Otsuka

JINARC®▼ (tolvaptan)

Healthcare professionals educational guide

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

Contents

Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AP	Alkaline phosphatase
AUC	Area under time-concentration curve
AVP	Arginine vasopressin
BT	Bilirubin-total
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
HCP	Healthcare professional
INR	International normalised ratio
PIL	Patient information leaflet
SmPC	Summary of product characteristics
WCBP	Women of child bearing potential
ULN	Upper limit of normal

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 involved in the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD) using Jinarc (tolvaptan).

This document summarises important information on the potential risk of hepatic toxicity and provides guidance on how to manage this risk. In addition, it provides important information about pregnancy prevention before and during the treatment with Jinarc.

This guide will enable you to:

- Understand what Jinarc is indicated for and how it should be used
- Be aware of warnings and precautions for use, (in particular idiosyncratic hepatic toxicity and the risk of dehydration and how it can be prevented, identified and managed)
- Provide important safety information to your patients
- Be aware of documents available that provide information on Jinarc and their purpose
- Be aware of the mechanism to report adverse events

This document does not replace the Summary of Product Characteristics (SmPC), which should be read thoroughly before prescribing or dispensing Jinarc. The patient should also be advised to read the Patient Information Leaflet (PIL). The SmPC and PIL for Jinarc can be found at www.medicines.org.uk/emc/

What is Jinarc?

Jinarc contains tolvaptan, which is a vasopressin antagonist that specifically blocks the binding of arginine vasopressin (AVP) at the V2 receptors of the distal portions of the nephron. Tolvaptan affinity for the human V2 receptor is 1.8 times that of native AVP (pharmacotherapeutic group: diuretics, vasopressin antagonists). Administration of Jinarc induces copious aquaresis.

What is Jinarc indicated for?

Jinarc (tolvaptan) is indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with Chronic Kidney Disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.

When is the use of Jinarc contraindicated?

The physician will need to determine if their patient is appropriate to receive Jinarc (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 (see page 7)

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 breast feeding

What dose of Jinarc should I prescribe?

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.

- The initial dose for Jinarc is 60 mg per day as a split-dose regimen of 45 mg + 15 mg (45 mg taken upon waking and 15 mg taken 8 hours later)
- Up titration to a split-dose regimen of 90 mg (60 mg + 30 mg) per day, and then to a split-dose regimen of 120 mg (90 mg + 30 mg) per day, if tolerated, should be attempted with at least weekly intervals between titration steps
- Patients have to be maintained on the highest tolerable dose. Patients may be down-titrated to lower doses based on tolerability
- Dose titration has to be performed carefully to ensure that high doses are not poorly tolerated through too rapid up-titration
- The aim of dose titration is to block activity of vasopressin at the renal V2 receptor as completely and constantly as possible, while maintaining acceptable fluid balance
- Tablets must be swallowed without chewing and with a glass of water
- Jinarc must not be taken with grapefruit juice

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

Posology in 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 (see page 6).

Condition	Details	Requirements
Raised liver enzymes (AST and/or ALT stabilised at no greater than 3 x ULN)	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.	Initiation: 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 testing must continue at increased time frequency. The advice of a hepatologist is recommended. On-going treatment: 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.
Severe hepatic impairment Cirrhosis	In patients with severe hepatic impairment the benefits and risks of treatment with Jinarc must be evaluated carefully.	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.

Dose adjustment is not needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). 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, the area under time-concentration curve (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.

What are the special warnings and precautions for use?

- Idiosyncratic hepatic toxicity (see page opposite)
- Access to water
- Dehydration
- Urinary outflow obstruction
- Fluid and electrolyte balance
- Serum sodium abnormalities
- Anaphylaxis
- Lactose intolerance
- Diabetes mellitus
- Uric acid increases
- Effect of Jinarc on glomerular filtration rate (GFR)

Please see Section 4.4 of the Jinarc SmPC for full details.

Idiosyncratic hepatic toxicity and safety measures

Jinarc 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). While these concomitant elevations were reversible with prompt discontinuation of Jinarc, they represent a potential for significant liver injury.

In post-marketing experience with Jinarc in ADPKD, acute liver failure requiring liver transplantation has been reported.

Prescribing physicians must comply fully with the safety measures required

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
- After 18 months of therapy, at regular 3-monthly intervals

Patients should not be started on Jinarc treatment if they show inability or unwillingness to comply with monthly liver function testing.

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 (see below), 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 testing must continue at increased time frequency. The advice of a hepatologist is recommended.

During treatment

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 interrupted immediately 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 reinitiated.

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

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Recommended guidelines for permanent discontinuation include:

- ALT or AST > 8-times Upper limit of Normal (ULN)
- ALT or AST > 5-times ULN for more than 2 weeks
- ALT or AST > 3-times ULN and (BT >2-times ULN or International Normalized Ratio (INR) >1.5)
- ALT or AST > 3-times ULN with persistent symptoms of hepatic injury (fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice)

If ALT and AST levels remain below 3 times the ULN, Jinarc therapy may be cautiously restarted, 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 you decide if it is appropriate to continue treatment in patients exhibiting signs and symptoms of liver injury and elevated liver enzymes. It summarises the information above.

It is important to report all adverse events, please find below how to report an adverse event (see page 11).

Access to water and dehydration

Jinarc may cause adverse reactions related to water loss such as thirst, polyuria, nocturia and pollakiuria. Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids.

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

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.

Volume status must be monitored in patients taking Jinarc because treatment with Jinarc may result in severe dehydration which constitutes a risk factor for renal dysfunction.

