PRODUCT MONOGRAPH

PrJINARC®

(tolvaptan)

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

Vasopressin V_2-receptor Antagonist

Otsuka Pharmaceutical Co., Ltd.
Tokyo, Japan 101-8535

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JINARC®

(tolvaptan tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Non-medicinal Ingredients**
Oral	Tablets, 15 mg, 30 mg 45 mg, 60 mg and 90 mg	Corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and FD&C Blue No. 2 Aluminum Lake as colorant

INDICATIONS AND CLINICAL USE

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

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, product-specific patient-prescriber agreement (PPAF) is required outlining relevant patient selection criteria to be considered, expected benefits and risks of treatment, and the need for mandatory hepatic function monitoring (see WARNINGS AND PRECAUTIONS, Hepatotoxicity, and DOSAGE AND ADMINISTRATION).

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

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, with relatively preserved renal function, i.e., estimated creatinine clearance (eCrCl) ≥60 mL/min, generally corresponding to a CKD-EPI eGFR ≥30 mL/min/1.73m^2, at the time of initiation of treatment.

JINARC treatment should be initiated and monitored by a physician experienced in the diagnosis and treatment of polycystic kidney disease.

Geriatrics (> 65 years of age): The safety and effectiveness of JINARC in geriatric patients has not been established.

Pediatrics (< 18 years of age): JINARC has not been studied in pediatric patients with ADPKD. Its use is not recommended in this patient population.

CONTRAINDICATIONS

JINARC (tolvaptan) is contraindicated in:

- hypovolemia
- hypernatremia
- patients who cannot perceive or respond to thirst
- patients with clinically relevant impairment of hepatic function (see WARNINGS AND PRECAUTIONS, Hepatotoxicity, and/or Hepatic Impairment, and DOSAGE AND ADMINISTRATION, Dosing Considerations, *Hepatic Impairment*)
- anuric patients (see WARNINGS AND PRECAUTIONS, Renal Impairment)
- pregnancy, nursing mothers
- patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

WARNING: IDIOSYNCRATIC HEPATIC TOXICITY
JINARC (tolvaptan) use has led to idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT & AST), rarely associated with concomitant elevations of total bilirubin (see Hepatotoxicity, below). To help mitigate the risk of liver injury, blood testing for hepatic transaminases and total bilirubin is required prior to initiation of JINARC, then hepatic transaminases continuing monthly for 18 months, every 3 months for the next 12 months, and then every 3-6 months thereafter during treatment with JINARC (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Dehydration

Due to a prominent aquaretic effect, treatment with tolvaptan may result in dehydration which constitutes a risk factor for renal dysfunction. If dehydration becomes evident, take appropriate action which may include the need to interrupt or reduce the dose of tolvaptan and increase fluid intake. Special care should be taken in patients having diseases that impair appropriate fluid intake or who are at an increased risk of water loss, e.g. in case of vomiting or diarrhea. JINARC should not be prescribed to patients who cannot perceive or respond to thirst (see CONTRAINDICATIONS).

Tolvaptan may cause undesirable effects related to water loss such as thirst, polyuria, nocturia, and pollakiuria. Therefore, it is imperative that patients should have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids. Patients should be instructed to drink water or other aqueous fluids at the first sign of thirst in order to avoid excessive thirst or dehydration (see DOSAGE AND ADMINISTRATION).

Patients should be generally encouraged to drink water while taking JINARC to avoid development of dehydration or hypernatremia, and to improve tolerability of tolvaptan.

Drugs metabolised by CYP3A or transported by P-gp

JINARC is a substrate of CYP3A and co-administration with CYP3A inhibitors or CYP3A inducers may lead to a change in exposure. Patient response should be monitored and the dose adjusted accordingly, as appropriate.

CYP3A Inhibitors

Substantial dose reduction of JINARC is required for patients prescribed strong CYP3A inhibitors, especially for those also having P-gp inhibitory properties, i.e., some azole antifungals (e.g., ketoconazole), some macrolides (e.g., clarithromycin), and some protease inhibitors (e.g., ritonavir, saquinavir) (see DOSAGE AND ADMINISTRATION, CYP3A Inhibitors).

Concomitant use with moderate CYP3A inhibitors, i.e., verapamil, fluconazole and erythromycin, also requires lowered dosing of JINARC (see DRUG INTERACTIONS, and DOSAGE AND ADMINISTRATION, CYP3A Inhibitors).

JINARC should not be taken with grapefruit juice.

CYP3A Inducers

Concomitant use of JINARC with strong CYP3A inducers should be avoided, e.g. rifampin, phenytoin, carbamazepine, St. John's Wort (see DRUG INTERACTIONS, and DOSAGE AND ADMINISTRATION, CYP3A Inducers).

P-gp Inhibitors

Reduction in the dose of JINARC may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors, such as cyclosporine and quinidine, based on clinical response (see DRUG INTERACTIONS, and DOSAGE AND ADMINISTRATION, P-gp Inhibitors). If P-gp inhibitors also act as strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, saquinavir), substantial dose reduction of JINARC is required (see DOSAGE AND ADMINISTRATION, CYP3A Inhibitors).

Hepatotoxicity

Tolvaptan has been associated with idiosyncratic drug-induced hepatocellular injury, as seen by elevations of serum alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations of total bilirubin.

In a double-blind, placebo-controlled trial in patients with ADPKD, elevation (>3 x upper limit of normal [ULN]) of ALT was observed in 4.4% (42/958) of patients on tolvaptan, and 1.0% (5/484) of patients on placebo, while elevation (>3xULN) of AST was observed in 3.1% (30/958) of patients on tolvaptan and 0.8% (4/484) patients on placebo (also, see ADVERSE REACTIONS, Hepatic Injury). Two (2/957, 0.2%) of these tolvaptan treated-patients, as well as a third patient from an extension open-label trial, exhibited increases in hepatic enzymes (>3xULN) with concomitant elevations in total bilirubin (>2xULN). The period of onset of hepatocellular injury, as reflected by ALT elevations >3xULN, was within 3 to 14 months after initiating treatment, and these increases were reversible, with ALT returning to <3xULN within 1 to 4 months. While these concomitant elevations were gradually reversible with prompt discontinuation of tolvaptan, they represent a potential for significant liver injury. Similar changes with other drugs have been associated with the potential to cause irreversible and potentially life-threatening liver injury. The incidence of hepatotoxicity does not appear to be dose related. To date, there is no evidence of hepatocellular injury with tolvaptan when used in patients not treated for ADPKD.

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

To mitigate the risk of significant and/or irreversible liver injury, blood testing for hepatic transaminases and total bilirubin is required prior to initiation of JINARC, then hepatic transaminases continuing monthly for 18 months, every 3 months for the next 12 months, and then at 3-6 month intervals thereafter during treatment with JINARC (see DOSING AND ADMINISTRATION, Dosing Considerations). Concurrent monitoring for symptoms that may indicate liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) is also warranted.

At the onset of symptoms or signs consistent with hepatic injury, or if abnormal ALT or AST increases are detected, JINARC administration must be immediately interrupted and repeat liver tests, i.e., ALT, AST, total bilirubin, alkaline phosphatase, should be obtained as soon as possible, ideally within 48-72 hours (see DOSING AND ADMINISTRATION, Dosing Considerations). Testing should continue at an increased frequency until symptoms/signs/laboratory abnormalities stabilise or resolve, at which point cautious re-initiation of JINARC may be considered.

Hypernatremia

During treatment initiation, patients should be frequently monitored for serum sodium and volume status. If serum sodium increases above the normal range, tolvaptan treatment must be down-titrated or discontinued promptly, with serum sodium carefully monitored and appropriate clinical measures taken, as necessary (see ADVERSE REACTIONS, Increases in Serum Sodium). Concomitant use with hypertonic saline solutions or drugs that may increase serum sodium concentrations should be avoided.

Hyperkalemia

Treatment with tolvaptan is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium. Serum potassium levels should be monitored carefully after initiation of tolvaptan, especially in those who are receiving drugs known to increase serum potassium levels, e.g. spironolactone.

Hyperuricemia

Treatment with tolvaptan may lead to increases in serum uric acid and clinical gout (see ADVERSE REACTIONS, Increases in Serum Uric Acid, and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Uric acid concentrations should be evaluated prior to initiation of JINARC therapy, and as indicated during treatment (see DOSAGE AND ADMINISTRATION, Increases in Serum Uric Acid).

Hypotension-related adverse events

In patients taking anti-hypertensive agents concomitantly with JINARC, an increased incidence of hypotension-related adverse events was observed (see ADVERSE REACTIONS, Co-administration with Anti-Hypertensive Medications), including dizziness and syncope. These findings were not seen in patients not taking anti-hypertensive drugs.

Serum sodium abnormalities

Serum sodium abnormalities, i.e., hyponatremia or hypernatremia, must be corrected prior to initiation of JINARC therapy (also, see CONTRAINDICATIONS).

Vasopressin analogues

In addition to V_2- receptor mediated renal aquaretic effects, tolvaptan blocks vascular vasopressin V_2-receptors involved in the release of coagulation factors (e.g., von Willebrand factor) from endothelial cells. Therefore, the effect of vasopressin analogues such as desmopressin may be attenuated in patients using these therapies concomitantly with tolvaptan. Accordingly, it is not recommended to administer JINARC together with vasopressin analogues.

Special Populations

Pregnant Women:

There are no adequate, well-controlled trials of JINARC in pregnant women. In animal trials with tolvaptan, cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased fetal weight, delayed fetal ossification, and embryo-fetal death occurred. JINARC use is contraindicated in pregnant women.

Women of childbearing potential should use adequate contraceptive measures during JINARC use.

Nursing Women:

It is not known whether JINARC is secreted into human milk. The presence of tolvaptan has been observed in the milk of lactating rats. Because many drugs are secreted into human milk and because of the potential for serious adverse reactions in nursing infants, treatment with JINARC is contraindicated in nursing women.

Pediatrics (< 18 years of age)**:**

JINARC has not been studied in pediatric patients with ADPKD. Its use is not recommended in this patient population.

Geriatrics (> 65 years of age)**:**

Safety and effectiveness in geriatric patients has not been studied.

Hepatic Impairment:

In hyponatremia studies, moderate or severe hepatic impairment was found to decrease the clearance and increase the volume of distribution of tolvaptan (see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, Dosing Considerations, *Hepatic Impairment*, and ACTION AND CLINICAL PHARMACOLOGY, Hepatic Insufficiency). The effects of such changes have not been studied in ADPKD patients, since these patients generally have normal liver function even in the presence of polycystic liver disease. JINARC is contraindicated in patients with clinically relevant impairment of hepatic function.

Renal Impairment:

JINARC is contraindicated in anuric patients, since it is not expected that tolvaptan would offer benefit in these patients. Further, no clinical trial data are available in patients with severe renal insufficiency, including those unable to make urine (see DOSAGE AND ADMINISTRATION, Dosing Considerations, *Renal Impairment*).

Potential for Cognitive and Motor Impairment

There are no controlled trials of the effects of tolvaptan on driving performance. When driving vehicles or using machines, it should be taken into account that occasionally dizziness, asthenia and syncope may occur.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse reaction profile of JINARC (tolvaptan) in the ADPKD indication is based on a clinical trial database of 1,444 treated patients, with 961patients treated with tolvaptan, 483 treated with placebo.

