

JINARC (tolvaptan) tablets

Indications and clinical use

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

- In order to select patients who might best benefit from the effects of JINARC, clinical trials evaluated ADPKD patients having a total kidney volume (TKV) ≥ 750 mL, and/or renal function corresponding to a CKD-EPI eGFR ≥ 25 mL/min/1.73m², at the time of initiation of treatment.
- JINARC treatment should be initiated and monitored under the supervision of a nephrologist or specialist with expertise in the management of patients with ADPKD and a full understanding of the benefits and risks of tolvaptan therapy including hepatic toxicity and monitoring requirements.
- Careful consideration and discussion of the appropriateness of JINARC treatment should be undertaken between the prescriber and patient before initiation of therapy, taking into account the potential benefits and risks of treatment. Upon mutual agreement to undertake treatment with JINARC, a signed, duly-documented, manufacturer and product-specific patient-prescriber agreement form (PPAF) is required outlining the relevant patient selection criteria to be considered, expected benefits and risks of treatment, and the need for mandatory hepatic function monitoring.
- **JINARC Controlled Hepatic Safety Monitoring and Distribution Programme:** JINARC is available for treatment of patients with ADPKD only through a manufacturer and product-specific controlled hepatic safety monitoring and distribution (HSMD) programme conducted and maintained by, or for, the market authorisation holder of JINARC. A duly signed manufacturer and product-specific PPAF is required for enrollment in the HSMD Programme. For more information on the programme, please call 1-844-254-6272.
- Safety and effectiveness have not been established in geriatrics (>65).

Therapeutic class

Vasopressin V₂-receptor antagonist

Mechanism of action†

JINARC is a selective vasopressin V₂-receptor antagonist with an affinity for the V₂-receptor that is 1.8 times that of native arginine vasopressin (AVP). Tolvaptan affinity for the V₂-receptor is 29 times greater than for the V_{1a}-receptor. When taken orally, tolvaptan inhibits the binding of vasopressin at the V₂-receptor in the kidney. The decreased binding of vasopressin to the V₂-receptor lowers adenylate cyclase activity resulting in a decrease in intracellular adenosine 3', 5'-cyclic monophosphate (cAMP) concentrations. 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. Inhibition of the V₂-receptor in the kidney epithelial cells also prevents aquaporin 2 containing vesicles from fusing with the plasma membrane, which in turn results in an increase in free water clearance, i.e., aquaresis, and a decrease in urine osmolality.

Dosing

JINARC is taken twice a day. The total daily dose is given as a split-dose regimen, with a higher dose taken in the morning, and a second, lower dose taken 8 hours later.

JINARC can be given with or without meals. Grapefruit and grapefruit juice should not be consumed with JINARC, due to a significant increase in tolvaptan concentrations.

All patients on JINARC should be encouraged to drink water liberally on an ongoing basis in order to match increased urine output, and reduce the likelihood of dehydration and hypernatremia from the aquaretic effects of JINARC. Treatment should be interrupted if the ability to drink or accessibility to water is limited.

Titration

The initial dose of JINARC is generally 60 mg/day and should be titrated upward (as shown) if tolerated.

Titration intervals should be at least 1 week. Titration should be done judiciously 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.

The dose should be up-titrated as shown:

Total daily dose	60 mg	90 mg	120 mg
as a split-dose regimen of	45 mg first thing in the morning	60 mg first thing in the morning	90 mg first thing in the morning
	15 mg 8 hours later	30 mg 8 hours later	30 mg 8 hours later

Patients should normally be maintained on the highest tolerated dose.

† Clinical significance has not been established.

Availability

Pr JINARC® is available in weekly combination blister packs of:

SKU	GTIN (UPC)	DIN
45+15 mg	694785040018	02437503
60+30 mg	694785040025	02437511
90+30 mg	694785040032	02437538



Storage requirements

Store JINARC at 15°C to 30°C.

Contraindications

JINARC is contraindicated in:

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

Most serious warnings and precautions

Idiosyncratic hepatic toxicity: JINARC use has led to idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT & AST), rarely associated with concomitant elevations of total bilirubin. To help mitigate the risk of liver injury, blood testing for hepatic transaminases and total bilirubin is required prior to initiation of JINARC, then blood testing for hepatic transaminases is required:

- monthly for 18 months
- every 3 months for the next 12 months
- every 3–6 months thereafter during treatment with JINARC

Therefore, JINARC is available for treatment of patients with ADPKD only through a controlled hepatic safety monitoring and distribution programme conducted and maintained by, or for, the market authorization holder of JINARC.

Other relevant warnings and precautions

- Risk of dehydration
- Interactions with moderate CYP3A inhibitors, CYP3A inducers or P-glycoprotein inhibitors
- Hepatotoxicity: Acute liver failure
- Anaphylaxis
- Hypernatremia: Concomitant use with hypertonic saline solutions or drugs that may increase serum sodium should be avoided
- Hyperkalemia
- Hyperuricemia
- Hypotension: Co-administration with antihypertensive medications may cause increase in hypotension-related adverse events, including dizziness or syncope
- Serum sodium abnormalities must be corrected prior to JINARC initiation
- Use of contraception in women of childbearing potential
- Vasopressin analogues: Co-administration not recommended
- Caution when driving vehicles or operating machinery

JINARC availability and support

JINARC is only available through the Hepatic Safety Monitoring and Distribution (HSMD) Programme, and managed in conjunction with patients' treating physicians.

Through the ORIJIN® Patient Support Program, patients on JINARC have access to:

- Financial/reimbursement assistance†
- Reminders for blood tests
- Pharmacy services and delivery of JINARC to their home or work
- JINARC.CA website and a newsletter program
- Nurses who can provide more information
- Home Bloodwork Program

For questions on how to obtain JINARC, or about the ORIJIN Patient Support Program and HSMD Programme, please call 1-844-2JINARC (254-6272). For medical information about JINARC, please call 1-877-341-9245.

For more information:

Consult the Product Monograph at jinarcmonograph.ca for adverse reactions, interactions, dosing, monitoring tests and conditions of clinical use. The Product Monograph is also available by calling 1-877-341-9245.

† Subject to ORIJIN Patient Support Program criteria.

Reference: 1. Pr JINARC® Product Monograph. Otsuka Canada Pharmaceutical Inc.



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