JINARC®
Tolvaptan

1. NAME OF THE MEDICINAL PRODUCT

Jinarc 15 mg tablets
Jinarc 30 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).

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.

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

Tolvaptan treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements (see 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, 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 (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 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. The morning dose of Jinarc is to be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food. Therapy must be interrupted if the ability to drink or the accessibility to water is limited (see section 4.4).

Tolvaptan 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), tolvaptan doses have to be reduced as follows:

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

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

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

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

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

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

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 tolvaptan (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 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

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 tolvaptan (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

Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in bilirubin-total (BT).
In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported.
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 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 (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 tolvaptan 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 48-72 hours). Testing must continue at increased time frequency until symptoms/signs/laboratory abnormalities stabilise or resolve, at which point Jinarc may be reinitiated.

If the abnormal liver tests results are determined to be definitively related to tolvaptan therapy, restarting therapy is not recommended. However, if bilirubin, ALT and AST levels remained below the permanent discontinuation threshold, and if it is determined that tolvaptan would still be beneficial for the patient, tolvaptan therapy may be cautiously reinitiated with more frequent monitoring at the same or a lower dose.
In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times upper limit of normal, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.

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.

If ALT and AST levels remain below 3-times the upper limit of normal (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

Tolvaptan 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 1-2 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. 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 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.

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) 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 tolvaptan 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 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. 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 tolvaptan (see section 4.3 Contraindications).

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) 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). 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.

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 m2). There are no data in patients with CKD stage 5. Tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on the pharmacokinetics of tolvaptan

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 tolvaptan exposure.
Co-administration of tolvaptan and ketoconazole resulted in a 440 % increase in area under time-concentration curve (AUC) and 248 % increase in maximum observed plasma concentration (C_{max}) for tolvaptan.
Co-administration of tolvaptan and fluconazole, a moderate CYP3A inhibitor, produced a 200 % and 80 % increase in tolvaptan AUC and C_{max}, respectively.
Co-administration of tolvaptan with grapefruit juice, a moderate to strong CYP3A inhibitor, produced a doubling of peak tolvaptan concentrations (C_{max}).
Dose reduction of tolvaptan is recommended for patients while taking moderate or strong CYP3A inhibitors (see 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 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. If P-gp inhibitors also act as strong CYP 3A inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, saquinavir), substantial dose reduction of tolvaptan is required.

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 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 tolvaptan 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
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
P-glycoprotein substrates: In-vitro studies indicate that tolvaptan 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 [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.

OATP1B1/OAT3/BCRP and OCT1: In-vitro studies indicate that tolvaptan or its oxobutyric metabolite may have the potential to inhibit OATP1B1, OAT3, BCRP and OCT1 transporters. Co-administration of tolvaptan (90 mg) with rosuvastatin (5 mg), a BCRP substrate, increased rosuvastatin C_{max} and AUC_t of 54 % and 69 %, respectively. If BCRP substrates (e.g. sulfasalazine) are co-administered with tolvaptan, 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 was 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 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

Pregnancy

There are no adequate data from the use of tolvaptan 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 tolvaptan is excreted in human breast milk. Studies in rats have shown excretion of tolvaptan 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. However, 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, tolvaptan has been associated with idiosyncratic elevations of blood alanine aminotransferases (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 tolvaptan therapy are tabulated below. The table is based on adverse events 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 events 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 tolvaptan 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 tolvaptan 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 tolvaptan 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 tolvaptan 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 to BPOM.

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 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

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 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 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 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.

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 tolvaptan in ADPKD through rate of total kidney volume (TKV) change (%) for tolvaptan-treated compared with placebo-treated subjects. In this trial a total of 1,445 adult patients (age 18-50 years) with evidence of rapidly-progressing, early ADPKD (meeting modified Ravine criteria, total kidney volume (TKV) $\geq$ 750 mL, estimated creatinine clearance $\geq$ 60 mL/min) were randomized 2:1 to treatment with tolvaptan or placebo. Patients were treated for up to 3 years.
'Tolvaptan (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 (CKD-EPI) with 79 % having hypertension and a mean TKV of 1,692 mL (height adjusted 972 mL/m). Approximately 35 % of subjects were chronic kidney disease (CKD) stage 1, 48 % CKD stage 2, and 17 % CKD stage 3 ($eGFR_{CKD-EPI}$). 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 tolvaptan (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 tolvaptan-treated subjects than for subjects receiving placebo: 2.80 % per year vs 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 tolvaptan-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 tolvaptan 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 tolvaptan-treated patients (hazard ratio,

