AUSTRALIAN PRODUCT INFORMATION
JINARC (TOLVAPTAN) TABLETS

Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations in bilirubin-total (BT). To help mitigate the risk of liver injury, blood testing for hepatic transaminases is required prior to initiation of JINARC, then continually monthly for 18 months, then every 3 months thereafter during treatment with JINARC. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

1 NAME OF THE MEDICINE

Tolvaptan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

JINARC tablets for oral use contain 15 mg, 30 mg, 45 mg, 60 mg or 90 mg of tolvaptan.

Tolvaptan is practically insoluble in water and the aqueous solubility of the drug substance is poor (~ 0.1 mg/250 mL) across all pH ranges. It is slightly soluble in ethyl acetate, sparingly soluble in ethanol, soluble in methanol and freely soluble in benzyl alcohol. The octanol: water partition coefficient was reported to be greater than 5000 at 25°C.

Excipients with known effect: lactose monohydrate.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

JINARC 15 mg Tablet: A blue triangular shallow-convex tablet debossed with “OTSUKA” and “15” on one side.

JINARC 30 mg Tablet: A blue round shallow-convex tablet debossed with “OTSUKA” and “30” on one side.

JINARC 45 mg Tablet: A blue square shallow-convex tablet debossed with “OTSUKA and “45” on one side.

JINARC 60 mg Tablet: A blue modified rectangular shallow convex tablet debossed with “OTSUKA” and “60” on one side.

JINARC 90 mg Tablet: A blue pentagonal shallow-convex tablet debossed with “OTSUKA” and “90” on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

JINARC is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

4.2 DOSE AND METHOD OF ADMINISTRATION

JINARC treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dosage

JINARC is to be administered twice daily in split dose regimens of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg. The morning dose is to be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food. According to these split dose regimens the total daily doses are 60, 90, or 120 mg.

Dose titration

The initial dose is 60 mg tolvaptan per day as a split-dose regimen of 45 mg + 15 mg (45 mg taken upon waking and prior the morning meal and 15 mg taken 8 hours later). The initial dose is to be titrated upward to a split-dose regimen of 90 mg tolvaptan (60 mg + 30 mg) per day and then to a target split-dose regimen of 120 mg tolvaptan (90 mg + 30 mg) per day, if tolerated, with at least weekly intervals between titrations. Dose titration has to be performed cautiously to ensure that high doses are not poorly tolerated through overly rapid up-titration. Patients may down-titrate to lower doses based on tolerability. Patients have to be maintained on the highest tolerable tolvaptan dose.

The aim of dose titration is to block activity of vasopressin at the renal V2 receptor as completely and constantly as possible, while maintaining acceptable fluid balance, in order to achieve optimal effects on TKV progression or diminution of renal function decline. Measurements of urine osmolality are recommended to monitor the adequacy of vasopressin inhibition and, if possible, an absolute urine osmolality of less than 300 mOsm/kg should be maintained at all times (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

Also, monitoring of plasma osmolality or serum sodium (to calculate plasma osmolality) and/or body weight should be considered to monitor the risk of dehydration secondary to the aquaretic effects of tolvaptan in case of patient's insufficient water intake.

The safety and efficacy of JINARC in CKD stage 5 have not been adequately explored and therefore tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5.

Therapy must be interrupted if the ability to drink or the accessibility to water is limited (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Tolvaptan must not be taken with grapefruit juice (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS

FOR USE, Interactions with other Medicines). Patients must be instructed to drink sufficient amounts of water or other aqueous fluids (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

At the onset of symptoms or signs consistent with hepatic injury or if abnormal ALT or AST increases are detected during treatment, JINARC administration must be interrupted and repeat tests including ALT, AST, BT and alkaline phosphatase (AP) must be obtained as soon as possible (ideally within 48-72 hours). Testing must continue at increased time frequency until symptoms/signs/laboratory abnormalities stabilise or resolve, at which point JINARC may be reinitiated.

If ALT and AST levels remain below 3-times the ULN, JINARC therapy may be cautiously continued, with frequent monitoring at the same or lower doses, as transaminase levels appear to stabilise during continued therapy in some patients.

Current clinical practice suggests that JINARC therapy is to 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 (BT >2-times ULN or International Normalized Ratio [INR] >1.5)
- ALT or AST >3-times ULN with persistent symptoms of hepatic injury noted above.

Dose adjustment for patients taking strong CYP3A inhibitors

In patients taking strong CYP3A inhibitors (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Interactions with other medicinal products), tolvaptan doses have to be reduced as follows:

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

Dose adjustment for patients taking moderate CYP3A inhibitors

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

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

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

Dosage adjustments for patients taking CYP 3A Inducers

Concomitant use of tolvaptan with strong CYP 3A inducers should be avoided (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

Elderly population

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

Renal impairment

Dose adjustment is not required in patients with renal impairment. No clinical trials in subjects with a creatinine clearance <10 mL/min or in patients undergoing dialysis have been conducted. The risk of hepatic damage in patients with severely reduced renal function (i.e. eGFR < 20) may be increased; these patients should be carefully monitored for hepatic toxicity. Data for patients in CKD stage 3 are more limited than for patients in stage 1 or 2 (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Hepatic impairment

In patients with severe hepatic impairment the benefits and risks of treatment with JINARC must be evaluated carefully. Patients must be managed carefully and liver enzymes must be monitored regularly (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

JINARC is contraindicated in patients with elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan (see Section 4.3 CONTRAINDICATIONS, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).

Paediatric population

The safety and efficacy of tolvaptan in children and adolescents has not yet been established. No data are available. Tolvaptan is not recommended in the paediatric age group.

Method of administration

For oral use.

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 LIST OF EXCIPIENTS
- Elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- Volume depletion
- Anuria
- Hypernatremia
- Patients who cannot perceive or respond to thirst
- Pregnancy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in pregnancy)
- Breastfeeding (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in lactation)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Idiosyncratic hepatic toxicity

Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in bilirubin-total (BT).

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

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. 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 BT (>2xULN). The period of onset of hepatocellular injury (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 reversible with prompt discontinuation of tolvaptan, they represent a potential for significant liver injury. Similar changes with other medicinal products have been associated with the potential to cause irreversible and potentially life-threatening liver injury.

Prescribing physicians must comply fully with the safety measures required below.

