▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

JINARC 15 mg tablets
JINARC 30 mg tablets
JINARC 45 mg tablets
JINARC 60 mg tablets
JINARC 90 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

JINARC 15 mg tablets
Each tablet contains 15 mg of tolvaptan.
Excipient(s) with known effect
Each 15 mg tablet contains approximately 35 mg lactose (as monohydrate).

JINARC 30 mg tablets
Each tablet contains 30 mg of tolvaptan.
Excipient(s) with known effect
Each 30 mg tablet contains approximately 70 mg lactose (as monohydrate).

JINARC 45 mg tablets
Each tablet contains 45 mg of tolvaptan.
Excipient(s) with known effect
Each 45 mg tablet contains approximately 12 mg lactose (as monohydrate).

JINARC 60 mg tablets
Each tablet contains 60 mg of tolvaptan.
Excipient(s) with known effect
Each 60 mg tablet contains approximately 16 mg lactose (as monohydrate).

JINARC 90 mg tablets
Each tablet contains 90 mg of tolvaptan.
Excipient(s) with known effect
Each 90 mg tablet contains approximately 24 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

JINARC 15 mg tablets
Blue, triangular, debossed with “OTSUKA” and “15” on one side.

JINARC 30 mg tablets
Blue, round, debossed with “OTSUKA” and “30” on one side.

JINARC 45 mg tablets
Blue, square, debossed with “OTSUKA” and “45” on one side.

JINARC 60 mg tablets
Blue, modified rectangular, debossed with “OTSUKA” and “60” on one side.

JINARC 90 mg tablets
Blue, pentagonal, 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 4 at initiation of treatment with evidence of rapidly progressing disease (see section 5.1).

4.2 Posology 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 JINARC therapy including hepatic toxicity and monitoring requirements (see section 4.4).

Posology

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 mg, 90 mg, or 120 mg.

Dose titration
The initial dose is 60 mg JINARC 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 JINARC (60 mg + 30 mg) per day and then to a target split-dose regimen of 120 mg JINARC (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 JINARC dose.

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 (see section 4.4).

Measurements of urine osmolality are recommended to monitor the adequacy of vasopressin inhibition. Periodic monitoring of plasma osmolality or serum sodium (to calculate plasma osmolarity) and/or body weight should be considered to monitor the risk of dehydration secondary to the aquaretic effects of JINARC in case of patient’s insufficient water intake.

The safety and efficacy of JINARC in CKD stage 5 have not been explored and therefore JINARC treatment should be discontinued if renal insufficiency progresses to CKD stage 5 (see section 4.4).

Therapy must be interrupted if the ability to drink or the accessibility to water is limited (see section 4.4).

JINARC must not be taken with grapefruit juice (see section 4.5). Patients must be instructed to drink sufficient amounts of water or other aqueous fluids (see section 4.4).

Dose adjustment for patients taking strong CYP3A inhibitors
In patients taking strong CYP3A inhibitors (see section 4.5), JINARC doses have to be reduced as follows:

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

Dose adjustment for patients taking moderate CYP3A inhibitors
In patients taking moderate CYP3A inhibitors, JINARC doses have to be reduced as follows:

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

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

Special populations

Elderly population
Increasing age has no effect on JINARC plasma concentrations. Limited data on the safety and effectiveness of JINARC in ADPKD patients aged over 55 are available (see section 5.1).

Renal impairment
JINARC is contraindicated in anuric patients (see section 4.3).

Dose adjustment is not required in patients with renal impairment.

No clinical trials in subjects with indices of glomerular filtration rate < 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. estimated glomerular filtration rate [eGFR] < 20) may be increased; these patients should be carefully monitored for hepatic toxicity. Data for patients in CKD early stage 4 are more limited than for patients in stage 1, 2 or 3 (see section 5.1). Limited data are available for patients with CKD late stage 4 (eGFR < 25 mL/min/1.73 m^2). No data are available for patients with CKD stage 5. JINARC treatment should be discontinued if renal insufficiency progresses to CKD stage 5 (see section 4.4).

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).

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 JINARC (see sections 4.3 and 4.4).

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 JINARC in children and adolescents has not yet been established. No data are available. JINARC is not recommended in the paediatric age group.

