I. Administrative Information

Application Number: NDA 204441
Application Holder: Otsuka Pharmaceutical Company, Ltd.
Initial REMS Approval: 04/2018

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


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


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

At all times

5. Get a blood test to check your liver.

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.
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:
<table>
<thead>
<tr>
<th>Target Audience</th>
<th>Communication Materials &amp; Dissemination Plans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare providers who are likely to prescribe JYNARQUE</td>
<td>REMS Letter: Letter for Healthcare Providers</td>
</tr>
<tr>
<td>1. Email within 60 calendar days of the date JYNARQUE is first commercially distributed and again 12 months later.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>2. Make available via a link from the JYNARQUE REMS Program Website.</td>
<td></td>
</tr>
<tr>
<td>3. Disseminate through field-based sales and medical representatives.</td>
<td></td>
</tr>
<tr>
<td>4. Disseminate through professional societies and request the letter or content be provided to their members.</td>
<td></td>
</tr>
<tr>
<td>5. Disseminate at Professional Meetings for 12 months from the date JYNARQUE is first commercially distributed.</td>
<td></td>
</tr>
</tbody>
</table>

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.

Reference ID: 4357323
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.

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) 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

<table>
<thead>
<tr>
<th>Field</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>First Name*</td>
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<tr>
<td>Middle Initial</td>
<td></td>
</tr>
<tr>
<td>Last Name*</td>
<td></td>
</tr>
<tr>
<td>Birthdate*</td>
<td></td>
</tr>
<tr>
<td>Sex*</td>
<td>□ Male □ Female</td>
</tr>
<tr>
<td>Race*</td>
<td>□ White □ Black or African American □ American Indian or Alaska Native □ Asian □ Native Hawaiian or Other Pacific Islander □ Other, Specify</td>
</tr>
<tr>
<td>Ethnicity*</td>
<td>□ Hispanic or Latino □ Not Hispanic or Latino</td>
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<tr>
<td>Address Line 1*</td>
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<tr>
<td>Address Line 2</td>
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<td>Phone*</td>
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<td>Mobile Phone*</td>
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<td>Email*</td>
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</table>

### 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

<table>
<thead>
<tr>
<th>Field</th>
<th>Value</th>
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<tbody>
<tr>
<td>First Name*</td>
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<tr>
<td>Last Name*</td>
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<tr>
<td>NPI No.*</td>
<td></td>
</tr>
<tr>
<td>Practice/Facility Name (where you see this patient):</td>
<td></td>
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<tr>
<td>Address Line 1:</td>
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<tr>
<td>City:</td>
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<tr>
<td>State:</td>
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<td>Zip code:</td>
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<td>Phone*</td>
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<td>Fax:</td>
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<td>Email:</td>
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</tbody>
</table>

### 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.
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 Agreement

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

Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.
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.
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*: ___________________________ Preferred Method of Contact: ___________________________
Email*: ___________________________ Authorized Representative Signature*: ___________________________ Date*: _____________
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.

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: 4357323
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*: ____________________________  Preferred Method of Contact: ________________________
Email*: ________________________________  

Authorized Representative Signature*: ___________________________________________  Date*:______________
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.

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

Reference ID: 4357323
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.
### HOW DOES THE JYNARQUE REMS WORK?

<table>
<thead>
<tr>
<th>Prescriber</th>
<th>Pharmacy (Outpatient &amp; Inpatient)</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Prescribing/Dispensing JYNARQUE</td>
<td>Before Starting JYNARQUE for each Patient</td>
<td>While on JYNARQUE Treatment for Each Patient</td>
</tr>
<tr>
<td>Prescriber certification</td>
<td>• 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</td>
<td>• 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</td>
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<tr>
<td>• Assess the patient’s liver function and appropriateness of initiating treatment</td>
<td>• 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</td>
<td>• Assess the patient’s liver function and appropriateness of continuing treatment</td>
</tr>
<tr>
<td>• Enroll the patient</td>
<td>• 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</td>
<td>• Review Patient Guide and 4 weeks after your first dose</td>
</tr>
<tr>
<td>• 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</td>
<td>• 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</td>
<td>• Get a blood test before your first dose</td>
</tr>
<tr>
<td>• Assess the patient’s liver function and appropriateness of initiating treatment</td>
<td>• 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</td>
<td>• Get a blood test at 2 weeks and 4 weeks after you start treatment</td>
</tr>
<tr>
<td>• Enroll the patient</td>
<td>• 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</td>
<td>• Get a blood test every month for the first 18 months of treatment and then every 3 months thereafter</td>
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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.

