Risk Evaluation and Mitigation Strategy (REMS) Document
JYNARQUE (tolvaptan) REMS Program

I. Administrative Information

Application Number: NDA 204441
Application Holder: Otsuka Pharmaceutical Company, Ltd.
Initial REMS Approval: 04/2018
Most Recent REMS Update: 12/2019

II. REMS Goal

The goal of the 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:
   a. the risk of serious and potentially fatal liver injury associated with the use of JYNARQUE

   b. the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

   c. 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:
   a. the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

3. Ensuring that patients are informed about:
   a. the risk of serious and potentially fatal liver injury associated with the use of JYNARQUE
   b. 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

III. REMS Requirements

Otsuka Pharmaceutical Company, Ltd. must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare Providers who prescribe JYNARQUE must:

To become certified to prescribe	1. Review the drug's Prescribing Information. 2. Review the following: Program Overview and Prescriber Training. 3. Successfully complete the Knowledge Assessment and submit it to the REMS Program. 4. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.

Before treatment initiation (first dose)	5. Counsel the patient on the risk of serious and potentially fatal liver injury and the requirement for liver function monitoring at baseline and at specific intervals during treatment using the Patient Guide. Provide a copy of the material to the patient. 6. Assess the patient's liver function and appropriateness of initiating treatment. Document and submit to the REMS Program using the Patient Enrollment Form. Provide a completed copy of the form to the patient. 7. Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS Program.
During treatment; 2 weeks and 4 weeks after treatment initiation, then monthly for the first 18 months and every 3 months thereafter	8. Assess the patient's liver function and appropriateness of continuing treatment.
During treatment; every 3 months for the first 18 months and every 6 months thereafter	9. Assess the patient's liver function and appropriateness of continuing treatment. Document appropriateness of continuing treatment and submit to the REMS Program using the Patient Status Form.
At all times	10. Report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS Program by phone, using the Liver Adverse Events Reporting Form, or using the Patient Status Form. 11. Report treatment discontinuation or transfer of care to the REMS Program.

2. Patients who are prescribed JYNARQUE:

Before treatment initiation	1. Review the Patient Guide. 2. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. 3. Get a blood test to check your liver. 4. Receive counseling from the prescriber on the risk of serious and potentially fatal liver injury and requirements to get blood tests using the Patient Guide.

During treatment; 2 weeks and 4 weeks after treatment initiation, then monthly for the first 18 months and every 3 months thereafter	5. Get a blood test to check your liver.
At all times	6. Inform the prescriber of signs and symptoms of serious liver injury.

3. Outpatient Pharmacies that dispense JYNARQUE must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy. 2. Have the authorized representative review the Program Overview. 3. Have the authorized representative enroll in the REMS Program by completing the Outpatient Pharmacy Enrollment Form and submitting it to the REMS Program. 4. Train all relevant staff involved in dispensing JYNARQUE using the Program Overview. 5. Establish processes and procedures to dispense no more than a 30 days supply.
Before dispensing	6. Obtain authorization to dispense each prescription by contacting the REMS Program to verify the prescriber is certified, and the patient is enrolled and authorized to receive the drug. 7. Dispense no more than 30 days supply.
To maintain certification to dispense	8. Have a new authorized representative enroll in the REMS Program by completing the Outpatient Pharmacy Enrollment Form and submitting it to the REMS Program if the authorized representative changes.

At all times	9. Report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS Program by phone or using the Liver Adverse Events Reporting Form. 10. Not distribute, transfer, loan, or sell JYNARQUE. 11. Maintain records documenting staff's completion of REMS training. 12. Maintain records that all processes and procedures are in place and are being followed. 13. Comply with audits carried out by Otsuka Pharmaceuticals or third party acting on behalf of the applicant to ensure that all processes and procedures are in place and are being followed.

4. Inpatient Pharmacies that dispense JYNARQUE must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy. 2. Have the authorized representative review the Program Overview. 3. Have the authorized representative enroll in the REMS Program by completing the Inpatient Pharmacy Enrollment Form and submitting it to the REMS Program. 4. Train all relevant staff involved in dispensing JYNARQUE using the Program Overview. 5. Establish processes and procedures to verify the prescriber is certified, and the patient is enrolled in the REMS Program. 6. Establish processes and procedures to dispense no more than a 15 days supply of JYNARQUE upon discharge of the patient.
Before dispensing	7. Verify the prescriber is certified and the patient is enrolled in the REMS Program.
At/upon discharge	8. Dispense no more than a 15 days supply.
To maintain certification to dispense	9. Have a new authorized representative enroll in the REMS Program by completing the Inpatient Pharmacy Enrollment Form and submitting it to the REMS Program if the authorized representative changes.

At all times	10. Report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS Program by phone or using the Liver Adverse Events Reporting Form. 11. Not distribute, transfer, loan, or sell JYNARQUE. 12. Maintain records documenting staff's completion of REMS training. 13. Maintain records that all processes and procedures are in place and are being followed. 14. Comply with audits carried out by Otsuka Pharmaceutical Company, Ltd or third party acting on behalf of the applicant to ensure that all processes and procedures are in place and are being followed.

5. Wholesalers that distribute JYNARQUE must:

To be able to distribute	1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies. 2. Train all relevant staff involved in distributing on the REMS requirements.
At all times	3. Distribute only to certified pharmacies. 4. Maintain and submit records of drug distribution to the REMS Program. 5. Comply with audits carried out by Otsuka Pharmaceutical Company, Ltd or third party acting on behalf of the applicant to ensure that all processes and procedures are in place and are being followed.

Otsuka Pharmaceutical Company, Ltd must provide training to healthcare providers who prescribe JYNARQUE.

The training includes the following educational materials: Program Overview, Prescriber Training and Prescriber Knowledge Assessment. The training must be available online and a hard copy format via mail or fax.

Otsuka Pharmaceutical Company, Ltd must provide training to pharmacies that dispense JYNARQUE.

The training includes the following educational material: Program Overview. The training must be available online and a hard copy format via mail or fax.

To inform healthcare providers about the REMS Program and the risks and safe use of JYNARQUE, Otsuka Pharmaceutical Company, Ltd must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials-& Dissemination Plans
Healthcare providers who are likely to prescribe JYNARQUE	REMS Letter: Letter for Healthcare Providers 1. Email within 60 calendar days of the date JYNARQUE is first commercially distributed and again 12 months later. a. Send by mail within 30 calendar days of the date the first email was sent if a healthcare provider's email address is not available or the email is undeliverable. b. Send a second email within 30 calendar days of the date the first email was sent if the first email is marked as unopened. 2. Make available via a link from the JYNARQUE REMS Program Website. 3. Disseminate through field-based sales and medical representatives. 4. Disseminate through professional societies and request the letter or content be provided to their members. 5. Disseminate at Professional Meetings for 12 months from the date JYNARQUE is first commercially distributed.

To support REMS Program operations, Otsuka Pharmaceutical Company, Ltd must:

1. Authorize dispensing for each patient based on receipt of the Patient Status Form on the following schedule. For the first 18 months: within 115 calendar days of the date of the first patient shipment, then within every 115 calendar days of the receipt of the last Patient Status Form. After the first 18 months of treatment: within every 205 calendar days of receipt of the last Patient Status Form. If a completed Patient Status Form is not received to authorize the continuation of treatment, the patient is not authorized to receive the drug until a completed form is received.
2. Establish and maintain a REMS Program website, www.JYNARQUErems.com. The REMS Program website must include the capability to complete prescriber and pharmacy certification or enrollment online, the capability to enroll and manage patients online including patient authorization status, and the option to print the PI and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).
3. Make the REMS Program website fully operational and all REMS materials available through website or call center by the date JYNARQUE is first commercially distributed.
4. Establish and maintain a REMS Program call center for REMS participants at [1-866-244-9446].
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the JYNARQUE REMS Program.
6. Ensure prescribers are certified in accordance with the requirements described above.
7. Ensure prescribers and pharmacies are able to complete the certification process online or by fax.
8. Ensure outpatient pharmacies are able to obtain authorization to dispense by phone and online.
9. Ensure prescribers are able to report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS Program [phone], using the Liver Adverse Events Reporting Form [online and fax] or using the Patient Status Form [online and fax].
10. Ensure pharmacies are able to report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS Program [phone] or using the Liver Adverse Events Reporting Form [online and fax].
11. Provide Program Overview and the Prescribing Information to REMS participants who (1) attempt to prescribe and are not yet certified or (2) inquire about how to become certified.
12. Notify prescribers and pharmacies within 2 business days after they become certified in the REMS Program.

13. Provide certified prescribers access to the database of certified pharmacies and enrolled patients.
14. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.
15. Establish and maintain a registry which includes a reporting and collection system for all patients to provide information on the incidence of serious and potentially fatal liver injury.
16. Ensure that once a report suggestive of serious liver injury is received, Otsuka Pharmaceutical Company, Ltd follows up with the healthcare provider to obtain all required data for the registry.

To ensure REMS participants' compliance with the REMS Program, Otsuka Pharmaceutical Company, Ltd must:

17. Ensure the Patient Status Form is received for each patient on the following schedule. For the first 18 months: if the form is not received within 95 calendar days of the date of receipt of the first patient shipment or the date the last Patient Status Form was received, Otsuka Pharmaceutical Company, Ltd must contact the prescriber to obtain the form. If the form is not received within 115 calendar days, the patient is not authorized to receive the drug until the form is received. After the first 18 months of treatment: if the form is not received for each patient within 185 calendar days, Otsuka Pharmaceutical Company, Ltd must contact the prescriber to obtain the form. If the form is not received within 205 calendar days, the patient is not authorized to receive the drug until the form is received.
18. Verify annually that the designated authorized representative for the pharmacy is the same. If different, the pharmacy must re-certify with a new authorized representative.
19. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: drug distribution and dispensing; certification of prescribers and pharmacies; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.
20. Establish a plan for addressing noncompliance with REMS Program requirements.
21. Monitor prescribers and pharmacies on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
22. Audit pharmacies no later than 180 days after they become certified, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
23. Take reasonable steps to improve implementation of and compliance with the requirements in the JYNARQUE REMS Program based on monitoring and evaluation of the JYNARQUE REMS Program.

IV. REMS Assessment Timetable

Otsuka Pharmaceuticals must submit REMS Assessments at 6 months and annually thereafter from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Otsuka Pharmaceuticals must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the JYNARQUE REMS**:**

Enrollment Forms

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient Enrollment Form

Pharmacy:

3. Outpatient Pharmacy Enrollment Form
4. Inpatient Pharmacy Enrollment Form

Training and Educational Materials

Prescriber:

5. Program Overview
6. Prescriber Training
7. Prescriber Knowledge Assessment

Patient:

8. Patient Guide

Pharmacy:

9. Program Overview

Patient Care Form

10. Patient Status Form
11. Liver Adverse Events Reporting Form

Communication Materials

12. Letter for Healthcare Providers

Other Materials

13. Program website

JYNARQUE® (tolvaptan) REMS PRESCRIBER ENROLLMENT FORM

JYNARQUE is available only through the JYNARQUE REMS, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program can prescribe, dispense, and receive JYNARQUE. Fields marked * are required.

