NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
Jinarc Tablets 15 mg (MAL24036007ARZ)
Jinarc Tablets 30 mg (MAL24036006ARZ)
Jinarc 45 mg and Jinarc 15 mg Tablets (MAL24036005ARZ)
Jinarc 60 mg and Jinarc 30 mg Tablets (MAL24036004ARZ)
Jinarc 90 mg and Jinarc 30 mg Tablets (MAL24036003ARZ)

ACTIVE INGREDIENT:
Tolvaptan 15mg
Tolvaptan 30mg
Tolvaptan 45mg + Tolvaptan 15mg
Tolvaptan 60mg+ Tolvaptan 30mg
Tolvaptan 90mg + Tolvaptan 30mg

PRODUCT REGISTRATION HOLDER:
Otsuka Pharmaceuticals (Malaysia) Sdn. Bhd.

PRODUCT MANUFACTURER:
Otsuka Pharmaceutical Co., Ltd, Japan

APPROVAL DATE:
7 March 2024 (DCA 394)

1.0 BACKGROUND INFORMATION

1.1 Approved Indication

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.

1.2 Approved Posology

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.

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.

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.

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

JINARC must not be taken with grapefruit juice. Patients must be instructed to drink sufficient amounts of water or other aqueous fluids.

Dose adjustment for patients taking strong CYP3A inhibitors
In patients taking strong CYP3A inhibitors, 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.

Renal impairment
JINARC is contraindicated in anuric patients.

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. 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.

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.

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.

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.

1.3 Method of administration

Oral use.

1.4 Pharmacological Aspects

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.

Pharmacokinetic Properties

<u>Absorption</u>
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.

<u>Distribution</u>
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 V_2 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/1.73m^2. An $eGFR_{CKD-EPI}$ decrease from 72.2 to 9.79 (mL/min/1.73m^2) was associated with a 32% reduction in total body clearance.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

- The proposed starting materials have been adequately justified in line with ICH Q11 (Guideline on Development and Manufacturer of Drug Substance) and acceptable specifications have been set. The manufacturing process of tolvaptan was sufficiently described and adequate in-process controls are applied during the manufacturing process. Acceptable specifications and control methods for intermediate products, starting materials and reagents have been presented.
- The characterisation of the API and its impurities are in accordance with the EMA Guideline on Chemistry of New Active Substances.
- The specification of API is controlled accordance to the in-house requirements. Batch analysis data for several batches were provided and the results were within the proposed specifications.
- The analytical methods used have been appropriately validated in accordance with the ICH Q2 (R1) (Validation of Analytical Procedures: Text and Methodology) guidelines.
- The stability studies on six batches were performed for 6 months at 40^{o}C/75%RH and for 60 months at 30°C/65%RH. The results of stability data showed that the API remains within the

specification. The stability studies were conducted in accordance with ICH Q1 (Guideline on Stability Testing of New Dug Substances and Products).

- The proposed re-test period for tolvaptan is 60 months, packed in polyethylene bag then packaged in another polyethylene bag and further packed in a fiber drum.

2.1.2 Finished Product

- The manufacturing process has been validated and the results fulfilled the expected acceptance criteria proving that the finished product manufacturing processes are robust and reproducible.
- The results of the stability studies support a shelf life of 36 months when stored below 30°C for single strength and 48 months for dual strength when stored below 25°C. The available 36 months long-term stability data at 30°C/75%RH for single strength and 48 months long-term stability data at 25°C/60%RH for dual strength, and 6 months of accelerated stability data at 40°C/75%RH for three commercial scale batches of finished product remain well within specifications to support the shelf life.
- The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form which are adequately described in the analysis protocol – description, identification, impurities, uniformity of dosage units, dissolution, assay and microbial limits.
- The products have passed the evaluation on analytical protocol and method validation in accordance with the International Council for Harmonization (ICH) Q2 (R1) guidelines.
- Certificate of Good Manufacturing Practice (GMP) compliance for the manufacturers were issued by Ministry of Health, Labour and Welfare, Japan.

2.2 Efficacy

- Efficacy of tolvaptan is supported by three pivotal phase III studies; TEMPO 3:4, TEMPO 4:4 and REPRISE.
- TEMPO 3:4 (156-04-251) is a 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.
- Additionally, applicant provided an extension study, TEMPO 4:4 (156-08-271) which is a multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease.

- REPRISE (156-13-210) is a Phase 3b, multi-centre, randomized-withdrawal, placebo-controlled, double-blind, parallel-group trial to compare the efficacy and safety of tolvaptan (45 to 120 mg/day, split-dose) in subjects with chronic kidney disease between late stage 2 to early stage 4 due to autosomal dominant polycystic kidney disease.

