

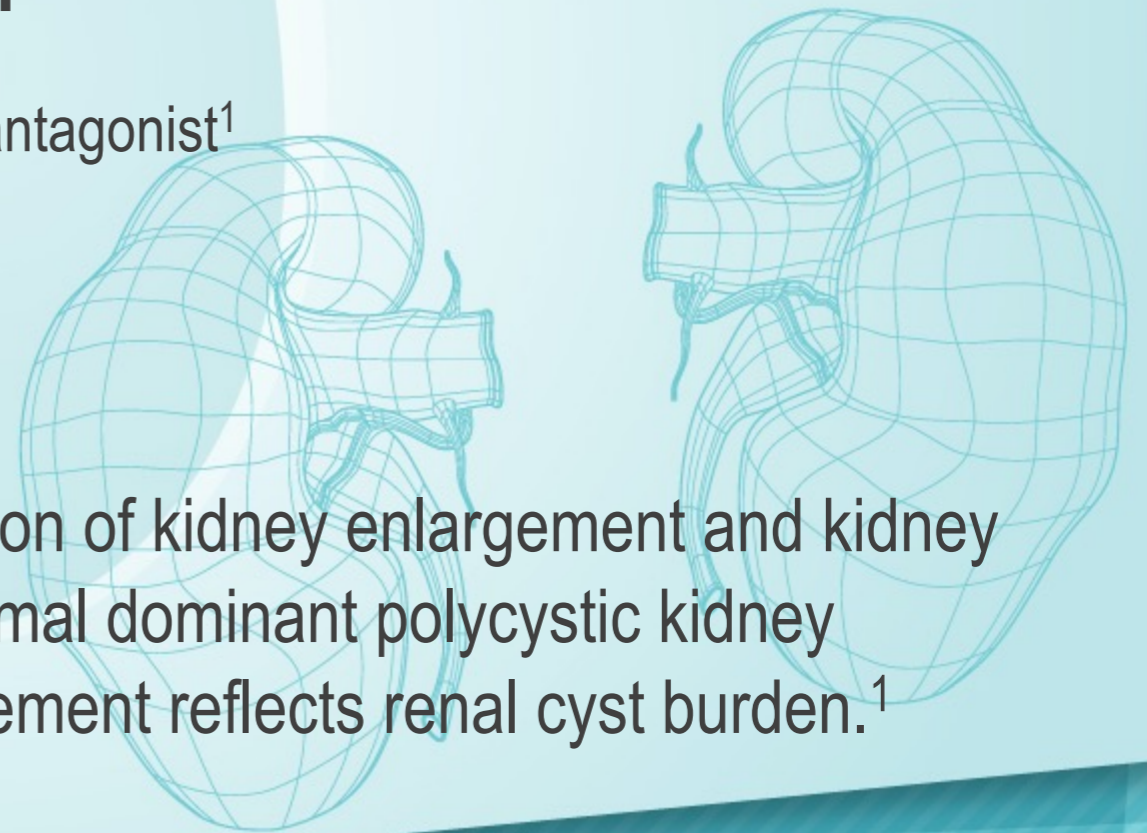
# A Treatment Option to Slow the Progression of Kidney Enlargement and Kidney Function Decline in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD):

Pr JINARC® (tolvaptan), a vasopressin V<sub>2</sub>-receptor antagonist<sup>1</sup>

## HCP Training Module

Pr JINARC® is indicated to slow the progression of kidney enlargement and kidney function decline in adult patients with autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, kidney enlargement reflects renal cyst burden.<sup>1</sup>

1. Pr JINARC® Product Monograph. Otsuka Canada Pharmaceutical Inc. October 23, 2019.



# Overview of ADPKD

## WHAT IS ADPKD?<sup>1</sup>

- ❑ An inherited disease with autosomal dominance<sup>1</sup>
- ❑ A form of nephropathy characterized by multiple kidney cysts that results in slow, gradual, and massive bilateral kidney enlargement<sup>1,2</sup>

## EPIDEMIOLOGY OF ADPKD

- ❑ Prevalence: 1:400-1:1000 live births<sup>1</sup>
- ❑ Affects approximately 35,000 people in Canada<sup>1</sup>
- ❑ More common than Huntington's disease, hemophilia, sickle cell disease, Down's syndrome, cystic fibrosis, and myotonic dystrophy combined<sup>3</sup>

ADPKD: autosomal dominant polycystic kidney disease

1. Cabellon M. Cystic Disease of the Kidney. In: Windus, David, editor. *Nephrology Subspecialty Consult*. 2<sup>nd</sup> edition. New York: Lippincott, Williams & Wilkins, 2008.

2. National Kidney Foundation. *Primer on Kidney Diseases*. New York: Saunders, 2005.

3. Belibi FA *et al*. *Expert Opin Investig Drugs* 2010; 19(3):315-28.

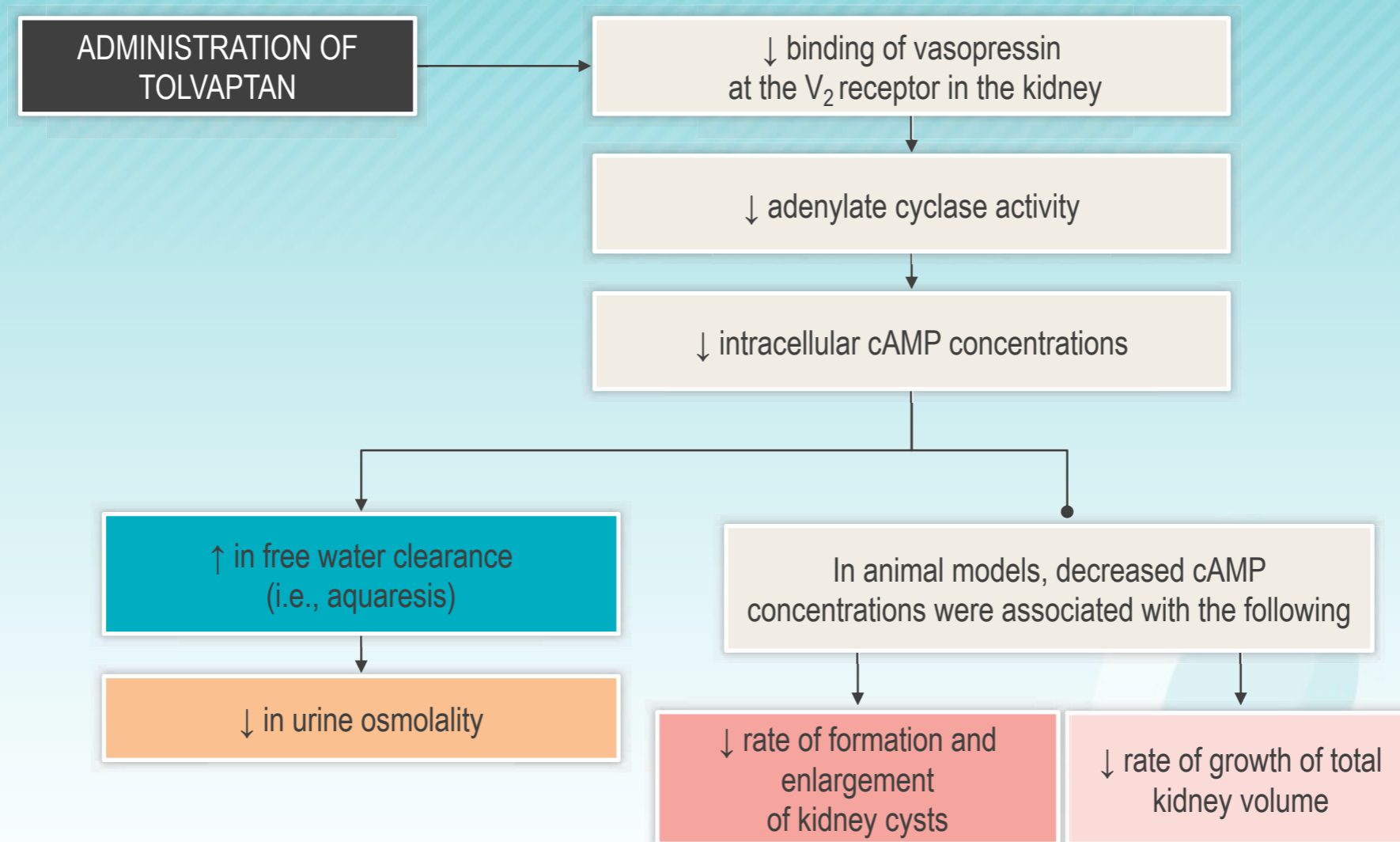
Pr JINARC®:

## A Treatment Option For Patients with ADPKD<sup>1</sup>

- ❑ Pr JINARC® is indicated to slow the progression of kidney enlargement and kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD)
- ❑ In ADPKD, kidney enlargement reflects renal cyst burden



# Mechanism of Action of Pr JINARC<sup>®1†</sup>



cAMP: adenosine 3', 5'-cyclic monophosphate

† Clinical significance has not been established.