Instructions:

1) **Review** the ***JYNARQUE Prescribing Information***, the ***REMS Program Overview***, and the ***Prescriber Training***.
2) **Complete** and **submit** the ***Prescriber Knowledge Assessment*** and this ***Prescriber Enrollment Form*** online at **www.JYNARQUErems.com**, or fax them to the REMS at **1-866-750-6820**.
3) **Complete** all mandatory fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the REMS will notify you upon successful certification.

**Indicates required field*

Prescriber Information

First Name*: _____ Middle Initial: _____ Last Name*: _____

National Provider Identifier No. (NPI)*: _____ State License No.: _____

Preferred Method of Contact: ☐ Phone ☐ Email ☐ Fax Preferred Time of Contact: ☐ AM ☐ PM

Credentials*: ☐ MD ☐ DO ☐ NP ☐ PA ☐ Other Specialty*: ☐ Nephrology ☐ Other: _____

Practice/Facility Name: _____

Address Line 1*: _____

Address Line 2: _____

City*: _____ State*: _____ Zip code*: _____

Phone*: _____ Fax*: _____ Email*: _____

Office Liaison First Name: _____ Office Liaison Last Name: _____

Office Liaison Email: _____

Prescriber Agreement

By signing this form, I agree JYNARQUE is only available through the REMS and I must comply with the following REMS requirements:

I have:

1. Reviewed the ***Prescribing Information***.
2. Reviewed the ***REMS Program Overview***.
3. Completed the ***Prescriber Training***.
4. Successfully completed the ***Prescriber Knowledge Assessment*** and submitted it to the REMS.

Before treatment initiation with the first dose I must:

1. Counsel the patient on the risk of serious and potentially fatal liver injury and the requirement for liver function monitoring at baseline, 2 weeks and 4 weeks after treatment initiation, then monthly for the first 18 months and then every 3 months thereafter using the ***Patient Guide***.
2. Provide a copy of the ***Patient Guide*** to the patient.
3. Assess the patient's liver function and appropriateness of initiating treatment.
4. Document appropriateness of initiating treatment using the ***Patient Enrollment Form***.
5. Enroll the patient by completing and submitting the ***Patient Enrollment Form*** to the REMS. Provide a copy of the form to the patient.

During treatment; at 2 weeks and 4 weeks after treatment initiation, then monthly for the first 18 months and every 3 months thereafter I must assess the patient's liver function and appropriateness of continuing treatment.

During treatment; every 3 months for the first 18 months and every 6 months thereafter I must:

1. Assess the patient's liver function and appropriateness of continuing treatment.
2. Document appropriateness of continuing treatment and submit to the REMS using the ***Patient Status Form***.

At all times, I must:

1. Report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS by phone, using the ***Liver Adverse Events Reporting Form***, or using the ***Patient Status Form***.
2. Report treatment discontinuation or transfer of care to the REMS.

I understand and acknowledge that:

1. I will only be able to prescribe JYNARQUE if certified in the REMS.
2. I will not share my credentials for the REMS website or allow others to sign into the website using my credentials.
3. I will allow Otsuka Pharmaceutical Company, Ltd and its agents to contact me via phone, mail, fax, or email to support administration of the REMS.
4. I will be contacted for further information regarding any reports of serious and potentially fatal liver injury and will be requested to provide pertinent laboratory test results.

Prescriber Signature*: _____ Date*: _____

Phone: 1-866-244-9446 | **www.JYNARQUErems.com** | **Fax: 1-866-750-6820**

Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

JYNARQUE®
(tolvaptan) tablets

Reference ID: 4528293

Otsuka

Otsuka America Pharmaceutical, Inc.

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan.
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA.
JYNARQUE is a registered trademark of Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan.

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JYNARQUE®
(tolvaptan) tablets

Fax#: 1-866-750-6820

JYNARQUE® (tolvaptan) REMS PATIENT ENROLLMENT FORM

JYNARQUE is available only through the JYNARQUE REMS, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program can prescribe, dispense, and receive JYNARQUE. Your certified healthcare provider will help you complete this form and provide you with a copy. Fields marked * are required.

Prescribers and Patients: Please complete this form online at www.JYNARQUErems.com or once completed, fax it to the REMS at 1-866-750-6820.

**Indicates required field*

Patient Information

First Name*: _____ Middle Initial: _____ Last Name*: _____

Birthdate*: _____ Sex*: ☐ Male ☐ Female

Race*: ☐ White ☐ Black or African American ☐ American Indian or Alaska Native
☐ Asian ☐ Native Hawaiian or Other Pacific Islander ☐ Other, Specify _____

Ethnicity*: ☐ Hispanic or Latino ☐ Not Hispanic or Latino

Address Line 1*: _____

Address Line 2: _____

City*: _____ State*: _____ Zip code*: _____

Phone*: _____ Mobile Phone*: _____ Email*: _____

Medical History

The information in this section is only collected to help determine if there are reasons why some people have elevations in their liver function tests and others do not.

Alcohol Classification*: ☐ Never Drank ☐ Ex-Drinker (stopped drinking at least 1 month ago) ☐ Current Drinker

Typical Alcohol Consumption (required for Current Drinker):

- ☐ Occasional (drink alcohol less than once each week)
- ☐ Light (1-2 beers, 1-2 glasses of wine, or 1-2 liquor drinks each week)
- ☐ Moderate (3-7 beers, 3-7 glasses of wine, or 3-7 liquor drinks each week)
- ☐ Heavy (more than 7 beers, more than 7 glasses of wine, or more than 7 liquor drinks each week)

Previously Treated with Tolvaptan Prior to REMS Enrollment*: ☐ Yes ☐ No

If yes, how long did you take tolvaptan? _____ years _____ months _____ days

Was this part of a clinical trial? ☐ Yes ☐ No

If yes, please provide clinical trial number/patient ID: _____

Prescriber Information

First Name*: _____ Last Name*: _____

NPI No.*: _____

Practice/Facility Name (where you see this patient): _____

Address Line 1: _____

City: _____ State: _____ Zip code: _____

Phone*: _____ Fax: _____ Email: _____

Prescriber Agreement

*Has the patient's liver function been assessed by evaluating ALT, AST, and bilirubin prior to enrolling this patient in the REMS?
☐ Yes ☐ No

If the answer is No, you must assess the patient's liver function by evaluating ALT, AST, and bilirubin prior to submitting this form to the REMS.

I have reviewed and discussed the risks of JYNARQUE and the requirements of the JYNARQUE REMS with this patient.

Prescriber Signature*: _____ Date*: _____

Healthcare Provider: Provide a copy of this form to the patient.

Phone: 1-866-244-9446 | www.JYNARQUErems.com | Fax: 1-866-750-6820

Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

JYNARQUE®
(tolvaptan) tablets

Reference ID: 4528293

JYNARQUE® (tolvaptan) REMS PATIENT ENROLLMENT FORM

Patient Agreement

Before my treatment begins, I will:

- Review the ***Patient Guide***.
- Enroll in the REMS by completing the ***Patient Enrollment Form*** with my healthcare provider. Enrollment information will be provided to the REMS.
- Get a blood test to check my liver.
- Receive counseling from my healthcare provider on the risk of serious liver problems and possibly death and requirements to get blood tests by using the ***Patient Guide***.

During treatment, I will get a blood test to check my liver:

- 2 weeks after my treatment begins,
- 4 weeks after treatment begins, and then
- every month after that for the first 18 months, and then
- every 3 months

I will contact my healthcare provider if I have any side effects, reactions, or symptoms after receiving JYNARQUE.

I understand and acknowledge that:

1. I have received, read, and understand the ***Patient Guide*** that my healthcare provider has given me.
2. JYNARQUE can cause serious side effects. It can cause serious liver problems and possibly death. This complication can be identified through monthly testing and awareness of side effects, reactions, or symptoms. My healthcare provider has reviewed with me the risks of treatment with JYNARQUE.
3. In order to receive JYNARQUE, I am required to be enrolled in the REMS, and my information will be stored in a database of all patients who receive JYNARQUE in the United States.
4. I should tell the REMS right away if I change my JYNARQUE healthcare provider, if my contact information changes, or if I discontinue JYNARQUE.
5. Otsuka Pharmaceutical Company, Ltd and its agents may contact me via phone, mail, fax, or email to support administration of the REMS.
6. Otsuka Pharmaceutical Company, Ltd and its agents may use and share my personal health information, including lab results and prescription data collected as part of the REMS for the purpose of the operations, analysis, and reporting of the REMS including enrolling me into, administering, and evaluating the REMS, coordinating the dispensing of JYNARQUE, and releasing my personal health information to the Food and Drug Administration (FDA), as necessary.

Patient or Legal Guardian Signature*: _____

Date*: _____

Printed Patient/Legal Guardian Name: _____

Healthcare Provider: Provide a copy of this form to the patient.

Phone: 1-866-244-9446 | www.JYNARQUErems.com | Fax: 1-866-750-6820

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JYNARQUE®
(tolvaptan) tablets

Reference ID: 4528293

JYNARQUE® (tolvaptan) REMS OUTPATIENT PHARMACY ENROLLMENT FORM

Instructions

JYNARQUE is available only through the JYNARQUE REMS, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program can prescribe, dispense, and receive JYNARQUE. Fields marked * are required.

Dispensing of JYNARQUE is limited to a small number of contracted outpatient pharmacies. These outpatient pharmacies must enroll in the REMS in order to dispense JYNARQUE. If you have any questions about the REMS, please call **1-866-244-9446**.

You must designate an authorized representative to complete and submit this form on behalf of this outpatient pharmacy.

Instructions for Authorized Representative:

1) **Review** the ***Prescribing Information*** and the ***REMS Program Overview***.
2) **Complete** and **submit** this ***Outpatient Pharmacy Enrollment Form*** and fax it to the JYNARQUE REMS at **1-866-750-6820**.

Complete all mandatory fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the REMS will notify the pharmacy upon successful certification.

**Indicates required field*

Outpatient Pharmacy Information:

Pharmacy Name*: _____

Pharmacy Address 1*: _____

City*: _____ State*: _____ Zip code*: _____

Pharmacy Address 2: _____

Pharmacy National Provider Information No. (NPI)*: _____

Authorized Representative Responsibilities

I am the Authorized Representative designated by my pharmacy to carry out the certification process and oversee implementation of and compliance with the REMS. By signing this form, I agree to comply with the requirements of REMS and as the Authorized Representative, understand that my Pharmacy must also comply with the REMS requirements:

1. Review the ***Prescribing Information*** and ***REMS Program Overview***.
2. Enroll in the REMS by completing the ***Outpatient Pharmacy Enrollment Form*** and submitting it to the REMS.
3. Train all relevant staff involved in dispensing JYNARQUE using the ***REMS Program Overview*** and maintain a record of training.
4. Establish processes and procedures to dispense no more than a 30 days' supply.
5. Inform the JYNARQUE REMS if the Authorized Representative changes and complete a new ***Outpatient Pharmacy Enrollment Form*** with the new Authorized Representative.