JINARC, at a total daily dose of 60-120 mg, has been evaluated for safety in 961 adult patients in the double-blind, placebo-controlled trial in ADPKD, with approximately 2,335 patient-years of exposure to tolvaptan. A total of 836 patients were treated with tolvaptan for at least 1 year and 742 patients treated with tolvaptan had at least 3 years of exposure.

The total safety database for tolvaptan is comprised of approximately 6,331 adult patients who participated in single and multiple-dose trials in ADPKD and other indications, and who had approximately 4,237 patient-years of exposure to tolvaptan.

The most commonly reported adverse reactions, consistent with the pharmacologic activity of tolvaptan, are thirst, polyuria, nocturia, and pollakiuria occurring in approximately 55%, 38%, 29% and 23% of patients, respectively. The most commonly reported serious adverse events (SAE) that occurred more frequently in tolvaptan patients compared to placebo patients, with ≥0.5% difference, included increased ALT (0.9% vs. 0.4%), increased AST (0.9% vs. 0.4%), chest pain (0.8% vs. 0.4%) and headache (0.5% vs. 0%).

Adverse events that led to discontinuation of tolvaptan were reported for 15.0% of patients, compared to 4.3% of placebo-treated patients, and included polyuria, pollakiuria, nocturia, thirst, abnormal hepatic function, and fatigue.

Idiosyncratic elevations of hepatic aminotransferases, i.e., ALT and AST, have been observed in ADPKD patients treated with JINARC, rarely associated with concomitant elevations in total bilirubin (see Clinical Trial Adverse Drug Reactions, *Hepatic Injury*, below, and WARNINGS AND PRECAUTIONS, Hepatotoxicity).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Table 1 below presents the incidence of treatment emergent adverse drug reactions occurring at a rate of 3% or greater and greater than placebo in the pivotal study, Trial 156-04-251, also known as TEMPO 3:4.

Table 1 **Incidence of Treatment-Emergent Adverse Drug Reactions in at Least 3% of Tolvaptan Subjects and Greater than Placebo in Trial 156-04-251**		
System Organ Class Preferred Term	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)
Cardiac disorders		
Palpitations	34 (3.5)	6 (1.2)
Gastrointestinal disorders		
Abdominal Distension	47 (4.9)	16 (3.3)
Constipation	81 (8.4)	12 (2.5)
Diarrhea	128 (13.3)	53 (11.0)
Dry Mouth	154 (16.0)	60 (12.4)
Dyspepsia	76 (7.9)	16 (3.3)
Gastroesophageal Reflux Disease	43 (4.5)	16 (3.3)
General disorders and administration site conditions		
Asthenia	57 (5.9)	27 (5.6)
Fatigue	131 (13.6)	47 (9.7)
Thirst	531 (55.3)	99 (20.5)
Metabolism and nutrition disorders		
Decreased Appetite	69 (7.2)	5 (1.0)
Hyperuricemia	37 (3.9)	9 (1.9)
Polydipsia	100 (10.4)	17 (3.5)
Musculoskeletal and connective tissue disorders		
Muscle Spasms	35 (3.6)	17 (3.5)
Nervous system disorders		
Dizziness	109 (11.3)	42 (8.7)
Headache	241 (25.1)	121 (25.1)
Psychiatric disorders		
Insomnia	55 (5.7)	21 (4.3)
Renal and urinary disorders		
Nocturia	280 (29.1)	63 (13.0)
Pollakiuria	223 (23.2)	26 (5.4)
Polyuria	368 (38.3)	83 (17.2)
Skin and subcutaneous tissue disorders		
Pruritus	33 (3.4)	13 (2.7)
Rash	40 (4.2)	9 (1.9)

Hepatic Injury

Elevations (>3 x ULN) of ALT were observed in 4.4% (42/958) of patients on tolvaptan, and 1.0% (5/484) of patients on placebo in Trial 156-04-251, while elevation (>3 x ULN) of AST was observed in 3.1% (30/958) of patients on tolvaptan and 0.8% (4/484) patients on placebo (see WARNINGS AND PRECAUTIONS, Hepatotoxicity). Elevations (>5 x ULN) of ALT were observed in 2.3% (22/958) of patients on tolvaptan, and 0.4% (2/484) of placebo-treated patients, while similar elevations of AST were observed in 1.9% (18/958), and 0.4% (2/484), respectively. Elevations (>10 x ULN) of ALT were observed in 1.3% (12/958) of tolvaptan-treated patients, and (>20 x ULN) in 0.6% (6/958), with none in placebo-treated patients. Elevations (>10 x ULN) of AST were observed in 1.0% (10/958) of tolvaptan-treated patients, and (>20 x ULN) in 0.3% (3/958), with none in placebo. Two (2/957, 0.2%) of these tolvaptan treated-patients, as well as a third patient from an extension open-label trial, exhibited increases in hepatic enzymes (>3 x ULN) with concomitant elevations in total bilirubin (>2 x ULN). In this pivotal trial, no cases of clinically-apparent hepatic failure were reported.

Co-administration with Anti-Hypertensive Medications

Among ADPKD patients taking anti-hypertensive medications, a higher incidence of dizziness, presyncope, and syncope was observed in patients treated with tolvaptan, compared to those treated with placebo, see Table 2, below (also, see WARNINGS AND PRECAUTIONS, Hypotension-related adverse events).

Table 2	**Incidence of Adverse Events Associated with Decreased Blood Pressure in Trial 156-04-251**						
System organ class	**Adverse Event**	**No anti−hypertensives**			**Anti−hypertensives**		
		Tolvaptan (N=129)	**Placebo (N=64)**	**Total (N=193)**	**Tolvaptan (N=832)**	**Placebo (N=419)**	**Total (N=1251)**
Nervous system disorders	Dizziness	8 (6.2%)	5 (7.8%)	13 (6.7%)	101 (12.1%)	37 (8.8%)	138 (11.0%)
	Dizziness exertional	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
	Dizziness postural	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.7%)	0 (0.0%)	6 (0.5%)
	Presyncope	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.4%)	0 (0.0%)	3 (0.2%)
	Syncope	3 (2.3%)	0 (0.0%)	3 (1.6%)	13 (1.6%)	3 (0.7%)	16 (1.3%)
Total		11 (8.5%)	5 (7.8%)	16 (8.3%)	116 (13.9%)	39 (9.3%)	155 (12.4%)

Adverse events are counted only once for the most severe of multiple occurrences of an event.

Increases in Serum Sodium

The overall incidence of hypernatremia, reported as an adverse event, in Trial 156-04-251 was 2.8% in patients treated with tolvaptan, compared to 1.0% in placebo-treated patients. The incidence of serum sodium > 150 mEq/L was 4.0%, and 1.4%, respectively. None of these events led to discontinuation of tolvaptan. Mean trough sodium levels were observed to be 1-3 mEq/L higher than placebo.

Increases in Serum Uric Acid

Decreased uric acid clearance by the kidney is a known effect of tolvaptan. Gout was observed in 2.9% (20/961) of patients on tolvaptan and 1.4% (7/483) patients on placebo, in Trial 156-04-251, with a higher incidence of the use of allopurinol (8.2% vs. 5.8%), benzbromarone (0.4% vs. 0.2%), and colchicine-containing medications (2.3% vs. 0.8%) to manage gout in patients on tolvaptan, compared to patients on placebo, respectively. Similarly, there was a higher incidence of increased blood uric acid (greater than 10 mg/dL), at 6.2% vs. 1.7%, reported in patients on tolvaptan compared to patients on placebo, respectively (see DOSAGE AND ADMINISTRATION, Increases in Serum Uric Acid). Mean serum uric acid levels increased about 0.9 mg/dL from baseline in patients treated with tolvaptan (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

<u>Less Common Clinical Trial Adverse Drug Reactions <3%</u>

The following adverse reactions occurred in <3% of ADPKD patients treated with tolvaptan and at a rate greater than placebo in the double-blind, placebo-controlled trial (n = 961 tolvaptan; n = 483 placebo), and are not mentioned elsewhere in the labeling:

Metabolism and Nutrition Disorders: dehydration, hyperglycemia
Respiratory, Thoracic and Mediastinal Disorders: dyspnea

Post-Market Adverse Drug Reactions
Angioedema, anaphylactic shock, and generalized rash, have been reported very rarely following administration of tolvaptan for indications not related to ADPKD.

DRUG INTERACTIONS

Overview
Tolvaptan is a substrate of CYP3A, and thus co-administration with CYP3A inhibitors or CYP3A inducers may lead to a change in tolvaptan exposure. Patient response should be monitored and the dose adjusted accordingly, as appropriate (see DOSAGE AND ADMINISTRATION). Tolvaptan does not inhibit or induce its own metabolism.

Non-clinical studies indicate that tolvaptan is a substrate and competitive inhibitor of p-glycoprotein; other transporters have not been studied.

There have been no trials performed to determine the potential interaction of tolvaptan with alcohol.

Drug-Drug Interactions

Effects of Other Drugs on Tolvaptan

CYP3A Inhibitors
Co-administration of a 30 mg single dose of tolvaptan with 200 mg QD ketoconazole resulted in a 440% increase in AUC and 248% increase in C_{max} for tolvaptan (see WARNINGS AND PRECAUTIONS, CYP3A Inhibitors).

CYP3A Inducers
Co-administration of a single oral dose of 240 mg of tolvaptan with 600 mg QD of rifampicin, a strong CYP3A4 inducer, at steady state decreased tolvaptan C_{max} and AUC_t by approximately 85% (see WARNINGS AND PRECAUTIONS, CYP3A Inducers).

P-gp Inhibitors
Co-administration of tolvaptan with P-gp inhibitors has not been studied in dedicated clinical studies (see WARNINGS AND PRECAUTIONS, P-gp Inhibitors).

Effects of Tolvaptan on Other Drugs

CYP3A substrates
In healthy subjects, tolvaptan, a CYP3A substrate, had no effect on the plasma concentrations of some other CYP3A substrates, e.g., warfarin or amiodarone. However, tolvaptan increased plasma levels of lovastatin by 1.3- to 1.4-fold, indicating a potential effect on weak substrates of CYP3A substrates.

Digoxin
Steady-state digoxin concentrations were statistically significantly increased (approximately 30% increase as determined by C_{max} and 20% increase as determined by AUC_τ), when digoxin was co-administered with multiple 60 mg doses (QD) of tolvaptan; *in vitro* studies indicate that tolvaptan is a substrate and

competitive inhibitor of p-glycoprotein. Patients receiving digoxin should be evaluated for excessive digoxin effects after adding tolvaptan.

Warfarin, Amiodarone, Furosemide, and Hydrochlorothiazide
Co-administration of tolvaptan does not appear to alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone) to a clinically significant degree.

Vasopressin Analogues
In addition to its renal aquaretic effect, tolvaptan is capable of blocking vascular vasopressin V_2 receptors involved in the release of coagulation factors (e.g., von Willebrand's factor) from endothelial cells. Therefore, the effect of vasopressin analogs such as desmopressin may be attenuated in patients using such analogs to prevent or control bleeding when co-administered with tolvaptan.

Drug-Food Interactions

Grapefruit Juice
Co-administration of tolvaptan with 240 mL of grapefruit juice produced a doubling of peak tolvaptan concentrations (C_{max}) but had no effect on tolvaptan elimination half-life (see WARNINGS AND PRECAUTIONS, CYP3A Inhibitors).

Drug-Herb Interactions
Interactions with herbal products have not been established; however, St John's Wort should be avoided while taking JINARC.

