

# JYNARQUE REMS (RISK EVALUATION AND MITIGATION STRATEGY) PRESCRIBER TRAINING

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**This training includes information about:**

- **Risk of serious and potentially fatal liver injury**
- **Requirements for baseline and regular monitoring and evaluation of your patient**
- **JYNARQUE REMS requirements**

## WHAT IS JYNARQUE?

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- JYNARQUE is a selective vasopressin V<sub>2</sub>-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)
- Please see Prescribing Information, including **BOXED WARNING**, for additional safety information

## **JYNARQUE HAS A BOXED WARNING**

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### **WARNING: RISK OF SERIOUS LIVER INJURY**

**JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported [see Warnings and Precautions (5.1)].**

**Measure ALT, AST and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter [see Warnings and Precautions (5.1)]. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.**

**Because of the risks of serious liver injury, JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program [see Warnings and Precautions (5.2)].**

## RISK ASSOCIATED WITH JYNARQUE: SERIOUS AND POTENTIALLY FATAL LIVER INJURY

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- JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine, or jaundice) can reduce the risk of severe hepatotoxicity
- In a 3-year placebo-controlled trial and its open-label extension (in which patients' liver tests were monitored every 4 months), evidence of serious hepatocellular injury (elevations of hepatic transaminases of at least 3 times ULN combined with elevated bilirubin at least 2 times the ULN) occurred in 0.2% (3/1487) of tolvaptan-treated patients compared to none of the placebo-treated patients
- To reduce the risk of significant or irreversible liver injury, assess ALT, AST, and bilirubin prior to initiation of JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter [see *Boxed Warning*]

## RISK ASSOCIATED WITH JYNARQUE: SERIOUS AND POTENTIALLY FATAL LIVER INJURY (CONT'D)

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- At the onset of signs or symptoms consistent with hepatic injury or if ALT, AST, or bilirubin increase to >2 times ULN, immediately discontinue JYNARQUE, obtain repeat tests as soon as possible (within 48-72 hours), and continue testing as appropriate. If laboratory abnormalities stabilize or resolve, JYNARQUE may be reinitiated with increased frequency of monitoring as long as ALT and AST remain below 3 times ULN
- Do not restart JYNARQUE in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3 times ULN during treatment with tolvaptan, unless there is another explanation for liver injury and the injury has resolved
- In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times upper limit of normal, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) reevaluation of liver test trends prior to reinitiating therapy with more frequent monitoring

## ADDITIONAL RISKS AND SAFETY INFORMATION

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- The information presented in this training program does not include a complete list of all safety information for JYNARQUE
- To review complete safety information on JYNARQUE, please refer to the Full Prescribing Information, including BOXED WARNING, for JYNARQUE at [www.JYNARQUErems.com](http://www.JYNARQUErems.com)

## WHAT IS THE JYNARQUE REMS?

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This Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage the risk of serious and potentially fatal liver injury associated with use of JYNARQUE and is required by the Food and Drug Administration (FDA) to ensure the benefits of JYNARQUE outweighs its risks.

JYNARQUE can cause serious and potentially fatal liver injury.

- To mitigate the risk of liver injury, monitoring for symptoms and signs is required
- Blood testing for hepatic transaminases and bilirubin is required prior to initiation of JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter
- Prompt recognition and response can help mitigate more serious injury

JYNARQUE is available only through the JYNARQUE REMS, a restricted distribution program.

## WHAT IS THE GOAL OF THE JYNARQUE REMS?

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The goal of JYNARQUE REMS is to mitigate the risk of serious and potentially fatal liver injury by:

1. Ensuring that healthcare providers are educated on the following:
  - The risk of serious and potentially fatal liver injury associated with the use of JYNARQUE
  - The requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information
  - The need to counsel patients about the risk of serious and potentially fatal liver injury and the need for monitoring at baseline and periodic monitoring as described in the Prescribing Information
2. Ensuring that healthcare providers adhere to:
  - The requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

## WHAT IS THE GOAL OF THE JYNARQUE REMS? (CONT'D)

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3. Ensuring that patients are informed about:
  - The risk of serious and potentially fatal liver injury associated with the use of JYNARQUE
  - The requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information
4. Enrollment of all patients in a registry to further support long-term safety and safe use of JYNARQUE