To mitigate the risk of significant and/or irreversible liver injury, blood testing for hepatic transaminases and bilirubin is required prior to initiation of JINARC, continuing monthly for 18 months and at regular 3-monthly intervals thereafter. Concurrent monitoring for symptoms that may indicate liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice) is recommended.

If a patient shows abnormal ALT, AST or BT levels prior to initiation of treatment which fulfil the criteria for permanent dicontinuation (see below) the use of tolvaptan is contraindicated

(see Section 4.3 CONTRAINDICATIONS). In case of abnormal baseline levels below the limits for permanent discontinuation treatment can only be initiated if the potential benefits of treatment outweigh the potential risks and liver function testing must continue at increased time frequency. The advice of a hepatologist is recommended.

During the first 18 months of treatment, JINARC can only be supplied to patients whose physician has determined that liver function supports continued therapy.

At the onset of symptoms or signs consistent with hepatic injury or if abnormal ALT or AST increases are detected during treatment, JINARC administration must be interrupted and repeat tests including ALT, AST, BT and alkaline phosphatase (AP) must be obtained as soon as possible (ideally within 48-72 hours). Testing must continue at increased time frequency until symptoms/signs/laboratory abnormalities stabilise or resolve, at which point JINARC may be reinitiated.

If ALT and AST levels remain below 3-times the upper limit of normal (ULN), JINARC therapy may be cautiously continued, with frequent monitoring at the same or lower doses, as transaminase levels appear to stabilise during continued therapy in some patients.

Current clinical practice suggests that JINARC therapy is to 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 (BT >2-times ULN or International Normalized Ratio [INR] >1.5)
- ALT or AST >3-times ULN with persistent symptoms of hepatic injury noted above.

Access to water

Tolvaptan may cause adverse reactions related to water loss such as thirst, polyuria, nocturia, and pollakiuria (see Section 4.8 ADVERSE EFFECTS). Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients have to be instructed to drink water or other aqueous fluids at the first sign of thirst in order to avoid excessive thirst or dehydration.

Additionally, patients have to drink 1-2 glasses of fluid before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia.

Dehydration

Volume status must be monitored in patients taking tolvaptan because treatment with tolvaptan may result in severe 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 must 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 diarrhoea. In such circumstances patients should be advised to cease tolvaptan treatment and seek urgent medical assistance.

Patients exposed to prolonged heat, humidity, exercise and intercurrent illness will be at greater risk of dehydration.

Urinary outflow obstruction

Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention.

Fluid and electrolyte balance

Fluid and electrolyte status must be monitored in all patients. Administration of tolvaptan induces copious aquaresis and may cause dehydration and increases in serum sodium (see Section 4.8 ADVERSE EFFECTS) and is contraindicated in hypernatraemic patients (see Section 4.3 CONTRAINDICATIONS). Therefore, serum creatinine, electrolytes and symptoms of electrolyte imbalances (e.g. dizziness, fainting, palpitations, confusion, weakness, gait instability, hyper-reflexia, seizures, coma) have to be assessed prior to and after starting tolvaptan to monitor for dehydration.

During long-term treatment electrolytes have to be monitored at least every three months.

Serum sodium abnormalities

Pretreatment sodium abnormalities (hyponatraemia or hypernatraemia) must be corrected prior to initiation with tolvaptan therapy.

Hyperkalemia

Treatment with tolvaptan is associated with an acute reduction of the extracellular fluid volume which could results 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.

Anaphylaxis

In post-marketing experience, anaphylaxis (including anaphylactic shock and rash generalised) has been reported very rarely following administration of tolvaptan. This type of reaction occurred after the first administration of tolvaptan. If an anaphylactic reaction or other serious allergic reactions occur, administration of tolvaptan must be discontinued immediately and appropriate therapy initiated. Since hypersensitivity is a contraindication (see Section 4.3 CONTRAINDICATIONS) treatment must never be restarted after an anaphylactic reaction or other serious allergic reactions.

Lactose

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

Diabetes mellitus

Diabetic patients with an elevated glucose concentration (e.g. in excess of 300 mg/dl) may present with pseudohyponatraemia. This condition must be excluded prior and during treatment with tolvaptan.

Tolvaptan may cause hyperglycaemia (see Section 4.8 ADVERSE EFFECTS). Therefore, diabetic patients treated with tolvaptan must be managed cautiously. In particular this applies to patients with inadequately controlled type II diabetes.

Uric acid increases

Decreased uric acid clearance by the kidney is a known effect of tolvaptan. In a double-blind, placebo-controlled trial of patients with ADPKD, potentially clinically significant increased uric acid (greater than 10 mg/dL) was reported at a higher rate in tolvaptan-patients (6.2%) compared to placebo-treated patients (1.7%). Adverse reactions of gout were reported more frequently in tolvaptan-treated patients (28/961, 2.9%) than in patients receiving placebo (7/483, 1.4%). In addition, increased use of allopurinol and other medicinal products used to manage gout were observed in the double-blind, placebo-controlled trial. Effects on serum uric acid are attributable to the reversible renal hemodynamic changes that occur in response to tolvaptan effects on urine osmolality and may be clinically relevant. However, events of increased uric acid and/or gout were not serious and did not cause discontinuation of therapy in the double-blind, placebo-controlled trial. Uric acid concentrations are to be evaluated prior to initiation of JINARC therapy, and as indicated during treatment based on symptoms.

Effect of tolvaptan on glomerular filtration rate (GFR)

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

Use in the elderly

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

Paediatric use

No data are available. Tolvaptan is not recommended in the paediatric age group.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other medicinal products on the pharmacokinetics of tolvaptan

CYP3A inhibitors

Concomitant use of medicinal products that are moderate (e.g. amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) or strong (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin, saquinavir) CYP3A inhibitors increase tolvaptan exposure. Co-administration of tolvaptan and ketoconazole resulted in a 440% increase in area under time-concentration curve (AUC) and 248% increase in maximum observed plasma concentration (C_{max}) for tolvaptan.

Co-administration of tolvaptan with 240mL grapefruit juice, a moderate to strong CYP3A inhibitor, produced a doubling of peak tolvaptan concentrations (C_{max}).

Dose reduction of tolvaptan is recommended for patients while taking moderate or strong CYP3A inhibitors (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients taking moderate or strong CYP3A inhibitors must be managed cautiously, in particular if the inhibitors are taken more frequently than once a day.