Pharmacodynamic Interactions

Concomitant Diuretic Use
Tolvaptan use alone produces a greater 24-hour urine volume than does furosemide or hydrochlorothiazide alone. However, concomitant administration of tolvaptan with furosemide or hydrochlorothiazide results in a 24-hour volume that is similar to that after tolvaptan administration alone.

Furosemide co-administered with tolvaptan produces a similar maximal rate of urine excretion compared to furosemide alone, and 70% higher than tolvaptan alone. HCTZ co-administered with tolvaptan produces a slightly higher maximal excretion rate compared to tolvaptan alone, and 66% higher compared to HCTZ alone.

DOSAGE AND ADMINISTRATION

JINARC (tolvaptan) treatment should be initiated and monitored by a physician experienced in the diagnosis and treatment of polycystic kidney disease (see INDICATIONS AND CLINICAL USE).

Upon mutual agreement to undertake treatment with JINARC, a signed, duly-documented, product-specific patient-prescriber agreement (PPAF) is required for all patients before initiation of JINARC (see INDICATIONS AND CLINICAL USE). This written agreement should be kept in good standing as long as JINARC treatment is continued.

Prior to initiation of treatment with JINARC, it is important to determine whether expected benefit-risk is deemed to be favourable for the individual patient to be treated. Patients most likely to benefit from JINARC appear to be those with rapidly progressive ADPKD, or at a stage of incipient rapid progression, but before widespread destruction of renal architecture has occurred. Factors associated with rapid progression of ADPKD include, large total renal cyst mass for a given age, as measured by total kidney volume (TKV), CKD Stage 2-3, rapid deterioration of renal function, presence of systemic hypertension or albuminuria (also see, Dosing Considerations, below). Conversely, ADPKD patients without evidence of hypertension, and especially those at an early stage of disease with excellent renal function, e.g., estimated creatinine clearance (eCrCL) ≥ 120 mL/min, consistent with renal glomerular (compensatory) hyperfiltration, appear to show little near-term benefit in terms of TKV progression or diminution of renal function decline.

All patients need to be apprised of the risk of idiosyncratic drug-induced liver injury associated with tolvaptan use in ADPKD (see WARNINGS AND PRECAUTIONS, Hepatotoxicity), and the need for ongoing monitoring of hepatic function during JINARC treatment.

In order to enhance the continuous evaluation of the long-term effects of tolvaptan in ADPKD, all patients to be initiated on JINARC should be offered participation in the Canadian JINARC patient outcomes registry.

Once JINARC treatment is instituted, all patients should be encouraged to drink water liberally on an ongoing basis in order to match increased urine output, to reduce the likelihood of dehydration and hypernatremia from the aquaretic effects of tolvaptan (see WARNINGS AND PRECAUTIONS, Dehydration).

Recommended Dose and Dosage Adjustment

JINARC is to be administered twice daily in split tolvaptan dose regimens of 45+15 mg, 60+30 mg, or 90+30 mg. According to these split-dose regimens, the total daily tolvaptan doses are 60, 90, or 120 mg, respectively.

The initial dosage for JINARC is generally 60 mg tolvaptan per day, as a split-dose regimen of 45+15 mg, with 45 mg taken upon waking, and 15 mg taken approximately 8 hours later. The initial dose should be titrated upward to a split-dose regimen of 90 mg tolvaptan (60+30 mg) per day, and then to a target split-dose regimen of 120 mg tolvaptan (90+30 mg) per day, if tolerated, with at least weekly intervals between titrations. Dose titration should be performed judiciously to ensure that high doses are not poorly tolerated through overly rapid up-titration. Physicians may down-titrate to lower doses based on patient tolerability, and up-titrate again when appropriate. Patients should normally be maintained on the highest tolerated dose of tolvaptan.

The aim of dose titration is to block activity of vasopressin at the renal V_2 receptor as completely and constantly as possible, while maintaining acceptable fluid balance, in order to achieve optimal effects on TKV progression or diminution of renal function decline. The adequacy of vasopressin suppression at a given dose of JINARC can be monitored through measurement of urine osmolality and may be used to optimise the clinical benefit of JINARC in ADPKD patients. Treatment with JINARC is more likely to achieve a better clinical response in patients with greater mean changes from baseline urine osmolality (see CLINICAL TRIALS, Figures 4 and 5). A target of a decrease of at least 300 mOsm/kg from baseline may be considered ideal in most cases, although a decrease of at least 200 mOsm/kg from baseline may be appropriate in those at moderate risk of disease progression and relatively early in their disease course, but still eligible for JINARC treatment. If possible, an absolute urine osmolality of less than 300 mOs/kg should be maintained at all times (see CLINICAL TRIALS).

Measurement of urine concentrating ability prior to initiation of JINARC will help determine the subsequent level of vasopressin blockade obtained with a particular dosage regimen of tolvaptan. Such subsequent measurements may then be useful in guiding dose titration with tolvaptan, particularly in patients in whom tolerability is dose limiting. Initial assessment of urine concentrating ability before initiation of JINARC should be carried out following complete overnight fluid restriction of 10-14 hours, using urine osmolality or specific gravity. During treatment with JINARC, measurement of urine osmolality or specific gravity should be carried out at trough before the morning dose, to determine the change in urine osmolality from baseline. However, patients then taking tolvaptan should not be restricted in their usual fluid intake overnight. Although not specifically evaluated, a urine specific gravity in the range of 1.005 generally corresponds to a Uosm < 300 mOsm/kg, although use of specific gravity measurement is considered less accurate than direct measurement of urine osmolality.

Patients should be told that unnecessary treatment interruption should be avoided, and that daily adherence to the recommended dosing regimen of JINARC is important in order to achieve best outcomes in terms of diminution of renal cyst progression and preservation of renal function (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

JINARC may be taken with or without meals.

Therapy should be interrupted if the ability to drink or accessibility to water is limited.

Dosing Considerations

Liver testing must be performed, including total bilirubin, prior to initiating treatment with JINARC to establish baseline liver function. JINARC is contraindicated in patients with clinically relevant impairment of hepatic function (also, see WARNINGS AND PRECAUTIONS, Hepatotoxicity, and/or Hepatic Impairment). Treatment with JINARC should not normally be initiated in patients with AST/ALT >3 x ULN. However, substantial hepatic cyst burden, without advanced impairment of hepatic function, should not serve as an impediment to initiation of JINARC treatment for ADPKD.

To mitigate the risk of significant and/or irreversible liver injury, regular and ongoing blood testing for hepatic transaminases is required during JINARC treatment, on a monthly basis for the first 18 months, then every 3 months for 12 months, and therafter at 3-6 month intervals during treatment with JINARC.

At the onset of symptoms or signs consistent with hepatic injury, or if abnormal ALT or AST increases are detected, JINARC administration must be immediately interrupted and repeat liver tests, i.e., ALT, AST, total bilirubin, alkaline phosphatase, should be obtained as soon as possible, ideally within 48-72 hours. Testing should continue at an increased frequency until symptoms/signs/laboratory abnormalities stabilise or resolve, at which point cautious re-initiation of JINARC may be considered.

Current clinical practice suggests that JINARC therapy should be interrupted upon confirmation of sustained or increasing transaminase levels, and permanently discontinued if significant increases and/or clinical symptoms of hepatic injury persist. 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** total bilirubin > 2xULN or INR > 1.5

- ALT or AST >3-times ULN, with persistent symptoms of hepatic injury as noted above.

If ALT and AST levels remain <3 x ULN, JINARC™ therapy may be cautiously continued with frequent monitoring, as transaminase levels appear to stabilise during continued therapy in some patients without increases in other liver function tests.

Hepatic Impairment
The effect of hepatic impairment on tolvaptan concentrations in treatment of ADPKD has not been studied. These patients should be managed cautiously and liver enzymes should be monitored regularly.

Due to its potential to induce hepatocellular injury, patients with clinically relevant impairment of hepatic function should not be treated with tolvaptan (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS, Hepatotoxicity).

Renal Impairment
Patients who are anuric, or at, or approaching end-stage-renal disease (ESRD), would not be expected to benefit from tolvaptan treatment (see WARNINGS AND PRECAUTIONS, Renal Impairment, and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency). Treatment should be avoided in these patients.

Increases in Serum Uric Acid
Tolvaptan use may lead to increases in serum uric acid and gout (see WARNINGS AND PRECAUTIONS, Hyperuricemia, ADVERSE REACTIONS, Increases in Serum Uric Acid, and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Uric acid concentrations should be evaluated prior to initiation of JINARC therapy, and as indicated during treatment.

CYP3A Inhibitors
Dose reduction of JINARC is required for patients prescribed strong CYP3A inhibitors (see WARNINGS AND PRECAUTIONS, Drugs metabolised by CYP3A or transported by P-gp, and DRUG INTERACTIONS).

Split-dose regimens of 120 mg/day, i.e., 90+30 mg per day, and 90 mg/day, i.e., 60+30 mg per day, should be down-adjusted to 30 mg once daily upon waking, and the split-dose regimen of 60 mg/day, i.e., 45+15 mg per day, to 15 mg once daily upon waking. Treatment should proceed with caution. If these adjusted doses are not well tolerated, further down-titration should be carried out or such combination treatment discontinued.

For patients taking moderate inhibitors of CYP3A concomitantly (see WARNINGS AND PRECAUTIONS, CYP3A Inhibitors), split-dose regimens should be down-adjusted by half, e.g., 120 mg/day, i.e., 90+30 mg per day, should be down-adjusted to 45+15 mg per day. With such down-adjustments, the second daytime dose should be maintained at 15 mg, and the first daily dose down-adjusted, as required.

CYP3A Inducers
Concomitant use of JINARC with strong CYP3A inducers should be avoided (see WARNINGS AND PRECAUTIONS, Drugs metabolised by CYP3A or transported by P-gp, and DRUG INTERACTIONS).

Missed Dose
If a patient misses a dose of JINARC, the patient should take their next dose at its scheduled time and

prescribed dose level.

Administration

Tolvaptan can be taken without regard to food or the timing of food. It should not be taken with grapefruit juice, or after eating grapefruit, as this may cause a significant increase in tolvaptan concentrations.

OVERDOSAGE

In healthy subjects, single oral doses of JINARC (tolvaptan) of up to 480 mg, and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials. 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, that is, 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.

If overdose occurs, estimation of the severity of poisoning is an important first step. A thorough history and details of overdose should be obtained, and a physical examination should be performed. The possibility of multiple drug involvement must be considered.

Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring, and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should be anticipated, which, if not matched by oral fluid ingestion, should be replaced with intravenous hypotonic fluids, while closely monitoring electrolytes and fluid balance.

ECG monitoring should begin immediately and continue until ECG parameters are within normal ranges. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (> 98%). Close medical supervision and monitoring should continue until the patient recovers.

For management of suspected drug overdose, consult the regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

JINARC (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 greater than for the V_{1a}-receptor. When taken orally, tolvaptan inhibits the binding of vasopressin at the V_2-receptor in the kidney. The decreased binding of vasopressin to the V_2-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 V_2-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.

Tolvaptan metabolites have no or weak antagonist activity for human V_2-receptors, compared with tolvaptan. *In vitro* studies have found both enantiomers of tolvaptan to be equally potent at the V_2 receptor.