## HOW DOES THE JYNARQUE REMS WORK?

	Before Prescribing/ Dispensing JYNARQUE	Before Starting JYNARQUE for Each Patient	While on JYNARQUE Treatment for Each Patient
<b>Prescriber</b>	Prescriber certification	<ul style="list-style-type: none"> <li>• <b>Counsel</b> the patient on the risk of serious and potentially fatal liver injury and the requirement for <b>liver function monitoring at baseline</b> and specific intervals during treatment</li> <li>• <b>Assess</b> the patient's liver function and appropriateness of initiating treatment</li> <li>• <b>Enroll</b> the patient</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Assess</b> the patient's liver function and appropriateness of continuing treatment at 2 weeks, 4 weeks, and monthly for the first 18 months of treatment and every 3 months thereafter</li> <li>• <b>Document</b> appropriateness of continuing treatment and submit to the REMS using the <b>Patient Status Form</b> every 3 months for the first 18 months of treatment and every 6 months thereafter</li> </ul>
<b>Pharmacy (Outpatient &amp; Inpatient)</b>	Pharmacy certification		<ul style="list-style-type: none"> <li>• <b>Outpatient: Obtain authorization</b> to dispense each prescription by contacting the REMS online or by phone to verify prescriber is certified and patient is enrolled. <ul style="list-style-type: none"> <li>— Dispense no more than a 30-day supply.</li> </ul> </li> <li>• <b>Inpatient: Verify</b> the prescriber is certified and the patient is enrolled in the REMS Program. <ul style="list-style-type: none"> <li>— Dispense no more than a 15-day supply at discharge.</li> </ul> </li> </ul>
<b>Patient</b>		<ul style="list-style-type: none"> <li>• Review <b>Patient Guide</b>.</li> <li>• Patient Enrollment</li> <li>• <b>Get</b> a blood test before your first dose.</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Get</b> a blood test at 2 weeks and 4 weeks after you start treatment.</li> <li>• <b>Get</b> a blood test every month for the first 18 months of treatment and then every 3 months thereafter.</li> </ul>

## WHAT ARE THE REQUIREMENTS OF THE JYNARQUE REMS?

In order to receive JYNARQUE, prescribers, pharmacies, and patients must comply with the requirements of the REMS.

Prescriber	Pharmacy (Outpatient & Inpatient)	Patient
<p><b>To prescribe JYNARQUE:</b></p> <ol style="list-style-type: none"> <li><b>1. Become certified</b> by completing a one-time certification process</li> <li>As you start patients on JYNARQUE, <b>counsel and evaluate baseline liver testing</b> prior to enrolling them into the REMS, and complete the prescription.</li> <li><b>Perform ongoing patient monitoring</b>, evaluate liver testing at 2 weeks, 4 weeks and monthly for the first 18 months of treatment and every 3 months thereafter.</li> <li><b>Complete a Patient Status Form</b> for each patient every 3 months for the first 18 months of treatment and every 6 months thereafter</li> </ol>	<p><b>To dispense JYNARQUE*:</b></p> <ol style="list-style-type: none"> <li><b>Designate an authorized representative, become certified, and recertify</b> if there is a change in the authorized representative.</li> <li><b>Train</b> staff and <b>comply</b> with REMS requirements.</li> <li><b>Outpatient: Obtain authorization</b> to dispense each prescription by contacting the REMS online or by phone to verify prescriber is certified, and the patient is enrolled and authorized to receive the drug. <ul style="list-style-type: none"> <li>— Dispense no more than a 30-day supply.</li> </ul> </li> <li><b>Inpatient: Verify</b> the prescriber is certified and the patient is enrolled in the REMS Program. <ul style="list-style-type: none"> <li>— Dispense no more than a 15-day supply at discharge.</li> </ul> </li> </ol>	<p><b>To receive JYNARQUE:</b></p> <ol style="list-style-type: none"> <li><b>Understand the risk</b> associated with JYNARQUE.</li> <li><b>Enroll</b> in the REMS by completing the <b>Patient Enrollment Form</b> with your healthcare provider.</li> <li><b>Complete</b> baseline liver testing before your first dose, 2 weeks and 4 weeks after your first dose and monthly for the first 18 months of treatment and every 3 months thereafter.</li> </ol>

\*JYNARQUE is not available to all pharmacies if you have any questions about the REMS or how to obtain JYNARQUE call 1-866-244-9446. Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center

