Jinarc®▼

(tolvaptan)

Healthcare Professional Educational Guide

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Contents

1. Glossary

ADPKD	Autosomal dominant polycystic kidney disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AP	Alkaline phosphatase
BT	Bilirubin-total
eGFR	Estimated glomerular filtration rate
HCP	Healthcare professional
INR	International normalized ratio
mL/min	Milliliters per minute
mg	Milligram
SmPC	Summary of product characteristics
WCBP	Women of child bearing potential
ULN	Upper limit of normal

2. What is the purpose of this guide?

This guide is provided by Otsuka Pharmaceutical Europe Limited for prescribers and other healthcare professionals (HCPs) who are responsible for the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD) using Jinarc® (tolvaptan).

This guide will enable you to:

- Understand what Jinarc® is indicated for and how it should be used
- Be aware of the important side effects of Jinarc® (in particular idiosyncratic hepatic toxicity and the risk of dehydration) and how they can be prevented, identified and managed
- Provide important safety information to your patients receiving Jinarc® and the need for regular monitoring
- Be aware of tools available to support the safe use of Jinarc® and their purpose
- Be aware of the mechanism to report adverse events.

Important: This guide summarises specific important information about Jinarc®. Before prescribing or dispensing Jinarc®, please read the Summary of Product Characteristics (SmPC) carefully, as it contains all the important information you need to know about Jinarc®.

3. What is Jinarc® and what is it indicated for?

Jinarc® contains tolvaptan, which blocks the effects of vasopressin at the V_2 receptor in the kidney, and is indicated 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.

4. When should treatment not be initiated with Jinarc®?

The physician will need to determine if their patient is appropriate to receive Jinarc® therapy (please see section 4.3 of the Jinarc® SmPC for the complete information on contraindications for Jinarc therapy). Due to the risk of hepatic toxicity with Jinarc® therapy for ADPKD, Jinarc® should not be used in patients with any of the following:

- 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®

- Inability or unwillingness to comply with monthly liver function testing.

Additionally, Jinarc® should not be used in patients with any of the following (included but not limited to):

- Volume depletion
- Inability to perceive or respond to thirst
- Female patients trying to become pregnant, Pregnant, or breastfeeding

5. What dose of Jinarc® should I prescribe?

The initial dosage for Jinarc® in patients with ADPKD is 60mg per day as a split-dose regimen of 45mg + 15mg (45mg taken upon waking and 15mg taken 8 hours later). Up titration to a split regime of 90mg (60mg + 30mg) per day, and then to a split dose regime of 120mg (90mg + 30mg) per day, if tolerated, should be attempted with at least weekly intervals between titration steps.

It is important to follow Jinarc® SmPC for the complete dosing instructions, including special considerations and information about interaction with other medications and supplements (see Jinarc® SmPC, section 4.2).

6. What are some of the special warnings and precautions for use pertaining to Jinarc therapy?

Please read section 4.2 (Posology and method of administration), section 4.4 (Special warnings and precautions for use) and section 4.5 (Interaction with other medicinal products and other forms of interaction) of the SmPC as they contain the complete and important information, including but not limited to hepatic toxicity and dehydration which are important to consider prior to prescribing Jinarc®.

Jinarc® has been associated with idiosyncratic elevations of blood ALT and AST with infrequent cases of concomitant elevations in BT. In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported.

7. How should I manage patients with existing hepatic impairment?

Dose adjustment is not needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). Limited information is available in patients with severe hepatic impairment (Child-Pugh class C). These patients should be managed cautiously and liver enzymes should be monitored regularly.

Jinarc® should be used in cirrhotic patients only when the need to treat outweighs the risk of treatment.

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.

8. How should I evaluate the liver function of patients on Jinarc therapy?

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 intervals (every 3 months) thereafter.

Prior to initiation:

If a patient has abnormal blood ALT, AST or BT levels prior to initiation of treatment which fulfil the criteria for permanent discontinuation, the use of Jinarc® is contraindicated. 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 monitoring must continue at increased time frequency. The advice of a hepatologist is recommended.

During the first 18 months of treatment:

During the first 18 months of treatment, Jinarc® will only be supplied to patients whose physician has determined that monitored 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 stopped 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 re-initiated.

Jinarc® therapy should be stopped upon confirmation of sustained or increasing transaminase levels and permanently discontinued if significant increases and/or clinical symptoms of hepatic injury persist.