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<th>Prescriber</th>
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<th>Patient</th>
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<tr>
<td>To prescribe JYNARQUE:</td>
<td>To dispense JYNARQUE*:</td>
<td>To receive JYNARQUE:</td>
</tr>
<tr>
<td>1. Become certified by completing a one-time certification process</td>
<td>1. Designate an authorized representative, become certified, and recertify if there is a change in the authorized representative</td>
<td>1. Understand the risks associated with JYNARQUE</td>
</tr>
<tr>
<td>2. As you start patients on JYNARQUE, counsel and evaluate baseline liver testing prior to enrolling them into the REMS, and complete the prescription</td>
<td>2. Train staff and comply with REMS requirements</td>
<td>2. Enroll in the REMS by completing the Patient Enrollment Form with your healthcare provider</td>
</tr>
<tr>
<td>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</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>4. Complete a Patient Status Form for each patient every 3 months for the first 18 months of treatment and every 6 months thereafter</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Become Certified (One-time)</th>
<th>Enroll Your Patients</th>
<th>Monitor Your Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before prescribing JYNARQUE:</strong></td>
<td><strong>Before starting each patient on JYNARQUE:</strong></td>
<td><strong>Once your patient is on JYNARQUE:</strong></td>
</tr>
</tbody>
</table>
| 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 | 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 Prescriber Knowledge Assessment | 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. 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 | 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* | 2. Submit a completed Patient Status Form to the REMS for each patient every 3 months. |
| 3. Upon completion of these steps, the REMS will notify you upon successful certification | 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 | 3. Report adverse events suggestive of serious and potentially fatal liver injury by contacting the REMS online or fax. |

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.  
*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 must notify the REMS.

Completed forms should be submitted to the REMS online at [www.JYNARQUErems.com](http://www.JYNARQUErems.com) or via fax to 1-866-750-6820. Patient Status Forms may be submitted by certified Prescribers online or fax. If completed by a delegate, the Patient Status Form should be submitted 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.

## PHARMACY REQUIREMENTS

<table>
<thead>
<tr>
<th>Become Certified</th>
<th>Ensure Compliance with REMS Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before dispensing JYNARQUE for the first time:</strong></td>
<td><strong>When dispensing JYNARQUE:</strong></td>
</tr>
</tbody>
</table>
| 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.  
   - 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.  
   - 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. | 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.  
   - Disperse no more than a 30-day supply.  
   - Inpatient: Verify the prescriber is certified and the patient is enrolled in the REMS Program.  
   - Disperse no more than a 15-day supply at discharge.  
   - 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.  
   - Maintain appropriate documentation that all processes and procedures are in place and are being followed.  
   - 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.  
   - 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.

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.
### PATIENT REQUIREMENTS

<table>
<thead>
<tr>
<th>Enroll and Complete Baseline Liver Testing</th>
<th>Complete Regular Liver Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before starting JYNARQUE:</td>
<td>Once your patient is on JYNARQUE:</td>
</tr>
<tr>
<td>1. Discuss and receive counseling from your healthcare provider on:</td>
<td>1. Complete liver testing at 2 weeks, 4 weeks and monthly for the first 18 months of treatment and every 3 months thereafter</td>
</tr>
<tr>
<td>a. The risk of serious and potentially fatal liver injury</td>
<td>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</td>
</tr>
<tr>
<td>b. The need for required blood testing before my first dose and regularly during treatment</td>
<td>3. Notify the REMS if you change your JYNARQUE healthcare provider, if your contact information changes, or if you discontinue treatment with JYNARQUE</td>
</tr>
<tr>
<td>2. Receive and read the Patient Guide</td>
<td></td>
</tr>
<tr>
<td>3. Complete the Patient Enrollment Form with your healthcare provider</td>
<td></td>
</tr>
<tr>
<td>4. Complete liver testing before your first dose of JYNARQUE</td>
<td></td>
</tr>
</tbody>
</table>

### JYNARQUE REMS RESOURCES

<table>
<thead>
<tr>
<th>Before Prescribing/Dispensing JYNARQUE</th>
<th>Before starting JYNARQUE for each Patient</th>
<th>While on JYNARQUE Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber</td>
<td>• Prescribing Information</td>
<td>• JYNARQUE REMS Patient Status Form</td>
</tr>
<tr>
<td></td>
<td>• JYNARQUE REMS Program Overview</td>
<td>• JYNARQUE REMS Liver Adverse Events Reporting Form</td>
</tr>
<tr>
<td></td>
<td>• JYNARQUE REMS Prescriber Training</td>
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</tr>
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<td>Pharmacy</td>
<td>• JYNARQUE REMS Program Overview</td>
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<td>• JYNARQUE Outpatient Pharmacy Enrollment Form</td>
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<tr>
<td>Patient</td>
<td>• JYNARQUE REMS Patient Guide</td>
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</tbody>
</table>

JYNARQUE is a selective vasopressin V1 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.
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.
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
WHAT IS JYNARQUE?