Before dispensing, I will ensure that all pharmacy staff must:

1. Obtain authorization to dispense each prescription by contacting the REMS by phone or checking the REMS website to verify the prescriber is certified, and the patient is enrolled and authorized to receive the drug.
2. Dispense no more than 30 days' supply.

Reference ID: 4528293

JYNARQUE® (tolvaptan) REMS OUTPATIENT PHARMACY ENROLLMENT FORM

Authorized Representative Responsibilities (cont'd)

At all times, I will ensure that all pharmacy staff must:

1. Report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS by phone or using the ***Liver Adverse Events Reporting Form***.
2. Not distribute, transfer, loan, or sell JYNARQUE.
3. Maintain records documenting staff's completion of REMS training.
4. Maintain and make available appropriate documentation reflecting that all processes and procedures are in place and are being followed for the REMS.
5. Comply with audits carried out by Otsuka Pharmaceutical Company, Ltd or third party acting on behalf of Otsuka Pharmaceutical Company, Ltd to ensure that all processes and procedures are in place and are being followed.

I understand and acknowledge that I must maintain compliance with the requirements of the REMS; otherwise, my pharmacy will no longer have the ability to dispense JYNARQUE.

Outpatient Pharmacy Authorized Representative Information:

First Name*: _____ Last Name*: _____ Middle Initial: _____

Telephone Number*: _____ Alternate Telephone Number: _____

Office Fax*: _____

Email*: _____ Preferred Method of Contact: _____

Authorized Representative Signature*: _____ Date*: _____

Phone: 1-866-244-9446 | www.JYNARQUErems.com | Fax: 1-866-750-6820

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JYNARQUE®
(tolvaptan) tablets

Reference ID: 4528293

JYNARQUE® (tolvaptan) REMS INPATIENT PHARMACY ENROLLMENT FORM

Instructions

JYNARQUE is available only through the JYNARQUE REMS, a restricted distribution program. Only prescribers, pharmacies, and patients enrolled in the program can prescribe, dispense, and receive JYNARQUE. Fields marked * are required.

Only inpatient pharmacies that are certified in the REMS may dispense JYNARQUE for a specific enrolled patient(s) being treated in the inpatient setting. Certified inpatient pharmacies are only authorized to order JYNARQUE from contracted distributors. If you have any questions about the REMS or need more information, please call **1-866-244-9446**.

You must designate an authorized representative to complete and submit this form on behalf of this inpatient pharmacy.

Instructions for Authorized Representative:

1) **Review** the ***Prescribing Information*** and the ***REMS Program Overview***.
2) **Complete** and **submit** this ***Inpatient Pharmacy Enrollment Form*** online at **www.JYNARQUErems.com**, or fax it to the REMS at **1-866-750-6820**.
3) **Complete** all mandatory fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the REMS will notify the pharmacy upon successful certification.

**Indicates required field*

Inpatient Pharmacy Information

Inpatient Pharmacy Name*: _____

Type*: ☐ Hospital ☐ Nursing home ☐ Hospice ☐ Mental facility ☐ Assisted Living ☐ Prison ☐ Rehabilitation Facility ☐ Other

Pharmacy Address Line 1*: _____

City*: _____ State*: _____ Zip code*: _____

Pharmacy Address Line 2: _____

Pharmacy National Provider Information No. (NPI)*: _____

Inpatient Pharmacy Ship to Address, if different than above

Pharmacy Address*: _____

City*: _____ State*: _____ Zip code*: _____

Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to carry out the certification process and oversee implementation of and compliance with the REMS. By signing this form, I agree to comply with the requirements of REMS and as the Authorized Representative, understand that my Pharmacy must also comply with the REMS requirements:

1. Review the ***Prescribing Information*** and ***REMS Program Overview***.
2. Enroll in the REMS by completing the ***Inpatient Pharmacy Enrollment Form*** and submitting it to the REMS.
3. Train all relevant staff involved in dispensing JYNARQUE using the ***REMS Program Overview***.
4. Establish processes and procedures to verify the prescriber is certified and the patient is enrolled in the REMS.
5. Establish processes and procedures to dispense no more than a 15 days' supply upon discharge of the patient.
6. Inform the REMS if the Authorized Representative changes and complete a new ***Inpatient Pharmacy Enrollment Form*** with the new Authorized Representative.

Before dispensing I will ensure that all pharmacy staff must:

1. Verify that the prescriber is certified and the patient is enrolled in the REMS.

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JYNARQUE® (tolvaptan) REMS INPATIENT PHARMACY ENROLLMENT FORM

Authorized Representative Responsibilities (cont'd)

At/upon discharge, I will ensure that all pharmacy staff must not dispense more than a 15 days' supply.

At all times, I will ensure that all pharmacy staff must:

1. Report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS by phone or using the ***Liver Adverse Events Reporting Form***.
2. Not distribute, transfer, loan, or sell JYNARQUE.
3. Maintain records documenting staff's completion of REMS training.
4. Maintain and make available appropriate documentation reflecting that all processes and procedures are in place and are being followed for the REMS.
5. Comply with audits carried out by Otsuka Pharmaceutical Company, Ltd or third party acting on behalf of Otsuka Pharmaceutical Company, Ltd to ensure that all processes and procedures are in place and are being followed.

I understand and acknowledge that I must maintain compliance with the requirements of the REMS; otherwise, my pharmacy will no longer have the ability to dispense JYNARQUE.

Inpatient Pharmacy Authorized Representative Information

First Name*: _____ Last Name*: _____ Middle Initial: _____
Telephone Number*: _____ Alternate Telephone Number: _____
Office Fax*: _____
Email*: _____ Preferred Method of Contact: _____

Authorized Representative Signature*: _____ Date*: _____

Phone: 1-866-244-9446 | www.JYNARQUErems.com | Fax: 1-866-750-6820

Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan.
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA.
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JYNARQUE REMS (RISK EVALUATION AND MITIGATION STRATEGY) PROGRAM OVERVIEW

This overview describes the requirements of the JYNARQUE REMS and the responsibilities of prescribers, pharmacies and patients.

If you have any questions regarding the REMS, please visit **www.JYNARQUErems.com** or call **1-866-244-9446**.

Phone: 1-866-244-9446 | www.JYNARQUErems.com | Fax: 1-866-750-6820

Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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WHAT IS THE JYNARQUE REMS?

- 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.
- **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.**

Reference ID: 4528293

HOW DOES THE JYNARQUE REMS WORK?

	Before Prescribing/ Dispensing JYNARQUE	Before Starting JYNARQUE for each Patient	While on JYNARQUE Treatment for Each Patient
Prescriber	Prescriber certification	• **Counsel** the patient on the risk of serious and potentially fatal liver injury and the requirement for **liver function monitoring at baseline** and specific intervals during treatment • **Assess** the patient's liver function and appropriateness of initiating treatment • **Enroll** the patient	• **Assess** 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 • **Document** appropriateness of continuing treatment and submit to the REMS using the ***Patient Status Form*** every 3 months for the first 18 months of treatment and every 6 months thereafter
Pharmacy (Outpatient & Inpatient)	Pharmacy certification		• **Outpatient: Obtain authorization** to dispense each prescription by contacting the REMS online or by phone to verify prescriber is certified, and patient is enrolled and authorized to receive the drug — Dispense no more than a 30-day supply • **Inpatient: Verify** the prescriber is certified and the patient is enrolled in the REMS Program — Dispense no more than a 15-day supply at discharge
Patient		• Review ***Patient Guide*** • Patient Enrollment • **Get** a blood test before your first dose	• **Get** a blood test at 2 weeks and 4 weeks after you start treatment • **Get** a blood test every month for the first 18 months of treatment and then every 3 months thereafter

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WHAT ARE THE REQUIREMENTS OF THE JYNARQUE REMS?

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

Prescriber	Pharmacy (Outpatient & Inpatient)	Patient
To prescribe JYNARQUE: 1. **Become certified** by completing a one-time certification process 2. As you start patients on JYNARQUE, counsel and evaluate baseline liver testing prior to enrolling them into the REMS, and complete the prescription 3. **Perform** ongoing patient monitoring, evaluate liver testing at 2 weeks, 4 weeks and monthly for the first 18 months of treatment and every 3 months thereafter 4. **Complete** a ***Patient Status Form*** for each patient every 3 months for the first 18 months of treatment and every 6 months thereafter	To dispense JYNARQUE*: 1. **Designate an authorized representative, become certified**, and **recertify** if there is a change in the authorized representative 2. **Train** staff and **comply** with REMS requirements 3. **Outpatient: Obtain authorization** 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 — Dispense no more than a 30-day supply 4. **Inpatient: Verify** the prescriber is certified and the patient is enrolled in the REMS Program — Dispense no more than a 15-day supply at discharge	To receive JYNARQUE: 1. **Understand the risks** associated with JYNARQUE 2. **Enroll** in the REMS by completing the ***Patient Enrollment Form*** with your healthcare provider 3. **Complete** 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

*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

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PRESCRIBER REQUIREMENTS

Become Certified (One-time)	Enroll Your Patients	Monitor Your Patients
Before prescribing JYNARQUE: 1. **Review** the following educational materials on JYNARQUE to understand the risks of severe and potentially fatal liver injury: • *Prescribing Information* • *JYNARQUE REMS Program Overview* • *JYNARQUE REMS Prescriber Training* 2. **Complete** and **submit** the *Prescriber Knowledge Assessment* and the *Prescriber Enrollment Form* to the REMS • *JYNARQUE REMS Prescriber Knowledge Assessment* • *JYNARQUE REMS Prescriber Enrollment Form* 3. Upon completion of these steps, the REMS will notify you upon successful certification	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: • JYNARQUE REMS *Patient Guide* 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	Once your patient is on JYNARQUE: 1. **Monitor** your patients on an ongoing basis. Assess the patient's liver function and appropriateness of continuing treatment 2 weeks and 4 weeks after treatment initiation, then monthly for the first 18 months and every 3 months thereafter 2. **Submit** a completed *Patient Status Form* to the REMS for each patient every 3 months for the first 18 months of treatment and every 6 months thereafter* 3. **Report** adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS by phone or submitting a completed *Liver Adverse Events Reporting Form* or a completed *Patient Status Form* 4. Inform the REMS if a patient is no longer under your care or has discontinued JYNARQUE

The completion of the laboratory test and the submission of the ***Patient Status Form*** are done at different intervals. At the time that the ***Patient Status Form*** is due, this form may also be used to report serious or potentially fatal liver injury events. However, 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 REMS will send a reminder to the certified prescriber of record when the ***Patient Status Form*** is due.