Recommended guidelines for permanent discontinuation include:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and (BT >2 x ULN or international normalised ratio (INR) >1.5)
- ALT or AST >3 x ULN with persistent symptoms of hepatic injury noted as 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.

A Jinarc® prescribing checklist has been developed to help HCPs decide whether to continue treatment in patients exhibiting signs and symptoms of liver injury and elevated liver enzymes.

It is important to report adverse events involving liver injury, including any AST or ALT rise exceeding 3 x ULN.

Please report Adverse Drug Reactions to Otsuka Pharmaceutical Europe LTD. Local representative Swixx Biopharma S.M.S.A Pharmacovigilance Department on telephone +30 214 444 9670, email: medinfo.malta@swixxbiopharma.com

9. What are some of the safety issues should I discuss with patients prescribed Jinarc®?

Liver injury

Patients should be informed about regular blood testing required to monitor and manage the risk of liver injury while taking Jinarc®. Monitoring for symptoms that may indicate liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) should also be discussed. Patients should be advised to report these side effects immediately if they occur.

Water loss and the risk of dehydration

Jinarc® may cause undesirable effects related to water loss such as thirst, polyuria, nocturia, and pollakiuria. Patients should be instructed to drink water or other aqueous fluids ahead of thirst, in order to avoid excessive thirst or dehydration. Additionally, patients should be advised to drink 1-2 glasses of fluid before bedtime regardless of perceived thirst, and to replenish fluids overnight with each episode of nocturia.

Ensure that patients are aware of diseases that may impair appropriate fluid intake or conditions that may increase the risk of water loss e.g. in case of vomiting or diarrhoea. Patients should be instructed to contact you in case they have experienced such conditions or have signs or symptoms of dehydration.

Fertility/Pregnancy/Lactation information

Jinarc® is contraindicated during conception and pregnancy as it may result in developmental abnormalities in the foetus. It is also contraindicated while breastfeeding.

Women of child-bearing potential (WCBP) should be advised to use effective and reliable method of contraception at least four weeks before starting therapy, during therapy and even in the case of dose interruptions, and for at least a further four weeks after stopping Jinarc®.

Female patients should be advised to report to the treating physician immediately if they are pregnant or think they may be pregnant while taking Jinarc® or within 30 days after stopping Jinarc®. Women should be advised not to breastfeed while taking Jinarc®.

Please refer to section 4.6, Fertility, pregnancy and lactation, of the Jinarc® SmPC for additional information.

10. What other tools are available to support the safe use of Jinarc®?

In addition to this guide, other tools available to support Health Care Professionals' and patients' use of Jinarc® include a Prescribing Checklist, Patient Education Brochure and Patient Alert Card. These are described in more detail below:

Prescribing Checklist:

The Prescribing Checklist is designed to assess the suitability of patients who have been identified as candidates for Jinarc® therapy. The checklist can be used at treatment initiation and regularly thereafter for monitoring patients to support the appropriate use of Jinarc®. At initiation, the checklist helps check contraindications and precautionary conditions to enable appropriate prescribing; it reminds the HCP to educate the patient in the correct use of the medicine. In the case of patients receiving on-going treatment, the checklist helps the HCP perform key checks to monitor the patient's condition and provides an algorithm to assist in optimising dosing based on tolerability.

Patient Education Brochure:
The Patient Education Brochure contains a summary of the key information that the patient should be aware of while on Jinarc® therapy. It should be given to patients so they can learn more about dosing plan, correct intake, and the safety issues to be aware of while taking Jinarc®. The Patient Education Brochure also advises patients to contact their prescribing doctor if they are concerned that they may be experiencing signs and symptoms of hepatic injury on treatment.

Patient Alert Card:
The Patient Alert Card contains important safety information about Jinarc® for patients and emergency carers. It includes information on hepatotoxicity, severe dehydration and advice should such symptoms occur. The Patient Alert Card should be filled out and given to the patient by their prescribing doctor or nurse. The patient should keep it with them in their wallet or bag at all times.

11. How should I report adverse drug reactions with Jinarc®?

Please report all suspected adverse drug reactions to Otsuka Pharmaceutical Europe LTD local representative Swixx Biopharma S.M.S.A Pharmacovigilance Department on +30 214 444 9670 (including out of hours), email medinfo.malta@swixxbiopharma.com and to the Medicines Authority ADR reporting form, which is available online at www.medicinesauthority.gov.mt/adrportal , and sent by post or email to:
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000

E: postlicensing.medicinesauthority@gov.mt

12. Where can I obtain further information?

For further information, please go to:

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