1. Pr JINARC<sup>®</sup> Product Monograph. Otsuka Canada Pharmaceutical Inc. October 23, 2019.

# Pr JINARC®: 2 Pivotal Trials in Patients with Earlier to Later Stages of ADPKD

## Design of the TEMPO 3:4 Trial<sup>1,2</sup>

### 3-year, placebo-controlled trial

- ❑ **Interventions:** Randomized trial with a 2 to 1 ratio
  - ❑ JINARC + standard of care vs. placebo + standard of care
  - ❑ Patients were titrated to receive the highest tolerable dose starting with morning and afternoon doses of 45 mg and 15 mg, respectively, with weekly increases to 60 mg and 30 mg, and then to 90 mg and 30 mg
  - ❑ All patients remained on standard concomitant medications
- ❑ **Subjects:** 1445 patients with ADPKD
  - ❑ Baseline TKV  $\geq$ 750 mL by MRI (mean baseline 1705 mL in JINARC group; 1668 mL in placebo group)
  - ❑ Baseline estimated creatinine clearance  $\geq$  60 mL/min (mean baseline 104 mL/min in both groups)
- ❑ **Baseline characteristics:**
  - ❑ Patient Distribution by CKD Stage: CKD Stage 1 (35%), CKD Stage 2 (48%) and CKD Stage 3 (17%)
- ❑ **Primary outcome:** Annual rate of TKV change (normalized as a percentage) for JINARC relative to placebo
- ❑ **Composite secondary outcome reflecting clinical progression:**
  - ❑ Worsening kidney function, defined as a persistent 25% reduction, i.e., reproduced over at least two weeks, in reciprocal serum creatinine during treatment (equivalent to a 33% increase in serum creatinine), from end of titration to last on-drug visit;
  - ❑ Medically significant kidney pain, defined as requiring prescribed leave, last-resort analgesics, narcotic or anti-nociceptive, radiologic or surgical interventions;
  - ❑ Worsening hypertension, defined as a persistent increase in blood pressure category, or an increase in anti-hypertensive medication(s); or
  - ❑ Worsening albuminuria, defined as a persistent increase in albumin/creatinine ratio category (seen at 2 of 3 successive assessments)
- ❑ **Additional secondary outcome:** Rate of kidney function change, measured by the reciprocal of the serum creatinine level and calculated as estimated glomerular filtration rate (eGFR<sub>CKD-EPI</sub>)

# Pr JINARC® : 2 Pivotal Trials in Patients with Earlier to Later Stages of ADPKD

## Design of the REPRISE Trial<sup>1,2</sup>

### 12 month, placebo-controlled trial

- ❑ **Interventions:** Randomized trial with a 1 to 1 ratio
  - ❑ JINARC + standard of care vs. placebo + standard of care
  - ❑ Patients were maintained on their highest tolerated dose for a period of 12 months but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses
  - ❑ All patients remained on standard concomitant medications
- ❑ **Subjects:** 1370 patients with ADPKD
  - ❑ Randomization was stratified according to the baseline estimated GFR ( $\leq 45$  or  $>45$  mL/min/1.73m<sup>2</sup>), patient age ( $\leq 55$  or  $>55$  years) and TKV ( $\leq 2000$  mL,  $>2000$  mL or unknown)
- ❑ **Baseline characteristics:**
  - ❑ Patient Distribution by CKD Stage: CKD Stage 2 (5.2%), CKD Stage 3a (30%), CKD Stage 3b (45.1%) and CKD Stage 4 (19.5%)
- ❑ **Primary outcome:** Annualized change in eGFR from pre-treatment baseline to post-treatment follow-up for JINARC relative to placebo
- ❑ **Key Secondary Endpoint:**
  - ❑ Slope of the change in the eGFR that was derived from individual slopes for each patient, with adjustment for the duration of the observation and with interpolation to 1 year

# Demonstrated efficacy results of Pr JINARC® in Patients with ADPKD: Key Results of the TEMPO Trial<sup>1,2</sup>

EFFICACY ENDPOINT		RESULTS			Relative reduction
		Tolvaptan	Placebo	p value	
Annual increase in total kidney volume (TKV), % per year • TKV results were due to a combination of the secretory and anti-proliferative effects of tolvaptan. The secretory effect is largely reversible upon discontinuation; see Product Monograph for more information.		2.8%	5.5%	<0.0001	49.2%
Composite endpoint: Clinical progression <sup>†</sup> ; events/100 person-years		44	50	0.01	13.5%
Component Analyses	Worsening hypertension	31	32	NS	–
	Worsening albuminuria	8	8	NS	–
	Clinically significant kidney pain	5	7	0.007 (nominal p-value)	35.8%
	Worsening kidney function	2	5	<0.001 (nominal p-value)	61.4%
Annual decrease in renal function, reciprocal of the sCr level		-2.6	-3.8	<0.001	31.6%
Annual decrease in renal function, eGFR		-2.7	-3.6	<0.0001	26.4%

NS; non-significant

<sup>†</sup> Composite of worsening kidney function, kidney pain, hypertension or albuminuria.

1. Pr JINARC® Product Monograph. Otsuka Canada Pharmaceutical Inc. October 23, 2019.

2. Torres VE *et al.* Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2012;367:2407–18.

# Demonstrated efficacy of Pr JINARC® in Patients with ADPKD: Key Results of the REPRISE Trial<sup>1</sup>

- ❑ 35% reduction in the rate of decline of kidney function was observed in JINARC patients (-2.34 vs. -3.61 with placebo, treatment effect of 1.27 mL/min/1.73m<sup>2</sup>/year, primary endpoint,  $p < 0.0001$ )
- ❑ Key secondary endpoint (eGFR slope) and all sensitivity analyses were significant ( $p \leq 0.0005$ )
- ❑ Subgroup analysis for the primary and key secondary endpoints demonstrated consistent treatment effects of JINARC for subjects in CKD Stages 2, 3a, 3b and 4

# Warning: Potential for Idiosyncratic Hepatic Toxicity<sup>1</sup>

## **WARNING: IDIOSYNCRATIC HEPATIC TOXICITY**

Pr JINARC<sup>®</sup> use has led to idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations of total bilirubin.

To help mitigate the risk of liver injury, blood testing for hepatic transaminases and total bilirubin is required prior to initiation of JINARC, then hepatic transaminases continuing monthly for 18 months, every 3 months for the next 12 months, and then every 3-6 months. Therefore, JINARC is available for treatment of patients with ADPKD only through a controlled hepatic safety monitoring and distribution programme conducted and maintained by, or for, the market authorization holder of JINARC.

## Warning: Potential for Idiosyncratic Hepatic Toxicity<sup>1</sup>

In the TEMPO trials, 3 individuals taking <sup>Pr</sup> JINARC<sup>®</sup> experienced ALT >3x ULN with bilirubin >2x ULN

- ❑ Includes 2 of 957 patients in the TEMPO 3:4 study and 1 in the TEMPO 4:4 study (extension open-label study)
- ❑ Monitoring for liver enzymes elevation was every 3-4 months
- ❑ All 3 returned to normal liver function after stopping JINARC<sup>†</sup>

In the REPRISE trial, all patients were monitored monthly for liver enzymes elevation and none of them showed this concomitant level of hepatic enzyme and bilirubin elevation. This suggests that monthly liver function monitoring during treatment helps detect liver enzyme elevation early on. In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported.

<sup>†</sup> These concomitant elevations were gradually reversible with prompt discontinuation of tolvaptan; however, they represent a potential for significant liver injury.

1. <sup>Pr</sup> JINARC<sup>®</sup> Product Monograph. Otsuka Canada Pharmaceutical Inc. October 23, 2019.