CYP3A inducers

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

P-gp Inhibitors

Reduction in the dose of tolvaptan may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors, such as cyclosporine and quinidine, based on clinical response (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). If P-gp inhibitors also act as strong CYP 3A inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, saquinavir), substantial dose reduction of tolvaptan is required (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Co-administration with medicinal products that increase serum sodium concentration

There is no experience from controlled clinical trials with concomitant use of tolvaptan and hypertonic saline, oral sodium formulations, and medicinal products that increase serum sodium concentration. Medicinal products with high sodium content such as effervescent analgesic preparations and certain sodium containing treatments for dyspepsia may also increase serum sodium concentration. Concomitant use of tolvaptan with medicinal products that increase serum sodium concentration may result in a higher risk for developing hypernatraemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) and is therefore not recommended.

Diuretics

Tolvaptan has not been extensively studied in ADPKD in combination with diuretics. While there does not appear to be a synergistic or additive effect of concomitant use of tolvaptan with loop and thiazide diuretics, each class of agent has the potential to lead to severe dehydration, which constitutes a risk factor for renal dysfunction. If dehydration or renal dysfunction becomes evident, appropriate action must be taken which may include the need to interrupt or reduce doses of tolvaptan and/or diuretics and increased fluid intake. Other potential causes of renal dysfunction or dehydration must be evaluated and addressed.

Effect of tolvaptan on the pharmacokinetics of other products

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). Tolvaptan increased plasma levels of lovastatin by 1.3- to 1.5-fold. Even though this increase has no clinical relevance, it indicates tolvaptan can potentially increase exposure to CYP3A4 substrates.

Transporter substrates

In vitro studies indicate that tolvaptan is a substrate and competitive inhibitor of P-glycoprotein (P-gp). In vitro studies indicate that tolvaptan or its oxobutyric metabolite may have the potential to inhibit OATP1B1, OATP1B3, OAT3, BCRP and OCT1 transporters.

Steady state digoxin concentrations were increased (1.3-fold in maximum observed plasma concentration [C_{max}] and 1.2-fold in area under the plasma concentration-time curve over the dosing interval [AUC_{τ}]) when co administered with multiple once daily 60 mg doses of tolvaptan. Patients receiving digoxin or other narrow therapeutic P-gp substrates (e.g. dabigatran) must therefore be managed cautiously and evaluated for excessive effects when treated with tolvaptan.

Statins commonly used in the tolvaptan phase 3 pivotal trial (e.g. rosuvastatin and pitavastatin) are OATP1B1 or OATP1B3 substrates, however no difference in AE profile was observed during the phase 3 pivotal trial for tolvaptan in ADPKD.

If OATP1B1 and OATP1B3 substrates (e.g. statins such as rosuvastatin and pitavastatin), OAT3 substrates (e.g. methotrexate, ciprofloxacin), BCRP substrates (e.g. sulfasalazine) or OCT1 substrates (e.g. metformin) are co-administered with tolvaptan, patients must be managed cautiously and evaluated for excessive effects of these medications.

Diuretics or non-diuretic anti-hypertensive drug(s)

Standing blood pressure was not routinely measured in ADPKD trials, therefore a risk of orthostatic/postural hypotension due to a pharmacodynamic interaction with tolvaptan cannot be excluded.

Co-administration with vasopressin analogues

In addition to its renal aquaretic effect, tolvaptan is capable of blocking vascular vasopressin V2 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 such analogues to prevent or control bleeding when co-administered with tolvaptan. It is not recommended to administer JINARC with vasopressin analogues.

Smoking and alcohol

Data related to smoking or alcohol history in ADPKD trials are too limited to determine possible interactions of smoking or alcohol with efficacy and safety of ADPKD treatment with tolvaptan.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility was unaffected in male and females rats given tolvaptan at oral doses up to 1000 mg/kg/day (yielding 1.9-times in males and 5.1-times in females the AUC in patients at the maximum recommended human dose [MRHD] of 120 mg per day). However, oestrus cycles were altered in rats at oral doses ≥ 300 mg/kg/day (3.8-times the clinical AUC at the MRHD).

Use in pregnancy (Category D)

Tolvaptan and/or it's metabolites were shown to cross the placent in rats and rabbits.

In rats treated with tolvaptan during organogenesis reduced fetal weights and delayed fetal ossification occurred at an oral dose of 1000mg/kg/day (yielding 17-times the clinical AUC at the MRHD).

Teratogenicity was noted in rabbits given 1000 mg/kg/day (7.5 times the exposure from the 120 mg/day human dose on an AUC basis). The effects were increased rates of emryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations. These adverse effects on embryofetal development were observed in conjuction with maternal toxicity (reduced maternal body weight gain and food consumption) although a direct effect of the drug cannot be excluded.

No teratogenic effects were seen in rabbits at 300 mg/kg/day (about 1.25 to 2.65 times the exposure in humans at the 120 mg/day dose, based on AUC). However, increasing the dose from 300 mg/kg/day to 1000 mg/kg/day increased abortions from 1/17 to 5/18 animals.

There are no adequate data from the use of tolvaptan in pregnant women. The potential risk for humans is unknown.

Women of childbearing potential must use adequate contraceptive measures during Jinarc use. Jinarc must not be used during pregnancy (see Section 4.3 CONTRAINDICATIONS)

Use in lactation

It is unknown whether tolvaptan is excreted in human breast milk. Studies in rats have shown excretion of tolvaptan in milk.

The potential risk for humans is unknown. Jinarc is contraindicated during breastfeeding (see Section 4.3 CONTRAINDICATIONS).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

JINARC has minor influence on the ability to drive or use machines. However, when driving vehicles or using machines it has to be taken into account that occasionally dizziness, asthenia or fatigue may occur.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The pharmacodynamically predictable and most commonly reported adverse reactions are thirst, polyuria, nocturia, and pollakiuria occurring in approximately 55%, 38%, 29% and 23% of patients, respectively. Furthermore, tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in bilirubin-total (BT).

Tabulated list of adverse reactions

The adverse reaction profile of tolvaptan in the ADPKD indication is based on a clinical trial database of 1444 treated patients (961 patients treated with tolvaptan, 483 treated with placebo) and is consistent with the pharmacology of the active substance. Adverse reactions associated with tolvaptan obtained from ADPKD clinical studies are tabulated below.