0.64; 95 % CI, 0.47 to 0.89; nominal p = 0.007). In contrast, there was no effect of tolvaptan 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 tolvaptan 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- tolvaptan 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 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 tolvaptan treatment, resulting in a total of 5 years on tolvaptan therapy no new safety signals were identified.

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

A total of 1,370 patients (age 18-65) with chronic kidney disease (CKD) with an eGFR between 25 and 65 mL/min/1.73 m^2 if younger than age 56; 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 56-65 were randomized to either tolvaptan (n = 683) or placebo (n = 687) and were treated for a period of 12 months.

For subjects randomized, the baseline, average estimated glomerular filtration rate (eGFR) was 41 mL/min/1.73 m^2 (CKD-Epidemiology formula) 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 30-45 mL/min/1.73 m^2).

The primary endpoint of the trial was the change in estimated glomerular filtration rate (eGFR) from pre-treatment baseline levels to post-treatment assessment. In patients treated with tolvaptan 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 tolvaptan 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 tolvaptan treatment vs. placebo in reducing the decline of annualized eGFR slope across all measured time points in the trial. These data also showed significant benefit from tolvaptan vs. 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 m2) at baseline.

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

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.

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, to minimise the unnecessary risk of increasing the maximal exposure the morning dose should be taken under fasted conditions (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

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, 60 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 (1.2times 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 aluminium lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Jinarc 15 mg tablets
Box of 3 blisters of 10 tablets — Reg. No.: DKL2118708510A1

Jinarc 30 mg tablets
Box of 3 blisters of 10 tablets — Reg. No.: DKL2118708510B1

Not all presentations may be marketed in Indonesia.

6.6 Special precautions for disposal

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

HARUS DENGAN RESEP DOKTER

Manufactured by:
Otsuka Pharmaceutical Co., Ltd.
Tokushima Itano Factory
13, Minami, Shishitoki, Matsutani, Itano-cho,
Itano-gun, Tokushima 779-0195
Japan

Packed and Released by:
PT Otsuka Indonesia
Jl. Sumber Waras No. 25, Lawang
Malang 65216, Indonesia

***Leaflet* kemasan: Informasi untuk pasien**
Jinarc 15 mg tablet
Jinarc 30 mg tablet
Tolvaptan

Baca seluruh isi *leaflet* ini secara saksama sebelum Anda memulai penggunaan obat karena leaflet ini berisi informasi yang penting bagi Anda.

- Simpan *leaflet* ini. Anda mungkin perlu untuk membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan dokter atau apoteker Anda
- Obat ini diresepkan hanya untuk Anda. Jangan diberikan pada orang lain. Hal ini dapat membahayakan mereka, bahkan jika mereka memiliki gejala penyakit yang sama dengan Anda.
- Jika Anda mengalami efek samping, informasikan pada dokter atau apoteker Anda. Ini termasuk semua kemungkinan efek samping yang tidak tercantum dalam *leaflet* ini. Lihat bagian 4.

1. Apa itu Jinarc dan apa kegunaannya

Jinarc adalah obat yang dikonsumsi untuk mengobati penyakit yang disebut "*Autosomal Dominant Polycystic Kidney Disease*" (ADPKD). Penyakit ini menyebabkan pertumbuhan kista berisi cairan di ginjal yang menekan jaringan sekitarnya dan menurunkan fungsi ginjal, yang mungkin dapat menyebabkan gagal ginjal. Jinarc dikonsumsi untuk mengobati ADPKD pada orang dewasa dengan penyakit ginjal kronik (CKD) tingkat 1 hingga 4 dengan bukti perburukan penyakit.