Table 1: Summary of Clinical Studies Conducted

Study Type & Design (n)	**Objective (s) of the Study**	**Results of Primary Endpoint**
TEMPO 3:4, 156-04-251 [*Torres, V. E., et al. New England Journal of Medicine, 2012*] Phase III, multinational, double-blind, randomized (2:1), placebo-controlled trial. n = 1445 patients in early stage of ADPKD Median age: 39 years (18 – 50 years) 129 sites in 15 countries Duration of study: 3 years	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.	<u>Primary endpoint:</u> 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, 0.980; p<0.0001). <u>Conclusion:</u> Tolvaptan, as compared with placebo, slowed the increase in total kidney volume and the decline in kidney function over a 3-year period in patients with ADPKD but was associated with a higher discontinuation rate, owing to adverse events.
TEMPO 4:4, 156-08-271 [*Torres, V. E., et al. Nephrology dialysis transplantation, 33(3), 477-489., 2018*]	<u>Primary objective:</u> To demonstrate whether tolvaptan modifies ADPKD progression as measured by changes in	<u>Primary endpoint:</u> ● TKV increased by 27.30% in early- versus 29.04% in delayed-treated subjects. TKV did not distinguish a difference in change (−1.7%) over the 5-year treatment between early- and delayed-treated subjects

Study Type & Design (n)	Objective (s) of the Study	Results of Primary Endpoint
Phase IIIb, multicenter, open-label, extension trial n = 871 patients completing TEMPO 3:4 Mean age: 42 years 106 sites in 13 countries Duration of study : 2 years	endpoints of total kidney volume (TKV) and renal function in early- versus delayed-treatment groups. <u>Secondary objective:</u> The change in eGFR from TEMPO 3:4 baseline to TEMPO 4:4 at month 24 in early- versus delayed-treatment groups.	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. ● Deceleration of TKV growth after reintroduction of tolvaptan at the initiation of TEMPO 4:4 in the early-treated subjects was correlated with the time delay between the two studies (R=-0.19, p<0.001) and observed mainly in the quartile with the longest off treatment duration (treatment effect from TEMPO 4:4 baseline to month 12 comparing Q4 to Q1 was -2.97% per year, p=0.06) <u>Secondary endpoint:</u> • The nominally significant difference between early- and delayed-treatment groups was maintained at each time point, demonstrating that the effect of tolvaptan on slowing renal function decline in TEMPO 3:4 was maintained for an additional 2 years in TEMPO 4:4 (3.15 mL/min/1.73 m^2; p<0.001) <u>Conclusion:</u> The results of TEMPO 4:4 support a sustained disease-modifying effect of tolvaptan on eGFR. The lack of a sustained treatment difference on TKV may be

Study Type & Design (n)	Objective (s) of the Study	Results of Primary Endpoint
		accounted for by limitations of the trial design, including loss of randomization and baseline imbalances ensuing TEMPO 3:4. The safety profile was similar to that observed in TEMPO 3:4.
REPRISE, 156-13-210 [*Torres, V. E., et al. New England Journal of Medicine, 2017*] Phase IIIb, multicenter, randomized-withdrawal (1:1), placebo-controlled, double-blind, parallel group trial n = 1370 patients involving patients with ADPKD who had late chronic kidney disease of stage 2 to early stage 4 Mean age: 47.3 years (18 - 65 years) 213 sites in 21 countries Duration of study : 1 year	To compare the efficacy of tolvaptan treatment in reducing the change in eGFR from pretreatment baseline to post-treatment follow-up, as compared with placebo.	<u>Primary endpoint:</u> Treatment difference in the change of eGFR from pretreatment baseline to post-treatment follow-up demonstrated a statistically significant difference ($p< 0.0001$) in favor of tolvaptan of 1.27 mL/min/1.73 m^2 /year (LS mean change of −2.34 mL/min/1.73 m^2 /year for tolvaptan vs −3.61 mL/min/1.73 m^2/year for placebo), which corresponds to a treatment difference of approximately ~ 35%. <u>Conclusion:</u> Tolvaptan resulted in a slower decline than placebo in the estimated GFR over a 1-year period in patients with later-stage ADPKD.

2.3 Safety

- The 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%).

- Based on the Periodic Safety Update Report (PSUR), the most frequently reported Preferred Term (PTs) were alanine aminotransferase increased (1132 events), aspartate aminotransferase increased (792 events), and hepatic function abnormal (583 events). Overall, the previously established favourable benefit-risk profile for tolvaptan has been reconfirmed by the efficacy and safety data that have become available during this reporting interval.
- Based on the Risk Management Plan (RMP), the important identified risks are liver injury, volume depletion, dehydration and associated sequelae such as renal dysfunction. Routine pharmacovigilance activities will be carried out to monitor routine adverse reaction reporting and signal detection. JINARC is only available through a restricted distribution programme, which is part of a risk management programme that Otsuka has put in place to manage the risk of idiosyncratic hepatic toxicity associated with the use of JINARC. Only prescribers and patients enrolled in the programme can prescribe and receive JINARC respectively. 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, including hepatic toxicity and monitoring requirements. Healthcare professionals are advised to inform their patients about regular blood testing required to monitor and manage the risk of liver injury while taking JINARC and to discuss with them the monitoring of symptoms that may indicate liver injury.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 394th meeting on 7th March 2024 has decided to approve the registration with the following indication:

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.