Table 1. Incidence of Treatment-emergent Adverse Events in at Least 2% of Subjects in Any Group in Trial 156-04-251 by MedDRA System Organ Class and Preferred Term

System Organ Class Preferred Term	Tolvaptan (N = 961) n (%)	Placebo (N = 483) n (%)	Total (N = 1444) n (%)
Total subjects with ≥ 1 TEAE[a]	941 (97.9)	469 (97.1)	1410 (97.6)
Blood and lymphatic system disorders			
Anaemia	27 (2.8)	24 (5.0)	51 (3.5)
Cardiac disorders			
Palpitations	**34 (3.5)**	**6 (1.2)**	**40 (2.8)**
Ear and labyrinth disorders			
Vertigo	24 (2.5)	18 (3.7)	42 (2.9)
Gastrointestinal disorders			
Abdominal Discomfort	29 (3.0)	10 (2.1)	39 (2.7)
Abdominal Distension	47 (4.9)	16 (3.3)	63 (4.4)
Abdominal Pain	62 (6.5)	32 (6.6)	94 (6.5)
Abdominal Pain Upper	63 (6.6)	42 (8.7)	105 (7.3)
Constipation	**81 (8.4)**	**12 (2.5)**	**93 (6.4)**
Diarrhoea	128 (13.3)	53 (11.0)	181 (12.5)
Dry Mouth	154 (16.0)	60 (12.4)	214 (14.8)
Dyspepsia	**76 (7.9)**	**16 (3.3)**	**92 (6.4)**
Gastroesophageal Reflux Disease	43 (4.5)	16 (3.3)	59 (4.1)
Nausea	98 (10.2)	57 (11.8)	155 (10.7)
Toothache	10 (1.0)	12 (2.5)	22 (1.5)
Umbilical Hernia	21 (2.2)	7 (1.4)	28 (1.9)
Vomiting	79 (8.2)	40 (8.3)	119 (8.2)
General disorders and administration site conditions			
Asthenia	57 (5.9)	27 (5.6)	84 (5.8)
Chest Pain	42 (4.4)	12 (2.5)	54 (3.7)

Table 1. Incidence of Treatment-emergent Adverse Events in at Least 2% of Subjects in Any Group in Trial 156-04-251 by MedDRA System Organ Class and Preferred Term			
Fatigue	131 (13.6)	47 (9.7)	178 (12.3)
Malaise	24 (2.5)	10 (2.1)	34 (2.4)
Oedema Peripheral	81 (8.4)	46 (9.5)	127 (8.8)
Pyrexia	45 (4.7)	42 (8.7)	87 (6.0)
Thirst	**531 (55.3)**	**99 (20.5)**	**630 (43.6)**
Hepatobiliary disorders			
Hepatic Cyst	13 (1.4)	10 (2.1)	23 (1.6)
Immune system disorders			
Seasonal Allergy	26 (2.7)	10 (2.1)	36 (2.5)
Infections and infestations			
Bronchitis	58 (6.0)	33 (6.8)	91 (6.3)
Cystitis	11 (1.1)	12 (2.5)	23 (1.6)
Ear Infection	22 (2.3)	7 (1.4)	29 (2.0)
Gastroenteritis	54 (5.6)	21 (4.3)	75 (5.2)
Gastroenteritis Viral	20 (2.1)	6 (1.2)	26 (1.8)
Influenza	75 (7.8)	38 (7.9)	113 (7.8)
Nasopharyngitis	211 (22.0)	111 (23.0)	322 (22.3)
Pharyngitis	16 (1.7)	16 (3.3)	32 (2.2)
Renal Cyst Infection	9 (0.9)	13 (2.7)	22 (1.5)
Rhinitis	14 (1.5)	11 (2.3)	25 (1.7)
Sinusitis	53 (5.5)	23 (4.8)	76 (5.3)
Upper Respiratory Tract Infection	82 (8.5)	42 (8.7)	124 (8.6)
Urinary Tract Infection	81 (8.4)	61 (12.6)	142 (9.8)
Viral Infection	21 (2.2)	13 (2.7)	34 (2.4)
Injury, poisoning and procedural complications			
Ligament Sprain	14 (1.5)	11 (2.3)	25 (1.7)
Investigations			
Alanine Aminotransferase Increased	39 (4.1)	17 (3.5)	56 (3.9)
Aspartate Aminotransferase Increased	36 (3.7)	16 (3.3)	52 (3.6)
Blood Creatinine Increased	135 (14.0)	71 (14.7)	206 (14.3)
Blood Urea Increased	10 (1.0)	12 (2.5)	22 (1.5)
Blood Uric Acid Increased	**24 (2.5)**	**6 (1.2)**	**30 (2.1)**
Gamma-glutamyl Transferase Increased	23 (2.4)	11 (2.3)	34 (2.4)
Weight Decreased	46 (4.8)	16 (3.3)	62 (4.3)
Weight Increased	46 (4.8)	19 (3.9)	65 (4.5)
Metabolism and nutrition disorders			
Decreased Appetite	**69 (7.2)**	**5 (1.0)**	**74 (5.1)**
Dehydration	18 (1.9)	11 (2.3)	29 (2.0)
Gout	**28 (2.9)**	**7 (1.4)**	**35 (2.4)**
Hypercholesterolaemia	26 (2.7)	12 (2.5)	38 (2.6)
Hyperglycaemia	6 (0.6)	10 (2.1)	16 (1.1)
Hypernatraemia	**27 (2.8)**	**5 (1.0)**	**32 (2.2)**
Hyperuricaemia	**37 (3.9)**	**9 (1.9)**	**46 (3.2)**
Polydipsia	**100 (10.4)**	**17 (3.5)**	**117 (8.1)**
Musculoskeletal and connective tissue disorders			
Arthralgia	69 (7.2)	28 (5.8)	97 (6.7)
Back Pain	133 (13.8)	88 (18.2)	221 (15.3)
Flank Pain	11 (1.1)	10 (2.1)	21 (1.5)
Muscle Spasms	35 (3.6)	17 (3.5)	52 (3.6)
Musculoskeletal Pain	37 (3.9)	17 (3.5)	54 (3.7)
Myalgia	50 (5.2)	16 (3.3)	66 (4.6)
Neck Pain	25 (2.6)	12 (2.5)	37 (2.6)
Pain In Extremity	42 (4.4)	27 (5.6)	69 (4.8)
Tendonitis	16 (1.7)	10 (2.1)	26 (1.8)
Nervous system disorders			
Dizziness	109 (11.3)	42 (8.7)	151 (10.5)