# Contraindications<sup>1</sup>

- ❑ Patients who have been asked to permanently discontinue tolvaptan
- ❑ Patients with known or suspected hypersensitivity to tolvaptan, benzazepine or benzazepine derivatives (e.g., mirtazapine) or any of the excipients
- ❑ Patients with hypovolemia
- ❑ Patients with hypernatremia
- ❑ Patients with anuria
- ❑ Patients who do not have access to fluids or who cannot respond to the physiologic sensation of thirst
- ❑ Patients with a history, signs or symptoms of significant liver impairment or injury, excluding uncomplicated polycystic liver disease
- ❑ Patients using strong CYP3A inhibitors, e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone
- ❑ Pregnancy
- ❑ Nursing women
- ❑ Patients with one of the following rare hereditary diseases: Galactose intolerance, Lapp lactase deficiency or Glucose-galactose malabsorption

# Key Elements and Goals of the Pr JINARC® Controlled Hepatic Safety Monitoring and Distribution (HSMD) Programme<sup>1</sup>

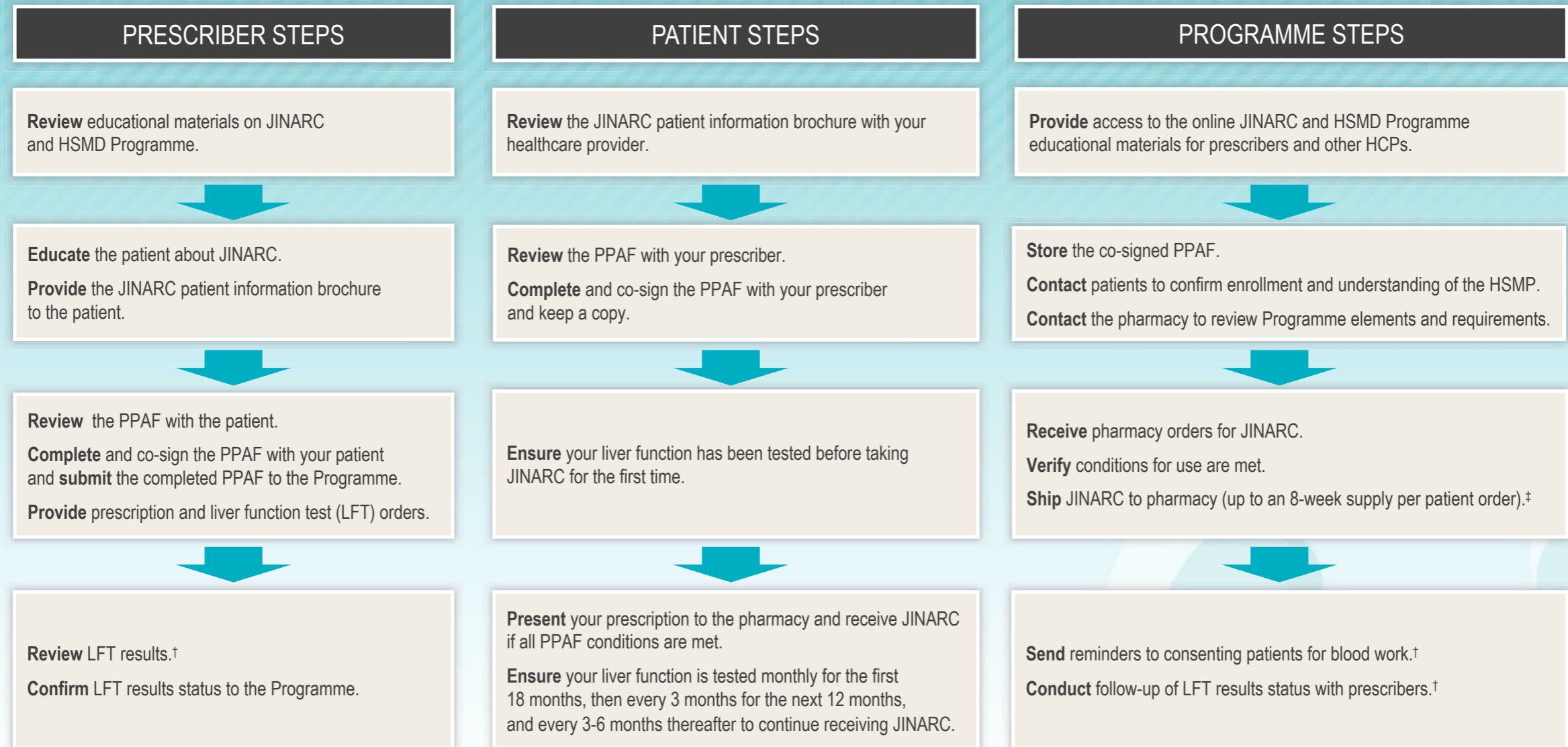
## GOALS

- ❑ To minimize the risk of liver injury associated with JINARC
- ❑ To ensure appropriate patient selection for the treatment with JINARC
- ❑ To document and ensure appropriate laboratory monitoring of hepatic function while on treatment
- ❑ To inform healthcare providers and patients about the risk of serious adverse events and safe use conditions of JINARC

## KEY PROGRAMME ELEMENTS

- ❑ Restriction of prescription to nephrologists or specialists with expertise in the management of patients with ADPKD and a full understanding of the benefits and risks of tolvaptan therapy including hepatic toxicity and monitoring requirements
- ❑ Deliver JINARC and HSMD Programme education to healthcare professionals
- ❑ Patient education
- ❑ Patient-prescriber agreement form (PPAF) prior to initiation of treatment
- ❑ Controlled distribution of JINARC supply to pharmacies
- ❑ Tracking liver enzymes and function tests

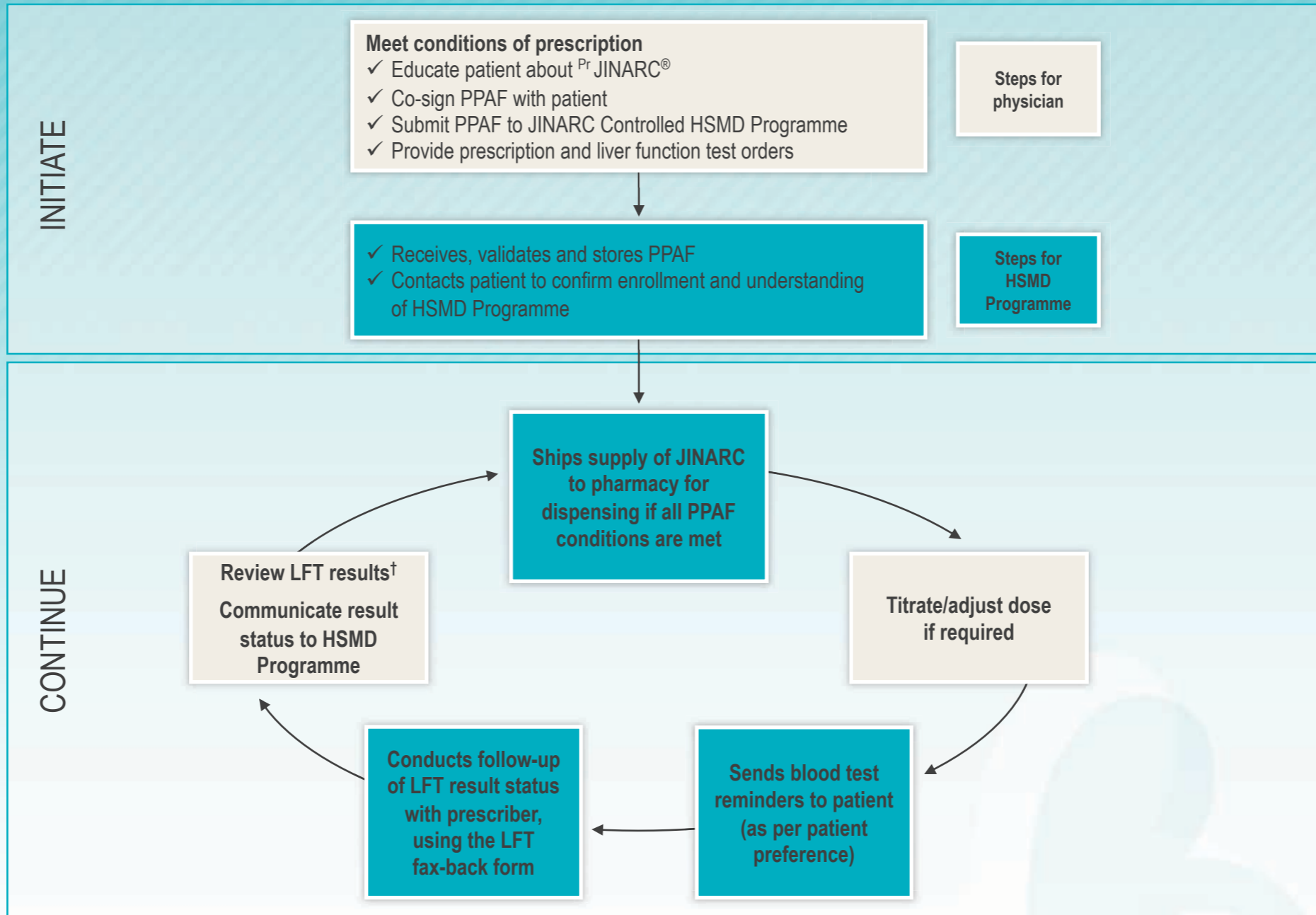
# Overview of Responsibilities in the Pr JINARC® Controlled Hepatic Safety Monitoring and Distribution Programme<sup>1</sup>



<sup>†</sup> Monthly for the first 18 months, then every 3 months until month 30, and every 3-6 months thereafter.