Method of administration

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 or to benzazepine or benzazepine derivatives (see section 4.4)
- Elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of JINARC (see section 4.4)
- Anuria
- Volume depletion
- Hypernatraemia
- Patients who cannot perceive or respond to thirst
- Pregnancy (see section 4.6)
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

Idiosyncratic hepatic toxicity

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

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

In a double-blind, placebo-controlled trial in patients with ADPKD, the period of onset of hepatocellular injury (by ALT elevations > 3 × ULN) was within 3 to 14 months after initiating treatment and these increases were reversible, with ALT returning to < 3 × ULN within 1 to 4 months. While these concomitant elevations were reversible with prompt discontinuation of JINARC, 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 (see section 4.8).

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 discontinuation (see below), the use of JINARC is contraindicated (see section 4.3). 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 clinically significant abnormal ALT or AST increases are detected during treatment, JINARC administration must be immediately interrupted and repeat tests including ALT, AST, BT and alkaline phosphatase (AP) must be obtained as soon as possible (ideally within 48 hours to 72 hours). Testing must continue at increased time frequency until symptoms/signs/laboratory abnormalities stabilise or resolve, at which point JINARC may be re-initiated.

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 Normalised Ratio[INR] > 1.5)
- ALT or AST > 3-times ULN with persistent symptoms of hepatic injury noted above.

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

Access to water

JINARC may cause adverse reactions related to water loss such as thirst, polyuria, nocturia, and pollakiuria (see section 4.8). 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). 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 to 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 JINARC because treatment with JINARC may result in severe dehydration which constitutes a risk factor for renal dysfunction. Accurate monitoring of body weight is recommended. A progressive reduction in body weight could be an early sign of progressive dehydration. If dehydration becomes evident, take appropriate action, which may include the need to interrupt or reduce the dose of JINARC 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.

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 JINARC induces copious aquaresis and may cause dehydration and increases in serum sodium (see section 4.8) and is contraindicated in hypernatraemic patients (see section 4.3). 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 JINARC to monitor for dehydration.

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

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

Anaphylaxis

In post-marketing experience, anaphylaxis (including anaphylactic shock and rash generalised) has been reported very rarely following administration of JINARC. This type of reaction occurred after the first administration of JINARC. Patients have to be carefully monitored during treatment. Patients with known hypersensitivity reactions to benzazepines or benzazepine derivatives (e.g. benazepril, conivaptan,

fenoldopam mesylate or mirtazapine) may be at risk for hypersensitivity reaction to JINARC (see section 4.3).

If an anaphylactic reaction or other serious allergic reactions occur, administration of JINARC must be discontinued immediately and appropriate therapy initiated. Since hypersensitivity is a contraindication (see section 4.3) treatment must never be restarted after an anaphylactic reaction or other serious allergic reactions.

Diabetes mellitus

Diabetic patients with an elevated glucose concentration (e.g. in excess of 300 mg/dL) may present with pseudo-hyponatraemia. This condition must be excluded prior and during treatment with JINARC.

JINARC may cause hyperglycaemia (see section 4.8). Therefore, diabetic patients treated with JINARC 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 JINARC. 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 JINARC-patients (6.2 %) compared to placebo-treated patients (1.7 %). Adverse reactions of gout were reported more frequently in JINARC-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 JINARC 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 JINARC on glomerular filtration rate (GFR)

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

Chronic Kidney Disease

Limited safety and efficacy data are available for JINARC in patients with CKD late stage 4 (eGFR < 25 mL/min/1.73 m^2). There are no data in patients with CKD stage 5. JINARC treatment should be discontinued if renal insufficiency progresses to CKD stage 5.

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on the pharmacokinetics of JINARC

CYP3A inhibitors
Concomitant use of medicinal products that are moderate CYP3A inhibitors (e.g. amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) or strong CYP3A inhibitors (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin) increase JINARC exposure.

Co-administration of JINARC 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

JINARC.

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

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

Dose reduction of JINARC is recommended for patients while taking moderate or strong CYP3A inhibitors (see section 4.2). 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 JINARC exposure and efficacy. Co-administration of JINARC with rifampicin reduces C_{max} and AUC for JINARC by about 85 %. Therefore, concomitant administration of JINARC with potent CYP3A inducers (e.g. rifampicin, rifabutin, rifapentine, phenytoin, carbamazepine, and St. John's Wort) is to be avoided.