Table 1. Incidence of Treatment-emergent Adverse Events in at Least 2% of Subjects in Any Group in Trial 156-04-251 by MedDRA System Organ Class and Preferred Term			
Dysgeusia	21 (2.2)	7 (1.4)	28 (1.9)
Headache	241 (25.1)	121 (25.1)	362 (25.1)
Hypoaesthesia	15 (1.6)	12 (2.5)	27 (1.9)
Migraine	22 (2.3)	10 (2.1)	32 (2.2)
Paraesthesia	19 (2.0)	13 (2.7)	32 (2.2)
Psychiatric disorders			
Anxiety	30 (3.1)	8 (1.7)	38 (2.6)
Depression	42 (4.4)	21 (4.3)	63 (4.4)
Insomnia	55 (5.7)	21 (4.3)	76 (5.3)
Stress	9 (0.9)	10 (2.1)	19 (1.3)
Renal and urinary disorders			
Haematuria	75 (7.8)	68 (14.1)	143 (9.9)
Nephrolithiasis	15 (1.6)	14 (2.9)	29 (2.0)
Nocturia	**280 (29.1)**	**63 (13.0)**	**343 (23.8)**
Pollakiuria	**223 (23.2)**	**26 (5.4)**	**249 (17.2)**
Polyuria	**368 (38.3)**	**83 (17.2)**	**451 (31.2)**
Renal pain	260 (27.1)	171 (35.4)	431 (29.8)
Respiratory, thoracic and mediastinal disorders			
Cough	77 (8.0)	38 (7.9)	115 (8.0)
Dyspnoea	22 (2.3)	6 (1.2)	28 (1.9)
Oropharyngeal Pain	46 (4.8)	18 (3.7)	64 (4.4)
Skin and subcutaneous tissue disorders			
Dry skin	**47 (4.9)**	**8 (1.7)**	**55 (3.8)**
Eczema	**19 (2.0)**	**3 (0.6)**	**22 (1.5)**
Pruritus	33 (3.4)	13 (2.7)	46 (3.2)
Rash	**40 (4.2)**	**9 (1.9)**	**49 (3.4)**
Vascular disorders			
Hypertension	310 (32.3)	174 (36.0)	484 (33.5)
Hypotension	30 (3.1)	15 (3.1)	45 (3.1)

Trial 156-04-251. IMP = investigational medicinal product; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: A TEAE is defined as an AE that occurred after start of IMP, or if the event was continuous from baseline and was serious; related to the IMP; or resulted in death, discontinuation, interruption, or reduction of IMP. Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA Preferred Term. Adverse events are censored 7 days after IMP end date. Note: Bolded rows indicate individual TEAEs that were reported in the tolvaptan group at a percent incidence at least twice that of the placebo group.

[a] Subjects with TEAEs in multiple SOCs were counted only once toward the total.

Description of selected adverse reactions

To mitigate the risk of significant or irreversible liver injury, blood testing for hepatic transaminases is required prior to initiation of JINARC treatment, continuing monthly for 18 months and at regular 3-monthly intervals thereafter (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The most frequent adverse reactions are related to water loss. It is therefore of greatest importance that patients have access to water and are able to drink sufficient amounts of fluids. The volume status of patients taking tolvaptan must be monitored to prevent dehydration (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Post-Marketing

The following adverse reactions have been reported during post-marketing surveillance of tolvaptan.The exact incidence of spontaneously reported adverse reactions is unknown:

- Anaphylaxis
- Generalised rash

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Contact the Poisons Information Centre on telephone 13 11 26 for advice on management of overdose.

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Tolvaptan is a Vasopressin antagonist: ATC code C03XA01.

Mechanism of action

Tolvaptan is a vasopressin antagonist that specifically blocks the binding of arginine vasopressin (AVP) at the V2 receptors of the distal portions of the nephron. Tolvaptan affinity for the human V2-receptor is 1.8 times that of native AVP.

Pharmacodynamic effects

The pharmacodynamic effects of tolvaptan have been determined in healthy subjects and subjects with autosomal dominant polycystic kidney disease (ADPKD) across chronic kidney disease (CKD) stages 1 to 4. Effects on free water clearance and urine volume are evident across all CKD stages with smaller absolute effects observed at later stages, consistent with the declining number of fully functioning nephrons. Acute reductions in mean total kidney volume were also observed following 3 weeks of therapy in all CKD stages, ranging from -4.6% for CKD stage 1 to -1.9% for CKD stage 4.

With the recommended split-dose regimens in patients with autosomal dominant polycystic kidney disease (ADPKD), tolvaptan inhibits vasopressin from binding to the V2-receptor in the kidney for the entire day, as indicated by increased urine output and decreased urine osmolality 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 and peaks 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.

Clinical trials

The primary focus of the clinical program for development of tolvaptan tablets for the treatment of ADPKD is a single pivotal, multinational, phase 3, randomised, placebo controlled trial in which the long-term safety and efficacy of oral split dose tolvaptan regimens (titrated between 60 mg/day and 120 mg/day) were compared with placebo in 1,445 adult subjects with ADPKD. In total, 14 clinical trials involving tolvaptan have been completed worldwide in support of the ADPKD indication, including 8 trials in the US, 1 in the Netherlands, 3 in Japan, 1 in Korea, and the multinational phase 3 pivotal trial.

In the pivotal double-blind, 36-month, placebo-controlled, multi-center trial (TEMPO 3:4), a total of 1444 adult patients (age 18-50 years) with early, rapidly-progressing ADPKD (meeting modified Ravine criteria, total kidney volume (TKV) ≥750 cc, estimated creatinine clearance ≥60 mL/min) were randomized 2:1 to treatment with tolvaptan or placebo, respectively. A total of 1444 patients were treated for up to 3 years, then followed for 14-42 days after treatment withdrawal. Randomization was stratified based on several predictors of more rapid progression, namely baseline hypertension status, kidney volume and renal function. Other known predictors of risk of rapid progression, not used in the stratification, include a family history of ADPKD with early end-stage renal disease (ESRD) or high bilateral cyst number. All patients remained on standard concomitant medications. Concomitant use of potent cytochrome P450 CYP 3A4 inhibitors was avoided. Investigational drug was up-titrated from a daily, oral split dose of 45 mg on waking plus 15 mg 9 hours later (45 mg/15 mg) weekly, as tolerated to 60 mg/30 mg then 90 mg/30 mg. Patients were to maintain the highest tolerated dose for 3 years, but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to drink adequate

water to avoid thirst or dehydration and at night before retiring. 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, MRI-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 and representative of regional populations with an average age of 39 years, with 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 m2 (CKD-EPI) and mean TKV was 1692 cc (height adjusted 972 cc/m). Using CKD-EPI eGFR, tolvaptan and placebo patients were distributed across Kidney Disease Outcomes Quality Initiative chronic kidney disease (KDOQI-CKD) stages 1 (34% and 36%), 2 (49% and 46%) and 3 (17% and 17%), respectively. 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. No anti-hypertensive medications were being taken by 23% of patients; in the remaining 77% of patients, 71% were taking agents acting on the renin-angiotensin system, 20% calcium channel blockers and, 18% beta blockers. Analgesics were used in 10% of patients for unspecified indications while an additional 5% of patients used these for kidney pain. Dietary restrictions for sodium, protein or caffeine were prescribed in 31%, 17% and 34% of patients, respectively.