<sup>‡</sup> With evidence of patient adherence to LFT testing, the Programme may supply up to a 12 week supply per patient order.

1. Pr JINARC® Product Monograph. Otsuka Canada Pharmaceutical Inc. October 23, 2019.



# Patient Selection Considerations for Pr JINARC® Treatment<sup>1-3</sup>

- ❑ Clinical trials of JINARC evaluated ADPKD patients with:<sup>†</sup>
  - ❑ TEMPO 3:4
    - Total kidney volume (TKV) ≥ 750 mL
    - Relatively preserved renal function: e.g., CKD-EPI eGFR ≥30 mL/min/1.73m<sup>2</sup> (eCrCl ≥60 mL/min)
  - ❑ REPRISE
    - CKD from late stage 2 to early stage 4
      - Patient age (<56): eGFR between 25 and 65 mL/min/1.73m<sup>2</sup>
      - Patient age (56-65): eGFR between 25 and 44 mL/min/1.73m<sup>2</sup>, plus eGFR decline >2.0 mL/min/1.73m<sup>2</sup>/year
  
- ❑ Factors associated with rapid progression of ADPKD include:
  - ❑ Large total renal cyst mass for a given age, as measured by TKV
  - ❑ CKD Stage 2–3
  - ❑ Rapid deterioration of renal function
  - ❑ Presence of systemic hypertension or albuminuria

<sup>†</sup> At the time of initiation of treatment.

1. Pr JINARC® Product Monograph. Otsuka Canada Pharmaceutical Inc. October 23, 2019.

2. Torres VE *et al.* Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2012;367:2407–2418.

3. Torres VE *et al.* Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med* 2017;377(20):1930-1942.

# The Patient-Prescriber Agreement Form (PPAF) for Pr JINARC®<sup>1</sup>

When the patient and provider decide to undertake treatment with JINARC, a signed, duly-documented, manufacturer- and product-specific, patient-prescriber agreement form (PPAF) is required

The PPAF outlines:

- Relevant patient selection criteria
- Expected risks and benefits of treatment
- Need for mandatory hepatic function monitoring
- Statement that the patient understands the benefits and risks of treatment and that they agree to take blood tests as prescribed by the doctor to start and remain on treatment

JINARC Patient-Prescriber Agreement Form (PPAF)		PRESCRIBER SECTION
Please return this completed and signed PPAF by fax to: 1-844-3JINARC (354-6272).		
<p>Pr JINARC® (tolvaptan) is available in Canada. JINARC can only be prescribed to patients who have completed and signed this form with their prescriber.</p> <p>The purpose of this Patient-Prescriber Agreement Form (PPAF) is to document the fully-considered engagement of both the patient and the prescriber to the treatment of autosomal dominant polycystic kidney disease (ADPKD) with JINARC ("Product"). In accordance with Health Canada requirements, the manufacturer of JINARC has implemented a safety monitoring initiative with regard to use of and access to JINARC. This initial step will also serve to confirm the patient enrollment into the JINARC Controlled Hepatic Safety Monitoring and Distribution Programme ("Programme"). The manufacturer of JINARC is Otsuka Canada Pharmaceutical Inc. ("Otsuka"). Otsuka is responsible for the Programme and may administer, in whole or in part with a designated third-party service provider, the Programme. JINARC is indicated to slow the progression of kidney enlargement and kidney function decline in patients with ADPKD. In ADPKD, kidney enlargement reflects renal cyst burden. Careful consideration and discussion of the appropriateness of JINARC treatment should be undertaken between the prescriber and patient before initiation of treatment, taking into account the potential benefits and risks of treatment, appropriate patient selection, and the need for mandatory ongoing hepatic function monitoring. Following mutual agreement to undertake treatment with JINARC, both the patient and their prescriber must complete, sign, and date this PPAF in person, together at the same time. The patient and prescriber must read each statement of their respective section(s) of this PPAF thoroughly, add their initials before each statement confirming that he/she understands the benefits and risks of treatment with JINARC and agrees to comply with the conditions for use prior to initiating JINARC. Please return all pages of this completed and signed PPAF by fax to: 1-844-3JINARC (354-6272). Incomplete information will result in delay. Please call 1-844-2JINARC (254-6272) if you have any questions regarding the Programme. A Programme nurse will contact the patient to acknowledge and confirm enrollment if the patient provides the required consent as specifically set out herein. JINARC is only distributed to pharmacies through a unique distributor who will verify with the Programme that there is a signed and valid PPAF on file prior to distributing JINARC. To allow the Programme specialty pharmacy to dispense JINARC, the prescriber should complete the prescription information section on this form. Both the patient and prescriber should keep a copy of the executed PPAF for their records. Should the patient's attending prescriber change, this PPAF will need to be renewed. In the event that there are material changes to the Programme, this PPAF or the Product Monograph for JINARC, the prescriber and the patient will be contacted and informed of such changes. The PPAF is specific to JINARC and cannot be used for any other product.</p>		
<p><b>PRESCRIBER NOTES</b></p> <p>As the PRESCRIBER of JINARC for the undersigned patient, I acknowledge that:</p> <p><input type="radio"/> I am a nephrologist or</p> <p><input type="radio"/> I am a specialist experienced in the management of autosomal dominant polycystic kidney disease (ADPKD). Please provide a brief description of your experience/training: _____</p> <p>I understand that JINARC is indicated to slow the progression of kidney enlargement and kidney function decline in patients with ADPKD. In ADPKD, kidney enlargement reflects renal cyst burden.</p> <p>I understand that JINARC is contraindicated in patients: who have been asked to permanently discontinue tolvaptan in the past, with known or suspected hypersensitivity to tolvaptan, benzazepine or benzazepine derivatives (e.g., mirtazapine) or any of the excipients; with hypovolemia, with hyponatremia, with anuria, who do not have access to fluids or who cannot respond to the physiologic sensation of thirst with a history signs or symptoms of significant liver impairment or injury, excluding uncomplicated polycystic liver disease, who are using strong CYP3A inhibitors; who are pregnant or nursing; or who have one of the following rare hereditary diseases: Galactose intolerance, Lapp lactase deficiency or Glucose-galactose malabsorption.</p> <p>I understand that JINARC has not been studied in pediatric patients (&lt;18 years of age) with ADPKD. Its use is therefore not recommended in this patient population. Also, patients who are at, or approaching, end-stage renal disease, would not be expected to benefit from JINARC treatment.</p> <p>I understand that the patients most likely to benefit from JINARC treatment according to the TEMPO 3:4 trial, appear to be those with rapidly progressive ADPKD or at a stage of incipient rapid progression, but before widespread destruction of renal architecture has occurred. Patients who are also likely to benefit from JINARC according to the REPRISE trial, appear to be those at high risk of progressive eGFR decline based on renal function for age (8 to 65 years of age with baseline eGFR between &lt;25 and 65 mL/min/1.73m<sup>2</sup>). I will comply with patient selection criteria as outlined in the totality of the JINARC Product Monograph.</p> <p>I have reviewed and understood the risks and potential benefits of JINARC, as well as the requirements of the Hepatic Safety Monitoring and Distribution Programme.</p> <p>I have counselled my patient about the potential risks and benefits of JINARC, the criteria for selecting him/her for this treatment, the appropriate use of JINARC, as well as the need for mandatory ongoing hepatic function testing.</p> <p>I have provided and reviewed the mandatory JINARC patient educational material with my patient.</p> <p>I understand the Hepatic Safety Monitoring and Distribution Programme will send me a liver function status report form for every liver function test required of the patient. I further understand that I or my delegate(s) must complete, sign and return this report to the Programme in order to ensure that the patient's pharmacy can continue to order and dispense JINARC to my patient. I acknowledge that failure to do so may lead to JINARC supply interruptions for this patient. I understand the Programme may contact me by phone, fax or by email after sending the liver function status report form to follow up on the availability of pending results for a given month or to provide me with information on the Programme.</p> <p>Prior to initiating and prescribing JINARC, I will confirm that my patient's liver function test (i.e., ALT and AST) levels are less than three (3) times the upper limit of normal, and total bilirubin has been assessed.</p> <p>I have reviewed the "Prescriber Privacy and Consent Declaration" on this form and I agree to its terms and conditions.</p>	<p><b>Prescriber Information</b></p> <p style="text-align: center; font-size: small;">Prescriber Stamp</p> <p>First name: _____</p> <p>Last name: _____</p> <p>Medical license #: _____</p> <p>Email address: _____</p> <p>Telephone number: _____</p> <p>Fax number: _____</p> <p>Street address: _____</p> <p>City: _____</p> <p>Province: _____ Postal code: _____</p> <p>Primary office contact person name (if different): _____</p> <p>Telephone number: _____</p> <p><b>Prescription Information</b></p> <p>Patient first name: _____</p> <p>Patient last name: _____</p> <p><b>JINARC oral tablets:</b></p> <p><input type="radio"/> 45/15 mg (60 mg)      One _____ mg tablet p.o. AM and one _____ mg tablet 8 hours later</p> <p><input type="radio"/> 60/30 mg (90 mg)      Disp: _____ weekly blister packs (14 tabs per pack)</p> <p><input type="radio"/> 90/30 mg (120 mg)      Refill x _____</p> <p style="font-size: x-small;">This original prescription constitutes a legal prescription for the patient for JINARC. The original copy of this prescription will be kept in my files and will not be re-used. Completion of this section is required for medication to be dispensed.</p> <p>Signature: <input checked="" type="checkbox"/> _____</p> <p>Date: _____</p>	