Jinarc mengandung zat aktif Tolvaptan yang menghambat efek vasopresin, sebuah hormon yang terlibat dalam pembentukan kista di ginjal pasien ADPKD. Dengan menghambat efek vasopresin, Jinarc memperlambat perkembangan kista di ginjal pasien ADPKD, mengurangi gejala dari penyakit dan meningkatkan produksi urin.

2. Apa yang perlu diketahui sebelum mengonsumsi Jinarc

Jangan mengonsumsi Jinarc:

- jika Anda **alergi** terhadap Tolvaptan atau bahan tambahan lain dalam obat ini (tercantum dalam bagian 6) atau jika Anda alergi terhadap benzazepine atau turunan benzazepine (contohnya benazepril, conivaptan, fenoldopam mesylate atau mirtazapine)
- jika Anda telah diberitahukan bahwa Anda mengalami peningkatan kadar enzim hati dalam darah yang tidak memungkinkan pengobatan dengan Tolvaptan
- jika ginjal Anda tidak berfungsi (tidak dapat memproduksi urin)
- jika Anda mengalami kondisi yang dikaitkan dengan volume darah yang sangat sedikit (contohnya dehidrasi yang berat atau perdarahan)
- jika Anda mengalami kondisi yang meningkatkan kadar natrium dalam darah Anda
- jika Anda tidak dapat merasakan rasa haus
- jika Anda hamil (lihat ''Kehamilan dan menyusui")
- jika Anda menyusui (lihat "Kehamilan dan menyusui")

Peringatan dan perhatian
Beritahu dokter Anda sebelum mengonsumsi Jinarc:

- jika Anda menderita penyakit hati
- jika Anda tidak dapat meminum cukup air (lihat "meminum cukup air" di bagian bawah) atau jika Anda harus membatasi pemasukan cairan Anda
- jika Anda memiliki kesulitan berkemih atau mengalami pembesaran prostat
- jika Anda memiliki kadar natrium dalam darah terlalu tinggi atau terlalu rendah
- jika Anda sebelumnya memiliki reaksi alergi terhadap benzazepine, Tolvaptan atau turunan benzazepine lainnya (contohnya benazepril, conivaptan, fenoldopam mesylate atau mirtazapine), atau terhadap bahan tambahan lainnya dalam obat ini (tercantum dalam bagian 6)
- jika Anda memiliki diabetes
- jika Anda telah diberitahukan bahwa Anda memiliki kadar asam urat yang tinggi dalam darah Anda (yang dapat menyebabkan serangan penyakit asam urat)
- Jika Anda memiliki penyakit ginjal lanjut

Jinarc dapat menyebabkan hati Anda tidak bekerja dengan baik. Oleh karena itu, mohon segera informasikan dokter Anda segera jika Anda memiliki gejala yang menunjukan kemungkinan masalah hati, seperti:

- mual
- muntah
- demam
- kelelahan
- kehilangan nafsu makan
- nyeri perut
- urin berwarna gelap
- penyakit kuning (kulit atau mata menguning)
- gatal pada kulit Anda
- gejala seperti flu (nyeri sendi dan otot dengan demam)

Selama pengobatan dengan Jinarc, dokter Anda akan melakukan pemeriksaan darah bulanan untuk memeriksa keadaan fungsi hati Anda.

<u>Meminum cukup air</u>
Jinarc menyebabkan kehilangan air dikarenakan terjadi peningkatan produksi urin Anda. Kehilangan air ini dapat menyebabkan efek samping seperti mulut kering dan kehausan atau bahkan efek samping yang lebih berat seperti masalah ginjal (lihat bagian 4). Karena itu penting bahwa Anda memiliki akses pada air dan Anda dapat minum dalam jumlah yang cukup saat Anda merasa haus. Sebelum tidur Anda harus minum 1 atau 2 gelas air walaupun Anda tidak merasa haus dan Anda harus minum air setelah Anda berkemih pada malam hari. Perhatian khusus harus diberikan jika Anda memiliki penyakit yang mengurangi asupan cairan yang sesuai atau jika Anda berisiko tinggi kehilangan air, misal dalam kasus muntah atau diare. Karena peningkatan produksi urin, maka penting bagi Anda untuk selalu memiliki akses ke toilet.