* If a patient has discontinued JYNARQUE treatment, the prescriber/prescriber delegate must notify the REMS.

Completed forms should be submitted to the REMS online at **www.JYNARQUErems.com** or via fax to **1-866-750-6820**. Patient Status Forms may be submitted by certified Prescribers or their delegate online or via fax.

Phone: 1-866-244-9446 | www.JYNARQUErems.com | Fax: 1-866-750-6820

Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

Reference ID: 4528293

PHARMACY REQUIREMENTS

Become Certified	Ensure Compliance with REMS Requirements
Before dispensing JYNARQUE for the first time: 1. **Designate** an authorized representative for the pharmacy. He or she will need to review the ***REMS Program Overview*** and will oversee implementation and ensure compliance with the REMS requirements 2. **Have the authorized representative complete and submit** the ***Outpatient Pharmacy Enrollment Form*** or ***JYNARQUE REMS Inpatient Pharmacy Enrollment Form*** • Outpatient dispensing of JYNARQUE is limited to a small number of contracted pharmacies that will be certified. The ***Outpatient Pharmacy Enrollment Form*** must be submitted via fax • Only inpatient pharmacies that are certified in the REMS may dispense JYNARQUE for a specific enrolled patient being treated in the inpatient setting. The ***Inpatient Pharmacy Enrollment Form*** may be completed online or via fax 3. Have the authorized representative ensure that all relevant staff involved in dispensing of JYNARQUE are trained on the REMS requirements and that a record of training is maintained by the pharmacy	**When dispensing JYNARQUE:** 1. Before dispensing JYNARQUE, **Outpatient: Obtain authorization** 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 — Dispense no more than a 30-day supply **Inpatient: Verify** the prescriber is certified and the patient is enrolled in the REMS Program — Dispense no more than a 15-day supply at discharge 2. **Report** adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS by phone or submitting a completed ***Liver Adverse Events Reporting Form*** 3. **Maintain** appropriate documentation that all processes and procedures are in place and are being followed 4. **Comply** with audits carried out by Otsuka Pharmaceuticals or third party acting on behalf of the manufacturer to ensure that all processes and procedures are in place and being followed 5. **Recertify** in the REMS if a new authorized representative is designated by completing and submitting the ***Outpatient Pharmacy Enrollment Form*** or ***Inpatient Pharmacy Enrollment Form***

JYNARQUE is not available to all pharmacies. If you have questions about the REMS or how to obtain JYNARQUE, call **1-866-244-9446**.

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PATIENT REQUIREMENTS

Enroll and Complete Baseline Liver Testing	Complete Regular Liver Testing
Before starting JYNARQUE: 1. **Discuss** and receive counseling from your healthcare provider on: a. The risk of serious and potentially fatal liver injury b. The need for required blood testing before my first dose and regularly during treatment 2. **Receive and read** the ***Patient Guide*** 3. **Complete** the ***Patient Enrollment Form*** with your healthcare provider 4. **Complete** liver testing before your first dose of JYNARQUE	**Once your patient is on JYNARQUE:** 1. **Complete** liver testing at 2 weeks, 4 weeks and monthly for the first 18 months of treatment and every 3 months thereafter 2. **Inform your healthcare provider** if you have any side effects, reactions, or symptoms after taking JYNARQUE, such as signs and symptoms of serious liver injury 3. **Notify** the REMS if you **change your JYNARQUE healthcare provider**, if your **contact information changes**, or if you **discontinue treatment with JYNARQUE**

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JYNARQUE REMS RESOURCES

	Before Prescribing/ Dispensing JYNARQUE	Before starting JYNARQUE for each Patient	While on JYNARQUE Treatment
Prescriber	• *Prescribing Information* • *JYNARQUE REMS Program Overview* • *JYNARQUE REMS Prescriber Training* • *JYNARQUE REMS Prescriber Knowledge Assessment* • *JYNARQUE REMS Prescriber Enrollment Form*		• *JYNARQUE REMS Patient Status Form* • *JYNARQUE REMS Liver Adverse Events Reporting Form*
Pharmacy	• *JYNARQUE REMS Program Overview* • *JYNARQUE REMS Inpatient Pharmacy Enrollment Form* • *JYNARQUE Outpatient Pharmacy Enrollment Form*		• *JYNARQUE REMS Liver Adverse Events Reporting Form*
Patient		• *JYNARQUE REMS Patient Guide*	

JYNARQUE is a selective vasopressin V_2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)

Please see the Prescribing Information, including **BOXED WARNING**, for more information.

Phone: 1-866-244-9446 | www.JYNARQUErems.com | Fax: 1-866-750-6820

Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

Reference ID: 4528293

ADDITIONAL QUESTIONS:

Please visit **www.JYNARQUErems.com** or call the JYNARQUE REMS at **1-866-244-9446** for more information about the JYNARQUE REMS.

Please see the Prescribing Information, including **BOXED WARNING**, for more information.

Phone: 1-866-244-9446 | **www.JYNARQUErems.com** | **Fax: 1-866-750-6820**

Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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Otsuka America Pharmaceutical, Inc.

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan.
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850.
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JYNARQUE REMS (RISK EVALUATION AND MITIGATION STRATEGY) PRESCRIBER TRAINING

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**

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WHAT IS JYNARQUE?

- JYNARQUE is a selective vasopressin V_2-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

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)]*.

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RISK ASSOCIATED WITH JYNARQUE: SERIOUS AND POTENTIALLY FATAL LIVER INJURY

- 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*]

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

- 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

- 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

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WHAT IS THE JYNARQUE REMS?

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?

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)

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

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HOW DOES THE JYNARQUE REMS WORK?

	Before Prescribing/ Dispensing JYNARQUE	Before Starting JYNARQUE for Each Patient	While on JYNARQUE Treatment for Each Patient
Prescriber	Prescriber certification	• **Counsel** the patient on the risk of serious and potentially fatal liver injury and the requirement for **liver function monitoring at baseline** and specific intervals during treatment • **Assess** the patient's liver function and appropriateness of initiating treatment • **Enroll** the patient	• **Assess** 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 • **Document** appropriateness of continuing treatment and submit to the REMS using the ***Patient Status Form*** every 3 months for the first 18 months of treatment and every 6 months thereafter
Pharmacy (Outpatient & Inpatient)	Pharmacy certification		• **Outpatient: Obtain authorization** to dispense each prescription by contacting the REMS online or by phone to verify prescriber is certified and patient is enrolled. — Dispense no more than a 30-day supply. • **Inpatient: Verify** the prescriber is certified and the patient is enrolled in the REMS Program. — Dispense no more than a 15-day supply at discharge.
Patient		• Review ***Patient Guide***. • Patient Enrollment • **Get** a blood test before your first dose.	• **Get** a blood test at 2 weeks and 4 weeks after you start treatment. • **Get** a blood test every month for the first 18 months of treatment and then every 3 months thereafter.

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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
To prescribe JYNARQUE: 1. **Become certified** by completing a one-time certification process 2. As you start patients on JYNARQUE, **counsel and evaluate baseline liver testing** prior to enrolling them into the REMS, and complete the prescription. 3. **Perform ongoing patient monitoring**, evaluate liver testing at 2 weeks, 4 weeks and monthly for the first 18 months of treatment and every 3 months thereafter. 4. **Complete a *Patient Status Form*** for each patient every 3 months for the first 18 months of treatment and every 6 months thereafter	**To dispense JYNARQUE*:** 1. **Designate an authorized representative, become certified,** and **recertify** if there is a change in the authorized representative. 2. **Train** staff and **comply** with REMS requirements. 3. **Outpatient: Obtain authorization** 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. — Dispense no more than a 30-day supply. 4. **Inpatient: Verify** the prescriber is certified and the patient is enrolled in the REMS Program. — Dispense no more than a 15-day supply at discharge.	**To receive JYNARQUE:** 1. **Understand the risk** associated with JYNARQUE. 2. **Enroll** in the REMS by completing the ***Patient Enrollment Form*** with your healthcare provider. 3. **Complete** 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.

*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

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PRESCRIBER REQUIREMENTS

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

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HOW DOES A PRESCRIBER BECOME CERTIFIED?

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?

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?

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)
   - Submit a completed ***Patient Status Form*** (via fax or online at www.JYNARQUEREMS.com)
4. Inform the REMS if a patient is no longer under your care or has discontinued JYNARQUE

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JYNARQUE REMS PATIENT STATUS FORM

- 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

- 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

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 × ULN (Upper limit of normal), or
  - ALT or AST >5 × ULN for more than 2 weeks, or
  - ALT or AST >3 × ULN and (TBL [Total Bilirubin] > 2× ULN or International Normalized Ratio [INR] >1.5) (TBL measurement can be within 30 days of the ALT elevation), or
  - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

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.

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

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

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, or call 1-800-FDA-1088.

PATIENT REGISTRY

- 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

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***.

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PRESCRIBERS WHO SUCCESSFULLY COMPLETE THE KNOWLEDGE ASSESSMENT WILL RECEIVE:

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.

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

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***.

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

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.

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JYNARQUE® (tolvaptan) REMS PRESCRIBER KNOWLEDGE ASSESSMENT

To become a certified prescriber in the JYNARQUE REMS, you must: complete this *Prescriber Knowledge Assessment* and the *Prescriber Enrollment Form*. You must answer ALL eight questions correctly to become certified.

1. Review the following materials:
- ***Prescribing Information*** • ***REMS Program Overview*** • ***Prescriber Training***

2. Complete your name, NPI number and phone number and answer all 8 questions

3. Submit your completed *Prescriber Knowledge Assessment* and *Prescriber Enrollment Form* to the REMS online at www.JYNARQUErems.com or via fax at 1-866-750-6820

If completed via fax, you will be notified by the REMS on the status of your certification within 2 business days upon receipt. When contacted, you will receive either:
- **Confirmation of your certification in the REMS or**
- **Instructions on how to retake the *Prescriber Knowledge Assessment*, if necessary**

**Indicates required field*

Prescriber Information

First Name*: _____ Middle Initial: _____ Last Name*: _____

National Provider Identifier No. (NPI)*: _____ Phone*: _____

Email: _____

Questions 1 – 8 Select the 1 best answer

Question 1
Before starting a new patient on JYNARQUE, I should
- ☐ Read the U.S. ***Prescribing Information*** (USPI), ***Prescriber Training***, and the ***REMS Program Overview***
- ☐ Counsel patients about the risk of serious and potentially fatal liver injury associated with JYNARQUE
- ☐ Order and review baseline hepatic labs
- ☐ All of the above

Question 2
Patients you identify as appropriate for JYNARQUE must enroll in the JYNARQUE REMS Program in order to be able to receive treatment ..... ☐ True ☐ False

Question 3
JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). ..... ☐ True ☐ False

Question 4
The primary counseling message I should tell my patients is:
- ☐ Do not drink alcohol before you take JYNARQUE
- ☐ Stop therapy if ALT or AST is >2 times the ULN
- ☐ There is a risk of serious and potentially fatal liver injury associated with JYNARQUE and that blood testing and monitoring is required
- ☐ Patients need to have blood tests every 18 months

Question 5
I will submit a ***Patient Status Form*** for each patient every 3 months for first 18 months of treatment and every 6 months thereafter. ..... ☐ True ☐ False

Question 6
I will educate my patients on JYNARQUE; the REMS; and the signs and symptoms of liver injury and what to do should they experience them, before I enroll them into the REMS. ..... ☐ True ☐ False

Question 7
Patients can take JYNARQUE and elect not to have blood tests done. ..... ☐ True ☐ False

Question 8
Only pharmacies enrolled in the REMS may dispense JYNARQUE to patients. ..... ☐ True ☐ False

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Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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Reference ID: 4528293

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JYNARQUE REMS (RISK EVALUATION AND MITIGATION STRATEGY) PATIENT GUIDE

Patients: Your healthcare provider will go over this patient guide with you. It is important to ask any questions you may have. Keep this guide for important safety information about the serious risks of JYNARQUE.