## PRESCRIBER REQUIREMENTS

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1. Become Certified
2. Enroll Your Patients
3. Monitor Your Patients

## HOW DOES A PRESCRIBER BECOME CERTIFIED?

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### Before prescribing JYNARQUE:

- 1. Review** the following educational materials on JYNARQUE to understand the risk of severe and potentially fatal liver injury:
  - **Prescribing Information**
  - **REMS Program Overview**
  - **Prescriber Training**
- 2. Successfully complete** the *Prescriber Knowledge Assessment* and **submit** it to the REMS
  - **Prescriber Knowledge Assessment**
- 3. Enroll in the REMS** by completing the *Prescriber Enrollment Form* and submitting it to the REMS
  - **Prescriber Enrollment Form**
- 4. Upon completion of these steps, the REMS will notify you upon successful certification**

## HOW DOES A PRESCRIBER ENROLL PATIENTS?

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### Before starting each patient on JYNARQUE:

- 1. Counsel** your patients on the risk of serious and potentially fatal liver injury and the requirement for liver function monitoring at baseline, 2 weeks, 4 weeks, and monthly for the first 18 months of treatment and every 3 months thereafter and share the resources below:
  - **Patient Guide**
  - **Provide a copy to your patient**
- 2. Order** and evaluate the baseline liver testing before each patient's first dose of JYNARQUE
- 3. Submit** a completed ***Patient Enrollment Form*** to the REMS and submit the prescription to the pharmacy
  - Provide a completed copy of the ***Patient Enrollment Form*** to the patient

## HOW DOES A PRESCRIBER MONITOR PATIENTS?

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### Once your patient is on JYNARQUE:

#### 1. **Monitor** your JYNARQUE patients on an ongoing basis

- Assess the patient's liver function and appropriateness of initiating and continuing treatment

#### 2. **Submit** a completed **Patient Status Form** to the REMS for each patient:

- Every 3 months for the first 18 months of treatment
- Every 6 months thereafter

#### 3. **Report** any Adverse Events suggestive of serious and potentially fatal liver injury to the REMS by doing any one of the following:

- Contact the JYNARQUE REMS Program at 1-866-244-9446
- Submit a completed **Liver Adverse Events Reporting Form** (via fax or online at [www.JYNARQUEREMS.com](http://www.JYNARQUEREMS.com))
- Submit a completed **Patient Status Form** (via fax or online at [www.JYNARQUEREMS.com](http://www.JYNARQUEREMS.com))

#### 4. Inform the REMS if a patient is no longer under your care or has discontinued JYNARQUE

## JYNARQUE REMS PATIENT STATUS FORM

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- A certified prescriber or delegate may complete and submit the **Patient Status Form** to the REMS on behalf of the certified prescriber of record
- The certified prescriber of record is responsible for compliance with the REMS requirements, including monitoring, evaluation and management of each patient under his/her care
- Prescribers will be contacted to obtain missing information, based on responses provided or if the form is not received
- Please note that if the prescriber does not submit the form, it may result in a delay of the patient receiving JYNARQUE
- The completion of the laboratory tests and the submission of the **Patient Status Form** are done at different intervals

## PRESCRIBER DELEGATE

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- A prescriber delegate may complete and submit the ***Patient Status Form*** to the REMS on behalf of the certified prescriber of record online or by fax
- A prescriber delegate is not required to enroll in the REMS
- The certified prescriber of record is responsible for compliance with the REMS requirements, including monitoring, evaluation and management of each patient under his/her care

## DEFINITION OF SERIOUS AND POTENTIALLY FATAL LIVER INJURY

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Liver injury events meeting any of the following criteria should be considered and reported as serious and potentially fatal liver injury.