Anak dan remaja
Jinarc belum diuji pada anak dan remaja (di bawah 18 tahun) dan penggunaannya tidak direkomendasikan pada kelompok usia tersebut.

Obat lainnya dan Jinarc

Beritahu dokter atau apoteker Anda jika Anda mengonsumsi, baru saja mengonsumsi atau mungkin mengonsumsi obat lainnya, termasuk obat yang diperoleh tanpa resep.

Obat-obatan di bawah ini dapat meningkatkan efek Jinarc:

- amprenavir, atazanavir, darunavir, ritonavir dan fosamprenavir (digunakan untuk mengobati HIV/AIDS)
- aprepitant (digunakan untuk menghindari mual dan muntah pada kemoterapi)
- crizotinib dan imatinib (digunakan untuk mengobati kanker)
- ketoconazole, fluconazole atau itraconazole (digunakan untuk mengobati infeksi jamur)
- antibiotik makrolida seperti eritromisin atau klaritromisin
- verapamil (digunakan untuk mengobati penyakit jantung dan tekanan darah tinggi)
- diltiazem (digunakan untuk mengobati tekanan darah tinggi dan nyeri dada)

Obat-obatan di bawah ini dapat menurunkan efek Jinarc:

- phenytoin atau carbamazepine (digunakan untuk mengobati epilepsi)
- rifampicin, rifabutin atau rifapentine (digunakan untuk mengobati tuberkulosis)
- St. John's Wort (obat herbal tradisional untuk menenangkan emosi dan gangguan kecemasan ringan)

Jinarc dapat meningkatkan efek dari obat-obatan di bawah ini:

- digoxin (digunakan untuk mengobati irama jantung yang tidak beraturan dan gagal jantung)
- dabigatran (digunakan untuk mengencerkan darah)
- methotrexate (digunakan untuk mengobati kanker, arthritis)
- ciprofloxacin (antibiotik)
- sulfasalazine (digunakan untuk mengobati penyakit radang usus atau radang sendi)
- metformin (digunakan untuk mengobati diabetes)

Jinarc dapat menurunkan efek dari obat-obatan di bawah ini:

- analog vasopresin seperti *desmopressin* (digunakan untuk meningkatkan faktor pembekuan darah atau untuk mengontrol pengeluaran urin atau mengompol).

Obat-obatan ini dapat mempengaruhi atau dipengaruhi oleh Jinarc:

- diuretik (digunakan untuk mempengaruhi pengeluaran urin). Jika dikonsumsi dengan Jinarc dapat meningkatkan risiko efek samping karena kehilangan cairan dan dapat menyebabkan penyakit ginjal.
- diuretik atau obat lain yang digunakan untuk pengobatan tekanan darah tinggi. Jika dikonsumsi dengan Jinarc dapat meningkatkan risiko tekanan darah rendah ketika akan berdiri dari keadaan duduk atau berbaring.
- obat-obatan yang dapat meningkatkan kadar natrium dalam darah atau yang mengandung banyak garam (contohnya, tablet yang dilarutkan dalam air dan obat gangguan pencernaan). Obat-obatan ini dapat meningkatkan efek Jinarc. Ada risiko peningkatan kadar natrium yang terlalu banyak dalam darah Anda.

Anda mungkin masih dapat mengonsumsi obat-obatan tersebut bersama dengan Jinarc. Dokter Anda akan dapat memutuskan apa yang sesuai untuk Anda.

Jinarc dengan makanan dan minuman
Jangan meminum jus *grapefruit* saat mengonsumsi Jinarc.

Kehamilan dan menyusui
Jangan mengonsumsi obat ini jika Anda hamil atau menyusui.

Wanita dalam usia subur harus menggunakan kontrasepsi yang dapat diandalkan selama penggunaan obat ini.

Jika Anda sedang hamil atau menyusui, merasa hamil atau merencanakan kehamilan, tanya saran dokter atau apoteker Anda sebelum mengonsumsi obat ini.

Berkendara dan menjalankan mesin
Beberapa orang dapat merasakan pusing, lemah atau letih setelah diberikan Jinarc. Jika ini terjadi pada Anda, jangan menyetir atau menggunakan peralatan atau mesin.