Pharmacodynamics

With the recommended split-dose regimens in patients with autosomal dominant polycystic kidney disease (ADPKD), 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 by about 250-300 mOsm/kg from baseline, or to below 300 mOsm/kg. Higher doses, e.g., 90+30 mg/day, reduced urine osmolality to below 300 mOsm/kg in a greater proportion of patients than the lower doses.

In healthy subjects or patients with CKD Stage 1 to 4 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 and 90 mg produce a peak effect of about 9 mL/min increase in urine excretion rate that 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. The offset of tolvaptan action is rapid with urine excretion rate returning to baseline within 24 hours following a 90 mg dose.

Increases in daily urine output in response to tolvaptan treatment are positively correlated with baseline renal function. Following a 90+30 mg split-dose regimen in patients with CKD Stage 1 or 2, the change in mean daily urine volume was about 4 L for a mean total daily volume of about 7 L. In Stage 4 patients, the mean change in daily urine volume was about 2 L for a total daily urine volume of about 5 L. Urine osmolality appears to be maximally suppressed at a urine excretion rate of about 4 mL/min or about 5 L/day.

The increase in free water excretion can result in an increase in serum sodium concentration unless fluid intake is increased to match urine output. Following a 90+30 mg split-dose regimen of tolvaptan in patients with CKD Stage 1 to 4, mean serum sodium concentrations were increased about 2 mEq/L.

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

With tolvaptan treatment, small decreases in glomerular filtration rate, as measured by iothalamate clearance, in the order of 6-10% are observed soon after JINARC initiation, and are independent of baseline renal function. It is noted that percent changes in renal plasma flow are highly correlated to percent changes in GFR, with these changes reversible upon discontinuation of tolvaptan. It is believed these changes may occur in response to the observed decrease in urine osmolality caused by tolvaptan.

Serum concentrations of creatinine and cystatin C are slightly increased in patients with CKD Stage 1 to 3, with creatinine changes 2-fold larger in patients with CKD Stage 4.

Uric acid clearance is decreased about 20%-25% in patients with $eGFR_{MDRD}$ >30 mL/min/1.73m^2. Mean uric acid values observed at baseline in the pivotal registration trial were 5.6 mg/dL (n= 948), increased to 6.4 mg/dL (n= 907) following 3 weeks of tolvaptan titration, and were 6.5 mg/dL (n= 721) following 36 months of treatment with tolvaptan (see WARNINGS AND PRECAUTIONS, Hyperuricemia). With placebo, mean uric acid values observed at baseline were 5.5 mg/dL (n= 482), increased to 5.6 mg/dL (n= 474) following 3 weeks of treatment, and were 5.9 mg/dL (n= 406) following 36 months of treatment.

After 3 weeks of tolvaptan treatment at doses from 90 to 120 mg/day, ADPKD patients demonstrated a total kidney volume (TKV) reduction of approximately 3.7%, p<0.0001 (see CLINICAL TRIALS, Figure 1). Treatment with tolvaptan appears more likely to achieve a greater response in patients with the greatest mean changes from baseline in urine osmolality (see CLINICAL TRIALS, Figures 4 and 5). Repeated "breakthrough" from inhibition, as indicated by a urine osmolality greater than plasma osmolality, i.e., > 300 mOsm/kg, may provide a stimulus for cyst cell division and progression of the disease.

In healthy subjects, no prolongation of the QT interval was observed with tolvaptan following multiple doses of 300 mg/day for 5 days.

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 examined. For single doses, area under the curve (AUC) increases proportionally with dose. After administration of doses ≥ 60 mg, however, C_{max} increases less than proportionally with dose. For multiple administration of 300 mg doses compared to 30 mg doses, C_{max} and AUC were only 4.2- and 6.4-fold higher. The pharmacokinetic properties of tolvaptan are stereospecific, with a steady-state ratio of the S-(-) to the R-(+) enantiomer of about 3.

Following oral administration of tolvaptan, peak concentrations are observed between 2 and 4 hours post-dose.

Moderate or severe hepatic impairment or congestive heart failure decrease the clearance and increase the volume of distribution of tolvaptan.

Absorption:
The absolute bioavailability of tolvaptan is 56% (range 42-80%). *In vitro* data indicate that tolvaptan is a substrate and inhibitor of P-gp.

Ingestion of a single dose of 90 mg of tolvaptan with a high-fat meal increased tolvaptan C_{max} 1.96-fold, with no increase in AUC. Similar intake of 60 mg and 30 mg increased tolvaptan C_{max} 1.4- and 1.2-fold, respectively, with no significant increase in AUC.

Distribution:
Tolvaptan is highly plasma protein bound (98%).

Metabolism:
Tolvaptan is extensively metabolized with less than 1% of the dose excreted unchanged in the urine.

Tolvaptan is a CYP3A substrate and does not appear to have clinically meaningful inhibitory activity. *In vitro* trials indicated that tolvaptan was extensively metabolized by the cytochrome P450 isoenzyme CYP3A4/5 and formed many metabolites, with fourteen identified in plasma, urine and feces. The metabolism of most tolvaptan metabolites was also mediated by CYP3A4/5.

Excretion:
Tolvaptan is eliminated entirely by non-renal routes, with 19% of a radioactive dose excreted as unchanged tolvaptan in the feces. The rest is metabolised mainly, if not exclusively, by CYP3A. After oral dosing, clearance is about 4 mL/min/kg and the terminal phase half-life is about 9 hours. The accumulation factor of tolvaptan with the once-daily regimen is 1.3 and the trough concentrations amount to ≤ 16% of the peak concentrations, suggesting a dominant half-life somewhat shorter than 9 hours. There is marked inter-

subject variation in peak and average exposure to tolvaptan with a percent coefficient of variation ranging between 30 and 60%.

Special Populations and Conditions

Pediatrics:
The pharmacokinetics of tolvaptan in patients under the age of 18 years have not been studied.

Geriatrics:
Age did not substantially influence the pharmacokinetic characteristics of tolvaptan following single-dose or multiple-dose administration of 60 mg tablets.

Gender:
Gender was found to have no significant effect on tolvaptan pharmacokinetics.

Race:
In an open-label crossover trial, 24 Japanese and 25 Caucasian men were administered a single 30 mg oral dose of tolvaptan. The mean tolvaptan C_{max} and AUC_{∞}values were only 5-15% higher in Japanese subjects compared to Caucasian subjects.

Hepatic Insufficiency:
In a population pharmacokinetic analysis of hyponatremia patients, moderate hepatic impairment was associated with a 19% decrease in tolvaptan clearance and severe hepatic impairment was associated with a 24% decrease in clearance and a 50% increase in volume of distribution. The effects of such changes have not been studied in ADPKD patients who typically have normal hepatic function despite having variable degrees of polycystic liver disease.

Renal Insufficiency:
Tolvaptan has been studied in subjects with varying degrees of renal function following a single 60-mg dose. Tolvaptan AUC_{∞} in subjects with CrCL<30 mL/min was approximately 1.9 times higher than that in subjects with CrCL>60 mL/min, but there was no correlation between tolvaptan AUC_{∞} and changes in pharmacodynamic endpoints (urine volume, fluid intake, creatinine and free water clearances, urinary excretions of creatinine, Na+ and K+). Tolvaptan increased free water clearance and suppressed urine osmolality to below 300 mOsm/kg in all subjects studied. Increases in urine output were positively correlated with baseline renal function and were significantly lower in patients with CKD Stage 4, i.e., GFR <30 mL/min).

No clinical trial data is available for tolvaptan in patients with a creatinine clearance <10 mL/min or in patients on chronic dialysis.

STORAGE AND STABILITY

Store JINARC at 15°C to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

JINARC (tolvaptan) is available in weekly combination blister packs of 45+15 mg, 60+30 mg, and 90+30 mg tablets. Each blister pack will contain a total of 14 tablets, 7 tablets of each strength, with one tablet from the row of the higher dose to be taken each morning and one tablet from the row of the lower dose to be taken each evening.

JINARC 15 mg tablets are non-scored, blue, triangular, shallow-convex, debossed with “otsuka” and “15” on one side.

JINARC 30 mg tablets are non-scored, blue, round, shallow-convex, debossed with “otsuka” and “30” on one side.

JINARC 45 mg tablets are non-scored, blue, square, shallow-convex, debossed with “otsuka” and “45” on one side.

JINARC 60 mg tablets are non-scored, blue, modified rectangular, shallow-convex, debossed with “otsuka” and “60” on one side.

JINARC 90 mg tablets are non-scored, blue, pentagonal, shallow-convex, debossed with “otsuka” and “90” on one side.

Inactive Ingredients: Corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and FD&C Blue No. 2 Aluminum Lake as colorant.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

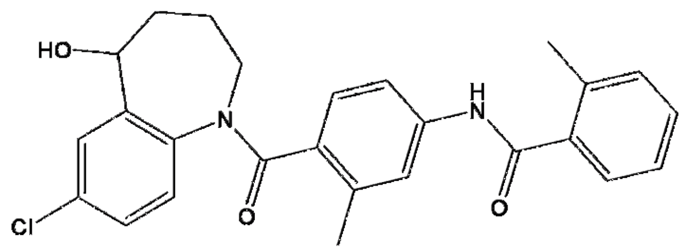
Drug Substance

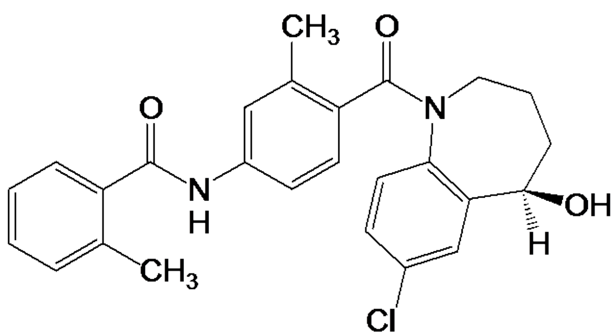
Common name: Tolvaptan

Chemical name: (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide

Molecular formula and molecular mass: $C_{26}H_{25}ClN_2O_3$ 448.94

Structural formula:





and enantiomer

Physicochemical properties: Tolvaptan is a white crystalline powder. It is practically insoluble in water (0.00005 w/v% at 25°C), and no pH dependence of solubility was observed. Tolvaptan is stable to light.

