any of the ingredients in tolvaptan tablets. See the end of this Medication Guide for a complete list of ingredients in tolvaptan tablets.
- are unable to urinate.

Before taking tolvaptan tablets, tell your healthcare provider about all your medical conditions, including if you:

- have a history of sodium levels that are too low.
- are pregnant or plan to become pregnant. It is not known if tolvaptan will harm your unborn baby. Tell your healthcare provider if you become pregnant or think that you may be pregnant.
- are breast-feeding or plan to breastfeed. It is not known if tolvaptan passes into your breast milk. Do not breastfeed during treatment with tolvaptan tablets. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take including prescription medicines, over-the-counter medicines, vitamins and herbal supplements.

- Taking tolvaptan tablets with certain medicines could cause you to have too much tolvaptan in your blood. Tolvaptan tablets should not be taken with certain medications. Your healthcare provider can tell you if it is safe to take tolvaptan tablets with other medicines.
- Do not start taking a new medicine without talking to your healthcare provider.
- Keep a list of your medicines to show your healthcare provider and pharmacist.

How should I take tolvaptan tablets?

- Take tolvaptan tablets exactly as your healthcare provider tells you to.
- Take tolvaptan tablets orally two times each day. Take the first dose of tolvaptan tablets when you wake up and take the second dose 8 hours later.
- Be sure to drink enough water so that you will not get thirsty or become dehydrated.
- If you miss a dose of tolvaptan tablets, take the next dose at your regular time.
- If you take too much tolvaptan tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking tolvaptan tablets?

- Do not drink grapefruit juice during treatment with tolvaptan tablets. This could cause you to have too much tolvaptan in your blood.

What are the possible side effects of tolvaptan tablets?
Tolvaptan tablets may cause serious side effects, including:
See "What is the most important information I should know about tolvaptan tablets?"

- **Too much sodium in your blood (hypernatremia) and loss of too much body fluid (dehydration).** In some cases, dehydration can lead to extreme loss of body fluid called hypovolemia. You should drink water when you are thirsty and throughout the day and night. Stop taking tolvaptan tablets and call your healthcare provider if you cannot drink enough water for any reason, such as not having access to water, or vomiting or diarrhea. Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fainting
  - weight loss
  - a change in the way your heart beats
  - feel confused or weak

The **most common side effects** of tolvaptan tablets include:

- thirst and drinking more fluid than normal
- making large amounts of urine, urinating often and urinating at night

These are not all the possible side effects of tolvaptan tablets.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store tolvaptan tablets?
Tolvaptan tablets come in a child-resistant package. Store tolvaptan tablets between 68°F to 77°F (20°C to 25°C).

Keep tolvaptan tablets and all medicines out of the reach of children.

General information about the safe and effective use of tolvaptan tablets.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use tolvaptan tablets for a condition for which it was not prescribed. Do not give tolvaptan tablets to other people, even if they have the same symptoms you have. It may harm them.

What are the ingredients in tolvaptan tablets?
Active ingredient: tolvaptan
Inactive ingredients: anhydrous lactose, colloidal silicon dioxide, copovidone, croscarmellose sodium, magnesium stearate, polysorbate, and indigotine aluminum lake 12 to 14% as colorant (45 mg, 60 mg and 90mg).

For more information about tolvaptan tablets, go to www.apotex.com or call 1-800-706-5575.

Rx Only

APOTEX INC.
Tolvaptan Tablets
15 mg, 30 mg, 45 mg, 60 mg and 90 mg

Manufactured by:	**Manufactured for:**
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Revised: October 2026

Rev. 5

This Medication Guide has been approved by the U.S. Food and Drug Administration.