Healthcare Providers: Review this patient guide with your patient, and provide your patient a copy to take home.

Phone: 1-866-244-9446 | www.JYNARQUErems.com | Fax: 1-866-750-6820

Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

WHAT IS JYNARQUE?

JYNARQUE is a prescription medicine used to slow kidney function decline in adults who are at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

It is not known if JYNARQUE is safe and effective in children.

Please also read the Medication Guide that comes with your medicine for more information about how to take JYNARQUE.

Reference ID: 4528293

WHAT IS THE MOST SERIOUS RISK OF JYNARQUE?

- JYNARQUE can cause serious liver problems that can lead to the need for a liver transplant or can lead to death

WHAT IS THE JYNARQUE REMS?

- 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
- Because of the risk of serious and potentially fatal liver injury, JYNARQUE is only available through a restricted distribution program called the JYNARQUE REMS
- The REMS educates patients and healthcare providers about these risks associated with JYNARQUE
- Requirements of the JYNARQUE REMS include the following:
  - You and your healthcare provider must be enrolled in the JYNARQUE REMS to receive and prescribe JYNARQUE
  - JYNARQUE is only available from pharmacies that participate in the REMS
- Your healthcare provider will do blood tests to check your liver before you start using JYNARQUE and regularly while you are being treated with JYNARQUE

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Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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WHAT DO I NEED TO DO BEFORE I START TREATMENT WITH JYNARQUE?

- Talk with your healthcare provider about:
  - The risk of serious liver problems that can lead to the need for a liver transplant or can lead to death
  - The required blood testing before your first dose and regularly during treatment
  - Signs or symptoms of liver injury
- Receive and read the ***Patient Guide***
- Agree to have important blood tests before you start, and regularly while you are taking JYNARQUE - to monitor your liver health
- Complete a ***Patient Enrollment Form*** with your healthcare provider to enroll in the JYNARQUE REMS

HOW WILL I RECEIVE JYNARQUE?

After you are enrolled in the REMS, the pharmacy will call you to schedule a shipment of JYNARQUE that will come right to your home.

- JYNARQUE is only available from pharmacies that participate in the REMS
- The pharmacy will only dispense a one month supply at a time

Reference ID: 4528293

WHAT DO I NEED TO DO WHILE I AM BEING TREATED WITH JYNARQUE?

- Get a blood test:
  - Before my treatment begins
  - At 2 weeks after my treatment begins
  - At 4 weeks after my treatment begins, and then
  - Every month after that for the first 18 months, and then
  - Every 3 months from then on
- Contact my healthcare provider if I have any side effects, reactions, or symptoms after receiving JYNARQUE (See **"What are the signs and symptoms of serious liver injury?"** below)
- Notify the JYNARQUE REMS Program Coordinating Center if you change your JYNARQUE healthcare provider, if your contact information changes, or if you stop treatment with JYNARQUE

JYNARQUE LIVER BLOOD TESTING TIMELINE

While taking JYNARQUE, you should stay in touch with your healthcare provider. You or your family members should tell your healthcare provider right away if you have any of the symptoms listed on the next page any time during treatment with JYNARQUE. Also, tell your healthcare provider about any other new symptoms you notice while taking JYNARQUE.

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WHAT ARE THE SIGNS AND SYMPTOMS OF SERIOUS LIVER INJURY?

You or your family member should contact your healthcare provider right away if you have any of the following symptoms:

- feeling tired
- loss of appetite
- nausea
- right upper stomach (abdomen) pain or tenderness
- vomiting
- fever
- rash
- itching
- yellowing of the skin and white part of the eye (jaundice)
- dark urine

WHERE CAN I FIND MORE INFORMATION ABOUT THE JYNARQUE REMS?

In addition to this guide, you will receive a Medication Guide that has important information about your prescription. If you would like more information, talk with your healthcare provider. You can also ask your healthcare provider for information about JYNARQUE that is written for healthcare providers.

If you have questions about the REMS, you can call the JYNARQUE REMS Program Coordinating Center.

Phone: 1-866-244-9446
Hours of Operation: 8 am-8 pm Eastern

Reference ID: 4528293

IF YOU HAVE ANY QUESTIONS ABOUT YOUR HEALTH OR MEDICINES, TALK TO YOUR HEALTHCARE PROVIDER.

To report negative side effects, contact Otsuka America Pharmaceutical, Inc. at **1-800-438-9927** or FDA at **1-800-FDA-1088** (**www.fda.gov/medwatch**).

Please see PRESCRIBING INFORMATION, including **BOXED WARNING**, and MEDICATION GUIDE.

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Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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JYNARQUE® (tolvaptan) REMS PATIENT STATUS FORM

This form must be regularly completed for all patients treated with JYNARQUE. At the time this form is due, this form may also be used to report adverse events suggestive of a serious or potentially fatal liver injury. Once completed, you may submit the form to the REMS by fax or online.

This form must be completed and submitted:
- every 3 months for the first 18 months of treatment and
- every 6 months thereafter.

Note:
The completion of the laboratory tests (see frequency below) and the submission of the ***Patient Status Form*** (per the schedule shown above) are done at different intervals.

Adverse events suggestive of serious and potentially fatal liver injury must be reported to the REMS by any one of the following actions:
- Contact the REMS Program Coordinating Center by phone
- Submit a completed ***Liver Adverse Events Reporting Form***
- Submit a completed ***Patient Status Form***

If an event is submitted via the *Patient Status Form*, it is not necessary to also complete and 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*.

**Indicates required field*

Patient Information

First Name*: _____ Last Name*: _____
Birthdate*: _____ REMS ID: _____
Address Line 1*: _____
Address Line 2: _____
City*: _____ State*: _____ Zip code*: _____

Prescriber Information

First Name*: _____ Last Name*: _____ REMS ID: _____
National Provider Identifier No. (NPI)*: _____ Practice/Facility Name: _____
Address Line 1: _____
Address Line 2: _____
City: _____ State: _____ Zip code: _____
Phone*: _____ Fax: _____ Email: _____

Patient Liver Monitoring and Authorization to Continue Treatment

*Following each treatment initiation, certified prescribers must assess each patient's liver function (ALT, AST, and bilirubin) and appropriateness of continuing treatment as follows:
- 2 weeks after treatment initiation
- 4 weeks after treatment initiation
- Monthly for the first 18 months; and then every 3 months

*Has the patient's liver function been assessed during this reporting period as described above?
☐ Yes ☐ No

*Is this patient authorized to continue to receive JYNARQUE?
☐ Yes ☐ No

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Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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JYNARQUE® (tolvaptan) REMS PATIENT STATUS FORM

Serious Adverse Events Reporting

*My patient experienced a serious and potentially fatal liver injury event? ☐ Yes ☐ No

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 × ULN (Upper limit of normal), or
  - ALT or AST >5 × ULN for more than 2 weeks, or
  - ALT or AST >3 × ULN and (TBL [Total Bilirubin] >2 × ULN or International Normalized Ratio [INR] >1.5) (TBL measurement can be within 30 days of the ALT elevation), or
  - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Event Information:
****Please see definition of seriousness criteria on page 3****
*Please select Yes or No for each seriousness criteria below:

Death* ☐ Yes ☐ No
Life-threatening* ☐ Yes ☐ No
Hospitalization* ☐ Yes ☐ No
Important Medical event* ☐ Yes ☐ No

*Treatment was discontinued due to this event ☐ Yes ☐ No ☐ Not available

Liver Laboratory Information:
Were the liver enzymes (ALT/AST) elevated > 3 x ULN?* ☐ Yes ☐ No ☐ Not available

Were there Symptoms of Liver Injury?* ☐ Yes ☐ No

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

Signature*: _____ Date*: _____

Print Name*: _____

Submitted by*: ☐ Prescriber Delegate ☐ Prescriber

Please Note:

A JYNARQUE certified prescriber or prescriber delegate may complete and submit this form 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.

If the patient has been discontinued from JYNARQUE treatment, the prescriber/prescriber delegate must notify the REMS.

Reference ID: 4528293

Definition of 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 Events
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.

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Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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JYNARQUE® (tolvaptan) REMS LIVER ADVERSE EVENTS REPORTING FORM

Adverse events suggestive of serious and potentially fatal liver injury must be reported to the REMS. Healthcare providers can complete and submit this form to the REMS by fax or online or they can report the information by calling the JYNARQUE REMS. Adverse events can also be reported to the REMS when the ***JYNARQUE REMS Patient Status Form*** is due. If an event is submitted via the ***Liver Adverse Event Report Form***, it is not necessary to also submit **the same event** on the ***Patient Status Form*** or contact the REMS Program Coordinating Center by phone. The ***Patient Status Form*** should still be submitted per the regular schedule outlined in the REMS.