CLINICAL TRIALS

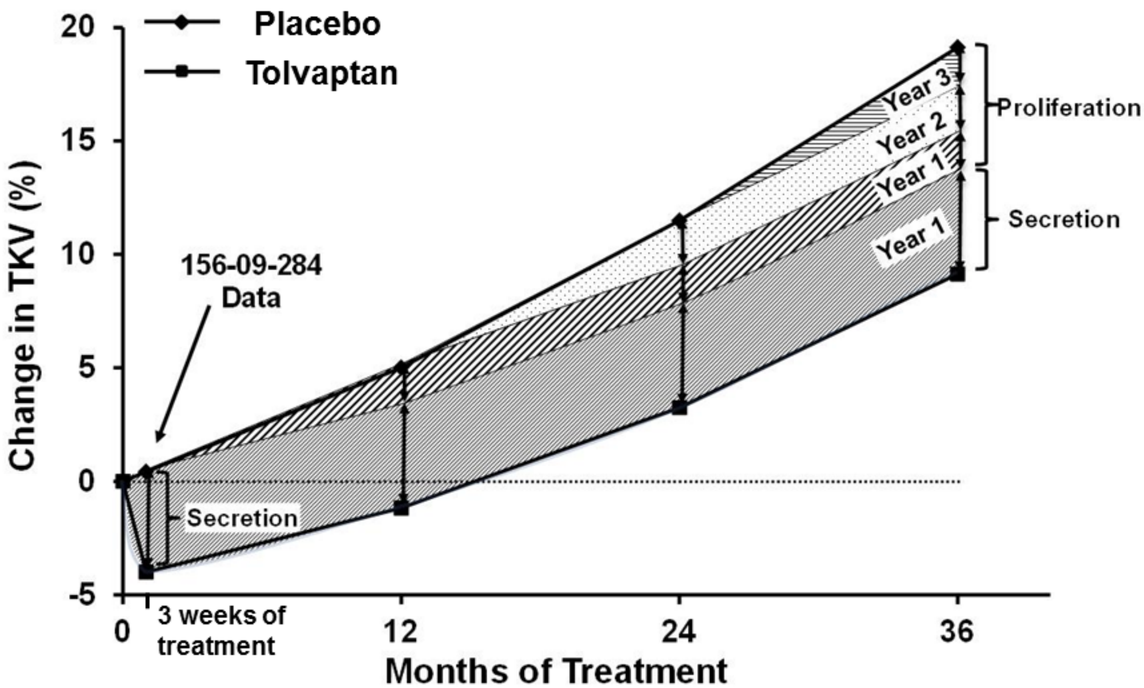
In the pivotal double-blind, 36-month, placebo-controlled, multi-center trial, called TEMPO 3:4 (Trial 156-04-251), a total of 1,445 adult patients (age 18-50 years) with early, rapidly-progressing ADPKD (meeting modified Ravine criteria, total kidney volume (TKV) ≥750 mL, and estimated creatinine clearance ≥60 mL/min) were randomised 2:1 to treatment with JINARC (tolvaptan) or placebo, respectively. A total of 1.444 patients were treated for up to 3 years, then followed for 14-42 days after treatment withdrawal. Randomisation was stratified based on several predictors of more rapid progression, namely baseline hypertension status, kidney volume and renal function. All patients remained on standard concomitant medications. Patients were evaluated at screening, baseline, during weekly titration steps and at intervals of at least 4 months for outcome, laboratory and safety assessments. At baseline and yearly visits, magnetic resonance imaging (MRI) of TKV and pharmacokinetic assessments were also performed. Patients who completed the study terminated treatment at 3 years, and were followed for a further period of 2-6 weeks to assess off-drug effects.

Tolvaptan (N=961) and placebo (N=484) groups were well matched, with an average age of 39 years, 52% being male, 84% Caucasian, 13% Asian and 3% other races. At baseline, 79% had hypertension, average estimated glomerular filtration rate (eGFR) was 82 mL/min/1.73 m^2 calculated by CKD-EPI, and mean TKV was 1,692 mL, with height-adjusted TKV (htTKV) 972 mL/m. Using $eGFR_{CKD\text{-}EPI}$, the distribution of tolvaptan and placebo patients at baseline across CKD stages was as follows: CKD Stage 1 (35%), 2 (48%), and 3 (17%). Within the study population receiving placebo, stratification factors successfully predicted more rapid progression in those who had larger kidneys, lower eGFR, or hypertension at baseline. All patients were encouraged to drink adequate water to avoid thirst or dehydration and at night before retiring.

The primary endpoint was the difference of the rate of change of TKV, normalised as a percentage. TKV increased in the tolvaptan group at a rate of 2.8% per year (95% CI, 2.5% to 3.1%), compared with 5.5% per year (95% CI, 5.1% to 6.0%) for placebo, representing a 49.2% reduction in growth rate averaged over 3 years ($p<0.0001$).

Analysis also indicated that the effect of treatment on TKV growth was greatest in the first year and included negative cyst growth for the tolvaptan group (−1.7%), compared with positive cyst growth in the placebo group (4.6%), for a treatment effect of −6.3%, a statistically significant difference between groups ($p < 0.0001$). However, tolvaptan has a short-term, so-called “secretory” effect on TKV, presumably due to its aquaretic effect, leading to a diminution of renal cyst fluid, which appears largely reversible upon discontinuation of tolvaptan (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). This phenomenon will thus apparently overstate the effect of tolvaptan on renal cyst proliferation in the first year when measured by TKV, see Figure 1 below. During the second and third years, kidney enlargement progressed in both groups. Further absolute reductions in TKV growth (relative to placebo) of 1.92% per year (95%CI 2.81 to 1.03%) and 1.78% per year (95%CI 2.77 to 0.78%) were observed at Year 2 and Year 3 of therapy, respectively.

Figure 1: Model of Tolvaptan's Effects on Total Kidney Volume



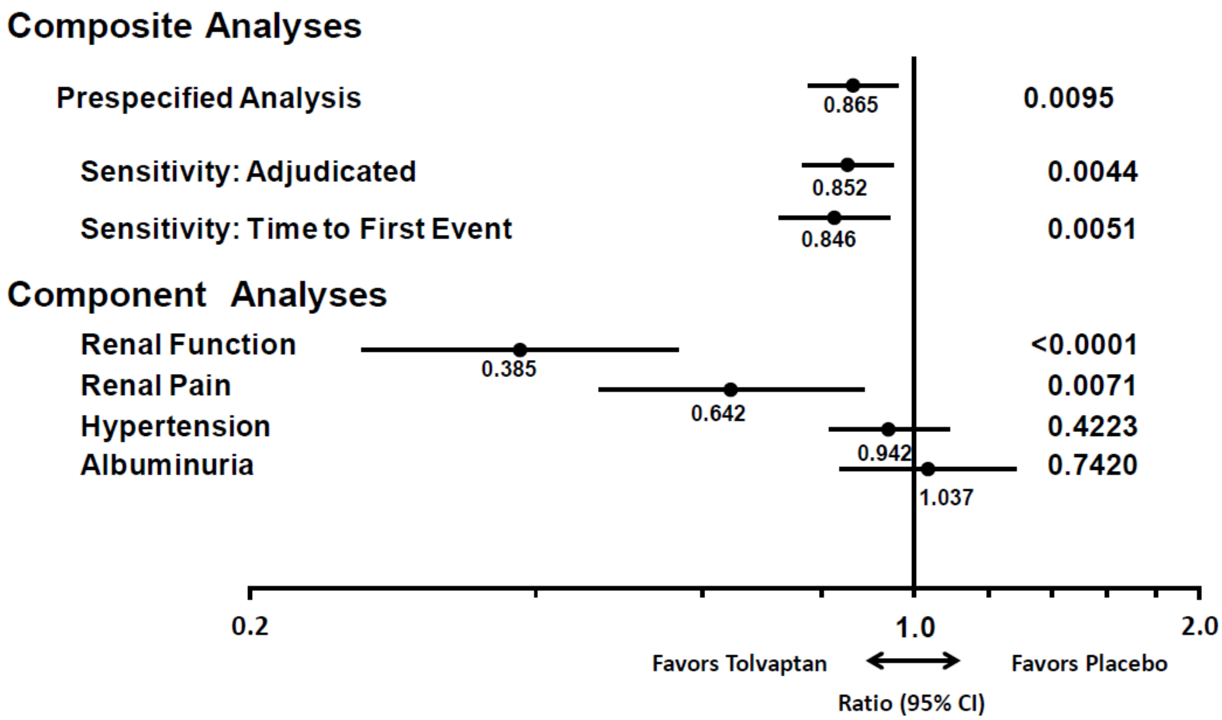
This Figure represents mixed–model repeated measures (MMRM) analysis of percent change in TKV over time for tolvaptan-treated patients (intention-to-treat dataset) from Trial 156–04–251 (TEMPO 3:4), overlaid with 3-week data from Trial 156–09–284.

Pre-specified secondary end-points were tested sequentially. The key secondary composite outcome endpoint, reflecting ADPKD progression, was evaluated using a time-to-event analysis, consisting of:

1) worsening kidney function, defined as a persistent 25% reduction, i.e., reproduced over at least two weeks, in reciprocal serum creatinine during treatment (equivalent to a 33% increase in serum creatinine), from end of titration to last on-drug visit;
2) medically significant kidney pain, defined as requiring prescribed leave, last-resort analgesics, narcotic or anti-nociceptive, radiologic or surgical interventions;
3) worsening hypertension, defined as a persistent increase in blood pressure category, or an increase in anti-hypertensive medication(s); or
4) worsening albuminuria, defined as a persistent increase in albumin/creatinine ratio category (seen at 2 of 3 successive assessments).

The rate of ADPKD-related events, as assessed by the key secondary composite outcome endpoint, was decreased by 13.5% in tolvaptan-treated patients, compared to placebo-treated patients (44 vs. 50 events; HR 0.87; 95% CI, 0.78 to 0.97; p=0.0095), see Figure 2, below.

Figure 2: Key Secondary Composite Endpoint of Clinical Progression Events in TEMPO 3:4

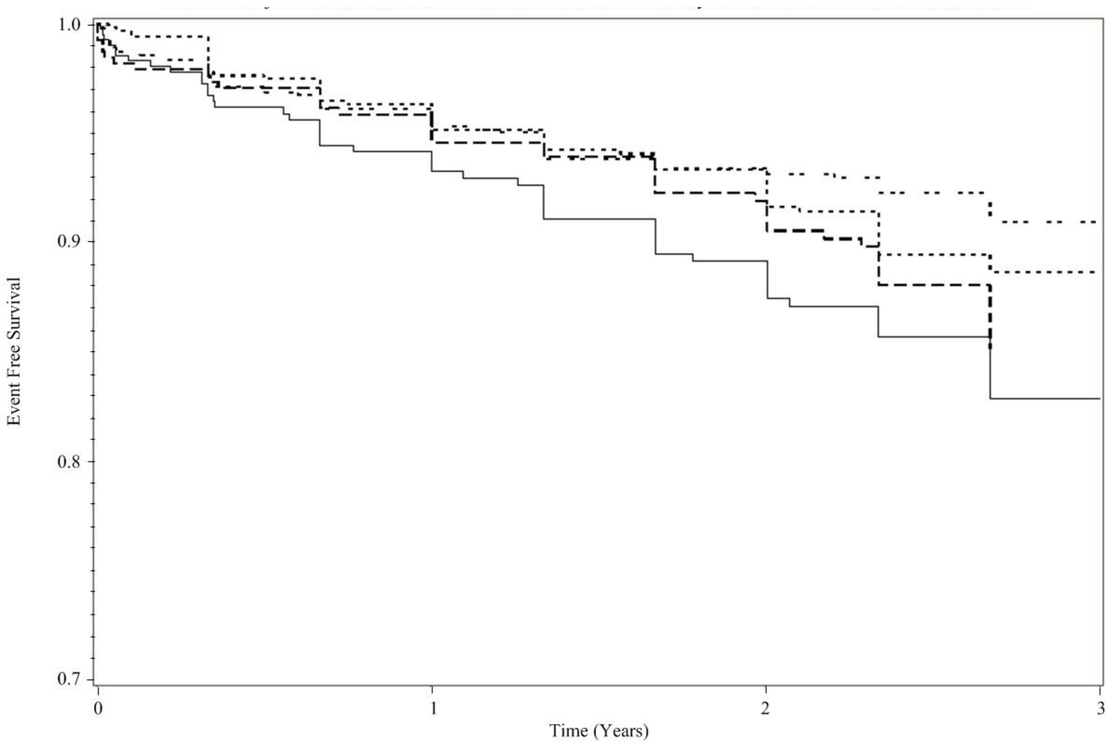


The result of the key secondary composite outcome endpoint is primarily attributed to effects on worsening kidney function and medically significant kidney pain. The renal function events were seen to occur 61.4% less often for tolvaptan compared with placebo (HR 0.39; 95% CI, 0.26 to 0.57; nominal p <0.0001), and renal pain events occurred 35.8% less often in tolvaptan-treated patients (HR 0.64; 95% CI, 0.47 to 0.89; nominal p=0.007), see Figure 2, above. In contrast, there was no effect of tolvaptan on either progression of hypertension or albuminuria. It should be noted, however, that 79% of patients were already hypertensive at baseline in both groups.