- 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)

- Please see Prescribing Information, including BOXED WARNING, for additional safety information
WARNING: RISK OF SERIOUS LIVER INJURY
JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported [see Warnings and Precautions (5.1)].

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

Because of the risks of serious liver injury, JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program [see Warnings and Precautions (5.2)].
RISK ASSOCIATED WITH JYNARQUE: SERIOUS AND POTENTIALLY FATAL LIVER INJURY

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

<table>
<thead>
<tr>
<th></th>
<th>Before Prescribing/Dispensing JYNARQUE</th>
<th>Before Starting JYNARQUE for Each Patient</th>
<th>While on JYNARQUE Treatment for Each Patient</th>
</tr>
</thead>
</table>
| **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 at 2 weeks and 4 weeks after you start treatment.  
|                      |                                        | • **Get** a blood test before your first dose. | • **Get** a blood test every month for the first 18 months of treatment and then every 3 months thereafter. |
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.

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<td>1. Understand the risk associated with JYNARQUE.</td>
</tr>
<tr>
<td>2. As you start patients on JYNARQUE, counsel and evaluate baseline liver testing prior to enrolling them into the REMS, and complete the prescription.</td>
<td>2. Train staff and comply with REMS requirements.</td>
<td>2. Enroll in the REMS by completing the Patient Enrollment Form with your healthcare provider.</td>
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<tr>
<td>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.</td>
<td>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.</td>
<td>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.</td>
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<td>4. Complete a Patient Status Form for each patient every 3 months for the first 18 months of treatment and every 6 months thereafter.</td>
<td>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.</td>
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*JYNARQUE is not available to all pharmacies if you have any questions about the REMS or how to obtain JYNARQUE call 1-866-244-9446. Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.
PREScriber REQUIREMENTS

1. Become Certified
2. Enroll Your Patients
3. Monitor Your Patients
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
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
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.
A prescriber delegate may complete and submit the Patient Status Form to the REMS on behalf of the certified prescriber of record.
• 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.
LIVER ADVERSE EVENTS REPORTING FORM

• Suggestive serious and potentially fatal liver injury events will be collected via phone or fax using the Liver Adverse Events Reporting Form.

• Healthcare providers must report Adverse Events suggestive of serious and potentially fatal liver injury by contacting the REMS:
  – By phone
  – Completing and submitting the Liver Adverse Events Reporting Form
    or
  – Completing and submitting the Patient Status Form

• Report treatment discontinuation or transfer of care to the REMS.
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**.
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.
You did not achieve 100%; you must re-take the Prescriber Knowledge Assessment.

You must successfully complete the Prescriber Knowledge Assessment within 3 attempts or you must re-review the Prescriber Training.
PREScribers who did not achieve 100% after 3 attempts will be presented the below message:

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.
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

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

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 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.
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.
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

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
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.

• 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

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

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

JYNARQUE LIVER BLOOD TESTING TIMELINE

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

JYNARQUE (tolvaptan) tablets

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

Confidential

Reference ID: 4357323
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.
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

* Indicates required field

Patient Information
First Name*: ___________________________ Last Name*: ___________________________
Birthdate*: ______________
Address Line 1*: ____________________________________________________________
Address Line 2: ______________________________________________________________
City*: ____________________ State*: ____________________ Zip code*: __________________

Prescriber Information
First Name*: ___________________________ Last Name*: ___________________________
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
*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

Reference ID: 4357323
Serious Adverse Events Reporting

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

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.
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 adverse events by calling the JYNARQUE REMS. The adverse events can also be reported to the REMS at the same time the JYNARQUE REMS Patient Status Form is due.