Jinarc mengandung laktosa
Jika Anda pernah diberitahukan dokter Anda bahwa Anda memiliki intoleransi terhadap beberapa jenis gula, informasikan dokter Anda sebelum mengonsumsi obat ini.

3. Cara penggunaan Jinarc

Jinarc hanya dapat diresepkan oleh dokter dengan spesialisasi pengobatan ADPKD. Selalu konsumsi obat ini persis seperti yang diinformasikan oleh dokter Anda. Periksa dengan dokter atau apoteker Anda jika Anda tidak yakin.

Dosis
Penggunaan Jinarc dalam satu hari dibagi menjadi dua dosis, yang satu lebih besar daripada yang lain. Dosis yang lebih tinggi harus dikonsumsi pada pagi hari setelah Anda bangun tidur, setidaknya 30 menit sebelum makan pagi. Dosis yang lebih rendah dikonsumsi 8 jam kemudian.

Kombinasi dosis antara lain:
45 mg + 15 mg
60 mg + 30 mg
90 mg + 30 mg

Pengobatan Anda biasanya dimulai dengan dosis 45 mg di pagi hari dan 15 mg delapan jam kemudian. Dokter Anda mungkin secara bertahap meningkatkan dosis Anda hingga kombinasi maksimum 90 mg saat bangun tidur pagi dan 30 mg setelah 8 jam. Untuk menemukan dosis terbaik, dokter Anda akan secara teratur memeriksa seberapa baik Anda menoleransi dosis yang ditentukan. Anda harus selalu mengonsumsi kombinasi dosis tertinggi yang dapat ditoleransi yang diresepkan oleh dokter Anda.
Jika Anda mengonsumsi obat lain yang dapat meningkatkan efek Jinarc, Anda mungkin dapat menerima dosis yang lebih rendah. Dalam hal ini, dokter Anda mungkin meresepkan Jinarc tablet dengan dosis 30 mg atau 15 mg Tolvaptan yang harus dikonsumsi sekali sehari pada pagi hari.

Cara penggunaan

Telan tablet tanpa dikunyah, dengan segelas air.
Dosis harian pertama di pagi hari dikonsumsi setidaknya 30 menit sebelum makan pagi. Dosis harian kedua dapat diminum dengan atau tanpa makanan.

Jika Anda meminum Jinarc lebih dari seharusnya
Jika Anda mengonsumsi lebih banyak tablet Jinarc dari pada dosis yang ditentukan, **minumlah banyak air dan segera hubungi dokter atau rumah sakit terdekat**. Ingatlah untuk membawa paket obat sehingga jelas apa yang telah Anda konsumsi. Jika Anda mengonsumsi dosis yang lebih tinggi di sore hari, Anda mungkin harus pergi ke toilet lebih sering di malam.

Jika Anda lupa mengonsumsi Jinarc
Jika Anda lupa untuk mengonsumsi Jinarc, Anda harus mengonsumsinya segera setelah Anda mengingatnya pada hari yang sama. Jika selama sehari penuh Anda tidak mengonsumsi obat Jinarc, minumlah dosis normal Anda pada hari berikutnya. **JANGAN** mengonsumsi dosis ganda untuk menebus dosis satuan yang terlupakan.

Jika Anda berhenti mengonsumsi Jinarc
Jika Anda berhenti mengonsumsi Jinarc, kista ginjal Anda dapat tumbuh secepat sebelum Anda memulai pengobatan dengan Jinarc. Oleh karena itu, Anda hanya boleh berhenti mengonsumsi Jinarc jika Anda melihat efek samping yang memerlukan perhatian medis segera (lihat bagian 4) atau jika dokter Anda memberi tahu Anda.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan dokter atau apoteker Anda.

4. Efek samping yang mungkin terjadi

Seperti obat lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping yang serius:

Jika Anda mengalami salah satu dari efek samping berikut, Anda mungkin memerlukan perhatian medis segera. Hentikan mengonsumsi Jinarc dan segera hubungi dokter atau pergi ke rumah sakit terdekat, jika Anda:

- kesulitan berkemih
- mengalami pembengkakan di wajah, bibir atau lidah, gatal, ruam secara umum, atau mengi berat atau sesak napas (gejala reaksi alergi)

Jinarc dapat menyebabkan hati Anda tidak berfungsi dengan baik.