- Development of any liver injury events leading to liver transplantation or resulting in a fatal outcome or considered to be life-threatening, or
- Development of any liver injury events meeting any of the laboratory criteria presented below:
  - ALT (Alanine aminotransferase) or AST (Aspartate aminotransferase)  $>8 \times$  ULN (Upper limit of normal), or
  - ALT or AST  $>5 \times$  ULN for more than 2 weeks, or
  - ALT or AST  $>3 \times$  ULN and (TBL [Total Bilirubin]  $> 2 \times$  ULN or International Normalized Ratio [INR]  $>1.5$ ) (TBL measurement can be within 30 days of the ALT elevation), or
  - ALT or AST  $>3 \times$  ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $>5\%$ )

## HOW TO REPORT AN EVENT SUGGESTIVE OF SERIOUS AND POTENTIALLY FATAL LIVER INJURY

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For the purposes of this REMS and event reporting, the liver injury may meet any of the following seriousness criteria:

- **Death:** Report if you suspect that the death was an outcome of the liver event, and include the date if known
- **Life-threatening:** Report if suspected that the patient was at substantial risk of dying at the time of the liver event, or use or continued use of product might have resulted in the death of the patient.
- **Hospitalization (initial or prolonged):** Report if admission to the hospital or prolongation of hospitalization was a result of the liver event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- **Important Medical Event:** Report when the liver event does not fit the other outcomes, but the liver event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

## HOW TO REPORT AN EVENT SUGGESTIVE OF SERIOUS AND POTENTIALLY FATAL LIVER INJURY (CONT'D)

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### Reporting Procedures:

If a patient experiences an event suggestive of serious and potentially fatal liver injury, it must be reported to the REMS by any of the following actions:

- 1) Submit a completed **Liver Adverse Event Reporting Form** online or by fax
- 2) Submit a completed **Patient Status Form** online or by fax
- 3) Contact the REMS Coordinating Center by phone

Report treatment discontinuation or transfer of care to the REMS

If an event is submitted via the **Patient Status Form**, it is not necessary to also submit a **Liver Adverse Event Reporting Form** or contact the REMS Program Coordinating Center by phone to report the same event. The **Patient Status Form** must still be submitted regularly – even if liver adverse events were already reported on the **Liver Adverse Event Reporting Form**

The **Liver Adverse Event Reporting Form** and **Patient Status Form** are available at [www.JYNARQUEREMS.com](http://www.JYNARQUEREMS.com)

**If an event of serious and potentially fatal liver injury is reported, you will be contacted for further information regarding the report. Pertinent laboratory test results will be requested.**

**To report any other type of adverse event, please contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927, visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088.**

## PATIENT REGISTRY

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- The JYNARQUE REMS includes enrollment of all patients in a registry. This is a reporting and collection system to provide information on the incidence of serious and potentially fatal liver injury
- The JYNARQUE REMS registry will:
  - Provide information on the incidence of serious and potentially fatal liver injury
  - Collect clinical information about patients identified as experiencing serious and potentially fatal liver injury
- Require Otsuka Pharmaceutical Company, Ltd. to follow up with a healthcare provider to obtain all required data

## NEXT STEPS

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Now that you have reviewed the requirements of the REMS in order to become certified you must complete the **Prescriber Knowledge Assessment**.

The next 8 slides will be questions about what you just reviewed. You are expected to achieve 100% on the Knowledge Assessment.

You will have 3 tries to successfully complete the **Prescriber Knowledge Assessment**.

If you do not successfully complete the **Prescriber Knowledge Assessment**, you will need to re-review the **Prescriber Training**.

## PRESCRIBERS WHO SUCCESSFULLY COMPLETE THE KNOWLEDGE ASSESSMENT WILL RECEIVE:

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You have successfully completed the ***Prescriber Knowledge Assessment***.

You must complete the ***Prescriber Enrollment Form*** and submit to the REMS before prescribing JYNARQUE.

You will receive a notification from the REMS confirming your certification. Upon receipt of this notification, you may prescribe JYNARQUE.

**PRESCRIBERS WHO DID NOT ACHIEVE 100% WILL  
BE PRESENTED THE BELOW MESSAGE:**

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You did not achieve 100%; you must re-take the ***Prescriber Knowledge Assessment***.

You must successfully complete the ***Prescriber Knowledge Assessment*** within 3 attempts or you must re-review the ***Prescriber Training***.

## PRESCRIBERS WHO DID NOT ACHIEVE 100% AFTER 3 ATTEMPTS WILL BE PRESENTED THE BELOW MESSAGE:

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You did not achieve 100% on the **Prescriber Knowledge Assessment** within the last 3 attempts.

You must re-review the **Prescriber Training** before attempting the **Prescriber Knowledge Assessment** again.



Otsuka America Pharmaceutical, Inc.

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[Month Year of Approval]

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**JYNARQUE**<sup>®</sup>  
(tolvaptan) tablets