1. Pr JINARC® Product Monograph. Otsuka Canada Pharmaceutical Inc. October 23, 2019.

# What to Do if Hepatic Toxicity Occurs with Pr JINARC®<sup>1</sup>

**At the onset of symptoms or signs consistent with hepatic injury, or if abnormal ALT or AST increases are detected:**

- ❑ JINARC administration must be immediately interrupted
- ❑ Repeat liver tests, i.e., ALT, AST, total bilirubin, alkaline phosphatase, must be obtained as soon as possible, ideally within 48-72 hours
- ❑ Liver testing should continue at an increased frequency until symptoms/signs/laboratory abnormalities stabilize or resolve, at which point cautious re-initiation of JINARC may be considered
- ❑ Any adverse event should be reported to Otsuka Canada Pharmaceutical Inc. at 1-877-341-9245

# When to Permanently Discontinue Pr JINARC® for Hepatic Toxicity<sup>1</sup>

JINARC treatment should be immediately interrupted upon confirmation of sustained or increasing transaminase levels, and permanently discontinued if significant increases and/or clinical symptoms of hepatic injury persist.

## Permanent discontinuation is recommended for:

- ALT or AST > 8x ULN
- ALT or AST > 5x ULN for more than 2 weeks
- ALT or AST > 3x times ULN **and** total bilirubin >2x ULN or INR >1.5
- ALT or AST > 3x times ULN, with persistent symptoms of hepatic injury

Permanent discontinuation from receiving tolvaptan is a contraindication and so once a patient has been permanently discontinued from receiving tolvaptan, treatment **must never be** restarted. The permanent discontinuation status of patients should be verified prior to initiation with tolvaptan.

# Tracking Hepatic Safety with Pr JINARC®

## Personnel from the JINARC Controlled HSMD Programme will send a monthly fax to each prescriber of tolvaptan

- Includes a list of all patients in the practice taking JINARC who are due for ALT/AST assessment
- For each patient, physician (or proxy) will need to tick off checkboxes indicating whether or not their JINARC patients:
  - Have done their blood work according to schedule
  - Have had normal or abnormal (>3x ULN) results from the ALT/AST testing
  - Have had any JINARC interruption or discontinuation, as well as permanent discontinuation
- Completed and signed form is to be returned by fax within 5 business days

**Pr JINARC® Controlled Hepatic Safety Monitoring and Distribution Programme**  
Liver Function Test Fax-Back Form

Below is an example of a form you will receive from the JINARC Hepatic Safety Monitoring and Distribution (HSMD) Programme. Once received, fill it out with your patient's most recent liver function test (LFT) results and fax back to the HSMD Programme.

To: <<Fax Number>> Date of Report << YYYY-MM-DD >>  
From: \*JINARC® Controlled Hepatic Safety Monitoring and Distribution Programme [1-844-254-6272]

Dear Dr: <<First Name Last Name>>, <<JINARC ID: Dr. JINARC ID Number>>

Our records indicate that a liver function test (LFT) report is due for each of the following patients treated with Pr JINARC®. In accordance with Health Canada requirements, the Hepatic Safety Monitoring and Distribution (HSMD) Programme must ensure follow-up and collection of transaminase results status for all patients treated with JINARC to facilitate its safe use. Please complete this form based on the most recent LFT results of your patient's transaminase levels and fax the form(s) to the JINARC HSMD Programme at 1-844-3JINARC (1-844-354-6272) by <<YYYY-MM-DD>>. Please note, if this report is not returned by its due date, your office will receive a follow-up call requesting this information as per the Programme requirements.

Patient Identifiers	ALT/AST Monitoring Frequency	ALT/AST Results Received?	Were ALT/AST levels >3x ULN?	JINARC Treatment Status (Please select, if applicable)	Please check if patient meets Product Monograph guidelines for permanent JINARC discontinuation <sup>1</sup>
Initial: prepopulated DOB: prepopulated JINARC ID #: prepopulated	<input type="checkbox"/> Monthly <input type="checkbox"/> Q3 months <input type="checkbox"/> Q6 months (prepopulated)	<input type="checkbox"/> Yes YYYY-MM-DD <input type="checkbox"/> No	<input type="checkbox"/> Yes! <input type="checkbox"/> No	<input type="checkbox"/> Treatment Interrupted <input type="checkbox"/> Treatment Discontinued YYYY-MM-DD	<input type="checkbox"/>

<sup>1</sup>At the onset of symptoms or signs consistent with hepatic injury or if abnormal ALT or AST increases are detected, JINARC administration must be immediately interrupted and repeat liver tests, i.e. ALT, AST, total bilirubin, alkaline phosphatase, must be obtained as soon as possible, ideally within 48-72 hours. Testing should continue until symptoms/signs/laboratory abnormalities stabilize or resolve, at which point cautious re-initiation of JINARC may be considered.

<sup>2</sup>JINARC supply will be permanently discontinued if any of the following conditions are met: ALT or AST >5 times ULN or >3 times ULN for more than 2 weeks; ALT or AST >3 times ULN and total bilirubin > 2 times ULN or NR > 1.5; ALT or AST > 3 times ULN with persistent symptoms of hepatic injury.

<sup>3</sup>Permanent discontinuation from receiving tolvaptan is a contraindication and so once a patient has been permanently discontinued from receiving tolvaptan, treatment must never be restarted. The permanent discontinuation status of patients should be verified prior to re-initiation of tolvaptan.

Note: Prescribers should report any adverse event associated with JINARC to Otsuka Canada Pharmaceutical Inc. at 1-877-560-9245.

**JINARC Interrupted Patients**  
Based on information the Programme has previously received, the following patients have had their treatment with JINARC interrupted. Please indicate if these patients will be resuming treatment.

Patient Identifiers	Date of Treatment Interruption	Will treatment be re-initiated?	Anticipated Re-initiation Date of JINARC
Initial: prepopulated DOB: prepopulated JINARC ID #: prepopulated	Prepopulated YYYY-MM-DD	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Please provide date, if available: YYYY-MM-DD

By signing this form, I confirm the prepopulated information to be correct, and I attest that the information provided on page X to page Y to be accurate and true.

Please print name: \_\_\_\_\_  
Signature of prescriber or delegate: \_\_\_\_\_  
X \_\_\_\_\_ Date: \_\_\_\_\_

If you have any questions, please do not hesitate to call us.  
Thank you.  
**JINARC Hepatic Safety Monitoring and Distribution Programme Team**

Programme Phone: 1-844-2JINARC (1-844-254-6272)  
Programme Fax Number: 1-844-3JINARC (1-844-354-6272)  
For important safety information and access to educational material, please visit [JINARC.ca](http://JINARC.ca)

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# Potential Drug Interactions with Pr JINARC®<sup>1</sup>

JINARC is a substrate of CYP3A and thus co-administration with CYP3A inhibitors or CYP3A inducers may lead to a change in exposure. Where dose adjustments are recommended or required, response should be monitored, and the dose adjusted accordingly.