**Indicates required field*

Patient Information

First Name*: _____ Last Name*: _____
Birthdate*: _____ REMS ID: _____
Address Line 1*: _____
Address Line 2: _____
City*: _____ State*: _____ Zip code*: _____

Prescriber Information

First Name*: _____ Last Name*: _____ REMS ID: _____
National Provider Identifier No. (NPI)*: _____ Practice/Facility Name: _____
Address Line 1: _____
Address Line 2: _____
City: _____ State: _____ Zip code: _____
Phone*: _____ Fax*: _____ Email*: _____

Serious Adverse Event Reporting

*My patient experienced a serious and potentially fatal liver injury event ☐ Yes ☐ No

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 × ULN (Upper limit of normal), or
  - ALT or AST >5 × ULN for more than 2 weeks, or
  - ALT or AST >3 × ULN and (TBL [Total Bilirubin] >2 × ULN or International Normalized Ratio [INR] >1.5) (TBL measurement can be within 30 days of the ALT elevation), or
  - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Event Information:
****Please see definition of seriousness criteria on page 2****

*Please select Yes or No for each seriousness criteria below:

Death*	☐ Yes	☐ No	Life-threatening*	☐ Yes	☐ No
Hospitalization*	☐ Yes	☐ No	Important Medical event*	☐ Yes	☐ No

*Treatment was discontinued due to this event ☐ Yes ☐ No ☐ Not available

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Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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Serious Adverse Event Reporting (continued)

Liver Laboratory Information:

Were the liver enzymes (ALT/AST) elevated > 3 x ULN?*

☐ Yes ☐ No ☐ Not available

Were there Symptoms of Liver Injury?*:

☐ Yes ☐ No

The patient's prescriber will be contacted for further information regarding this report of a serious and potentially fatal liver injury event. Pertinent laboratory results will be requested.

Signature*: _____ Date*: _____

Print Name*: _____

If the patient has been discontinued from JYNARQUE treatment, the prescriber/prescriber delegate must notify the REMS.

Definition of 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 Events
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.

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IMPORTANT DRUG WARNING

[Month/Day/Year]

JYNARQUE REMS Letter for Healthcare Providers

Subject: Risk of serious and potentially fatal liver toxicity associated with JYNARQUE (tolvaptan)

Dear Healthcare Provider:

The purpose of this letter is to inform you about the risk of serious and potentially fatal liver injury associated with JYNARQUE (tolvaptan) and the need to monitor for this risk. JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). Tolvaptan, currently approved and marketed as SAMSCA, should not be used to treat ADPKD, as the risks associated with JYNARQUE require a REMS for safe use of the drug.

The U.S. Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of JYNARQUE outweigh its risks. JYNARQUE is only available through a restricted distribution program — the JYNARQUE REMS. Only prescribers, pharmacies, and patients enrolled in the REMS can prescribe, dispense, and receive JYNARQUE.

Serious Risk of JYNARQUE:

JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the postmarketing ADPKD experience. JYNARQUE is contraindicated in patients with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease.

As part of the JYNARQUE REMS:

- Healthcare providers must be trained and specially certified to prescribe JYNARQUE. REMS training materials and enrollment forms may be obtained by calling 1-866-244-9446 or visiting www.JYNARQUErems.com.
- Patients being treated with JYNARQUE must be enrolled in the REMS by completing a ***Patient Enrollment Form*** with their prescriber.
- Prescribers must 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. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of liver injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.
- During treatment, prescribers must also regularly complete and submit the ***Patient Status Form***. A prescriber delegate acting on behalf of the prescriber may also complete and submit this form.

— Healthcare providers must promptly report any suspected adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS by phone, using the ***Liver Adverse Events Reporting Form***, or using the ***Patient Status Form***.

— It is important for you to know that JYNARQUE will only be available through the JYNARQUE REMS, which will require distribution through certified pharmacies.

Adverse Events Reporting

To report negative side effects, contact Otsuka America Pharmaceutical, Inc. at **1-800-438-9927** or FDA at **1-800-FDA-1088 (www.fda.gov/medwatch)**

Additional details about prescriber responsibilities, enrollment and educational materials for JYNARQUE REMS can be found at **www.JYNARQUErems.com**. For more information, contact the JYNARQUE REMS at **1-866-244-9446**.

The information in this letter is not intended as a complete description of benefits and risks associated with the use of JYNARQUE. Please see accompanying Prescribing Information.

Sincerely,

Robert McQuade, PhD

EVP, Chief Strategic Officer

Otsuka Pharmaceutical Development and Commercialization, Inc.

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JYNARQUE REMS (Risk Evaluation and Mitigation Strategy)

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.

Acute liver failure requiring liver transplantation has been reported in the post-marketing autosomal dominant polycystic kidney disease (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.

PRESCRIBERS

Click here to learn how to prescribe JYNARQUE

To prescribe JYNARQUE:

1. **Become certified** by completing a one-time certification process.
2. As you start patients on JYNARQUE, **counsel and evaluate baseline liver testing** prior to enrolling them into the REMS, and complete the prescription.
3. **Perform** ongoing patient monitoring, evaluate liver testing at 2 weeks, 4 weeks and monthly for the first 18 months of treatment and every 3 months thereafter.
4. **Complete** a ***Patient Status Form*** for each patient every 3 months for the first 18 months of treatment and every 6 months thereafter.

PHARMACIES (OUTPATIENT & INPATIENT)

Click here to learn how to dispense JYNARQUE

To dispense JYNARQUE:

1. **Designate an authorized representative, become certified**, and **recertify** if there is a change in the authorized representative.
2. **Train** staff and **comply** with REMS requirements.
3. **Outpatient: Obtain authorization** 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.
   - Dispense no more than a 30-day supply.
4. **Inpatient: Verify** the prescriber is certified and the patient is enrolled in the REMS Program.
   - Dispense no more than a 15-day supply at discharge.

PATIENTS

Click here to learn how to receive JYNARQUE

To receive JYNARQUE:

1. **Understand the risks** associated with JYNARQUE.
2. **Enroll** in the REMS by completing the ***Patient Enrollment Form*** with your healthcare provider.
3. **Complete** 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.

PDFs for Download

Resources for Healthcare Providers

- *JYNARQUE REMS Program Overview*
- *JYNARQUE REMS Prescriber Training*
- *JYNARQUE REMS Prescriber Knowledge Assessment*
- *JYNARQUE REMS Prescriber Enrollment Form*
- *JYNARQUE REMS Patient Guide*
- *JYNARQUE REMS Patient Enrollment Form*
- *JYNARQUE REMS Patient Status Form*
- *JYNARQUE REMS Liver Adverse Events Reporting Form*
- *JYNARQUE REMS Letter for Healthcare Providers*

Resources for Pharmacies

- *JYNARQUE REMS Program Overview*
- *JYNARQUE REMS Inpatient Pharmacy Enrollment Form*
- *JYNARQUE REMS Outpatient Pharmacy Enrollment Form*

Resources for Patients

- *JYNARQUE REMS Patient Guide*
- *JYNARQUE REMS Patient Enrollment Form*

- *Programa REMS de JYNARQUE Guía para el Paciente*
- *Programa REMS de JYNARQUE Formulario de Inscripción del Paciente*

- *JYNARQUE REMS 患者指南*
- *JYNARQUE REMS 患者登記表*

Indication

JYNARQUE is a selective vasopressin V2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

To learn more about the serious risks associated with JYNARQUE, please refer to the US Prescribing Information including Boxed Warning, JYNARQUE REMS Program Overview and JYNARQUE REMS Patient Guide.

[Month Year of Approval] XXXXXXXXXXXXX

To report negative side effects,
contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927
or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch)

For JYNARQUE REMS Program Information call:
PHONE: 1-866-244-9446
FAX: 1-866-750-6820

Manufactured by Otsuka Pharmaceutical Co., Ltd. Tokyo 101-8535 Japan.
Marketed and distributed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA.
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Prescribers

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

1. Ensuring that healthcare providers are educated on the following:
   a. the risk of serious and potentially fatal liver injury associated with the use of JYNARQUE
   b. the requirement for monitoring at baseline and periodic monitoring as described in the *Prescribing Information*
   c. 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:
   a. the requirement for monitoring at baseline and periodic monitoring as described in the *Prescribing Information*
3. Ensuring that patients are informed about:
   a. the risk of serious and potentially fatal liver injury associated with the use of JYNARQUE
   b. 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

Prescriber Requirements

How do I become certified in the JYNARQUE REMS?

1. Review the following educational materials on JYNARQUE to understand the risks of severe and potentially fatal liver injury:
   - *Prescribing Information*
   - *REMS Program Overview*
   - *Prescriber Training*
2. Successfully complete and submit the *Prescriber Knowledge Assessment*:
   a. Online
   b. By Fax
3. Complete and submit the *Prescriber Enrollment Form*:
   a. Online
   b. By Fax

How do I enroll a patient in the JYNARQUE REMS?

1. Counsel the patient on the risk of serious and potentially fatal liver injury and the requirement for regular monitoring using the *Patient Guide*
2. Order and evaluate baseline liver monitoring and attest that this monitoring is complete prior to the first prescription for JYNARQUE
3. Complete the *Patient Enrollment Form* with each patient prior to prescribing JYNARQUE:
   a. Online
   b. By Fax

Once a patient is on JYNARQUE, how often should I monitor patients?

- Order and review liver laboratory tests (liver transaminases and total bilirubin) at 2 weeks and 4 weeks after treatment initiation, then monthly for 18 months; then every 3 months thereafter. Assess the patient's liver function and appropriateness of continuing treatment.
- Submit a completed *Patient Status Form* to the REMS for each patient every 3 months for the first 18 months of treatment and every 6 months thereafter. A certified prescriber may assign a delegate to submit the *Patient Status Form* via fax on behalf of the certified prescriber:
  - Online
  - By fax

How should I report liver adverse events?

- Adverse events suggestive of serious and potentially fatal injury liver must be reported to the REMS Program.
  - Healthcare providers can complete and submit the *Liver Adverse Events Reporting Form*:
    - Online
    - By Fax
  - Healthcare providers can report adverse events by calling the JYNARQUE REMS at 1-866-244-9446
- The adverse events can also be reported to the REMS at the same time the *Patient Status Form* is due.

PDFs for Download

Resources for Prescribers

- *JYNARQUE REMS Program Overivew*
- *JYNARQUE REMS Prescriber Training*
- *JYNARQUE REMS Prescriber Knowledge Assessment*
- *JYNARQUE REMS Prescriber Enrollment Form*
- *JYNARQUE REMS Patient Guide*
- *JYNARQUE REMS Patient Enrollment Form*
- *JYNARQUE REMS Patient Status Form*
- *JYNARQUE REMS Liver Adverse Events Reporting Form*
- *JYNARQUE REMS Letter for Healthcare Providers*

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Patients

What is JYNARQUE?

JYNARQUE is a prescription medicine used to slow kidney function decline in adults who are at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)

It is not known if JYNARQUE is safe and effective in children.

Who should not take JYNARQUE?

Do not take JYNARQUE if you:

- have a history of liver problems or have signs or symptoms of liver problems excluding polycystic liver disease
- cannot feel if you are thirsty or cannot replace fluids by drinking
- have been told that the amount of sodium (salt) in your blood is too high or too low
- are dehydrated
- are allergic to tolvaptan or any of the ingredients in JYNARQUE. See the Medication Guide for a complete list of ingredients in JYNARQUE
- are unable to urinate

How do I become enrolled in the JYNARQUE REMS?