Co-administration with medicinal products that increase serum sodium concentration
There is no experience from controlled clinical trials with concomitant use of JINARC and hypertonic sodium chloride solution, 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 JINARC with medicinal products that increase serum sodium concentration may result in a higher risk for developing hypernatraemia (see section 4.4) and is therefore not recommended.

Diuretics
JINARC 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 JINARC 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 JINARC and/or diuretics and increased fluid intake. Other potential causes of renal dysfunction or dehydration must be evaluated and addressed.

Effect of JINARC on the pharmacokinetics of other products

CYP3A substrates
In healthy subjects, JINARC, a CYP3A substrate, had no effect on the plasma concentrations of some other CYP3A substrates (e.g. warfarin or amiodarone). JINARC increased plasma levels of lovastatin by 1.3- to 1.5-fold. Even though this increase has no clinical relevance, it indicates JINARC can potentially increase exposure to CYP3A4 substrates.

Transporter substrates
P-glycoprotein substrates: In-vitro studies indicate that JINARC is a substrate and competitive inhibitor of P-glycoprotein (P-gp). 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 [AUCτ]) when co-administered with multiple once daily 60 mg doses of JINARC. 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 JINARC.

OATP1B1/OAT3/BCRP and OCT1: In-vitro studies indicate that JINARC or its oxobutyric metabolite may have the potential to inhibit OATP1B1, OAT3, BCRP and OCT1 transporters. Co-administration of JINARC (90 mg) with rosuvastatin (5mg), a BCRP substrate, increased rosuvastatin C_{max} and AUC_{τ} of 54% and 69%, respectively. If BCRP substrates (e.g. sulfasalazine) are co-administered with JINARC, patients must be managed cautiously and evaluated for excessive effects of these medicinal products.
Administration of rosuvastatin (OATP1B1 substrate) or furosemide (OAT3 substrate) to healthy subjects with elevated oxobutyric acid metabolite (inhibitor of OATP1B1 and OAT3) plasma concentrations did not

meaningfully alter the pharmacokinetics of rosuvastatin or furosemide. Statins commonly used in the tolvaptan phase 3 pivotal trial (e.g. rosuvastatin and pitavastatin) are OATP1B1 or OATP1B3 substrates, however no difference in adverse events profile were observed during the phase 3 pivotal trial for tolvaptan in ADPKD.
If OCT1 substrates (e.g. metformin) are co-administered with tolvaptan, patients must be managed cautiously and evaluated for excessive effects of these medicinal products.

Diuretics or non-diuretic anti-hypertensive medicinal product(s)
Standing blood pressure was not routinely measured in ADPKD trials. Therefore, a risk of orthostatic/postural hypotension due to a pharmacodynamic interaction with JINARC cannot be excluded.

Co-administration with vasopressin analogues
In addition to its renal aquaretic effect, JINARC is capable of blocking 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 such analogues to prevent or control bleeding when co-administered with JINARC. 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 JINARC.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of JINARC in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). JINARC is not recommended in women of childbearing potential not using contraception.

JINARC is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether JINARC is excreted in human breast milk. Studies in rats have shown excretion of JINARC in milk. A risk for the newborns/infants cannot be excluded. JINARC is contraindicated during breast-feeding (see section 4.3).

Fertility

Studies in animals showed effects on fertility (see section 5.3). The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

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

4.8 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, JINARC has been associated with idiosyncratic elevations of blood alanine aminotransferase (ALT; 4.4 %) and aspartate aminotransferases (AST; 3.1 %) with infrequent cases of concomitant elevations in bilirubin-total (BT; 0.2 %).

Tabulated list of adverse reactions

The incidences of the adverse drug reactions (ADRs) associated with JINARC therapy are tabulated below. The table is based on adverse reactions reported during clinical trials and/or post-marketing use.

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

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse reactions is qualified as "not known".