RECOMMENDATION(S)	EXAMPLES
Concomitant use with strong CYP3A4 inhibitors is contraindicated as it may lead to significant increase in tolvaptan exposure.	Ketoconazole, clarithromycin, ritonavir, saquinavir
Concomitant use with moderate CYP3A inhibitors also requires lowered dosing of JINARC	Verapamil, fluconazole, erythromycin
JINARC should not be taken with grapefruit juice	
Concomitant use of JINARC with strong CYP3A inducers should be avoided	Rifampin, phenytoin, carbamazepine, St. John's Wort
Reduction in the dose of JINARC may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors. However, concomitant use with those P-gp inhibitors that also act as strong CYP3A inhibitors is contraindicated	Cyclosporine, quinidine

# Other Warnings and Precautions with Pr JINARC®<sup>1</sup>

<b>Dehydration</b>	<ul style="list-style-type: none"> <li>Patients should be generally encouraged to drink water while taking JINARC to avoid development of dehydration or hypernatremia., and to improve tolerability of tolvaptan</li> </ul>
<b>Anaphylaxis</b>	<ul style="list-style-type: none"> <li>Anaphylaxis has been reported very rarely following the first administration of tolvaptan. Patients have to be carefully monitored during treatment</li> <li>Since hypersensitivity is a contraindication, treatment must never be restarted after an anaphylactic reaction or other serious allergic reaction</li> </ul>
<b>Hypernatremia</b>	<ul style="list-style-type: none"> <li>During treatment initiation, patients should be frequently monitored for serum sodium and volume status</li> <li>If serum sodium increases above the normal range, tolvaptan treatment must be down-titrated or discontinued promptly</li> </ul>
<b>Hyperkalemia</b>	<ul style="list-style-type: none"> <li>Treatment with tolvaptan could result in increased serum potassium</li> <li>Serum potassium levels should be monitored carefully after initiation of tolvaptan</li> </ul>
<b>Hyperuricemia</b>	<ul style="list-style-type: none"> <li>Treatment with tolvaptan may lead to increases in serum uric acid and clinical gout</li> <li>Uric acid concentrations should be evaluated prior to initiation of JINARC treatment, and as indicated during treatment</li> </ul>
<b>Hypotension</b>	<ul style="list-style-type: none"> <li>Increased incidence of hypotension-related AEs (e.g., dizziness, syncope) was observed in patients taking concomitant anti-hypertensives</li> </ul>
<b>Serum sodium abnormalities</b>	<ul style="list-style-type: none"> <li>Must be corrected prior to initiation of JINARC treatment</li> </ul>
<b>Vasopressin analogues</b>	<ul style="list-style-type: none"> <li>Concomitant treatment with JINARC is not recommended</li> </ul>
<b>Special populations</b>	<ul style="list-style-type: none"> <li>Women of childbearing potential must have effective contraceptive measures prior to and during JINARC use</li> <li>JINARC has not been studied in pediatric patients (&lt;18 years) with ADPKD</li> <li>Safety and effectiveness in geriatric patients have not been studied</li> <li>JINARC is contraindicated in patients with clinically relevant impairment of hepatic function</li> <li>JINARC is contraindicated in anuric patients</li> </ul>
<b>Cognitive &amp; motor impairment</b>	<ul style="list-style-type: none"> <li>No controlled trials of the effects of tolvaptan on driving performance</li> <li>Occasionally, dizziness, asthenia and syncope may occur</li> </ul>

# Recommended Dosing of Pr JINARC® (tolvaptan) in patients with ADPKD<sup>1</sup>

Dosing	
Regimen overview	2 doses daily: One (larger dose) upon waking and one (smaller dose) 8 hours later
Available dosages	45+15 mg, 60+30 mg, 90+30 mg
Usual initial dosage	45+15 mg
Target dose	Highest tolerated dose, up to 90+30 mg
Titration	At least weekly intervals between titrations

The aim of dose titration is to block the activity of vasopressin at the renal V<sub>2</sub> receptor as completely and constantly as possible, while maintaining acceptable fluid balance, in order to achieve optimal effects on TKV progression or diminution of renal function decline.

The adequacy of vasopressin suppression at a given dose of JINARC can be monitored through measurement of urine osmolality and may be used to optimize the clinical benefit of JINARC in ADPKD patients.

Name \_\_\_\_\_

Address \_\_\_\_\_

**R<sub>x</sub>**

*JINARC 45+15 mg (60 mg)  
oral tablets*

*Sig: One 45 mg tablet  
po AM and one 15 mg  
tablet  
8 hours later*

*Disp: 4 blister packs  
(56 tablets)*

MD \_\_\_\_\_

Signature \_\_\_\_\_

# Recommended Dosing of Pr JINARC® (tolvaptan) in patients with ADPKD<sup>1</sup>

- Attributes of patients who can benefit from JINARC:
  - TEMPO 3:4
    - Have rapidly-progressing ADPKD (meeting modified Ravine criteria)
    - Are at early stage of CKD
    - TKV  $\geq$ 750 mL
    - Estimated creatinine clearance  $\geq$ 60 mL/min
  - REPRISE
    - Have high risk of progressive eGFR decline based on renal function for age (18 to 65 years of age with baseline eGFR between 25 and 65 mL/min/1.73m<sup>2</sup>)

Prior to initiation of treatment with JINARC, it is important to determine whether expected benefit-risk is deemed to be favourable for the individual patient to be treated.

# Canadian Pr JINARC® Patient Outcomes Registry

**In order to enhance the continuous evaluation of the long-term effects of tolvaptan in patients with ADPKD, all patients to be initiated on JINARC should be offered participation in the Canadian JINARC patient outcomes registry<sup>1</sup>**

## Key data to be captured:

- Total mortality, and mortality attributable to renal and hepatic causes
- Time to renal replacement therapy (i.e., dialysis and transplantation)

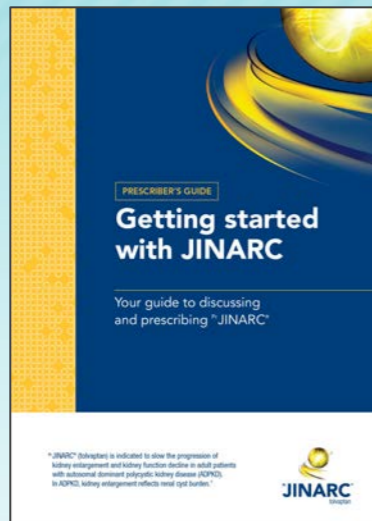
*JINARC is not indicated for the measurements listed above.*

## Other variables:

- Patient characteristics
- Disease history and baseline disease status
- Clinical variables (e.g., markers of renal function)
- Patient-reported outcomes
- Discontinuations (and reasons)

# Practical Information for the Pr JINARC® Prescriber

Resources available for the JINARC prescriber include:



Prescriber guide



Patient-prescriber agreement form (PPAF)



Patient information booklet

These resources are available from your Otsuka representative, through [JINARC.CA](http://JINARC.CA), and by calling 1-844-2JINARC (1-844-254-6272)

# Pr JINARC® in Patients with ADPKD: Conclusions<sup>1</sup>

- ❑ Pr JINARC® is indicated to slow the progression of kidney enlargement and kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD)
- ❑ JINARC demonstrated efficacy vs. placebo in a number of endpoints in the TEMPO 3:4 and REPRISE trials
- ❑ Hepatic safety has been identified as a concern with JINARC
  - ❑ Participation in the HSMD Programme is mandatory for prescribers and patients

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## ❑ Attributes of patients who can benefit from JINARC:

### ❑ TEMPO 3:4

- Have rapidly-progressing ADPKD (meeting modified Ravine criteria)
- Are at early stage of CKD
- TKV  $\geq 750$  mL
- Estimated creatinine clearance  $\geq 60$  mL/min

### ❑ REPRISE

- Have high risk of progressive eGFR decline based on renal function for age (18 to 65 years of age with baseline eGFR between 25 and 65 mL/min/1.73m<sup>2</sup>)

**What is the full indication for Pr JINARC® in patients with autosomal dominant polycystic kidney disease (ADPKD)?**

- a) To improve kidney function in patients with ADPKD
- b) To slow the progression of kidney function decline in patients with ADPKD
- c) To stop the progression of kidney enlargement in patients with ADPKD
- d) To slow the progression of kidney enlargement and kidney function decline in patients with ADPKD
- e) None of the above

**What is the full indication for Pr JINARC® in patients with autosomal dominant polycystic kidney disease (ADPKD)?**

**d IS CORRECT.**

The exact wording in the product monograph is: “Pr JINARC® is indicated to slow the progression of kidney enlargement and kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD).”

This information is found on slide 3 of the HCP Training Module.

1

**What is the full indication for Pr JINARC® in patients with autosomal dominant polycystic kidney disease (ADPKD)?**

**INCORRECT.**

**The correct answer is **d****

**To slow the progression of kidney enlargement and kidney function decline in patients with ADPKD**

---

The exact wording in the product monograph is: “Pr JINARC® is indicated to slow the progression of kidney enlargement and kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD).”

This information is found on slide 3 of the HCP Training Module.

2

**What was the approximate mean total kidney volume (TKV) at baseline among subjects in the TEMPO 3:4 trial comparing <sup>Pr</sup> JINARC<sup>®</sup> to placebo in ADPKD?**

- a) 750 mL
- b) 1200 mL
- c) 1700 mL
- d) 2100 mL
- e) None of the above

**What was the approximate mean total kidney volume (TKV) at baseline among subjects in the TEMPO 3:4 trial comparing Pr JINARC<sup>®</sup> to placebo in ADPKD?**

**C IS CORRECT.**

The entry criterion to be included in the TEMPO 3:4 study was a TKV of 750 mL or greater. The mean TKV at baseline was 1705 mL in the tolvaptan group and 1668 mL in the placebo group.

