Public Summary of the Risk Management Plan (RMP)

JINARC® (tolvaptan)

Film-coated tablets: 15mg, 30mg, 45mg, 60mg, 90mg

Based on Part VI of EU RMP Version 15.0

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Marketing Authorisation Holder:
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Jinarc is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/ Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Jinarc in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Otsuka Pharmaceuticals (Switzerland) GmbH is fully responsible for the accuracy and correctness of the content of the published RMP summary of Jinarc.

1.1 Summary of the Risk Management Plan for Jinarc

1.1.1 VI.1: Summary of the Risk Management Plan for Jinarc

This is a summary of the risk management plan (RMP) for Jinarc. The RMP details important risks of Jinarc, how these risks can be minimised, and how more information will be obtained about tolvaptan's risks and uncertainties (missing information).

Jinarc's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how this product should be used.

This summary of the RMP for Jinarc should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of tolvaptan’s RMP.

1.1.2 I: The Medicine and What it is Used for

Jinarc is authorised in the EEA under indication to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease (see SmPC for the full indication). It contains tolvaptan as the active substance and it is given by oral tablet administration.

1.1.3 II: Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Jinarc, together with measures to minimise such risks and the proposed studies for learning more about its risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine’s packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g., prescription only) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Jinarc, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, (including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Jinarc is not yet available, it is listed under ‘missing information’ below.

1.1.3.1 II.A: A List of Important Risks and Missing Information

Important risks of Jinarc are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Jinarc. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 1.1.3.1-1 II.A-1: List of Important Risks and Missing Information for Jinarc (from Part II: Module SVIII)

Important identified risks	• Liver Injury in ADPKD Patients • Volume depletion, dehydration and associated sequelae such as renal dysfunction
Important potential risks	• None
Missing information	• Pregnancy outcome data • Off-label use • Use in hepatic impaired patients • Use in ADPKD patients over the age of 55 years • Long term use of Jinarc in routine medical practice

1.1.3.2 II.B: Summary of Important Risks for Jinarc

Table 1.1.3.2-1 Important Identified Risk: Liver Injury in ADPKD Patients

Evidence for linking the risk to the medicine	The risk of developing hepatotoxicity involves a complex interplay between the chemical properties of the drug, environmental factors (e.g., the use of concomitant drugs or alcohol), age, sex, and underlying diseases. The most extensively documented risk factors are concomitant drug use and diseases. The mechanisms underlying tolvaptan-induced liver injury cannot be determined based on the available data. However, the prolonged latency to onset and the relatively prompt recurrence upon re-challenge would support involvement of the adaptive immune system. Engagement of adaptive immunity could also potentially account for the progression and prolonged resolution phases characteristically observed after discontinuing tolvaptan treatment. In view of the liver safety signal emerging from review of the ADPKD clinical trial database, liver safety data from the preapproval clinical trials for cirrhosis, congestive heart failure, and hyponatraemia were reviewed by the experts and no signal was found.Watkins_2015

Table 1.1.3.2-1 Important Identified Risk: Liver Injury in ADPKD Patients	
Risk factors and risk groups	**ADPKD** The liver enzyme elevations seen with Jinarc characteristically had an onset between 3 and 18 months of treatment. The injury typically progressed by biochemical criteria for weeks after discontinuation of treatment and resolved slowly over one to several months. HLA alleles have been identified as patient risk factors for liver injury due to certain drugs. If HLA alleles that infer risk for liver injury in tolvaptan treated patients are identified (i.e., missing information), a personalized medicine approach to improve liver safety might be feasible.
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc Prescribing Information** • **Section Contraindications** • **Section Warnings and Precautions** **Jinarc PL** • **Section When should Jinarc not be taken?** • **Section When is caution advised when taking Jinarc?** Medicinal product subject to restricted medical prescription **Additional risk minimisation measures** Several education materials are available: • Patient Education Brochure • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Alert Card
Additional pharmacovigilance activities	**Jinarc** • PASS 156-12-299 • Adjudication of cases of liver injury by a panel of independent experts of a Hepatic Adjudication Committee (HAC)

Table 1.1.3.2-2 Important Identified Risk: Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction	
Evidence for linking the risk to the medicine	**ADPKD** 2.7.4 Summary of Clinical Safety and Clinical Study Report 156-04-251 and 2.7.4 Summary of Clinical Safety and Clinical Study Report 156-13-210 for NDA resubmission.