*Indicates required field

Patient Information

First Name*: ___________________________  Last Name*: ___________________________
Birthdate*: ________
Address Line 1*: ____________________________________________________________
Address Line 2: __________________________________________________________
City*: _______________  State*: ___________________________  Zip code*: _______________

Prescriber Information

First Name*: ___________________________  Last Name*: ___________________________
National Provider Identifier No. (NPI)*: ________  Practice/Facility Name: ___________________________
Address Line 1: ____________________________________________________________
Address Line 2: __________________________________________________________
City: _______________  State: ___________________________  Zip code: _______________
Phone*: ___________________________  Fax: ___________________________  Email: ___________________________

Serious Adverse Events Reporting

*My patient experienced a serious and potentially fatal liver injury event □

You may be contacted for further information on any reported events by the JYNARQUE REMS.

Signature*: ___________________________  Date*: ___________________________
Print Name: ___________________________
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](http://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.
Acute liver failure requiring liver transplantation has been reported in the post-marketing autoseomal 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

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:
   a. Prescribing Information
   b. REMS Program Overview
   c. 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 liver injury must be reported to the REMS Program.
  - Healthcare providers can complete and submit the Liver Adverse Events Reporting Form:
    a. Online
    b. By Fax
- Healthcare providers can report adverse events by calling the JYNARQUE REMS at 1-866-244-9466.
- The adverse events can also be reported to the REMS at the same time the Patient Status Form is due.

Reference ID: 4357323
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 eat 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 regular 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.
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 population. 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 1-866-750-4820.
   - **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 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.
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.

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
JYNARQUE is a trademark of Otsuka Pharmaceutical Co., Ltd. Tokyo 101-8535 Japan

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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

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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# 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
- 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 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 参考指南
- JYNARQUE REMS 患者登记表

## Resources for Pharmacies

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

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

* NPI Number: 

* Email: 

CONTINUE
Prescriber Certification

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

To report negative side effects, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-888-FDA-1080 (www.fda.gov/medwatch).

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

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Marketed and distributed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850
JYNARQUE is a trademark of Otsuka Pharmaceutical Co., Ltd. Tokyo 101-8535 Japan

© 2018 Otsuka America Pharmaceutical, Inc.
Prescriber Certification

WHAT IS JYNARQUE?

- 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)

- Please see Prescribing Information, including BOXED WARNING, for additional safety information
Prescriber Certification

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)].

To report negative side effects, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-888-FDA-1088 (www.fda.gov/medwatch)
For JYNARQUE REMS Program Information call:
PHONE: 1-866-264-9446
FAX: 1-866-750-4820

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Marketed and distributed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850
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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]
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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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

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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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 outweigh 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.

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: 1-866-750-5400

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WHAT IS THE GOAL OF THE JYNARQUE REMS?

The goal of JYNARQU 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

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: 1-864-750-4820

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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
Prescriber Certification

HOW DOES THE JYNARQUE REMS WORK?

<table>
<thead>
<tr>
<th>Prescriber</th>
<th>Before Prescribing/Dispensing JYNARQUE</th>
<th>Before Starting JYNARQUE for Each Patient</th>
<th>While on JYNARQUE Treatment for Each Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. 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.</td>
<td>2. Assess the patient's liver function and appropriateness of initiating treatment.</td>
<td>3. Assess the patient's liver function and appropriateness of continuing treatment.</td>
</tr>
<tr>
<td></td>
<td>2. Assess the patient's liver function and appropriateness of initiating treatment.</td>
<td>3. Enroll the patient.</td>
<td>4. 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.</td>
</tr>
<tr>
<td>Pharmacy (Outpatient &amp; Inpatient)</td>
<td>Pharmacy Certification</td>
<td>4. 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.</td>
<td>5. 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.</td>
</tr>
<tr>
<td>Patient</td>
<td>5. Review Patient Guide.</td>
<td>6. Get a blood test at 2 weeks and 4 weeks after you start treatment.</td>
<td>7. Get a blood test every month for the first 18 months of treatment and then every 3 months thereafter.</td>
</tr>
</tbody>
</table>

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: 1-888-244-9446
FAX: 1-866-750-0820

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Prescriber Certification

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.

<table>
<thead>
<tr>
<th>Prescriber</th>
<th>Pharmacy (Outpatient &amp; Inpatient)</th>
<th>Patient</th>
</tr>
</thead>
</table>
| To prescribe JYNARQUE:  
1. Become certified by completing a once-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 4 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. 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.  
4. Dispense no more than a 30-day supply.  
4. Inpatient: Verify the prescriber is certified and the patient is enrolled in the REMS Program.  
5. 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 1-800-244-3946. Healthcare providers must report cases of liver injury to the REMS Program Coordinating Center.

