

# Tolvaptan

RX

## JINARC®

15mg & 30mg Tablet  
Diuretic (Vasopressin Antagonist)

**FORMULATION:**  
Each tablet contains 15 mg or 30 mg of tolvaptan.

**PRODUCT DESCRIPTION:**  
Tolvaptan (JINARC®) 15 mg tablets  
Blue, triangular (major axis: 6.58 mm, minor axis: 6.20 mm), shallow-convex, debossed with "OTSUKA" and "15" on one side.

Tolvaptan (JINARC®) 30 mg tablets  
Blue, round (diameter: 8 mm), shallow-convex, debossed with "OTSUKA" and "30" on one side.

**INDICATIONS:**  
Tolvaptan (JINARC®) is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease (see *Pharmacodynamics*).

**DOSAGE AND ADMINISTRATION:**  
Tolvaptan (JINARC®) is to be administered twice daily in split dose regimens of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg. 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. According to these split dose regimens the total daily doses are 60, 90, or 120 mg. Tablets must be swallowed without chewing and with a glass of water.

**Dose titration:**  
The initial dose is 60 mg tolvaptan per day as a split-dose regimen of 45 mg + 15 mg (45 mg taken upon waking and the remainder meal and 15 mg taken before bed). The initial dose is to be increased to a split-dose regimen of 90 mg + 30 mg per day, if tolerated, with at least weekly intervals between titrations. Dose titration has to be performed carefully to ensure that high doses are not poorly tolerated through overly rapid up-titration. Patients may down-titrate to lower doses based on tolerability. Patients have to be maintained on the highest tolerable tolvaptan dose.

The aim of dose titration is to block activity of vasopressin at the renal V2 receptor as completely and constantly as possible, while maintaining acceptable fluid balance (see *Special Warnings and Precautions For Use*). Measurements of urine osmolarity are recommended to monitor the adequacy of vasopressin inhibition. Periodic monitoring of plasma osmolarity or serum sodium (to calculate plasma osmolarity) and/or body weight should be considered to monitor the risk of dehydration secondary to the aqueous effects of tolvaptan in case of patient's insufficient water intake. The safety and efficacy of Tolvaptan (JINARC®) in CKD stage 5 have not been adequately explored and therefore tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5. The morning dose of Tolvaptan (JINARC®) is to be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food. Therapy must be discontinued if the ability to drink or the accessibility to water is limited (see *Special Warnings and Precautions For Use*).

**PRECAUTION:**  
Tolvaptan treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements (see *Special Warnings and Precautions For Use*).

Tolvaptan must not be taken with grapefruit juice (see *Drug Interactions*). Patients must be instructed to drink sufficient amounts of water or other aqueous fluids (see *Special Warnings and Precautions For Use*).

**IMPORTANT PRECAUTION:**  
*Dose adjustment for patients taking strong CYP3A inhibitors*  
In patients taking strong CYP3A inhibitors (see *Drug Interactions*), tolvaptan doses have to be reduced as follows:

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

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

**Elderly population**  
Increasing age has no effect on tolvaptan plasma concentrations. However, the safety and effectiveness of tolvaptan in ADPKD patients aged over 50 years has not yet been established.

**Renal impairment**  
Tolvaptan is contraindicated in anuric patients (see *Contraindications*).

**Serum sodium abnormalities**  
Pre-treatment sodium abnormalities (hyponatraemia or hypernatraemia) must be corrected prior to initiation with tolvaptan therapy.

**Anaphylaxis**  
In post-marketing experience, anaphylaxis (including anaphylactic shock and rash generalised) has been reported very rarely following administration of tolvaptan. This type of reaction occurs after the first administration of tolvaptan. Patients have to be carefully monitored during treatment. Patients with known hypersensitivity reactions to benzazepines or benzepine derivatives (e.g. benzepril, conivaptan, belindopril, mesyate or mirtazapine) may be at risk for hypersensitivity reaction to tolvaptan (see *Contraindications*).

**Breast-feeding**  
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. Tolvaptan (JINARC®) is contraindicated during breast-feeding (see *Contraindications*).

**Paediatric population**  
Tolvaptan (JINARC®) contains lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**CONTRAINDICATIONS:**

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to benzazepine or benzepine derivatives (see *Special Warnings and Precautions For Use*).

• 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 (see *Special Warnings and Precautions For Use*).