Table 1.1.3.2-2 Important Identified Risk: Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction	
Risk factors and risk groups	Patients with an inability or a compromised capacity to perceive and communicate thirst would be at risk of severe dehydration without appropriate medical intervention. This would include bedridden and unconscious subjects. Patients who are concomitantly treated with diuretics may be at risk of severe dehydration and subsequent renal impairment. Special populations which may be at higher risk also include those with a fluid overload in extravascular compartments, but with intravascular contraction. These groups include subjects with hepatic cirrhosis, and potentially some subjects with heart failure.
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc Prescribing Information** • **Section Contraindications** • **Section Warnings and Precautions** **Jinarc PL** • **Section When should Jinarc not be taken?** • **Section When is caution advised when taking Jinarc?** Medicinal product subject to restricted prescription **Additional risk minimization measures**: • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Education Brochure • Patient Alert Card **Additional pharmacovigilance activities**: None

Table 1.1.3.2-3 Missing Information: Pregnancy Outcome Data	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc Prescribing Information** • **Section Contraindications** • **Section Pregnancy, lactation** **Jinarc PL** • **Section When should Jinarc not be taken?** • **Section Can Jinarc be taken during pregnancy or while breastfeeding?** Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Education Brochure **Additional pharmacovigilance activities:** • PASS (156-12-299)

Table 1.1.3.2-4 Missing Information: Off-label Use	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc Prescribing Information** • **Section: Indications/Uses** • **Section: Dosage/Administration** **Jinarc Package Leaflet (PL)** • **Section What is Jinarc and what is it used for?** Medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** PASS 156-12-299

Table 1.1.3.2-5 Missing Information: Use in Hepatic Impaired Patients	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc Prescribing Information** • **Section: Dosage/Administration** • **Section: Warnings and Precautions** • **Section: Pharmacokinetics** **Jinarc Package Leaflet (PL)** • **Section: When should Jinarc not be taken?** • **Section: When is caution advised when taking Jinarc?** • **Section: What side effects can Jinarc have?** Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** None

Table 1.1.3.2-6 Missing Information: Use in ADPKD Patients over the age of 55 years	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc Prescribing Information** • **Section: Dosage/Administration** • **Section: Pharmacodynamics** • **Section: Pharmacokinetics** **Jinarc Package Leaflet (PL)** • **Not applicable** Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** Protocol PASS 156-12-299

Table 1.1.3.2-7 Missing Information: Long-term Use of Jinarc in Routine Medical Practice	
Risk minimisation measures	**Routine risk minimisation measures:** **Jinarc Prescribing Information** • **Section**: Pharmacodynamics **Jinarc Package Leaflet (PL)** • **Not applicable** Medicinal product subject to restricted medical prescription **Additional risk minimisation measures:** None **Additional pharmacovigilance activities:** PASS 156-12-299

1.1.4 II.C: Post-authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

Table 1.1.4-1	**Ongoing and Planned Additional Pharmacovigilance Activities for the ADPKD Indication (Jinarc)**			
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
Jinarc PASS **156-12-299** Ongoing	Jinarc PASS: In the EU/EFTA 2,100 patients who are treated according to the decision of the treating physician will be followed prospectively for a minimum of 2 years and a maximum of 5 years monitor the risk of liver injury in the real-life setting. To compliment this prospective study, a large multi-national retrospective database analysis at predetermined periods post-licensing will allow monitoring of off label use. In addition, there will be an assessment of ADPKD related morbidity and mortality, including longer-term effects on GFR decline and progression of disease leading to dialysis or trans-plantation. The objective of the PASS is to prospectively collect information on the safety of Jinarc when used in a real-life setting. A retrospective study to assess safety concerns associated with longer term use will also be included.	Hepatotoxicity and missing information: Off label use, Use in patients over the age of 50 years in ADPKD patients, Use and potential risks in pregnant women, including frequency and outcome of pregnancies associated with the use of Jinarc, and Long term use of Jinarc in routine medical practice. In addition, ADPKD related morbidity and mortality will be assessed.	Started FPFV: Planned LPLV: Retrospective database analysis: Interim Report 1 Interim Report 2 Final Study Report:	31 Oct 2016 31 Mar 2024 Predetermined periods post-licensing to be clarified in the full protocol 22 Oct 2019 14 NOV 2022 Planned Q1 2025

1.1.5 II.C.2 Other Pharmacovigilance Activities in Post-authorisation Development Plan

Table 1.1.5-1 Other Additional Pharmacovigilance Activity for the ADPKD Indication (Jinarc)				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Hepatic Adjudication Committee (HAC) adjudication of cases of liver injury. Ongoing	To help assess the effectiveness of risk minimisation activities for liver injury with the use of tolvaptan in ADPKD.	Follow-up on incidence of cases in clinical trials to assess if rules for withdrawal of tolvaptan are effective Risk of Liver injury in ADPKD patients	All cases of suspected liver injury, both from the clinical trials and from the post-marketing settings. are assessed by the HAC and 3 quarterly reports are issued in addition to annual Liver Safety Summary (LSS) report being produced on ongoing basis.	Ongoing