The next sequentially ordered secondary endpoint was the slope of kidney function decline, assessed as change in estimated glomerular filtration rate ($eGFR_{CKD-EPI}$) during treatment from end of titration to last on-drug visit. The tolvaptan-treated patients had a 26.4% reduction in the rate of renal function decline, compared to placebo, -2.7 versus -3.6 mL/min/1.73m^2/year, respectively, p <0.0001. Note that initiation of tolvaptan is associated with a generally reversible, prompt decline in GFR, likely due to hemodynamic factors (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Preliminary analyses for urine osmolality (Uosm) suggest that the greatest degree of efficacy, as related to outcomes of events of worsening renal function or renal pain, is seen when Uosm was suppressed by at least -300 mOsm/kg. A lesser degree of efficacy (when compared with other groups of Uosm suppression) is seen for the group between -105 and -300 mOsm/kg, see Figure 3 below.

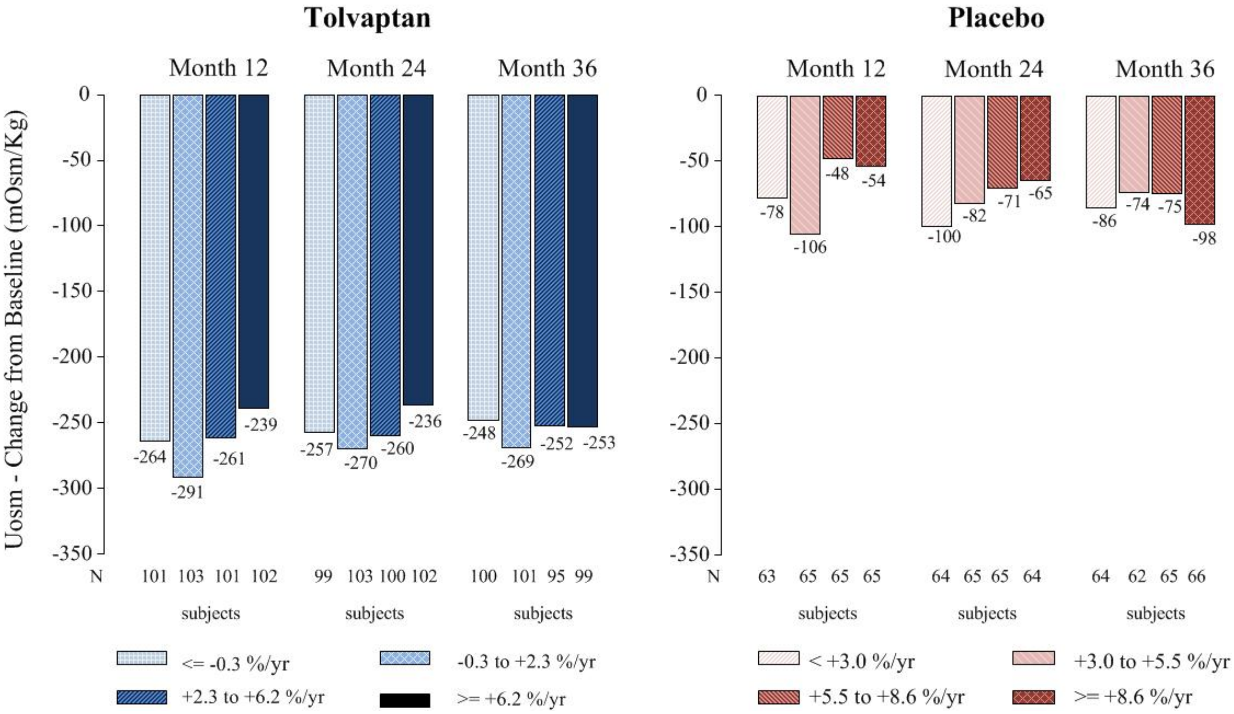
Figure 3: Time to Events of Worsening Renal Function or Kidney Pain, derived from the Key Secondary Composite Endpoint, in TEMPO 3:4 (Trial 156-04-251)



Change of urine osmolality from End of Titration/Week 3 to Baseline; -- --- -- (-1119 to -300 mOsm/kg), ---- (-300 to -105 mOsm/kg), —— (-105 to 0 mOsm/kg), and —— (0 to + 545 mOsm/kg)

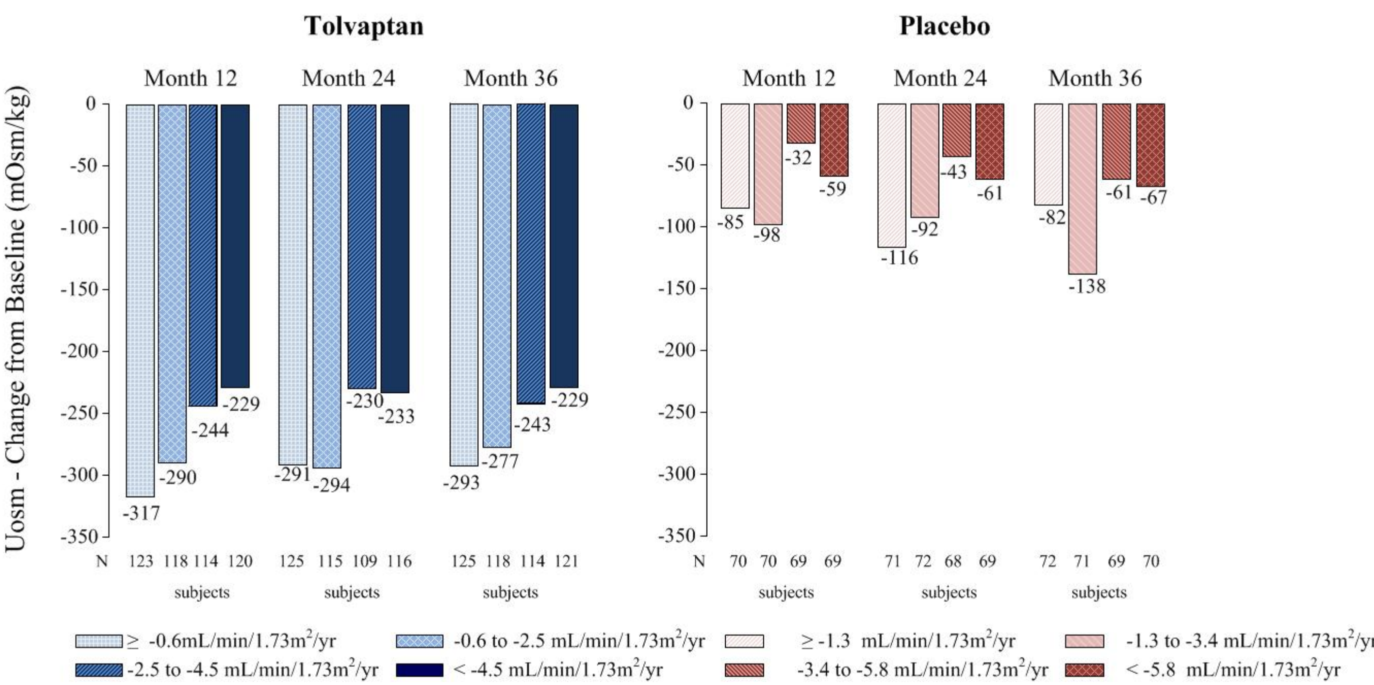
Patients treated with tolvaptan demonstrating greater changes in urine osmolality from baseline appeared to have better responses in terms of slowing progression of TKV and renal function decline, see Figures 4 and 5, respectively, below. Note that best responses are represented by the lightest coloured bars to the left, and worst responses in darkest coloured bars presented to the right, for both endpoints of TKV and renal function decline in all tolvaptan and placebo panels. Although a threshold effect seems to have been reached for TKV with any tolvaptan treatment, with all quartiles achieving a mean change in urine osmolality from baseline of at least 200 mOsm/kg and no apparent correlation of relative changes of urine osmolality on TKV growth, there is an apparent correlation of change of urine osmolality from baseline and attenuation of renal function decline, see Figure 5, below. Placebo shows no such effect.

Figure 4: Mean Change from Baseline in Urine Osmolality in Trial 156-04-251, by Quartile of TKV Growth Rate



Quartiles of TKV Growth Rates, ranging from < -0.3 %/year growth to ≥ 6.2 %/year growth for tolvaptan, and from < 3.0 %/year growth to ≥ 8.6 %/year for placebo.

Figure 5: Mean Change from Baseline in Urine Osmolality in Trial 156-04-251, by Quartile of Renal Function Decline, as Measured by Slope of $eGFR_{CKD-EPI}$

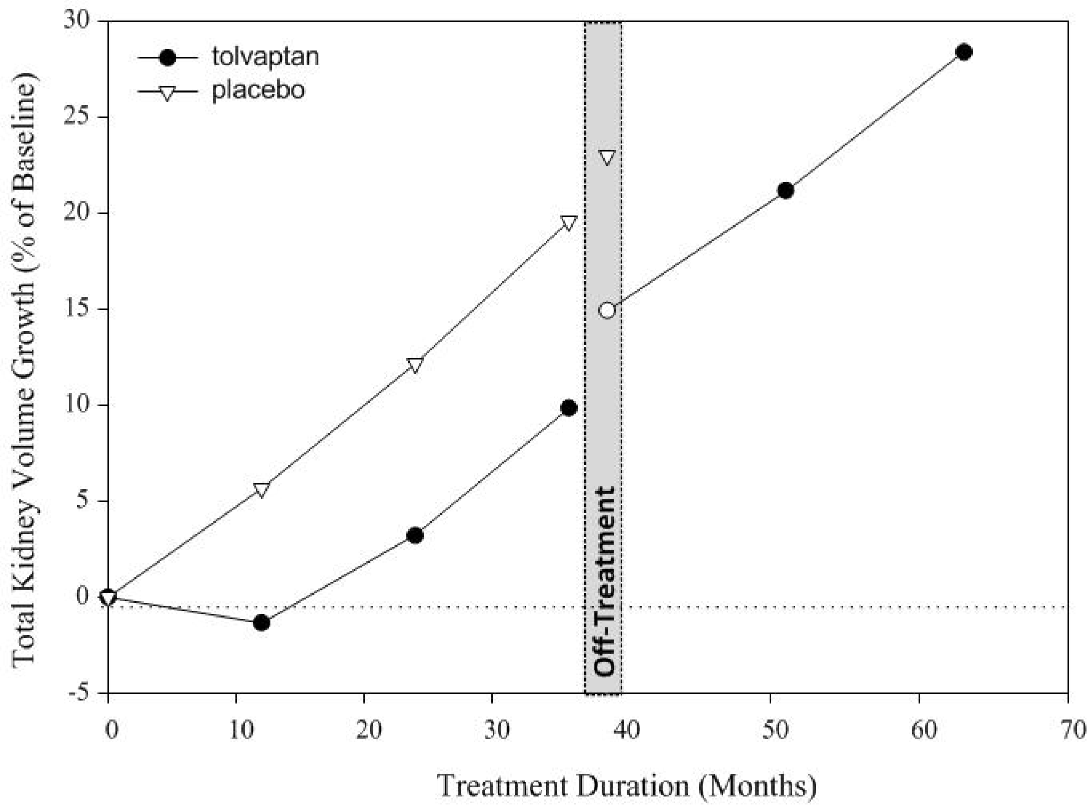


Quartiles of Renal Function Decline, ranging from < 0.6 mL/min/1.73m^2/year to > 4.5 mL/min/1.73m^2/year of renal function decline for tolvaptan, and from < 1.3 mL/min/1.73m^2/year to > 5.8 mL/min/1.73m^2/year of renal function decline for placebo

Following completion of TEMPO 3:4 (Trial 156-04-251), and after a three-month washout period, all placebo-treated and tolvaptan-treated patients were offered ongoing tolvaptan treatment in Study 156-08-271, an open-label extension study.