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: 1-866-750-6402

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Prescriber Certification

PREScriber Requirements

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

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: 1-866-750-6280

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Prescriber Certification

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
Prescriber 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

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: 1-866-284-9446
FAX: 1-866-750-6180

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Prescriber Certification

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](http://www.JYNARQUEREMS.com))
   - Submit a completed **Patient Status Form** (via fax or online at [www.JYNARQUEREMS.com](http://www.JYNARQUEREMS.com))

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

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

To report adverse events, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1080 [www.fda.gov/medwatch]
For JYNARQUE REMS Program Information call:
PHONE: 1-866-746-9446
FAX: 1-866-750-6800

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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.
- 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.

To report negative side effects, contact Otsuka America Pharmaceutical, Inc. at 1-800-436-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).
For JYNARQUE REMS Program Information call:
PHONE: 1-866-294-9446
FAX: 1-866-750-4820

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Prescriber Certification

LIVER ADVERSE EVENTS REPORTING FORM

- Suggestive serious and potentially fatal liver injury events will be collected via phone or fax using the Liver Adverse Events Reporting Form
- Healthcare providers must report Adverse Events suggestive of serious and potentially fatal liver injury by contacting the REMS:
  - By phone
  - Completing and submitting the Liver Adverse Events Reporting Form or
  - Completing and submitting the Patient Status Form
- Report treatment discontinuation or transfer of care to the REMS

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/modwatch)

For JYNARQUE REMS Program Information call:
PHONE: 1-866-244-9446
FAX: 1-866-750-6830

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Prescriber Certification

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.
Prescriber Certification

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**.
Prescriber Certification

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.
Prescriber Certification

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.
Prescriber Certification

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.

To report negative side effects, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1080 [www.fda.gov/medwatch]

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Prescriber Certification

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
Prescriber Certification

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
Prescriber Certification

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
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
Prescriber Certification

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
Prescriber Certification

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
Prescriber Certification

Question 7:

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

- True
- False
Prescriber Certification

Question 8:

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

- True
- False
Prescriber Knowledge Assessment

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

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 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
Prescriber Enrollment

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 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.JYNARQUE-rems.com, or fax them to the REMS at 1-866-750-8020.
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 verification.

Prescriber Information

*Last Name
State License #:

First Name
Preferred Method of Contact:

Middle Initial
Preferred Time of Contact:

*NH Number
Credential:


Practice/Facility Name

Address Line 1

Address Line 2

City

State

Zip

*Phone
Fax

Email

Office Liaison First Name

Office Liaison Last Name

Office Liaison Email


Prescriber Agreement

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 10 months and then every 2 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 appropriate baseline of initiating treatment using the Patient Enrollment Form.
5. Enroll the patient by completing and submitting the Patient Enrollment Forms to the REMS. Provide a copy of the form to the patient.

During treatment: 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 appropriate baseline 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.

*Signature

Reset
Submit
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 1-866-750-6620.
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)
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 Inpatient Pharmacy Enrollment Form.
2. Complete and submit the Inpatient Pharmacy Enrollment Form for the patient, www.JYNARQUEPharmacy.com, or fax it to the REMS at 1-866-775-8400.
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)

* Inpatient Pharmacy Name

Type:
Hospital
Mental facility
Rehabilitation facility
Other

* Pharmacy Address Line 1

City
State
Zip

Inpatient Pharmacy Ship to Address, if different from above

Pharmacy Address

City
State
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 Inpatient Pharmacy Enrollment Form.
2. Email to the REMS by completing the Inpatient Pharmacy Enrollment Form and submitting it to the REMS.
3. Ensure all pharmacist staff involved in dispensing JYNARQUE is informed of the REMS Program Overview.
4. Establish procedures to ensure compliance with the REMS.
5. Establish procedures and requirements to verify that no more than 15 days’ supply is dispensed upon discharge of the patient.
6. Inform the REMS of any changes to the Authorized Representative and complete a new Inpatient Pharmacy Enrollment Form with the new Authorized Representative.

Before dispensing I will ensure that all pharmacy staff:

1. Verify the prescription is certified and the patient is certified to the REMS.
2. Upon discharge, I will ensure that all pharmacy staff must dispense no more than 15 days’ supply.

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

1. Report adverse events suggestive of serious and potentially fatal injury by contacting the REMS by phone, using the Liver ADR Ph.D. E-mail, and/or calling the REMS.
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 all processes and procedures are in place and are being followed for the REMS.
5. Comply with all policies and procedures as in place and as being followed.

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

[Signature]

Submit