Otsuka

JINARC®▼ (tolvaptan)

Healthcare professional educational guide

This non-promotional material has been developed and funded by Otsuka Pharmaceuticals UK Ltd and is intended for Irish HCPs treating patients with Jinarc▼ (tolvaptan)

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 normalised ratio
mL/min	Milliliters per minute
mg	Milligram
SmPC	Summary of Product Characteristics
WCBP	Women of childbearing potential
ULN	Upper Limit of Normal

2. What is the purpose of this guide?

This guide is provided by Otsuka Pharmaceuticals (U.K.) Ltd 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 it is appropriate for his/her patient to receive treatment with Jinarc® (please refer to section 4.3 of the Jinarc® SmPC for a complete list of contraindications to Jinarc treatment).

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®

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

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

5. Idiosyncratic hepatic toxicity and safety measures

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.

5.1 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).

In patients with severe hepatic impairment (Child-Pugh class C) 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 tolvaptan.

5.2 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. 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.

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

Jinarc® can 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.

Current clinical practice suggests that Jinarc® therapy should be interrupted 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 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.

Summary table

Hepatic injury	Yes	No
Is the patient showing any signs or symptoms of liver injury? (fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice). If the answer is Yes, treatment with JINARC® should be immediately interrupted, the cause investigated and the occurrence reported using the reporting mechanism below.		

Liver function test results	Recommended action
Clinically significant abnormal ALT or AST increases	Interrupt JINARC® treatment and investigate the cause of the raised liver enzyme(s) and repeat tests including ALT, AST, BT and alkaline phosphatase (AP) as soon as possible. Report associated adverse events using the reporting mechanism indicated below. Testing must continue at increased time frequency until symptoms/ signs/ laboratory abnormalities stabilise or resolve, at which point JINARC® maybe reinitiated.
Liver function results stabilise If ALT and AST levels remain < 3 x ULN	Restart JINARC® treatment cautiously at same or lower dose with frequent monitoring and report associated adverse events using the reporting mechanism indicated below.
ALT or AST > 8 x ULN	Permanently discontinue treatment and report associated adverse events using the reporting mechanism indicated below.
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 signs or symptoms of hepatic injury (as noted above)	

6. What are some of the safety issues I should discuss with my 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, 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 at the first sign 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.

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.

Please refer to section 4.4 in the SmPC, 'Special warnings and precautions for use' for further information.

Pregnancy and lactation information

Jinarc® is contraindicated during 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.

7. 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 Guide 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 Guide

The Patient Guide 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 risks of liver injury, dehydration and pregnancy prevention while taking Jinarc®. The Patient Guide 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.

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

▼Jinarc® is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected adverse reactions to Otsuka Pharmaceuticals (U.K.) Ltd Pharmacovigilance Department by telephone on **+353 (0) 1695 0725** (including out of hours), by fax on **+44 (0) 1895 207 115** or by email at **opuksafety@otsuka.co.uk**

Healthcare professionals can also report suspected adverse reactions via HPRA Pharmacovigilance, website: **www.hpra.ie**

9. Where can I obtain further information?

For further information, please contact Otsuka Medical Information at **medical.information@otsuka-europe.com** or telephone **+353 1 695 0725**.