If dehydration becomes evident, take appropriate action which may include the need to interrupt or reduce the dose of Jinarc 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 see Jinarc SmPC for full details.

Pregnancy, lactation and breastfeeding

Pregnancy

Jinarc is contraindicated in pregnancy.

There are no adequate data from the use of Jinarc in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Women of childbearing potential must use effective and reliable contraceptive measures at least four weeks before starting therapy, during Jinarc use and even in the case of dose interruptions, and for at least a further four weeks after stopping Jinarc. Jinarc must not be used during pregnancy.

Pregnancy and pregnancy outcomes should be reported; please find below how to report them (see page 11).

Lactation and breastfeeding

It is unknown whether Jinarc is excreted in human breast milk. Studies in rats have shown excretion of tolvaptan in milk. The potential risk for humans is unknown.

Jinarc is contraindicated while breastfeeding. 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.

What safety issues should I discuss with patients taking Jinarc?

Liver injury

Patients should be informed about the regular blood testing required (monthly for the first 18 months of treatment and at regular 3-monthly intervals thereafter) to monitor and manage the risk of liver injury while taking Jinarc.

Monitoring for signs and symptoms that may indicate liver injury, such as nausea, vomiting, fever, tiredness, loss of appetite, pain in the abdomen, dark urine, yellowing of skin or eyes (jaundice), itching of skin, flu-like syndrome (joint and muscle pain with fever), should also be discussed. Patients should be advised to report these side effects to their doctor immediately if they occur.

Water loss and dehydration

Jinarc causes water loss because it increases urine production. This water loss may result in side effects such as dry mouth and thirst or even more severe side effects (like kidney problems). Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids.

Patients have to 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 have to 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. Grapefruit juice must not be taken.

Patients must talk to their doctor if they cannot drink enough water or if they have to restrict their fluid intake. They should also be advised to take special care in situations which increase their chances of becoming dehydrated such as vomiting or diarrhoea.

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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.

Patients should be advised to seek medical attention if they suspect they are becoming dehydrated. Symptoms of dehydration may include increased thirst, dark yellow and strong-smelling urine, feeling dizzy or lightheaded, feeling tired, decreased urination, dry mouth, lips, eyes or skin. Patients should know that if dehydration is left untreated, it can become severe.

Severe dehydration is a medical emergency and requires immediate medical attention; symptoms can include unusual tiredness, weak/rapid pulse, confusion, dizziness, not urinated all day, fits (seizures).[1]

Pregnancy prevention before and during Jinarc treatment

Jinarc is contraindicated in pregnancy. Therefore, patients should be advised not to become pregnant while taking Jinarc.

Women of child-bearing potential (WCBP) should be advised to use effective and reliable method of contraception for 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.

WCBP 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.

What other tools are available to support the appropriate use of Jinarc?

In addition to this HCPs guide, there are other items available to support HCP's and patients' use of Jinarc. These are described in more detail below.

Jinarc Summary of Product Characteristics

Available at **www.medicines.org.uk/emc/** for GB and **www.emcmedicines.com/northernireland** for Northern Ireland.

Healthcare professionals training slides

These slides contain much of the information you will read in this guide. They summarise important information on the potential risk of hepatic toxicity and provide guidance on how to manage this risk. They provide important information about pregnancy prevention before and during the treatment with Jinarc. In addition, they provide important safety information to be given to your patients and the mechanism to report adverse events.

The slides are available on the Jinarc training portal for HCPs: **www.jinarctraining.co.uk/**

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1 NHS dehydration – available at https://www.nhs.uk/conditions/Dehydration/ (last accessed Aug 2021).

Healthcare professionals prescribing checklist

A prescribing checklist has been made available and is designed to help you assess the suitability of patients who have been identified as candidates for Jinarc therapy, as well as their suitability for ongoing treatment.

The checklist can be used at treatment initiation and regularly thereafter to help you monitor patients, to support the appropriate use of Jinarc and to minimise the risk to patients. It may be downloaded by HCPs from **www.jinarctraining.co.uk/** and is also available printed from Otsuka upon request.

Patient/carer education brochure

The patient/carer education brochure contains a summary of the key information that the patients should be aware of while on Jinarc therapy.

It should be given to patients so they can learn more about the dosing plan, correct use, most important safety issues and monitoring requirements 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 or severe dehydration on treatment.

It may be downloaded by HCPs from **www.jinarctraining.co.uk/** and is also available printed from Otsuka upon request.

Patient alert card

The patient alert card contains important safety information about Jinarc for patients and carers. It includes information on hepatic toxicity, severe dehydration and advice should such symptoms occur. The patient alert card should be filled out and given to the patient by their prescribing HCP. The patient should keep it with them in their wallet or bag at all times.

It may be downloaded by HCPs from **www.jinarctraining.co.uk/** and is also available printed from Otsuka upon request.

Jinarc Patient Information Leaflet

Contained in the product packaging.

How should I report adverse events, including pregnancy and pregnancy outcomes with Jinarc?

Adverse events should be reported. Reporting forms and information can be found at **www.mhra.gov.uk/yellowcard**. Adverse events should also be reported to Otsuka at **opuksafety@otsuka.co.uk** or by calling **0808 168 6726**.

Pregnancy and pregnancy outcomes should also be reported using the same details provided above.

Where can I obtain further information?

For further information, please contact Otsuka Medical Information at **medical.information@otsuka-europe.com** or call **0203 747 5300**.

Please refer to Jinarc SmPC available at **www.medicines.org.uk/emc/** for GB and **www.emcmedicines.com/northernireland** for Northern Ireland.