This information is found on slide 5 of the HCP Training Module.

**What was the approximate mean total kidney volume (TKV) at baseline among subjects in the TEMPO 3:4 trial comparing <sup>Pr</sup> JINARC<sup>®</sup> to placebo in ADPKD?**

**INCORRECT.**

**The correct answer is **C****

**1700 mL**

---

The entry criterion to be included in the TEMPO 3:4 study was a TKV of 750 mL or greater. The mean TKV at baseline was 1705 mL in the tolvaptan group and 1668 mL in the placebo group.

This information is found on slide 5 of the HCP Training Module.

**What were the percent annual increases in TKV for the <sup>Pr</sup> JINARC<sup>®</sup> and placebo groups in the TEMPO 3:4 trial?**

- a) Placebo: 2.8%; JINARC: 5.5%
- b) Placebo: 0.2%; JINARC: 4.2%
- c) Placebo: 4.2%; JINARC: 0.2%
- d) Placebo: 5.5%; JINARC: 2.8%
- e) None of the above

**What were the percent annual increases in TKV for the Pr JINARC<sup>®</sup> and placebo groups in the TEMPO 3:4 trial?**

**d IS CORRECT.**

This was a statistically significant difference ( $p < 0.0001$ ). This represents a 49.2% reduction in growth rate averaged over 3 years ( $p < 0.0001$ ).

- TKV results were due to a combination of the secretory and anti-proliferative effects of tolvaptan. The secretory effect is largely reversible upon discontinuation; see Product Monograph for more information.

This information is found on slide 7 of the HCP Training Module.

What were the percent annual increases in TKV for the <sup>Pr</sup> JINARC<sup>®</sup> and placebo groups in the TEMPO 3:4 trial?

**INCORRECT.**

The correct answer is **d**

Placebo: 5.5%; JINARC: 2.8%

---

This was a statistically significant difference ( $p < 0.0001$ ). This represents a 49.2% reduction in growth rate averaged over 3 years ( $p < 0.0001$ ).

- TKV results were due to a combination of the secretory and anti-proliferative effects of tolvaptan. The secretory effect is largely reversible upon discontinuation; see Product Monograph for more information.

This information is found on slide 7 of the HCP Training Module.

4

**How many patients in the Pr JINARC® clinical trials experienced an increase in alanine aminotransferase (ALT) 3 times the upper limit of normal, together with a bilirubin increase to twice the upper limit of normal?**

- a) 0
- b) 1
- c) 2
- d) 3

**How many patients in the Pr JINARC® clinical trials experienced an increase in alanine aminotransferase (ALT) 3 times the upper limit of normal, together with a bilirubin increase to twice the upper limit of normal?**

**d IS CORRECT.**

In clinical trials, 3 individuals taking JINARC experienced ALT greater than 3 times the upper limit of normal concomitantly with total bilirubin greater than twice the upper limit of normal. This includes 2 of 957 patients in the TEMPO study and 1 in an open-label study. All 3 of these individuals returned to normal liver function after stopping JINARC within 1 to 4 months.

This information is found on slide 10 of the HCP Training Module.

**How many patients in the Pr JINARC® clinical trials experienced an increase in alanine aminotransferase (ALT) 3 times the upper limit of normal, together with a bilirubin increase to twice the upper limit of normal?**

**INCORRECT.**

**The correct answer is **d****

**3**

---

In clinical trials, three individuals taking JINARC experienced ALT greater than three times the upper limit of normal concomitantly with total bilirubin greater than twice the upper limit of normal. This includes 2 of 957 patients in the TEMPO study and 1 in an open-label study. All 3 of these individuals returned to normal liver function after stopping JINARC within 1 to 4 months.

This information is found on slide 10 of the HCP Training Module.

**How often is blood testing for hepatic transaminases required for the first 18 months following the initiation of Pr JINARC®?**

- a) Every other week
- b) Monthly
- c) Every other month
- d) Every three months
- e) Every six months
- f) Blood testing is not required for JINARC

**How often is blood testing for hepatic transaminases required for the first 18 months following the initiation of Pr JINARC®?**

**b IS CORRECT.**

The warning in the JINARC product monograph states: “JINARC use has led to idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations of total bilirubin. To help mitigate the risk of liver injury, blood testing for hepatic transaminases and for total bilirubin is required prior to initiation of JINARC, then hepatic transaminases continuing monthly for 18 months, every 3 months for the next 12 months, and then every 3-6 months thereafter during treatment with JINARC.”

This information is found on slide 9 of the HCP Training Module.

**How often is blood testing for hepatic transaminases required for the first 18 months following the initiation of Pr JINARC®?**

**INCORRECT.**

**The correct answer is **b****

**Monthly**

---

The warning in the JINARC product monograph states: “JINARC use has led to idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations of total bilirubin. To help mitigate the risk of liver injury, blood testing for hepatic transaminases and total bilirubin is required prior to initiation of JINARC, then hepatic transaminases continuing monthly for 18 months, every 3 months for the next 12 months, and then every 3-6 months thereafter during treatment with JINARC.”

This information is found on slide 9 of the HCP Training Module.

**For which liver test results should Pr JINARC® be permanently discontinued?**

- a) ALT or AST >3 times ULN
- b) ALT or AST >3 times ULN, with persistent symptoms of hepatic injury
- c) ALT or AST >3 times ULN, and total bilirubin > 2x ULN or INR > 1.5
- d) ALT or AST >5 times ULN, for more than 2 weeks
- e) ALT or AST >8 times ULN
- f) b, c, d and e
- g) All of the above

**For which liver test results should Pr JINARC® be permanently discontinued?**

**f IS CORRECT.**


The JINARC product monograph states that permanent discontinuation is recommended for:

- ALT or AST >8x ULN;
- ALT or AST >5x ULN for more than 2 weeks;
- ALT or AST >3x times ULN and total bilirubin >2x ULN or INR >1.5; or
- ALT or AST >3x times ULN, with persistent symptoms of hepatic injury.

This information is found on slide 18 of the HCP Training Module.

**For which liver test results should Pr JINARC® be permanently discontinued?**

**INCORRECT.**

**The correct answer is** 

**b, c, d and e**

The JINARC product monograph states that permanent discontinuation is recommended for:

- ALT or AST > 8x ULN;
- ALT or AST > 5x ULN for more than 2 weeks;
- ALT or AST > 3x times ULN and total bilirubin >2x ULN or INR >1.5; or
- ALT or AST > 3x times ULN, with persistent symptoms of hepatic injury.

This information is found on slide 18 of the HCP Training Module.

**According to the TEMPO 3:4 trial, patients most likely to benefit from Pr JINARC® appear to be those with rapidly progressive ADPKD, or at a stage of incipient rapid progression. Which of the following is/are (a) factor(s) associated with rapid progression of ADPKD?**

- a) Large total renal cyst mass for a given age, as measured by TKV
- b) CKD Stage 2–3
- c) Rapid deterioration of renal function
- d) Presence of systemic hypertension or albuminuria
- e) a and c
- f) a, c and d
- g) All of the above

**According to the TEMPO 3:4 trial, patients most likely to benefit from Pr JINARC® appear to be those with rapidly progressive ADPKD, or at a stage of incipient rapid progression. Which of the following is/are (a) factor(s) associated with rapid progression of ADPKD?**

**g IS CORRECT.**

Based on TEMPO 3:4, patients most likely to benefit from JINARC appear to be those with rapidly progressive ADPKD, or at a stage of incipient rapid progression, but before widespread destruction of renal architecture. The factors associated with rapid progression of ADPKD include: large total renal cyst mass for a given age, as measured by TKV; CKD Stage 2–3; rapid deterioration of renal function; and presence of systemic hypertension or albuminuria.

This information is found on slide 15 of the HCP Training Module.

According to the TEMPO 3:4 trial, patients most likely to benefit from Pr JINARC® appear to be those with rapidly progressive ADPKD, or at a stage of incipient rapid progression. Which of the following is/are (a) factor(s) associated with rapid progression of ADPKD?

**INCORRECT.**

The correct answer is **g**

All of the above

---

Based on TEMPO 3:4, patients most likely to benefit from JINARC appear to be those with rapidly progressive ADPKD, or at a stage of incipient rapid progression, but before widespread destruction of renal architecture. The factors associated with rapid progression of ADPKD include: large total renal cyst mass for a given age, as measured by TKV; CKD Stage 2–3; rapid deterioration of renal function; and presence of systemic hypertension or albuminuria.

This information is found on slide 15 of the HCP Training Module.

