

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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.

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.

Further information about the evaluation of Jinarc's benefits can be found in Jinarc's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

<https://www.ema.europa.eu/en/medicines/human/EPAR/jinarc>

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 (eg, 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.

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 0-1 II.A-1: List of Important Risks and Missing Information for Jinarc (from Part II: Module SVIII)	
Important identified risks	<ul style="list-style-type: none"> • Liver Injury in ADPKD Patients • Volume depletion, dehydration and associated sequelae such as renal dysfunction
Important potential risks	<ul style="list-style-type: none"> • None
Missing information	<ul style="list-style-type: none"> • 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

II.B: Summary of Important Risks for Jinarc

Table 0-1 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 (eg, the use of concomitant drugs or

Table 0-1	Important Identified Risk: Liver Injury in ADPKD Patients
	<p>alcohol), age, sex, and underlying diseases. The most extensively documented risk factors are concomitant drug use and diseases.^{62,63}</p> <p>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.⁶¹</p> <p>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.⁶¹</p>
Risk factors and risk groups	<p>ADPKD</p> <p>The liver enzyme elevations seen with Jinarc characteristically had an onset between 3 and 18 month 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 (ie, missing information), a personalized medicine approach to improve liver safety might be feasible.</p>
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>Jinarc SmPC</p> <ul style="list-style-type: none"> • Section 4.3 • Section 4.4 <p>Jinarc PL</p> <ul style="list-style-type: none"> • Section 2 • Section 4 <p>Medicinal product subject to restricted medical prescription</p> <p>Additional risk minimisation measures</p> <p>Details of prescriber’s education, certification in the prescriber’s registry and reassurance of prescriber’s certification prior to the dispensation of Jinarc shall be agreed by the MAH with each National Competent Authority</p> <p>Several education materials are available:</p> <ul style="list-style-type: none"> • Patient Education Brochure • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Alert Card

Table 0-1 Important Identified Risk: Liver Injury in ADPKD Patients	
Additional pharmacovigilance activities	<p>Jinarc</p> <ul style="list-style-type: none"> • PASS 156-12-299 • Ajudication of cases of liver injury by a panel of independent experts of a Hepatic Adjudication Committee (HAC)

Table 0-2 Important Identified Risk: Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction	
Evidence for linking the risk to the medicine	<p>ADPKD</p> <p>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.</p>
Risk factors and risk groups	<p>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.</p> <p>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.</p>
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>Jinarc SmPC</p> <ul style="list-style-type: none"> • Section 4.3 • Section 4.4 <p>Jinarc PL</p> <ul style="list-style-type: none"> • Section 2 • Section 4 <p>Medicinal product subject to restricted perscription</p> <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Education Brochure • Patient Alert Card <p>Additional pharmacovigilance activities: None</p>

Table 0-3 Missing Information: Pregnancy Outcome Data	
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>Jinarc SmPC</p> <ul style="list-style-type: none"> • Section 4.3 • Section 4.6 <p>Jinarc PL</p> <ul style="list-style-type: none"> • Section 2 <p>Medicinal product subject to restricted medical prescription</p> <p>Additional risk minimisation measures:</p> <ul style="list-style-type: none"> • Healthcare Professional Education Guide • Jinarc Prescribing Checklist • Patient Education Brochure <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • PASS (156-12-299)

Table 0-4 Missing Information: Off-label Use	
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>Jinarc SmPC</p> <ul style="list-style-type: none"> • Section 4.1 • Section 4.2 <p>Jinarc PL</p> <ul style="list-style-type: none"> • Section 1 <p>Medicinal product subject to restricted medical prescription. Pack size</p> <p>Additional risk minimisation measures: None</p> <p>Additional pharmacovigilance activities:</p> <p>PASS 156-12-299</p>

Table 0-5 Missing Information: Use in Hepatic Impaired Patients	
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>Jinarc SmPC</p> <ul style="list-style-type: none"> • Section 4.2 • Section 4.4 • Section 5.2 <p>Jinarc PL</p> <ul style="list-style-type: none"> • Section 2 • Section 4 <p>Medicinal product subject to restricted medical prescription</p> <p>Additional risk minimisation measures: None</p> <p>Additional pharmacovigilance activities: None</p>

Table 0-6 Missing Information: Use in ADPKD Patients over the age of 55 years	
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>Jinarc SmPC</p> <ul style="list-style-type: none"> • Section 4.2 • Section 5.1 • Section 5.2 <p>Jinarc PL</p> <ul style="list-style-type: none"> • Not applicable <p>Medicinal product subject to restricted medical prescription</p> <p>Additional risk minimisation measures: None</p> <p>Additional pharmacovigilance activities: Protocol PASS 156-12-299</p>

Table 0-7 Missing Information: Long-term Use of Jinarc in Routine Medical Practice	
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>Jinarc SmPC</p> <ul style="list-style-type: none"> • Section 5.1 <p>Jinarc PL</p> <ul style="list-style-type: none"> • Not applicable <p>Medicinal product subject to restricted medical prescription</p> <p>Additional risk minimisation measures: None</p> <p>Additional pharmacovigilance activities: PASS 156-12-299</p>

II.C: Post-authorisation Development Plan

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

Table 0-1 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 postlicensing will allow monitoring of off label use. In addition, there will be an assessment of ADPKD related morbidity and mortality, ncluding 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 Final Study Report:	31 Oct 2016 31 Mar 2024 Predetermined periods post- licsning to be clarified in the full protocol 31 Dec 2022 Planned Q1 2025

II.C.2 Other Studies in Post-authorisation Development Plan

Table 0-2 Other Studies in Post-authorisation Development Plan for the ADPKD Indication (Jinarc)				
Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
<p>Hepatic Adjudication Committee (HAC) adjudication of cases of liver injury.</p> <p>Ongoing</p>	<p>To help assess the effectiveness of risk minimisation activities for liver injury with the use of tolvaptan in ADPKD.</p>	<p>Follow-up on incidence of cases in clinical trials to assess if rules for withdrawal of tolvaptan are effective</p> <p>Risk of Liver injury in ADPKD patients</p>	<p>All cases of suspected liver injury, both from the clinical trials and from the postmarketing 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.</p>	<p>Ongoing</p>