	Very common	**Common**	**Uncommon**	**Not known**
Immune system disorders				Anaphylactic shock, Generalised rash
Metabolism and nutrition disorders	Polydipsia	Dehydration, Hypernatraemia, Decreased appetite, Hyperuricaemia, Hyperglycaemia, Gout		
Psychiatric disorders		Insomnia		
Nervous system disorders	Headache, Dizziness	Dysgeusia, Syncope		
Cardiac disorders		Palpitations		
Respiratory, thoracic and mediastinal disorders		Dyspnoea		
Gastrointestinal disorders	Diarrhoea, Dry mouth	Abdominal pain, Abdominal distension, Constipation, Dyspepsia, Gastroesophageal reflux disease		
Hepatobiliary disorders		Abnormal hepatic function		Acute hepatic failure[1]
Skin and subcutaneous tissue disorders		Dry skin, Rash, Pruritus, Urticaria		
Musculoskeletal and connective tissue disorders		Arthralgia Muscle spasms Myalgia		
Renal and urinary disorders	Nocturia, Pollakiuria, Polyuria			

General disorders and administration site conditions	Fatigue, Thirst	Asthenia		
Investigations		Alanine aminotransferase increased, Aspartate aminotransferase increased, Weight decreased, Weight increased	Bilirubin increased	

[1] observed in post-marketing with JINARC in ADPKD. Liver transplantation was necessary.

Description of selected adverse reactions

Laboratory results
Elevation (> 3 × upper limit of normal [ULN]) of ALT was observed in 4.4 % (42/958) of patients on JINARC and 1.0 % (5/484) of patients on placebo, while elevation (> 3 × ULN) of AST was observed in 3.1 % (30/958) of patients on JINARC and 0.8 % (4/484) patients on placebo in a double-blind, placebo-controlled trial in patients with ADPKD. Two (2/957, 0.2 %) of these JINARC treated-patients, as well as a third patient from an extension open label trial, exhibited increases in hepatic enzymes (> 3 × ULN) with concomitant elevations in BT (> 2 × ULN).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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.

4.9 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 JINARC 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 JINARC 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 JINARC because of its high binding affinity for human plasma protein (> 98 %).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics, vasopressin antagonists, ATC code: C03XA01.

Mechanism of action

Tolvaptan is a vasopressin antagonist that specifically blocks the binding of arginine vasopressin (AVP) at the V_2 receptors of the distal portions of the nephron. Tolvaptan affinity for the human V_2 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 ADPKD across 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.

Clinical efficacy and safety

The primary focus of the clinical program for development of JINARC tablets for the treatment of ADPKD is a single pivotal, multi-national, phase 3, randomised, placebo-controlled trial in which the long-term safety and efficacy of oral split dose JINARC 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 JINARC 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.

The phase 3 pivotal trial (TEMPO 3:4, 156-04-251) included subjects from 129 centres in the Americas, Japan, Europe and other countries. The primary objective of this trial was to evaluate the long-term efficacy of JINARC in ADPKD through rate of total kidney volume (TKV) change (normalised as percentage; %) for JINARC-treated compared with placebo-treated subjects. In this trial a total of 1,445 adult patients (age 18 to 50 years) with evidence of rapidly-progressing, early ADPKD (meeting modified Ravine criteria, TKV ≥ 750 mL, estimated creatinine clearance ≥ 60 mL/min) were randomised 2:1 to treatment with JINARC or placebo. Patients were treated for up to 3 years.

JINARC (n = 961) and placebo (n = 484) groups were well matched in terms of gender with an average age of 39 years. The inclusion criteria identified patients who at baseline had evidence of early disease progression. At baseline, patients had average estimated glomerular filtration rate (eGFR) of 82 mL/min/1.73 m^2 (Chronic Kidney Disease-Epidemiology Collaboration; CKD-EPI) with 79 % having hypertension and a mean TKV of 1,692 mL (height adjusted 972 mL/m). Approximately 35 % of subjects were CKD stage 1, 48 % CKD stage 2, and 17 % CKD stage 3 ($eGFR_{CKD\text{-}EPI}$). While these criteria were useful in enriching the study population with patients who were rapidly progressing, subgroup analyses based on stratification criteria (age, TKV, GFR, Albuminuria, Hypertension) indicated the presence of such risk factors at younger ages predicts more rapid disease progression.

The results of the primary endpoint, the rate of change in TKV for subjects randomised to JINARC (normalised as percentage, %) to the rate of change for subjects on placebo, were highly statistically significant. The rate of TKV increase over 3 years was significantly less for JINARC-treated subjects than for subjects receiving placebo: 2.80 % per year *versus* 5.51 % per year, respectively (ratio of geometric mean 0.974; 95 % CI 0.969 to 0.980; $p < 0.0001$).