**True or false: Completion of the Patient-Prescriber Agreement Form (PPAF) for Pr JINARC® is a mandatory requirement for the prescription of JINARC.**

- a) True
- b) False

**True or false: Completion of the Patient-Prescriber Agreement Form (PPAF) for Pr JINARC® is a mandatory requirement for the prescription of JINARC.**

**a IS CORRECT.**

When the patient and provider decide to undertake treatment with JINARC, a signed, duly-documented, manufacturer- and product-specific, patient-prescriber agreement form (PPAF) is required. The PPAF outlines: relevant patient selection criteria; expected risks and benefits of treatment; need for mandatory hepatic function monitoring; and a statement that the patient understands the benefits and risks of treatment and that they agree to take blood tests as prescribed by the doctor to start and remain on treatment.

This information is found on slide 16 of the HCP Training Module.

**True or false: Completion of the Patient-Prescriber Agreement Form (PPAF) for Pr JINARC® is a mandatory requirement for the prescription of JINARC.**

**INCORRECT.**

**The correct answer is **a****

**True**

---

When the patient and provider decide to undertake treatment with JINARC, a signed, duly-documented, manufacturer- and product-specific, patient-prescriber agreement form (PPAF) is required. The PPAF outlines: relevant patient selection criteria; expected risks and benefits of treatment; need for mandatory hepatic function monitoring; and a statement that the patient understands the benefits and risks of treatment and that they agree to take blood tests as prescribed by the doctor to start and remain on treatment.

This information is found on slide 16 of the HCP Training Module.

9

Pr JINARC<sup>®</sup> is a substrate of which hepatic isoenzyme(s)?

- a) CYP1A
- b) CYP2A
- c) CYP2B
- d) CYP2C
- e) CYP3A
- f) a and e
- g) None of the above

Pr JINARC® is a substrate of which hepatic isoenzyme(s)?

**e** IS CORRECT.

JINARC is a substrate of CYP3A. The recommendations based on this are the following: Concomitant use with strong CYP3A4 inhibitors is contraindicated as it may lead to significant increase in tolvaptan exposure; concomitant use with moderate CYP3A inhibitors also requires lowered dosing of JINARC; JINARC should not be taken with grapefruit juice; concomitant use of JINARC with strong CYP3A inducers should be avoided; and reduction in the dose of JINARC may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors. However, concomitant use with those P-gp inhibitors that also act as strong CYP3A inhibitors is contraindicated.

This information is found on slide 20 of the HCP Training Module.

Pr JINARC<sup>®</sup> is a substrate of which hepatic isoenzyme(s)?

**INCORRECT.**

**The correct answer is** **e**

**CYP3A**

JINARC is a substrate of CYP3A. The recommendations based on this are the following:

Concomitant use with strong CYP3A4 inhibitors is contraindicated as it may lead to significant increase in tolvaptan exposure; concomitant use with moderate CYP3A inhibitors also requires lowered dosing of JINARC; JINARC should not be taken with grapefruit juice; concomitant use of JINARC with strong CYP3A inducers should be avoided; and reduction in the dose of JINARC may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors. However, concomitant use with those P-gp inhibitors that also act as strong CYP3A inhibitors is contraindicated.

This information is found on slide 20 of the HCP Training Module.

10

**What is the recommended starting dose of Pr JINARC®?**

- a) 45 mg once daily
- b) 45 mg upon waking, 15 mg approx. 8 hours later
- c) 60 mg once daily
- d) 60 mg upon waking, 30 mg approx. 8 hours later
- e) 90 mg once daily
- f) 90 mg upon waking, 30 mg approx. 8 hours later
- g) None of the above

What is the recommended starting dose of Pr JINARC®?

**b** IS CORRECT.

The product monograph states that the 45+15 mg regimen is the usual initial dose. Patients should be titrated to the highest tolerated dose, up to 90+30 mg. It is recommended that there be at least weekly intervals between titrations.

This information is found on slide 22 of the HCP Training Module.

10

What is the recommended starting dose of Pr JINARC®?

**INCORRECT.**

The correct answer is **b**

45 mg upon waking, 15 mg approx. 8 hours later

---

The product monograph states that the 45+15 mg regimen is the usual initial dose. Patients should be titrated to the highest tolerated dose, up to 90+30 mg. It is recommended that there be at least weekly intervals between titrations. This information is found on slide 22 of the HCP Training Module.

# Safety Information (1/4)<sup>1</sup>

## Indications and clinical use:

Pr JINARC<sup>®</sup> is indicated to slow the progression of kidney enlargement and kidney function decline in adult patients with autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, kidney enlargement reflects renal cyst burden.

- ❑ In order to select patients who might best benefit from the effects of JINARC, clinical trials evaluated ADPKD patients having a total kidney volume (TKV)  $\geq 750$  mL, and/or renal function corresponding to a CKD-EPI eGFR  $\geq 25$  mL/min/1.73m<sup>2</sup>, at the time of initiation of treatment.
- ❑ JINARC treatment should be initiated and monitored under the supervision of a nephrologist or specialist with expertise in the management of patients with ADPKD and a full understanding of the benefits and risks of tolvaptan therapy including hepatic toxicity and monitoring requirements.
- ❑ Careful consideration and discussion of the appropriateness of JINARC treatment should be undertaken between the prescriber and patient before initiation of therapy, taking into account the potential benefits and risks of treatment. Upon mutual agreement to undertake treatment with JINARC, a signed, duly-documented, manufacturer- and product-specific, patient-prescriber agreement form (PPAF) is required outlining the relevant patient selection criteria to be considered, expected benefits and risks of treatment, and the need for mandatory hepatic function monitoring.
- ❑ **JINARC Controlled Hepatic Safety Monitoring and Distribution Programme:** JINARC is available for treatment of patients with ADPKD only through a manufacturer- and product-specific controlled hepatic safety monitoring and distribution (HSMD) programme conducted and maintained by, or for, the market authorisation holder of JINARC. A duly signed manufacturer and product-specific PPAF is required for enrollment in the HSMD Programme. For more information on the programme, please call 1-844-254-6272.
- ❑ Safety and effectiveness have not been established in geriatrics (>65).

# Safety Information (2/4)<sup>1</sup>

## Contraindications:

Pr JINARC<sup>®</sup> is contraindicated in:

- ❑ Patients who have been asked to permanently discontinue tolvaptan
- ❑ Patients with known or suspected hypersensitivity to tolvaptan, benzazepine or benzazepine derivatives (e.g., mirtazapine) or any of the excipients
- ❑ Patients with hypovolemia
- ❑ Patients with hypernatremia
- ❑ Patients with anuria
- ❑ Patients who do not have access to fluids or who cannot respond to the physiologic sensation of thirst
- ❑ Patients with a history, signs, or symptoms of significant liver impairment or injury, excluding uncomplicated polycystic liver disease
- ❑ Patients using strong CYP3A inhibitors, e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone
- ❑ Pregnancy
- ❑ Nursing women
- ❑ Patients with one of the following rare hereditary diseases: Galactose intolerance, Lapp lactase deficiency, or Glucose-galactose malabsorption

# Safety Information (3/4)<sup>1</sup>

## Most serious warnings and precautions:

**Idiosyncratic hepatic toxicity:** Pr JINARC<sup>®</sup> use has led to idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST), rarely associated with concomitant elevations of total bilirubin. To help mitigate the risk of liver injury, blood testing for hepatic transaminases and for total bilirubin is required prior to initiation of JINARC, then blood testing for hepatic transaminases is required:

- monthly for 18 months
- every 3 months for the next 12 months
- every 3-6 months thereafter during treatment with JINARC

Therefore, JINARC is available for treatment of patients with ADPKD only through a controlled hepatic safety monitoring and distribution programme conducted and maintained by, or for, the market authorization holder of JINARC.

# Safety Information (4/4)<sup>1</sup>

## Other relevant warnings and precautions:

- ❑ Risk of dehydration
- ❑ Interactions with moderate CYP3A inhibitors, CYP3A inducers or P-glycoprotein inhibitors
- ❑ Hepatotoxicity: Acute liver failure
- ❑ Anaphylaxis
- ❑ Hyponatremia: Concomitant use with hypertonic saline solutions or drugs that may increase serum sodium should be avoided
- ❑ Hyperkalemia
- ❑ Hyperuricemia
- ❑ Hypotension: Co-administration with antihypertensive medications may cause increase in hypotension-related adverse events, including dizziness or syncope

- ❑ Serum sodium abnormalities must be corrected prior to Pr JINARC<sup>®</sup> initiation
- ❑ Use of contraception in women of childbearing potential
- ❑ Vasopressin analogues: Co-administration not recommended
- ❑ Caution when driving vehicles or operating machinery

## For more information:

Consult the Product Monograph at [jinarcmonograph.ca](http://jinarcmonograph.ca) for adverse reactions, interactions, dosing, monitoring tests, and conditions of clinical use. The Product Monograph is also available by calling 1-877-341-9245.

1. Pr JINARC<sup>®</sup> Product Monograph. Otsuka Canada Pharmaceutical Inc. October 23, 2019.



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