Konsultasikan dengan dokter Anda jika mengalami gejala mual, muntah, demam, kelelahan, kehilangan nafsu makan, nyeri perut, urin berwarna gelap, penyakit kuning (kulit atau mata menguning), gatal pada kulit Anda atau nyeri sendi dan otot disertai demam.

Efek samping lainnya:
Sangat Umum: dapat terjadi pada lebih dari 1 orang dari 10 orang

- haus (membutuhkan minum air yang banyak)
- sakit kepala
- pusing
- diare
- mulut kering
- peningkatan kebutuhan untuk berkemih, berkemih saat malam atau berkemih lebih sering
- kelelahan

Umum: dapat terjadi pada hingga 1 orang dari 10 orang

- dehidrasi
- peningkatan kadar natrium, asam urat dan gula darah
- perubahan rasa
- asam urat
- penurunan nafsu makan
- pingsan
- sulit tidur
- jantung berdebar-debar
- sesak napas
- sakit perut
- perut penuh atau kembung atau tidak nyaman
- sembelit
- dada terasa perih atau panas
- fungsi hati tidak normal
- kulit kering
- ruam
- gatal
- gatal-gatal pada ruam (*hives*)
- nyeri sendi
- kejang otot
- nyeri otot
- kelemahan secara umum
- peningkatan kadar enzim hati dalam darah
- penurunan berat badan
- peningkatan berat badan

Tidak umum: dapat terjadi pada hingga 1 orang dari 100 orang

- peningkatan bilirubin (zat yang dapat menyebabkan kulit atau mata menguning) dalam darah

Tidak diketahui: frekuensi tidak dapat diestimasi dari data yang tersedia

- reaksi alergi (lihat bagian atas)
- ruam pada umumnya
- gagal hati akut (*ALF*)

Pelaporan efek samping
Jika Anda mengalami efek samping, beritahu dokter atau apoteker Anda. Hal ini termasuk semua kemungkinan efek samping yang tidak tercantum dalam *leaflet* ini. Anda juga dapat melaporkan efek samping secara langsung ke BPOM. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara penyimpanan Jinarc

Jauhkan Jinarc dari jangkauan anak-anak.

Jangan mengonsumsi obat ini setelah tanggal kedaluwarsa yang tertera pada karton dan blister setelah kedaluwarsa (EXP). Tanggal kedaluwarsa mengacu pada tanggal terakhir pada bulan tersebut.

Simpan dalam kemasan asli untuk melindungi dari cahaya dan kelembapan.

Jangan membuang obat melalui air limbah atau limbah rumah tangga. Tanyakan pada apoteker Anda cara membuang obat yang sudah tidak digunakan. Langkah ini akan membantu melindungi lingkungan.

6. Isi dari kemasan dan informasi lainnya

Apa saja yang terkandung dalam Jinarc
Zat aktif adalah tolvaptan.
Setiap tablet Jinarc 15 mg mengandung Tolvaptan 15 mg.
Setiap tablet Jinarc 30 mg mengandung Tolvaptan 30 mg.

Zat tambahan lainnya adalah *lactose monohydrate* (lihat bagian 2), *maize starch, microcrystalline cellulose, hydroxypropylcellulose, magnesium stearate, indigo carmine aluminium lake*.

Bentuk sediaan dan isi kemasan Jinarc
Jinarc dengan kekuatan yang berbeda memiliki perbedaan pada bentuk dan *embossing*:
15 mg tablet: biru, segitiga, *debossed* dengan “OTSUKA” dan “15” pada salah satu sisi.
30 mg tablet: biru, bulat, *debossed* dengan “OTSUKA” dan “30” pada salah satu sisi.

Obat Anda tersedia dalam kemasan di bawah ini:
Tablet Jinarc 15 mg: Dus, 3 blister @ 10 tablet
Nomor registrasi: DKL2118708510A1
Tablet Jinarc 30 mg: Dus, 3 blister @ 10 tablet
Nomor registrasi: DKL2118708510B1

HARUS DENGAN RESEP DOKTER

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