Pre-specified secondary endpoints 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- medicinal product 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
4) worsening albuminuria

The relative rate of ADPKD-related events was decreased by 13.5 % in JINARC-treated patients, (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 JINARC compared with placebo (hazard ratio, 0.39; 95 % CI, 0.26 to 0.57; nominal $p < 0.0001$), while renal pain events were 35.8 % less likely in JINARC-treated patients (hazard ratio, 0.64; 95 % CI, 0.47 to 0.89; nominal $p = 0.007$). In contrast, there was no effect of JINARC on either progression of hypertension or albuminuria.

TEMPO 4:4 is an open-label extension study that included 871 subjects that completed TEMPO 3:4 from 106 centres across 13 countries. This trial evaluated the effects of JINARC on safety, TKV and eGFR in subjects receiving active treatment for 5 years (early-treated), compared with subjects treated with placebo for 3 years, then switched to active treatment for 2 years (delayed-treated).

The primary end point for TKV did not distinguish a difference in change (−1.7 %) over the 5-year treatment between early- and delayed-treated subjects at the pre-specified threshold of statistical significance ($p = 0.3580$). Both groups' TKV growth trajectory was slowed, relative to placebo in the first 3 years, suggesting both early- and delayed- JINARC treated subjects benefitted to a similar degree.

A secondary endpoint testing the persistence of positive effects on renal function indicated that the preservation of eGFR observed by the end of the TEMPO 3:4 pivotal trial (3.01 to 3.34 mL/min/1.73 m^2 at follow-up visits 1 and 2) could be preserved during open-label treatment. This difference was maintained in the pre-specified mixed effect model repeat measurement (MMRM) analysis (3.15 mL/min/1.73 m^2, 95 % CI 1.462 to 4.836, $p = 0.0003$) and with sensitivity analyses where baseline eGFR data were carried forward (2.64 mL/min/1.73 m^2, 95 % CI 0.672 to 4.603, $p = 0.0086$). These data suggest that JINARC can slow the rate of renal function decline, and that these benefits persist over the duration of therapy.

Longer term 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.

Genotyping for *PKD1* and *PKD2* genes was conducted in a majority of patients entering the open-label extension study (TEMPO 4:4) but the results are not yet known.

Following an additional 2 years of JINARC treatment, resulting in a total of 5 years on JINARC therapy no new safety signals were identified.

The phase 3, multi-centre, international, randomised-withdrawal, placebo-controlled, double-blind trial 156-13-210 compared the efficacy and safety of JINARC (45 mg/day to 120 mg/day) to placebo in patients able to tolerate JINARC during a five-week titration and run-in period on JINARC. The trial utilised a randomised withdrawal design, to enrich for patients that were able to tolerate JINARC for a 5-week, single-blind pre-randomisation period consisting of a 2-week titration period and 3-week run-in period. The design was used to minimise the impact of early discontinuation and missing data on trial endpoints.

A total of 1,370 patients (age 18 to 65 years) with CKD with an eGFR between 25 and 65 mL/min/1.73 m^2 if younger than age 56 years; or eGFR between 25 and 44 mL/min/1.73 m^2, plus eGFR decline > 2.0 mL/min/1.73 m^2/year if between age 56 to 65 years were randomised to either JINARC (n = 683) or placebo (n = 687) and were treated for a period of 12 months.

For subjects randomised, the baseline, average eGFR was 41 mL/min/1.73 m^2 (CKD-EPI) and historical TKV, available in 318 (23 %) of subjects, averaged 2,026 mL. Approximately 5 %, 75 % and 20 % had an eGFR 60 mL/min/1.73 m^2 or greater (CKD stage 2), or less than 60 and greater than 30 mL/min/1.73 m^2 (CKD stage 3) or less than 30 but greater than 15 mL/min/1.73 m^2 (CKD stage 4), respectively. The CKD stage 3 can be subdivided further to stage 3a, 30 %, (eGFR 45 mL/min/1.73 m^2 to less than 60 mL/min/1.73 m^2) and stage 3b, 45 %, (eGFR between 30 and 45 mL/min/1.73 m^2).