In order to be enrolled in the REMS and start taking JYNARQUE, you must:

1. Discuss with your healthcare provider and understand:
   - The risk of serious liver problems that can lead to the need for a liver transplant or can lead to death
   - The need for required blood testing before your first dose and regularly during treatment
   - How to identify signs or symptoms of liver injury
2. Read the *Patient Guide*
3. Agree to have important blood tests before you start, and regularly while you are taking JYNARQUE, to monitor your liver health
4. Complete a *Patient Enrollment Form* with your healthcare provider

What do I need to do while taking JYNARQUE?

To help reduce your risk of liver problems, your healthcare provider will do a blood test to check your liver:

- Before you start taking JYNARQUE
- At 2 weeks and 4 weeks after you start treatment with JYNARQUE
- Then monthly for 18 months during treatment with JYNARQUE
- And every 3 months from then on

How will I get my JYNARQUE medicine?

You will receive your medicine by mail. Only certain pharmacies can fill your JYNARQUE prescription. The pharmacies that are part of the REMS will fill your prescription for JYNARQUE and ship to your home.

PDFs for Download

Resources for Patients

- *JYNARQUE REMS Patient Guide*
- *JYNARQUE REMS Patient Enrollment Form*

- *Programa REMS de JYNARQUE Guía para el Paciente*
- *Programa REMS de JYNARQUE Formulario de Inscripción del Paciente*

- *JYNARQUE REMS 患者指南*
- *JYNARQUE REMS 患者登記表*

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Pharmacies

Outpatient dispensing of JYNARQUE is limited to a small number of contracted certified outpatient pharmacies. Only inpatient pharmacies that are certified in the REMS may dispense JYNARQUE for a specific enrolled patient being treated in the inpatient setting.

Contact the REMS to obtain contact information for certified outpatient pharmacies and distributors who are authorized to ship to certified inpatient pharmacies.

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.

To become certified, pharmacies must:

1. Designate an authorized representative for the pharmacy. He or she will need to review the ***REMS Program Overview*** and will oversee implementation and ensure compliance with the REMS requirements.
2. Have the authorized representative complete and submit the ***Outpatient Pharmacy Enrollment Form*** or the ***Inpatient Pharmacy Enrollment Form***.
   - Outpatient Pharmacies:
     - Complete and fax the ***Outpatient Pharmacy Enrollment Form*** to the REMS at 1-866-750-6820.
   - Inpatient Pharmacies:
     - Complete and submit the ***Inpatient Pharmacy Enrollment Form***:
       - Online
       - By Fax
3. Have the authorized representative ensure that all relevant staff involved in dispensing of JYNARQUE are trained on the REMS requirements and that a record of training is maintained by the pharmacy.

To Ensure Compliance with REMS requirements, pharmacies must:

1. Before dispensing JYNARQUE,

   Outpatient: Obtain authorization 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.
   - Dispense no more than a 30-day supply.

   Inpatient: Verify the prescriber is certified and the patient is enrolled in the REMS Program.
   - Dispense no more than a 15-day supply at discharge.
2. **Report** any adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS by phone or submitting a completed ***Liver Adverse Events Reporting Form***. You will be contacted for more information about these events.
3. **Maintain** appropriate documentation that all processes and procedures are in place and are being followed.
4. **Comply** with audits carried out by Otsuka Pharmaceutical Company,Ltd or third party acting on behalf of the manufacturer to ensure that all processes and procedures are in place and being followed.
5. **Recertify** in the REMS if a new authorized representative is designated by completing and submitting the ***Outpatient Pharmacy Enrollment Form*** or the ***Inpatient Pharmacy Enrollment Form***.

Login is available for certified pharmacies.

PDFs for Download

Resources for Pharmacies

- *JYNARQUE REMS Program Overview Guide*
- *JYNARQUE REMS Inpatient Pharmacy Enrollment Form*
- *JYNARQUE REMS Outpatient Pharmacy Enrollment Form*

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or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch)

For JYNARQUE REMS Program Information call:
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FAX: 1-866-750-6820

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Contact us

Phone

1-866-244-9446

Fax

1-866-750-6820

Hours of Operation

Monday - Friday
8:00-8:00 PM
Eastern

To report any adverse events suggestive of liver injury, please contact the JYNARQUE REMS Program Coordinating Center.

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Login

Please enter your User Name

Login

If you have not received a user name, please contact the JYNARQUE REMS at 1-866-244-9446

User Name

LOGIN

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Resources

Resources for Prescribers

- *JYNARQUE REMS Program Overview*
- *JYNARQUE REMS Prescriber Training*
- *JYNARQUE REMS Prescriber Knowledge Assessment*
- *JYNARQUE REMS Prescriber Enrollment Form*
- *JYNARQUE REMS Patient Guide*
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- *JYNARQUE REMS Patient Status Form*
- *JYNARQUE REMS Liver Adverse Events Reporting Form*
- *JYNARQUE REMS Letter for Healthcare Providers*

Resources for Patients

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- *JYNARQUE REMS 患者指南*
- *JYNARQUE REMS 患者登記表*

Resources for Pharmacies

- *JYNARQUE REMS Program Overview*
- *JYNARQUE REMS Inpatient Pharmacy Enrollment Form*
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Prescriber Certification

1 NPI Validation • • • 2 Review Materials • • • 3 Knowledge Assessment • • • 4 Online Enrollment

To begin, please complete all required fields below. Required fields are denoted by "*".

*NPI Number:

*Email

CONTINUE

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JYNARQUE® (tolvaptan) tablets

JYNARQUE REMS (RISK EVALUATION AND MITIGATION STRATEGY) PRESCRIBER TRAINING

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

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To report negative side effects,
contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927
or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch)

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Prescriber Certification

JYNARQUE® (tolvaptan) tablets

WHAT IS JYNARQUE?

- JYNARQUE is a selective vasopressin V_2-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

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or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch)

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Prescriber Certification

JYNARQUE® (tolvaptan) tablets

JYNARQUE HAS A **BOXED** WARNING

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)]*.

[Month Year of Approval] XXXXXXXXXXXXX

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Reference ID: [redacted]

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JYNARQUE® (tolvaptan) tablets

RISK ASSOCIATED WITH JYNARQUE: SERIOUS AND POTENTIALLY FATAL LIVER INJURY

- 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*]

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

- 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

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JYNARQUE® (tolvaptan) tablets

ADDITIONAL RISKS AND SAFETY INFORMATION

- 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

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JYNARQUE® (tolvaptan) tablets

WHAT IS THE JYNARQUE REMS?

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.

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Prescriber Certification

JYNARQUE® (tolvaptan) tablets

WHAT IS THE GOAL OF THE JYNARQUE REMS?

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

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JYNARQUE® (tolvaptan) tablets

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

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

[Month Year of Approval] XXXXXXXXXXXXX

To report negative side effects,
contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927
or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch)

For JYNARQUE REMS Program Information call:
PHONE: 1-866-244-9446
FAX: 1-866-750-6820

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Reference ID: [illegible]

Prescriber Certification

JYNARQUE® (tolvaptan) tablets

HOW DOES THE JYNARQUE REMS WORK?

	Before Prescribing/ Dispensing JYNARQUE	Before Starting JYNARQUE for Each Patient	While on JYNARQUE Treatment for Each Patient
Prescriber	Prescriber certification	• **Counsel** the patient on the risk of serious and potentially fatal liver injury and the requirement for **liver function monitoring at baseline** and specific intervals during treatment • **Assess** the patient's liver function and appropriateness of initiating treatment • **Enroll** the patient	• **Assess** 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 • **Document** appropriateness of continuing treatment and submit to the REMS using the ***Patient Status Form*** every 3 months for the first 18 months of treatment and every 6 months thereafter
Pharmacy (Outpatient & Inpatient)	Pharmacy certification		• **Outpatient: Obtain authorization** to dispense each prescription by contacting the REMS online or by phone to verify prescriber is certified and patient is enrolled. — Dispense no more than a 30-day supply. • **Inpatient: Verify** the prescriber is certified and the patient is enrolled in the REMS Program. — Dispense no more than a 15-day supply at discharge.
Patient		• Review ***Patient Guide***. • Patient Enrollment • **Get** a blood test before your first dose.	• **Get** a blood test at 2 weeks and 4 weeks after you start treatment. • **Get** a blood test every month for the first 18 months of treatment and then every 3 months thereafter.

[Month Year of Approval] XXXXXXXXXXXXX

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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
To prescribe JYNARQUE: 1. **Become certified** by completing a one-time certification process 2. As you start patients on JYNARQUE, **counsel and evaluate baseline liver testing** prior to enrolling them into the REMS, and complete the prescription. 3. **Perform ongoing patient monitoring**, evaluate liver testing at 2 weeks, 4 weeks and monthly for the first 18 months of treatment and every 3 months thereafter. 4. **Complete a *Patient Status Form*** for each patient every 3 months for the first 18 months of treatment and every 6 months thereafter	**To dispense JYNARQUE*:** 1. **Designate an authorized representative, become certified,** and **recertify** if there is a change in the authorized representative. 2. **Train** staff and **comply** with REMS requirements. 3. **Outpatient: Obtain authorization** 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. — Dispense no more than a 30-day supply. 4. **Inpatient: Verify** the prescriber is certified and the patient is enrolled in the REMS Program. — Dispense no more than a 15-day supply at discharge.	**To receive JYNARQUE:** 1. **Understand the risk** associated with JYNARQUE. 2. **Enroll** in the REMS by completing the ***Patient Enrollment Form*** with your healthcare provider. 3. **Complete** 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.

*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

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PRESCRIBER REQUIREMENTS

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

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HOW DOES A PRESCRIBER BECOME CERTIFIED?

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**

[Month Year of Approval] XXXXXXXXXXXX

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HOW DOES A PRESCRIBER ENROLL PATIENTS?

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

[Month Year of Approval] XXXXXXXXXXXXX

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HOW DOES A PRESCRIBER MONITOR PATIENTS?

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)
   - Submit a completed ***Patient Status Form*** (via fax or online at www.JYNARQUEREMS.com)
4. Inform the REMS if a patient is no longer under your care or has discontinued JYNARQUE

[Month Year of Approval] XXXXXXXXXXXXX

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JYNARQUE REMS PATIENT STATUS FORM

- 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

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PRESCRIBER DELEGATE

- 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

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DEFINITION OF SERIOUS AND POTENTIALLY FATAL LIVER INJURY

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 × ULN (Upper limit of normal), or
  - ALT or AST >5 × ULN for more than 2 weeks, or
  - ALT or AST >3 × ULN and (TBL [Total Bilirubin] > 2× ULN or International Normalized Ratio [INR] >1.5) (TBL measurement can be within 30 days of the ALT elevation), or
  - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

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.

[Month Year of Approval] XXXXXXXXXXXXX

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

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

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, or call 1-800-FDA-1088.

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PATIENT REGISTRY

- 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

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NEXT STEPS

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***.

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PRESCRIBERS WHO SUCCESSFULLY COMPLETE THE KNOWLEDGE ASSESSMENT WILL RECEIVE:

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.

