Tolvaptan™

(Tolvaptan)

Tablet

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COMPOSITION:

Tolvaptan Tablet 15 mg:

Each tablet contains:

Tolvaptan ..... 15 mg.

Product Specs.: Innovator

Tolvaptan Tablet 45 mg:

Each tablet contains:

Tolvaptan ..... 45 mg.

Product Specs.: Innovator

INDICATIONS:

Tolvaptan is 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 4 at initiation of treatment with evidence of rapidly progressing disease.

POSOLOGY:

- Tolvaptan should be initiated by ADPKD specialists aware of its hepatic risks.
- It is taken twice daily in split doses (45 + 15 mg, 60 + 30 mg, or 90 + 30 mg), giving total daily doses of 60–120 mg.
- Take the morning dose 30 minutes before food; the second dose may be taken with or without food.

Dose titration:

Start Tolvaptan at 60 mg/day (45 mg + 15 mg), increasing weekly to 90 mg/day and then 120 mg/day if tolerated.

Maintain the highest tolerable dose and monitor hydration and osmolality.

Stop if CKD reaches stage 5 or if fluid intake is limited.

Avoid grapefruit juice and ensure adequate water intake.

Dose adjustment for patients taking strong CYP3A inhibitors:

In patients taking strong CYP3A inhibitors, tolvaptan doses have to be reduced as follows:

Tolvaptan daily split-dose	Reduced dose (once daily)
90 mg + 30 mg	30 mg (further reduction to 15 mg if 30 mg are not well tolerated)
60 mg + 30 mg	30 mg (further reduction to 15 mg if 30 mg are not well tolerated)
45 mg + 15 mg	15 mg

Dose adjustment for patients taking moderate CYP3A inhibitors:

In patients taking moderate CYP3A inhibitors, tolvaptan doses have to be reduced as follows:

Tolvaptan daily split-dose	Reduced split-dose
90 mg + 30 mg	45 mg + 15 mg
60 mg + 30 mg	30 mg + 15 mg
45 mg + 15 mg	15 mg + 15 mg

Further reductions have to be considered if patients cannot tolerate the reduced tolvaptan doses.

SPECIAL POPULATIONS:

- ***Elderly:***
  - Increasing age has no effect on tolvaptan plasma concentrations. Limited data on the safety and effectiveness of tolvaptan in ADPKD patients aged over 55 are available.
- ***Renal Impairment:***
  - Contraindicated in anuria, no dose change needed otherwise.
  - Stop if CKD reaches stage 5.
- ***Hepatic Impairment:***
  - Avoid in liver injury; monitor enzymes.
  - No adjustment for mild/moderate impairment.
- ***Paediatric Population:***
  - Not studied or recommended.

METHOD OF ADMINISTRATION:

- Oral use
- Tablets must be swallowed without chewing and with a glass of water.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance
- Elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment
- Anuria
- Volume depletion
- Hypernatremia
- Patients who cannot perceive or respond to thirst
- Pregnancy
- Breast-feeding

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

- ***Idiosyncratic Hepatic Toxicity:***
  - Tolvaptan may cause idiosyncratic liver injury, with elevated ALT/AST and occasionally bilirubin.
  - Rare cases of acute liver failure requiring transplantation have occurred
  - Liver enzyme rises usually appear within 3–14 months of treatment and are reversible after discontinuation, but may become severe or life-threatening if unmonitored.
- ***Liver Injury:***
  - Measure ALT, AST, and bilirubin before treatment, monthly for 18 months, then every 3 months.
  - Monitor for hepatic symptoms (fatigue, anorexia, nausea, abdominal pain, vomiting, fever, rash, pruritus, dark urine, jaundice).
  - Do not start if ALT/AST/bilirubin meet discontinuation thresholds.
  - *Interrupt* if significant ALT/AST rise or hepatic symptoms occur; repeat tests within 48–72 h.
  - *Permanently discontinue if:*
    - ALT/AST >8× ULN
    - ALT/AST >5× ULN for >2 weeks
    - ALT/AST >3× ULN with bilirubin >2× ULN or INR >1.5
    - ALT/AST >3× ULN with symptoms
  - *Re-initiate* cautiously if ALT/AST <3× ULN and stable.

Hydration:

- Ensure access to water; drink to thirst.
- Advise 1–2 glasses before bedtime and during nocturia.
- Monitor body weight and volume status; adjust dose or fluid intake if dehydration occurs.

Urinary Outflow:

- Ensure unobstructed urine flow; caution in partial obstruction (e.g., prostatic hypertrophy).

Electrolytes:

- Correct serum sodium abnormalities before treatment.
- Monitor electrolytes and renal function before and during therapy.
- Tolvaptan is contraindicated in hypernatraemia.
- Check electrolytes at least every 3 months during long-term use.

Hypersensitivity/Anaphylaxis:

- Rare anaphylaxis reported, usually after first dose.
- Discontinue immediately, if reaction occurs; do not re-challenge.
- Use caution in benzazepine hypersensitivity.

Diabetes:

- Exclude pseudohyponatremia (glucose >300 mg/dL).
- Monitor glucose; may cause hyperglycaemia, especially in uncontrolled type II diabetes.

Uric Acid:

- May increase serum uric acid and risk of gout; monitor as indicated.

Renal Function:

- Reversible GFR reduction may occur at initiation.
- Limited data in CKD stage 4 (eGFR <25 mL/min/1.73 m²); discontinue if CKD stage 5 develops.