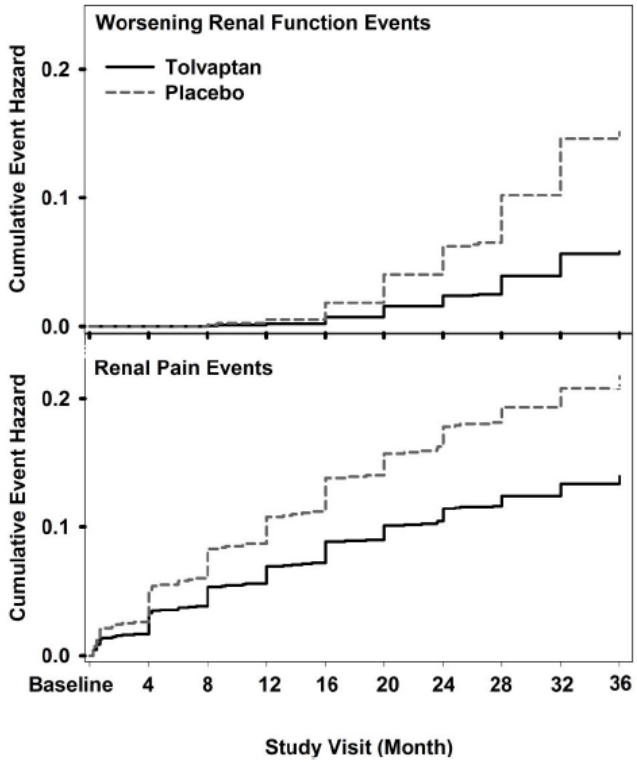
The primary endpoint (TKV slope) was the intergroup difference for rate of change of TKV normalized as a percentage. TKV increased in the tolvaptan group at a rate of 2.80% per year (95% confidence interval [CI], 2.5% to 3.1%) compared with 5.51% per year (95% CI, 5.1% to 6.0%) for placebo representing a 49.2% reduction in growth rate averaged over 3 years ($p<0.0001$).

Pre-specified secondary end-points were tested sequentially. The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of:
1) worsening kidney function (defined as a persistent [reproduced over at least 2 weeks] 25% reduction in reciprocal serum creatinine during treatment (from end of titration to last on-drug visit); 2) medically significant kidney pain (defined as requiring prescribed leave, last-resort analgesics, narcotic and anti-nociceptive, radiologic or surgical interventions); 3) worsening hypertension (defined as a persistent increase in blood pressure category or an increased anti-hypertensive prescription); 4) worsening albuminuria (defined as a persistent [reproduced at 2 of 3 successive assessments] increase in albumin/creatinine ratio category).

The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (44 vs. 50 events; hazard ratio, 0.87; 95% CI, 0.78 to 0.97; p=0.0095).

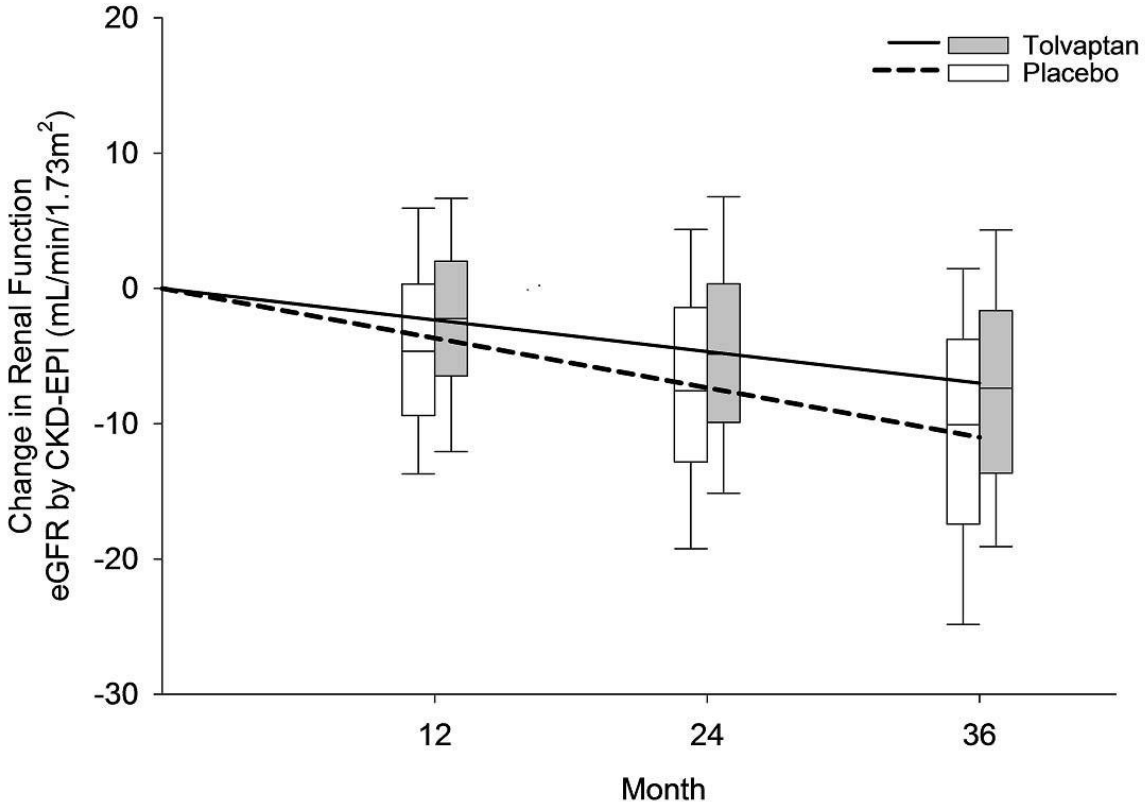
The result of the key secondary composite endpoint is primarily attributed to effects on worsening kidney function and medically significant kidney pain. The renal function events were 61.4% less likely for tolvaptan compared with placebo (2 events per 100 person-years of follow-up in the tolvaptan group vs. 5 in the placebo group; hazard ratio, 0.39; 95% CI, 0.26 to 0.57; nominal $p <0.0001$, Figure 1), while renal pain events were 35.8% less likely in tolvaptan-treated patients (5 events per 100 person-years of follow-up in the tolvaptan group vs. 7 in the placebo group; hazard ratio, 0.64; 95% CI, 0.47 to 0.89; nominal p=0.007, Figure 1). In contrast, there was no effect of tolvaptan on either progression of hypertension or albuminuria.