Interim analysis of TKV progression and eGFR decline over a total of 5 years for tolvaptan-treated patients and 3 years for placebo-treated patients are presented below in Figures 6 and 7, respectively.

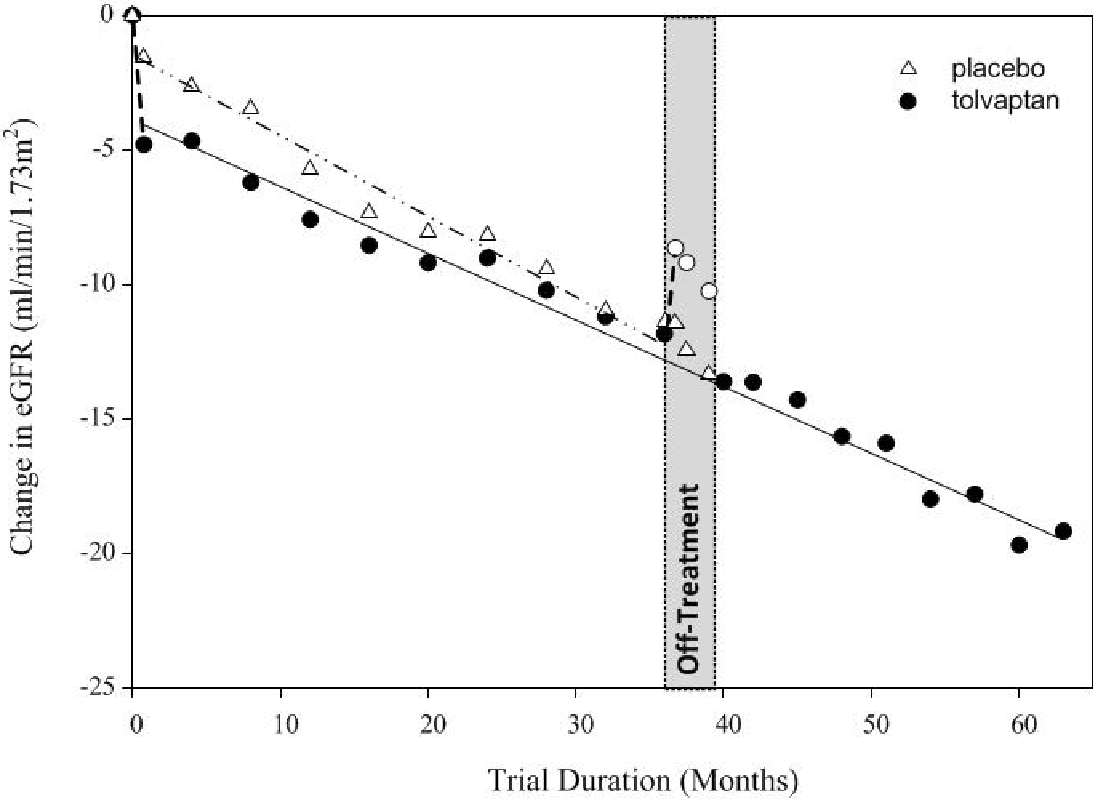
Figure 6: Percent Change in Total Kidney Volume (TKV) from Baseline, from Trials 156-04-251 and 156-08-271



Average TKV change from baseline for patients receiving tolvaptan (solid circles) or placebo (open triangles) during the three years of placebo-controlled Trial 156-04-251 are shown, followed by an average of 3 months post-treatment (open circles or triangles), and then, for the previously tolvaptan-treated patients, two further years of treatment with tolvaptan in the open-label extension study, Trial 156-08-271 (solid circles).

An initial increase in TKV growth is seen after interrupting active therapy, returning to a slowed level of growth after resuming therapy.

Figure 7: Change in Renal Function from Baseline, from Trials 156-04-251 and 156-08-271



Average eGFR change from baseline for patients receiving tolvaptan (solid circles) or placebo (open triangles) during the three years of placebo-controlled Trial 156-04-251 are shown, followed by off-treatment measurements for approximately 3 months post-treatment (open circles or triangles), and then, for the patients previously treated with tolvaptan in Trial 156-04-251, two further years of treatment with tolvaptan in the open-label extension study, Trial 156-08-271(solid circles).

An initial decline in eGFR (- -) is seen, attributed to acute hemodynamic effects of tolvaptan, and thereafter the rate of decline is significantly slowed, $p < 0.0001$, relative to placebo-treated patients (-••- N=422). Upon discontinuing active therapy (see off-treatment period), eGFR rebounds in tolvaptan-treated patients, corresponding to a reversal of tolvaptan-induced acute hemodynamic effects, and is significantly improved relative to placebo-treated patients (- - N=557). Upon resumption of active treatment (approximately 3 months later) the acute hemodynamic effect is seen once again, and eGFR decline continues at the previously slower rate of decline during the additional two years of study (—— N=501 completed).

DETAILED PHARMACOLOGY

Arginine vasopressin (AVP) is a neuropeptide hormone which causes vasoconstriction via V_{1a}-receptors and promotes water reabsorption in the kidneys via V_2-receptors, both of which are G-protein-coupled transmembrane receptors. The V_2-receptors are primarily responsible for the anti-diuretic effects of AVP. Patients with various disorders, including congestive heart failure, liver cirrhosis, and syndrome of inappropriate secretion of anti-diuretic hormone (SIADH), are at risk of experiencing excess water retention or inadequate water disposal due to increased vasopressin secretion. JINARC (tolvaptan) is a competitive, non-peptide vasopressin antagonist drug that blocks the binding of arginine vasopressin at the V_2-receptors of the distal nephron, thereby inducing water diuresis (aquaresis), but notably without the depletion of electrolytes.

Pharmacodynamics

In vitro antagonistic effects of tolvaptan were investigated in binding experiments using a human endocervical carcinoma cell line (HeLa cells) expressing human AVP receptor subtypes (V_{1a}, V_{1b}, and V_2). Tolvaptan inhibited [^{3}H]AVP binding to the V_2-receptors in a concentration-dependent manner, with an inhibition constant (K_i) of 0.43 ± 0.06 nM, which was approximately 1.8 times higher than that of AVP (K_i = 0.78 ± 0.08 nM). Tolvaptan also inhibited [^{3}H]AVP binding to the V_{1a}-receptors with a K_i of 12.3 ± 0.8 nM, but the affinity is approximately 29 times weaker than that for V_2-receptors. On the other hand, tolvaptan did not inhibit [^{3}H]AVP binding to the V_{1b}-receptors even at 100 nM.

The affinities of tolvaptan for rat and canine AVP receptors were investigated by measuring the inhibition of [^{3}H]AVP binding to membrane preparations prepared from rat liver (V_{1a}), canine platelet (V_{1a}), and rat and canine kidney (V_2). Tolvaptan concentration-dependently inhibited [^{3}H]AVP binding to rat AVP V_{1a}- and V_2-receptors with K_i of 345 ± 54 nM and 1.33 ± 0.26 nM, and to canine AVP V_{1a}- and V_2-receptors with K_i of 40.3 ± 12.0 nM and 0.66 ± 0.09 nM, respectively. Thus tolvaptan was approximately 259- and 61-times more selective for V_2-receptors than for V_{1a}-receptors in rats and dogs.

TOXICOLOGY

Single-Dose Toxicity

Single-dose toxicity trials of tolvaptan were conducted by the oral route at doses of up to 2,000 mg/kg in Sprague-Dawley rats and Beagle dogs. No mortality or clinical signs indicative of toxicity were observed in rats or dogs. The minimum lethal dose was not determined in the single-dose trials in rats or dogs. There were no apparent gender differences in sensitivity to the acute effects of tolvaptan in either rats or dogs. There was no macroscopic evidence of target organ toxicity at any dose level.

Repeat-Dose Toxicity

Repeat-dose oral toxicity trials were conducted in Sprague-Dawley rats and Beagle dogs for up to 26 weeks and 52 weeks, respectively. In rats, the No Observed Adverse Effect Level (NOAEL) was 1,000 mg/kg/day in both sexes in the 4-week and 13-week repeated oral dose toxicity trials. In the 26-week trial at doses of 30, 100 and 1,000 mg/kg/day, the results showed neither overt toxicity nor target organ toxicity even at 1,000 mg/kg/day. However, 3 females given 1,000 mg/kg/day were euthanized in a moribund state (dehydration). Therefore, the NOAEL in this trial was estimated to be 1,000 mg/kg/day in the males and 100 mg/kg/day in the females (serum drug concentration at the fourth week of administration: C_{max} was 1.37 and 3.42 μg/mL and AUC_{0-24h} was 12.72 and 20.76 μg·h/mL in the males and females, respectively).

In dogs, the NOAEL was 1,000 mg/kg/day in both sexes in the 4-week and 13-week administration. In the 52-week administration trial at doses of 30, 100 and 1,000 mg/kg/day, the results showed no notable target organ toxicity even at 1000 mg/kg/day. However, one male and 2 females given 1,000 mg/kg/day were sacrificed in a moribund state because of decreases in body weight and food consumption. Therefore, the NOAEL in this trial was estimated to be 100 mg/kg/day in both sexes (serum drug concentration at 52nd week of administration: C_{max} was 5.46 and 6.05 μg/mL and AUC_{0-24h} was 31.45 and 42.35 μg·h/mL in the males and females, respectively).

Genotoxicity

The genotoxic potential of JINARC (tolvaptan) was assessed in a battery of *in vitro* and *in vivo* test systems. Tolvaptan exhibited no genotoxic potential at concentrations up to 5,000 μg/plate in the bacterial (*Salmonella typhimurium* and *Escherichia coli*) reverse-mutation test, up to 200 μg/mL in the forward gene mutation test in mouse lymphoma cells, following pulse treatment at up to 100 μg/mL (in the presence or absence of metabolic activation) or with continuous treatment at up to 40 μg/mL (in the presence or absence of metabolic activation) in the chromosomal aberration test using Chinese hamster lung fibroblast cell line (CHL) or at doses up to 2,000 mg/kg in rat micronucleus test using bone marrow cells from male and female rats administered tolvaptan.