The primary endpoint of the trial was the change in eGFR from pre-treatment baseline levels to post-treatment assessment. In patients treated with JINARC the reduction in eGFR was significantly less than in patients treated with placebo ($p < 0.0001$). The treatment difference in eGFR change observed in this trial is

1.27 mL/min/1.73 m^2, representing a 35 % reduction in the LS means of change in eGFR of -2.34 mL/min/1.73 m^2 in JINARC group relative to a -3.61 mL/min/1.73 m^2 in placebo group observed over the course of one year. The key secondary endpoint was a comparison of the efficacy of JINARC treatment *versus* placebo in reducing the decline of annualised eGFR slope across all measured time points in the trial. These data also showed significant benefit from JINARC *versus* placebo ($p < 0.0001$).

Subgroup analysis of the primary and secondary endpoints by CKD stage found similar, consistent treatment effects relative to placebo for subjects in stages 2, 3a, 3b and early stage 4 (eGFR 25 to 29 mL/min/1.73 m^2) at baseline.

A pre-specified subgroup analysis suggested that JINARC had less of an effect in patients older than 55 years of age, a small subgroup with a notably slower rate of eGFR decline.

5.2 Pharmacokinetic properties

Absorption

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, the morning dose should be taken under fasted conditions to minimise the unnecessary risk of increasing the maximal exposure (see section 4.2).

Distribution

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.

Biotransformation

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

Elimination

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/non-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. For split-dose regimens of 30 mg/day, 60 mg/day and 120 mg/day in ADPKD patients, tolvaptan exposure (AUC) increases linearly.

Pharmacokinetics in special populations

Age
Clearance of tolvaptan is not significantly affected by age.

Hepatic impairment
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. No clinically significant changes have been seen in clearance for doses ranging from 5 to 60 mg. 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 impairment
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

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential. Teratogenicity was noted in rabbits given 1,000 mg/kg/day (2.6 times the exposure at the maximum human recommended dose of 120 mg/day). No teratogenic effects were seen in rabbits at 300 mg/kg/day (1.2 times the exposure at the maximum human recommended dose of 120 mg/day). In a peri- and post-natal study in rats, delayed ossification and reduced pup bodyweight were seen at the high dose of 1,000 mg/kg/day.

Two fertility studies in rats showed effects on the parental generation (decreased food consumption and body weight gain, salivation), but tolvaptan did not affect reproductive performance in males and there were no effects on the foetuses. In females, abnormal oestrus cycles were seen in both studies.
The no observed adverse effect level (NOAEL) for reproduction in females (100 mg/kg/day) was about 4.4-times the exposure at the maximum human recommended dose of 120 mg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Indigo carmine (E 132) aluminium lake
Low-substituted hydroxypropyl cellulose

6.2 Incompatibilities

Not applicable.

6.3 Nature and contents of container

JINARC 15 mg tablets

30 tablets in 3 aluminium/aluminium foil blisters with 10 x 15 mg tablets

JINARC 30 mg tablets

30 tablets in 3 aluminium/aluminium foil blisters with 10 x 30 mg tablets

JINARC 15 mg tablets + JINARC 45 mg tablets

14 tablets in 1 PVC/aluminium foil blister with 7 × 15 mg and 7 × 45 mg tablets
28 tablets in 2 PVC/aluminium foil blisters with 7 × 15 mg and 7 × 45 mg tablets
56 tablets in 4 PVC/aluminium foil blisters with 7 × 15 mg and 7 × 45 mg tablets

JINARC 30 mg tablets + JINARC 60 mg tablets

14 tablets in 1 PVC/aluminium foil blister with 7 × 30 mg and 7 × 60 mg tablets
28 tablets in 2 PVC/aluminium foil blisters with 7 × 30 mg and 7 × 60 mg tablets
56 tablets in 4 PVC/aluminium foil blisters with 7 × 30 mg and 7 × 60 mg tablets

JINARC 30 mg tablets + JINARC 90 mg tablets

14 tablets in 1 PVC/aluminium foil blister with 7 × 30 mg and 7 × 90 mg tablets
28 tablets in 2 PVC/aluminium foil blisters with 7 × 30 mg and 7 × 90 mg tablets
56 tablets in 4 PVC/aluminium foil blisters with 7 × 30 mg and 7 × 90 mg tablets

Not all presentations may be available locally.

6.4 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT UNDER LICENCE FROM

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