Figure 1: cumulative Hazard Function for Time to Multiple Events of Worsening Kidney Function and Kidney Pain



The next sequentially ordered secondary endpoint of slope of kidney function decline was 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 with placebo (-2.7 versus - 3.7 (mL/min/1.73 m2), p <0.0001, Figure 2). Figure 2 represents slope of renal function for tolvaptan (solid) and placebo (dashed) change from end of titration baseline (i.e., end of Week 3). Box plots derived from mixed effect model repeat measurement (MMRM) analyses to each indicated 12-month visit with 5th, 25th, mean, 75th and 95th percentiles of change from end of titration for tolvaptan (grey) and placebo (white) groups.

Figure 2: Change in Renal Function (eGFR CKD-EPI)



Subgroup analysis of all endpoints above (change in TKV, key composite [including time to worsening of kidney function and time to medically significant kidney pain] and change in slope of decline in renal function) demonstrated consistent efficacy (directional) in all pre-specified subgroups, including those stratified by age, gender, race, geographical location, baseline hypertension, baseline eGFR and baseline TKV.

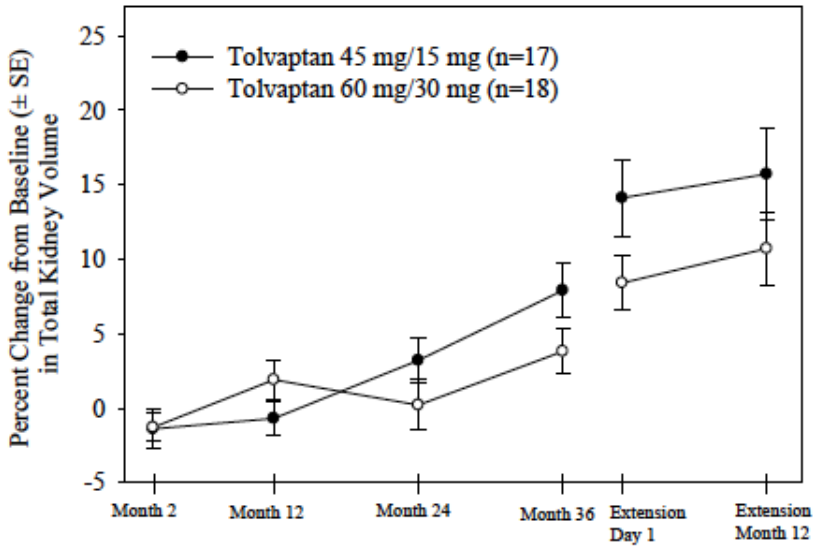
Patients were not genotyped to separate into ADPKD type 1 and 2 and it is not known whether JINARC has comparable efficacy in these subgroups.

In a long-term, open-label, multi-center dose ranging trial (TEMPO 2:4) in 46 adult patients (age 18-50 years) with ADPKD (meeting modified Ravine criteria and an estimated GFR ≥30 mL/min) patients were titrated in weekly intervals for the first 4 weeks among split doses of 30 mg/15 mg (down-titration to 15 mg/15 mg allowed for tolerability) to 90 mg/30 mg, then maintained at their maximal tolerated dose (MTD) through Month 2 (Titration Period). Following a determination of final long-term dosing regimens based on objective criteria (trough spot urine osmolality <300 mOsm/kg, median tolerability) using data from the Titration Period, patients were randomly allocated to a fixed high dose regimen (60 mg/30 mg) and fixed low dose regimen (45 mg/15 mg) for up to Month 36 (Fixed-dose Period). All patients discontinued treatment at the end of this phase of the trial and after a period of 4-6 months had an option to enter an Extension Period of treatment for an additional 12 months.

All 46 of the patients who entered the Titration Period were treated in the Fixed-dose Period, including 22 patients in the tolvaptan 45 mg/15 mg group and 24 patients in the tolvaptan 60 mg/30 mg group. Over the course of 36 to 48 months of open-label tolvaptan treatment, 39/46 patients (84.8%) completed the 36-month portion of the trial and 35/35 patients (100%) completed the 12-month Extension. At Month 36, TKV increased from baseline in both groups, with a higher mean (SD) percent increase seen in the tolvaptan 45 mg/15 mg group

(9.86% [11.81%]) compared with the tolvaptan 60 mg/30 mg group 5.06% [9.77%]; nominal p =0.0553). The mean (SD) annual rate of change from predose baseline in eCrCLCG was −2.17 (14.45) mL/min/year in the tolvaptan 45 mg/15 mg group and −0.450 (4.86) mL/min/year in the tolvaptan 60 mg/30 mg group. Upon withdrawal from treatment, TKV increased at higher rates than while on treatment. Upon resumption of treatment, in the extension phase rates of TKV growth again slowed (Figure 3). These results support that patients treated with higher doses of tolvaptan have a greater treatment effect and that continued treatment is required to maintain benefits and provided support for the dosing recommendations in the pivotal trial discussed above.

Figure 3: Change from Baseline in Total Kidney Volume by assigned dose-regimen in patients in TEMPO 2:4



Data are not currently available to show whether long-term therapy with JINARC continues to slow the rate of renal function decline and affect clinical outcomes of ADPKD, including delay in the onset of end-stage renal disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and distribution

After oral administration, tolvaptan is rapidly absorbed with peak plasma concentrations occurring about 2 hours after dosing. The absolute bioavailability of tolvaptan is about 56%.