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

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***.

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

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.

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Question 1:

Before treating each patient with JYNARQUE, I should.

- ○ Read the ***U.S. Prescribing Information*** (USPI), ***Prescriber Training***, and the ***REMS Program Overview***
- ○ Counsel patients about the risk of serious and potentially fatal liver injury associated with JYNARQUE
- ○ Order and review baseline liver labs
- ○ All of the above

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SUBMIT

Reference ID: 4528293

Prescriber Certification

NPI Validation • Review Materials • 3 Knowledge Assessment • 4 Online Enrollment

Question 2:

Patients you identify as appropriate for JYNARQUE must enroll in the JYNARQUE REMS in order to be able to receive treatment

- ○ True
- ○ False

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Question 3:

JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

- ○ True
- ○ False

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Prescriber Certification

Question 4:

The primary counseling message I should tell my patients is:

- ○ Do not drink alcohol before you take JYNARQUE
- ○ Stop therapy if ALT or AST is > 2 times the ULN
- ○ There is a risk of serious and potentially fatal liver injury associated with JYNARQUE and that blood testing and monitoring is required
- ○ Patients need to have blood tests every 18 months

[Month Year of Approval] XXXXXXXXXXXXX

To report negative side effects,
contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927
or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch)

For JYNARQUE REMS Program Information call:
PHONE: 1-866-244-9446
FAX: 1-866-750-6820

Manufactured by Otsuka Pharmaceutical Co., Ltd. Tokyo 101-8535 Japan.
Marketed and distributed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA.
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Question 5:

I will submit a ***Patient Status Form*** for each patient every 3 months for first 18 months of treatment and every 6 months thereafter.

- ○ True
- ○ False

[Month Year of Approval] XXXXXXXXXXXXX

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Question 6:

I will educate my patients on JYNARQUE; the REMS; and the signs and symptoms of liver injury and what to do should they experience them, before I enroll them into the REMS.

- ○ True
- ○ False

[Month Year of Approval] XXXXXXXXXXXXX

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Question 7:

Patients can take JYNARQUE and elect not to have blood tests done.

- ○ True
- ○ False

[Month Year of Approval] XXXXXXXXXXXXX

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Question 8:

Only pharmacies enrolled in the REMS may dispense JYNARQUE to patients.

- ○ True
- ○ False

[Month Year of Approval] XXXXXXXXXXXXX

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SUBMIT

Prescriber Knowledge Assessment

NPI Validation • Review Materials • 3 Knowledge Assessment • 4 Online Enrollment

You have successfully completed the JYNARQUE Knowledge Assessment. You must complete the JYNARQUE REMS Prescriber Enrollment Form and submit to the JYNARQUE REMS Program before prescribing JYNARQUE. You will receive a notification from the JYNARQUE REMS Program confirming your certification in the JYNARQUE REMS Program. Upon receipt of this notification, you may prescribe JYNARQUE.

COMPLETE ONLINE ENROLLMENT

Download Training Certificate

[Month Year of Approval] XXXXXXXXXXXXX

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Prescriber Knowledge Assessment

You did not achieve 100%. Please retake the Knowledge Assessment. You must successfully complete the Knowledge Assessment within 3 attempts or you must re-review the training module.

REVIEW TRAINING SLIDES

RETAKE KNOWLEDGE ASSESSMENT

[Month Year of Approval] XXXXXXXXXXXXX

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Prescriber Enrollment

NPI Validation • Review Materials • Knowledge Assessment • 4 Online Enrollment

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Instructions:

1. **Review** the ***Prescribing Information***, the ***REMS Program Overview***, and the ***Prescriber Training***.
2. **Complete** and **submit** the ***Prescriber Knowledge Assessment*** and this ***Prescriber Enrollment Form*** online at www.JYNARQUErems.com, or fax them to the REMS at 1-866-750-6820.
3. **Complete** all mandatory fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the REMS will notify you upon successful certification.

Prescriber Information

*NPI Number:

*State License #:

*First Name

Middle Initial

*Last Name

Preferred Method of Contact:
○ Phone ○ Email ○ Fax

Preferred Time of Contact:
○ AM ○ PM

*Credentials
○ MD ○ DO ○ NP
○ PA ○ Other

*Specialty
☐ Nephrology
☐ Other

Practice/Facility Name

*Address Line 1

Address Line 2

*City

*State
-- Please Select --

*Zip

*Phone

*Fax

*Email

Office Liaison First Name

Office Liaison Last Name

Office Liaison Email

Prescriber Agreement

By completing, checking the below attestation and submitting this form, I agree to comply with the following REMS requirements.

I have:

1. Reviewed the ***Prescribing Information***
2. Reviewed the ***REMS Program Overview***
3. Completed the ***Prescriber Training***
4. Successfully completed the ***Knowledge Assessment*** and submitted it to the REMS

Before treatment initiation with the first dose I must:

1. Counsel the patient on the risk of serious and potentially fatal liver injury and the requirement for liver function monitoring at baseline, 2 weeks and 4 weeks after treatment initiation, then monthly for the first 18 months and then every 3 months thereafter using the ***Patient Guide***.
2. Provide a copy of the ***Patient Guide*** to the patient.
3. Assess the patient's liver function and appropriateness of initating treatment.
4. Document appropriateness of initiating treatment using the ***Patient Enrollment Form***.
5. Enroll the patient by completing and submitting the ***Patient Enrollment Form*** to the REMS. Provide a copy of the form to the patient.

During treatment; at 2 weeks and 4 weeks after treatment initiation, then monthly for the first 18 months and every 3 months thereafter I must thereafter I must assess the patient's liver function and appropriateness of continuing treatment.

During treatment; every 3 months for the first 18 months and every 6 months thereafter I must:

1. Assess the patient's liver function and appropriateness of continuing treatment.
2. Document appropriateness of continuing treatment and submit to the REMS using the ***Patient Status Form***.

At all times, I must:

1. Report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS by phone, using the ***Liver Adverse Events Reporting Form***. or using the ***Patient Status Form***..
2. Report treatment discontinuation or transfer of care to the REMS.

I understand and acknowledge that:

1. I will only be able to prescribe JYNARQUE if certified in the REMS.
2. I will not share my credentials for the REMS website or allow others to sign into the website using my credentials
3. I will allow Otsuka Pharmaceutical Company, Ltd and its agents to contact me via phone, mail, fax, or email to support administration of the REMS.
4. I will be contacted for further information regarding any reports of serious and potentially fatal liver injury and will be requested to provide pertinent laboratory test results.

☐ *Signature

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[Month Year of Approval] XXXXXXXXXXXXX

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Inpatient Pharmacy Enrollment Form

Instructions

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Only inpatient pharmacies that are certified in the REMS may dispense JYNARQUE for a specific enrolled patient(s) being treated in the inpatient setting. Certified inpatient pharmacies are only authorized to order JYNARQUE from contracted distributors If you have any questions about the REMS or need more information, please call 1-866-244-9446.

You must designate an authorized representative to complete and submit this form on behalf of this inpatient pharmacy.

Instructions for Authorized Representative:

1. **Review** the ***Prescribing Information*** and the ***REMS Program Overview***.
2. **Complete** and **submit** this ***Inpatient Pharmacy Enrollment Form*** online at www.JYNARQUErems.com, or fax it to the REMS at 1-866-750-6820.
3. **Complete** all mandatory fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the REMS will notify the pharmacy upon successful certification.

Inpatient Pharmacy Information

* Pharmacy National Provider Information No. (NPI)

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Inpatient Pharmacy Enrollment Form

Instructions

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Only inpatient pharmacies that are certified in the REMS may dispense JYNARQUE for a specific enrolled patient(s) being treated in the inpatient setting. Certified inpatient pharmacies are only authorized to order JYNARQUE from contracted distributors If you have any questions about the REMS or need more information, please call 1-866-244-9446.

You must designate an authorized representative to complete and submit this form on behalf of this inpatient pharmacy.

Instructions for Authorized Representative:

1. **Review** the ***Prescribing Information*** and the ***REMS Program Overview***.
2. **Complete** and **submit** this ***Inpatient Pharmacy Enrollment Form*** online at www.JYNARQUErems.com, or fax it to the REMS at 1-866-750-6820.
3. **Complete** all mandatory fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the REMS will notify the pharmacy upon successful certification.

Inpatient Pharmacy Information

* Pharmacy National Provider Information No. (NPI)

RESET

* Inpatient Pharmacy Name

* Type

- Hospital
- Nursing Home
- Hospice
- Mental facility
- Assisted Living
- Prison
- Rehabilitation Facility
- Other

* Pharmacy Address Line 1

Pharmacy Address Line 2

* City

* State

-- Please Select --

* Zip

Inpatient Pharmacy Ship to Address, if different from above

Pharmacy Address

City

State

-- Please Select --

Zip Code

Inpatient Pharmacy Authorized Representative Information

* First Name

Middle Initial

* Last Name

* Telephone Number

Alternate Telephone Number

* Office Fax

* Email

Preferred Method of Contact

Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to carry out the certification process and oversee implementation of and compliance with the REMS. By signing this form, I agree to comply with the requirements of REMS and as the Authorized Representative, understand that my Pharmacy must also comply with the REMS requirements:

1. Review the ***Prescribing Information*** and ***REMS Program Overview***.
2. Enroll in the REMS by completing the ***Inpatient Pharmacy Enrollment Form*** and submitting it to the REMS.
3. Train all relevant staff involved in dispensing JYNARQUE using the ***REMS Program Overview***.
4. Establish processes and procedures to verify the prescriber is certified, the patient is enrolled in the REMS.
5. Establish processes and procedures to verify that no more than a 15 days' supply is dispensed upon discharge of the patient.
6. Inform the REMS if the Authorized Representative changes and complete a new ***Inpatient Pharmacy Enrollment Form*** with the new Authorized Representative.

Before dispensing I will ensure that all pharmacy staff must:

1. Verify that the prescriber is certified and the patient is enrolled in the REMS

At/upon discharge, I will ensure that all pharmacy staff must not dispense more than a 15 days' supply.

At all times, I will ensure that all pharmacy staff will:

1. Report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS by phone, using the ***Liver Adverse Events Reporting Form***.
2. Not distribute, transfer, loan, or sell JYNARQUE.
3. Maintain records documenting staff's completion of REMS training.
4. Maintain and make available appropriate documentation reflecting that all processes and procedures are in place and are being followed for the REMS.
5. Comply with audits carried out by Otsuka Pharmaceutical Company, Ltd or third party acting on behalf of Otsuka Pharmaceutical Company, Ltd to ensure that all processes and procedures are in place and are being followed.

I understand and acknowledge that I must maintain compliance with the requirements of the REMS; otherwise, my pharmacy will no longer have the ability to dispense JYNARQUE.

* Signature

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY R SOUTHWORTH
12/03/2019 04:50:21 PM