Carcinogenicity

The carcinogenic potential of tolvaptan was evaluated in one 104-week oral carcinogenicity trial in mice and one 104-week oral carcinogenicity trial in rats. Dose levels for the mouse carcinogenicity trial were 0, 10, 30 and 60 mg/kg/day in males and 0, 10, 30 and 100 mg/kg/day in females. The dose levels for the rat carcinogenicity trial were 0, 100, 300 and 1000 mg/kg/day in males and 0, 30, 100, 300 and 1,000 mg/kg/day in females. Oral (gavage) administration of tolvaptan to $B6C3F_1$ mice or Sprague-Dawley rats for 104 weeks was not associated with a decrease in survival or an increase in the incidence of neoplastic or non-neoplastic drug-related findings in males or females. The highest doses tested in mice resulted in exposures (AUC_{0-24h}) that were just below (females; 4.3317 μg·h/mL) and below (males; 2.8595 μg·h/mL) the exposure in humans at the MRHD (120 mg). The highest dose tested in rats resulted in exposures (AUC_{0-24h}) that were approximately 2-times (males; 12.716 μg·h/mL) and 5-times (females; 33.449 μg·h/mL) greater than the exposure in humans at steady state at the MRHD of 120 mg.

Reproductive and Developmental Toxicity Trials

In trials of effects on fertility and reproductive performance in Sprague-Dawley rats, tolvaptan did not impair reproductive performance at doses up to 1,000 mg/kg/day in males and 100 mg/kg/day in females (approximately 81- and 8-times the MRHD on a mg/m^2 basis, respectively). Fertility was not affected at 1,000 mg/kg/day in males and females. The drug-related effect of altered estrous cycles due to prolongation of diestrus was observed in females given 300 and 1,000 mg/kg/day. The NOAEL was less than 100 mg/kg/day for general toxicologic effects in males and females, 100 mg/kg/day for reproductive performance in females and 1,000 mg/kg/day for reproductive performance in males and for fetal development.

In trials of embryo-fetal development, tolvaptan did not cause any developmental toxicity in rats at maternal doses up to 100 mg/kg/day (8-times the MRHD on a mg/m^2 basis) or in New Zealand White rabbits at maternal doses up to 300 mg/kg/day (49-times the MRHD on a mg/m^2 basis). Dose-dependent maternal toxicity was evident in rats at 100 mg/kg/day and higher and in rabbits at 30 mg/kg/day and higher. The NOAEL in rats was 10 mg/kg/day for general toxicologic effects in the parental generation (F_0) dams, 1,000 mg/kg/day for reproductive performance in F_0 dams and 100 mg/kg/day for embryo-fetal development in first generation (F_1) fetuses. Maternal toxicity in female rats consisted of decreased food consumption and body weight (100 mg/kg/day and higher) and developmental toxicity of the F_1 fetuses consisted of decreased body weight and delayed ossification (1,000 mg/kg/day).

In rabbits, the NOAEL was 10 mg/kg/day for general toxicologic effects in F_0 dams, and 100 mg/kg/day for reproductive performance in F_0 dams and 300 mg/kg/day for embryo-fetal development in F_1 fetuses. Maternal toxicity in female rabbits consisted of decreased food consumption and body weight (30 mg/kg and higher). In addition, maternal changes in physiology were examined in dams given 1,000 mg/kg and the changes included increased urine volume, decreased urine osmolality, increased water consumption and increased plasma sodium and chloride concentration as well as plasma osmolality and plasma AVP levels. Maternal reproductive performance, as assessed by the ability to maintain pregnancy, was altered at dose levels of 300 mg/kg and higher where a dose-dependent incidence of abortion was observed. There was also evidence of developmental toxicity in rabbits at the maternally toxic dose of 1,000 mg/kg (162-times the MRHD on a mg/m^2 basis). This developmental toxicity consisted of increased incidences of embryo-fetal death, microphthalmia, open eyelids, cleft palate, brachymelia (zygopodium malformations) and fused phalanx.

Teratogenicity of tolvaptan was further investigated in rabbits. The sensitive period of teratogenicity was during gestation Days 6 to 11, and the maximum sensitivity was shown to be during gestation Days 9 to 11. A toxicokinetics trial in pregnant rabbits showed that 13-day repetitive administration of tolvaptan caused a decrease in exposure level (AUC) of unchanged compound to approximately 1/10 of that at the first administration.

In the prenatal and postnatal trial in pregnant rats, tolvaptan had no effect on offspring development at doses up to 100 mg/kg/day following oral administration to pregnant rats from gestation Day 7 through lactation Day 21. Increased perinatal death and decreased body weight of F_1 generation animals during the lactation period and after weaning were observed in the 1,000 mg/kg/day group. The NOAEL was less than 10 mg/kg/day for general toxicologic effects in F_0 dams, and 1,000 mg/kg/day for reproductive performance in F_0 dams and 100 mg/kg/day in terms of effects on offspring development.

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PART III: CONSUMER INFORMATION
PrJINARC®
Tolvaptan Tablets

This leaflet is part III of a three-part "Product Monograph" published when JINARC was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JINARC. Contact your doctor, nurse or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
JINARC is used in adults to treat autosomal dominant kidney disease (ADPKD).
ADPKD is a genetic disorder which leads to the growth of multiple cysts (sacs filled with fluid) on the kidneys. Over time, the cysts grow in size, which can damage the way your kidneys work, and may ultimately lead to kidney failure.

JINARC should only be prescribed by a doctor experienced in the diagnosis and treatment of polycystic kidney disease.

What it does:
JINARC works by blocking the effects of a hormone called vasopressin, which promotes cyst growth in the kidneys in patients with ADPKD. By blocking the effects of the hormone, JINARC is able to reduce the growth of the cysts in the kidneys and should help protect your kidneys from damage and failure.

Because of the way that JINARC works, you will produce more urine causing you to urinate more frequently during the day and at night. This may become less pronounced over time.

Before starting this medication:
Before taking JINARC you should discuss carefully with your doctor if this medication is suitable for you, taking into consideration the potential benefits and risks involved. Once you and your doctor have agreed that JINARC is suitable for you, your doctor will ask that you sign a patient-prescriber agreement form (PPAF), stating that you understand the benefits and risks of treatment and that you agree to take blood tests as prescribed by your doctor to start and remain on treatment.

When it should not be used:
Do not take JINARC if:
- you can not replace fluids by drinking or you can not feel if you are thirsty
- you have elevated sodium (salt) in your blood
- you have a condition associated with a low blood volume
- your liver is not functioning properly and in a way that is of concern to your doctor. The presence of hepatic cysts in and of themselves should not be an impediment to initiation of JINARC treatment.
- you are pregnant or plan to become pregnant. It is not known if JINARC will harm your unborn baby.
- you are breast-feeding. It is not known if JINARC passes into your breast milk. You and your healthcare provider should decide if you will take JINARC or breast-feed. You should not do both.
- your body is not able to make any urine. JINARC will not help your condition.
- have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in JINARC.
- you are allergic to tolvaptan or any non-medicinal ingredients in the formulation.

What the medicinal ingredient is:
tolvaptan

What the non-medicinal ingredients are:
Corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and FD&C Blue No. 2 Aluminum Lake as colorant.

What dosage forms it comes in:
Weekly combination blister packs of 45+15 mg, 60+30 mg, and 90+30 mg tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions – Liver damage
Your doctor will arrange blood tests before you start treatment with JINARC and then at regular intervals during treatment to check for changes in your liver function.

To prevent pregnancy while on JINARC treatment, women of childbearing potential should use adequate contraceptive measures.

BEFORE you use JINARC talk to your doctor, nurse or pharmacist if you:
- have difficulty urinating or have an enlarged prostate
- are dehydrated or suffer from excessive vomiting, diarrhea or sweating
- have low levels of sodium in your blood
- have high potassium levels in your blood

- have high levels of uric acid in your blood or gout
- are taking medication to treat high blood pressure
- are less than 18 years old

Driving and using machines: Before doing tasks which require special attention, wait until you know how you respond to JINARC. Dizziness, weakness and fainting can occur.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with JINARC: clarithromycin, ketoconazole, ritonavir, saquinavir, rifampicin, phenytoin, carbamazipine, St. John's Wort, cyclosporin, quinidine, verapamil, erythromycin, fluconazole, hypertonic saline solutions, drugs that increase serum sodium concentrations, drugs known to increase serum potassium levels (such as spironolactone), digoxin, consuming grapefruit juice, or vasopressin drugs, such as desmopressin, used to control bleeding.

PROPER USE OF THIS MEDICATION

Always take JINARC exactly as your doctor has prescribed. Check with your doctor, nurse or pharmacist if you are not sure.

You can take JINARC with or without food.

While taking JINARC you will produce more urine, urinate more frequently, and urinate at night. If this causes you concern, consult your doctor, nurse or pharmacist. This side-effect should become less pronounced with time.

To prevent becoming dehydrated, have water available to drink at all times while taking JINARC. Unless your doctor tells you otherwise, drink plenty of water during the day and one or two glasses before going to bed. If you suffer from vomiting, diarrhea or any other condition that might cause you to become dehydrated while taking JINARC call your doctor.

<u>Blood tests:</u>
During treatment with JINARC, your doctor will arrange blood tests to check for changes in your liver function, as follows:

- before starting treatment with JINARC
- every month for the first 18 months, then
- every 3 months for the next 12 months, and
- every 3 - 6 months thereafter during treatment

<u>Usual adult dose:</u>

- JINARC is to be taken twice a day in two different doses. There are three possible dose combinations that your doctor may prescribe:
  - 45+15 mg, for a total daily dose of 60 mg, or
  - 60+30 mg, for a total daily dose of 90 mg, or
  - 90+30 mg, for a total daily dose of 120 mg.
- Take one tablet of the higher dose (45 mg, 60 mg or 90 mg) in the morning.
- 8 hours later take one tablet of the lower dose (15 mg or 30 mg).
- This schedule was designed to give you the best balance between the amount of medicine in your body and possible side effects (especially night time urination).
- Do not drink grapefruit juice during treatment with JINARC. This could cause you to have too great of a drug effect, while taking JINARC.

<u>Overdose</u>: If you think you have taken too much JINARC contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

<u>Missed Dose:</u>
Do not miss or skip doses of JINARC. If you miss a dose, take your next dose at the scheduled time and prescribed level. Do not take 2 doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Thirst
- Increased amount of urine
- Increased frequency of urination during the day and at night
- Headache
- Constipation, diarrhea, dry mouth, indigestion, decreased appetite
- Fatigue, weakness, dizziness
- Trouble sleeping
- Muscle spasms
- Rash, itching

If any of these affects you severely, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor, nurse or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
Common	**Increased levels of potassium in the blood:** irregular heart beats, muscle weakness and generally feeling unwell		√	
Common	**Increased levels of uric acid in the blood/Gout:** joint pain, commonly in the big toe, followed by redness, swelling, warmth		√	
Uncommon	**Dehydration:** increased thirst, dry mouth and/or skin, fatigue, decreased amount of urine, headache, dizziness, irregular heart beats			√
Rare or Uncommon	**Liver Disorder:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
Rare or Uncommon	**Angioedema and Severe Allergic Reactions*:*** swelling of the face, eyes, or tongue, difficulty swallowing, wheezing, hives and generalized itching, rash, fever, abdominal cramps, chest discomfort or tightness, difficulty breathing, unconsciousness.			√

This is not a complete list of side effects. For any unexpected effects while taking JINARC contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store JINARC between 15ºC to 30ºC.

Keep JINARC out of sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**
    Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.otsukacanada.com

or by contacting the marketer, Otsuka Canada Pharmaceutical Inc., at:
1-877-341-9245.

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