DRUG INTERACTIONS:

Effect of other drugs on Tolvaptan:

CYP3A Inhibitors:

Some medicines, including certain antibiotics, antifungals, calcium channel blockers, and HIV medications, can increase the levels of tolvaptan in your blood. This may increase the risk of side effects. Grapefruit juice can also raise tolvaptan levels. Your doctor may need to adjust your dose if you take these medicines.

CYP3A inducers:

Medicines such as rifampicin, phenytoin, carbamazepine, and St. John's Wort can reduce tolvaptan levels and make it less effective. These medicines should generally be avoided while taking tolvaptan.

Co-administration with medicinal products that increase serum sodium concentration:

Medicines or foods with high sodium may increase your risk of high blood sodium. These should be avoided while taking tolvaptan.

Diuretics:

Loop and thiazide diuretics may increase the risk of dehydration and kidney problems. Your doctor may need to adjust doses or recommend extra fluids.

Effect of Tolvaptan on Other Drugs:

CYP3A substrates:

Tolvaptan may slightly increase the levels of some medicines processed by CYP3A, such as statins, but this is usually not clinically significant.

Transporter substrates:

Tolvaptan can affect medicines like digoxin or dabigatran. Your doctor will monitor you carefully if you take these medicines. Tolvaptan may also affect other medicines including certain statins or metformin, so close monitoring is recommended.

Diuretics or non-diuretic anti-hypertensives:

Tolvaptan may increase the risk of low blood pressure, especially when standing.

Co-administration with vasopressin analogues:

Tolvaptan may reduce the effect of medicines like desmopressin, so using them together is not recommended.

Smoking and alcohol:

There are limited information on how smoking or alcohol affects tolvaptan. Discuss with your doctor if you smoke or drink alcohol.

FERTILITY, PREGNANCY & LACTATION:

Pregnancy:

There are no or limited amount of data from the use of tolvaptan in pregnant women. Tolvaptan is not recommended in women of childbearing potential not using contraception. Tolvaptan is contraindicated during pregnancy.

Breast-feeding:

It is unknown whether tolvaptan is excreted in human breast milk. Tolvaptan is contraindicated during breast-feeding.

Fertility:

Studies in animals showed effects on fertility. The potential risk for humans is unknown.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Tolvaptan has a minor effect on the ability to drive or use machines; dizziness, asthenia, or fatigue may occasionally occur.

ADVERSE EFFECTS:

All ADRs are listed by system organ class and frequency; very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

	Very Common	Common	Uncommon	Not Known
Immune system disorders				Anaphylactic shock, Generalised rash
Metabolism and nutrition disorders	Polydipsia	Dehydration, Hypernatraemia, Decreased appetite, Hyperuricaemia, Hyperglycaemia, Gout		
Psychiatric disorders		Insomnia		
Nervous system disorders	Headache, Dizziness	Dysgeusia, Syncope		
Cardiac disorders		Palpitations		
Respiratory, thoracic and mediastinal disorders		Dyspnoea		
Gastrointestinal disorders	Diarrhoea, Dry mouth	Abdominal pain, Abdominal distension, Constipation, Dyspepsia, Gastroesophageal reflux disease		
Hepatobiliary disorders		Abnormal hepatic function		Acute hepatic failure
Skin and subcutaneous tissue disorders		Dry skin, Rash, Pruritus, Urticaria		
Musculoskeletal and connective tissue disorders		Arthralgia, Muscle spasms, Myalgia		
Renal and urinary disorders	Nocturia, Pollakiuria, Polyuria			
General disorders and administration site conditions	Fatigue, Thirst	Asthenia		
Investigations		Alanine aminotransferase increased, Aspartate aminotransferase increased, Weight decreased, Weight increased	Bilirubin increased	Blood creatine phosphokinase increased

PHARMACOLOGICAL PROPERTIES:

Pharmacotherapeutic group:

Diuretics, vasopressin antagonists,

ATC code: C03XA01.

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. Tolvaptan affinity for the human V2 receptor is 1.8 times that of native AVP.

PHARMACOKINETIC PROPERTIES:

Absorption:

Tolvaptan is rapidly absorbed, reaching peak plasma levels ~2 hours post-dose with ~56% bioavailability. A high-fat meal doubles C_{max} without affecting AUC; morning doses should be taken fasting to avoid excessive exposure.

Distribution:

Plasma concentrations plateau at ≥300 mg, suggesting absorption saturation. Tolvaptan is ~98% protein-bound.

Metabolism:

Extensively metabolized by CYP3A; 14 metabolites identified, all minor and mostly inactive. Terminal half-life is ~8 hours, with steady state after the first dose.

Elimination:

Less than 1% excreted unchanged in urine. About 40% of radioactivity recovered in urine and 59% in feces; unchanged tolvaptan accounts for ~32% of fecal radioactivity.

OVERDOSE:

There is no specific antidote for tolvaptan overdose. Expected effects include hypernatremia, polyuria, thirst, and dehydration or hypovolemia. Management involves monitoring vital signs, electrolytes, ECG, and fluid balance, with continued water and electrolyte replacement until aquaresis subsides. Dialysis is unlikely to be effective due to > 98% plasma protein binding.

INSTRUCTIONS:

This medicinal product does not require any special storage conditions.

– Store below 30°C.

– Protect from heat, sunlight & moisture.

– Keep out of the reach of children.

– To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Tolvaptan Tablet 15 mg : Pack of 1 x 10 tablets.

Tolvaptan Tablet 45 mg : Pack of 1 x 10 tablets.

ہدایات:

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

گرمی، دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATIONS PLEASE CONTACT:

CCL

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