• Anuria

• Volume depletion

• Hypernatraemia

• Patients who cannot perceive or respond to thirst

• Pregnancy (see *Fertility, Pregnancy and Lactation*)

• Breast-feeding (see *Fertility, Pregnancy and Lactation*)

**Urinary acid increases**  
Decreased uric acid clearance by the kidney is a known effect of tolvaptan. In a double-blind, placebo-controlled trial of patients with ADPKD, potentially clinically significant increased uric acid (greater than 10 mg/dL) was reported at a higher rate in tolvaptan-patients (6.2 % compared to placebo-treated patients (1.7 %). Adverse reactions of gout were reported more frequently in tolvaptan-treated patients (28% vs. 24%) than in patients receiving placebo (7/483, 1.4%). In addition, increased use of allopurinol and other medicinal products to manage gout were observed in the double-blind, placebo-controlled trial. Effects on serum uric acid are attributable to the reversible renal hemodynamic changes that occur in response to tolvaptan effects on urine osmolarity and may be clinically relevant. However, events of increased uric acid and/or gout were not serious and did not cause

discontinuation of therapy in the double-blind, placebo-controlled trial. Uric acid concentrations are to be evaluated prior to initiation of Tolvaptan (JINARC®) therapy, and as indicated during treatment based on symptoms.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE:**

**Idiosyncratic Hepatic Toxicity**

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).

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

**Effect of tolvaptan on glomerular filtration rate (GFR)**

A reversible reduction in GFR has been observed in ADPKD trials at the initiation of tolvaptan treatment.

**DRUG INTERACTIONS:**

**Effect of other medicinal products on the pharmacokinetics of Tolvaptan**

**CYP3A inhibitors**

Concomitant use of medicinal products that are moderate CYP3A inhibitors (e.g. ampravatin, aripiprant, atazanavir, ciprofloxacin, erlotinib, darunavir/ritonavir, diltiazem, erythromycin, flucloxacil, itraconazole, losartan, mafosfamide, matinib, verapamil) or strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, ritonavir, clarithromycin) increase tolvaptan exposure.

Co-administration of tolvaptan and ketoconazole resulted in a 440 % increase in area under time-concentration curve (AUC) and 248 % increase in maximum observed plasma concentration ( $C_{max}$ ) for tolvaptan.

Co-administration of tolvaptan and flucloxacil, a moderate CYP3A inhibitor, produced a 200 % and 80 % increase in tolvaptan AUC and  $C_{max}$ , respectively.

Co-administration of tolvaptan with grapefruit juice, a moderate to strong CYP3A inhibitor, produced a doubling of peak tolvaptan concentrations ( $C_{max}$ ).

Dose reduction of tolvaptan is recommended for patients while taking moderate or strong CYP3A inhibitors (see *Dose and Administration*). Patients taking moderate or strong CYP3A inhibitors must be managed cautiously, in particular if the inhibitors are taken more frequently than once a day.

**CYP3A inducers**

Concomitant use of medicinal products that are potent CYP3A inducers (e.g., rifampicin) will decrease tolvaptan exposure and efficacy. Co-administration of tolvaptan with rifampicin reduces  $C_{max}$  and AUC for tolvaptan by about 85 %. Therefore, concomitant administration of tolvaptan with potent CYP3A inducers (e.g., rifampicin, rifabutin, rifapentine, phenytoin, carbamazepine, and St. John's Wort) is to be avoided.

If a patient shows abnormal ALT, AST or BT levels prior to initiation of treatment which fulfil the criteria for permanent discontinuation (see below) the use of tolvaptan is contraindicated (see *Contraindications*). In the second daily dose can be taken with or without food. According to these split dose regimens the total daily doses are 60, 90, or 120 mg. Tablets must be swallowed without chewing and with a glass of water.

**Dose titration:**

The initial dose is 60 mg tolvaptan per day as a split-dose regimen of 45 mg + 15 mg (45 mg taken upon waking and the remainder meal and 15 mg taken before bed). The initial dose is to be increased to a split-dose regimen of 90 mg + 30 mg per day, if tolerated, with at least weekly intervals between titrations. Dose titration has to be performed carefully to ensure that high doses are not poorly tolerated through overly rapid up-titration. Patients may down-titrate to lower doses based on tolerability. Patients have to be maintained on the highest tolerable tolvaptan dose.

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