Co-administration of tolvaptan with a high-fat meal increased peak concentrations of tolvaptan up to 2-fold but left AUC unchanged. Even though the clinical relevance of this finding is not known, to minimise the unnecessary risk of increasing the maximal exposure the morning dose should be taken under fasted conditions (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Following single oral doses of ≥ 300 mg, peak plasma concentrations appear to plateau, possibly due to saturation of absorption. Tolvaptan binds reversibly (98%) to plasma proteins.

Metabolism

Tolvaptan is extensively metabolised in the liver almost exclusively by CYP3A. Tolvaptan is a weak CYP3A4 substrate and does not appear to have any inhibitory activity.

In vitro studies indicated that tolvaptan has no inhibitory activity for CYP3A. Fourteen metabolites have been identified in plasma, urine and faeces; all but one were also metabolised by CYP3A. Only the oxobutyric acid metabolite is present at greater than 10% of total plasma radioactivity; all others are present at lower concentrations than tolvaptan.

Tolvaptan metabolites have little to no contribution to the pharmacological effect of tolvaptan; all metabolites have no or weak antagonist activity for human V2 receptors when compared with tolvaptan.

Excretion

The terminal elimination half-life is about 8 hours and steady-state concentrations of tolvaptan are obtained after the first dose.

Less than 1% of intact active substance is excreted unchanged in the urine. Radio labelled tolvaptan experiments showed that 40% of the radioactivity was recovered in the urine and 59% was recovered in the faeces, where unchanged tolvaptan accounted for 32% of radioactivity. Tolvaptan is only a minor component in plasma (3%).

Linearity

Following single oral doses, C_{max} values show less than dose proportional increases from 30 to 240 mg and then a plateau at doses from 240 to 480 mg, AUC increases linearly.

Following multiple once daily dosing of 300 mg, tolvaptan exposure was only increased 6.4-fold when compared to a 30 mg dose. Based on calculations from 4 different studies in split-dose regimens of 30, 60 and 120 mg/day in ADPKD patients, tolvaptan exposure (AUC) increases approximately linearly.

Pharmacokinetics in special populations

Elderly

Clearance of tolvaptan is not significantly affected by age.

Hepatic Dysfunction

The effect of mildly or moderately impaired hepatic function (Child-Pugh classes A and B) on the pharmacokinetics of tolvaptan was investigated in 87 patients with liver disease of various origins. For single doses of 10-60 mg, C_{max} and AUC_{∞} increase linearly with dose. Although mean C_{max} values for 30 and 60 mg doses do not appear to be much higher compared to healthy subjects, 1.07 – to 1.65-fold, AUC values are 1.56- to 2.75-fold higher. Following multiple dosing (QD, 13 days) tolvaptan concentrations also appear to accumulate 1.7- to 1.6-fold. Clearance following a single dose is about half that of healthy subjects and following multiple dosing is about a third that of healthy subjects. Very limited information is available in patients with severe hepatic impairment (Child-Pugh class C).

In a population pharmacokinetic analysis in patients with hepatic oedema, AUC of tolvaptan in severely (Child-Pugh class C) and mildly or moderately (Child-Pugh classes A and B) hepatic impaired patients were 3.1 and 2.3 times higher than that in healthy subjects.

Renal Dysfunction

In a population pharmacokinetic analysis for patients with ADPKD, tolvaptan concentrations were increased, compared to healthy subjects, as renal function decreased below eGFR of 60 mL/min/1.73 m^2. An $eGFR_{CKD-EPI}$ decrease from 72.2 to 9.79 (mL/min/1.73 m^2) was associated with a 32% reduction in total body clearance.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tolvaptan tested negative for genotoxicity in in vitro (bacterial reverse mutation assay, mammalian forward mutation assay and chromosomal aberration test in Chinese hamster lung fibroblast cells) and in vivo (rats micronucleus assay) test systems.

Carcinogenicity

Up to two years of oral administration of tolvaptan to male and female rats at doses up to 1000 mg/kg/day (yielding 1.3- and 3.4-times respectively, the AUC for tolvaptan in patients at the MRHD), to male mice at doses up to 60 mg/kg/day (relative exposure, 0.3) and to female mice at doses up to 100 mg/kg/day (relative exposure, 0.4) did not increase the incidence of tumours. The predictive value of these studies is limited by the inability to obtain high multiples of clinical exposure to tolvaptan. However, negative findings in genotoxicity assays and the absence of pre-neoplastic lesions observed in these and other studies lend support to tolvaptan being unlikely to pose a particular carcinogenic risk in patients.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Inactive ingredients include maize starch, hyprolose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and indigo carmine aluminium lake as colorant.

6.2 INCOMPATIBILITIES

Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C.

Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

The following pack sizes and configurations are available:

JINARC 15 mg Tablets are available in a PVC/Aluminium blister of 7 or 28 tablets

JINARC 30 mg Tablets are available in a PVC/Aluminium blister of 7 or 28 tablets

JINARC Combination Pack of 15 mg + 45 mg Tablets are available in a PVC/Aluminium foil blister in a wallet card of 56 tablets.

JINARC Combination Pack of 30 mg + 60 mg Tablets are available in a PVC/Aluminium foil blister in a wallet card of 56 tablets.

JINARC Combination Pack of 30 mg + 90 mg Tablets are available in a PVC/Aluminium foil blister in a wallet card of 56 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

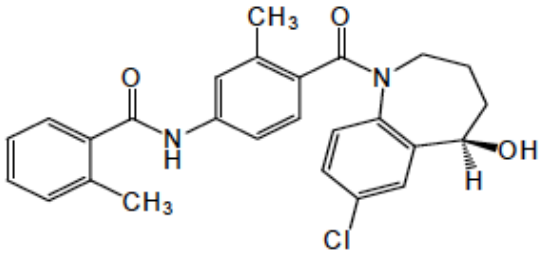
Chemical Structure

Tolvaptan is a vasopressin V_2 receptor antagonist.

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

The empirical formula of tolvaptan is $C_{26}H_{25}ClN_2O_3$

Molecular Weight: 448.94



and enantiomer

CAS Number

CAS Registry Number for tolvaptan is 150683-30-0.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Otsuka Australia Pharmaceutical Pty Ltd
Suite 2.03, Level 2
9 Help Street
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www.otsuka.com.au

Under the licence of Otsuka Pharmaceutical Co., Ltd., Japan

9 DATE OF FIRST APPROVAL

24 March 2017

10 DATE OF REVISION

11 May 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat to meet the requirements of the current form for product information (PI)
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE	New text regarding acute liver failure added based on postmarketing experience.