

Risk Evaluation and Mitigation Strategy (REMS) Document

JYNARQUE (tolvaptan) REMS Program

I. Administrative Information

Application Number: NDA 204441
Application Holder: Otsuka Pharmaceutical Company, Ltd.
Initial REMS Approval: 04/2018
Most Recent REMS Update: 11/2020

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)	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 8. Assess the patient's liver function and appropriateness of continuing treatment.
During treatment; every 3 months for the first 18 months and every 6 months thereafter	<ol style="list-style-type: none"> 9. Assess the patient's liver function and appropriateness of continuing treatment. Document appropriateness of continuing treatment and submit to the REMS Program using the Patient Status Form.
At all times	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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.
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During treatment; 2 weeks and 4 weeks after treatment initiation, then monthly for the first 18 months and every 3 months thereafter	5. Get a blood test to check your liver.
At all times	6. Inform the prescriber of signs and symptoms of serious liver injury.

3. Outpatient Pharmacies that dispense JYNARQUE must:

To become certified to dispense	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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 except to certified pharmacies. 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.
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4. Inpatient Pharmacies that dispense JYNARQUE must:

To become certified to dispense	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 7. Verify the prescriber is certified and the patient is enrolled in the REMS Program.
At/upon discharge	<ol style="list-style-type: none"> 8. Dispense no more than a 15 days supply.
To maintain certification to dispense	<ol style="list-style-type: none"> 9. Have a new authorized representative enroll in the REMS Program by completing the Inpatient Pharmacy Enrollment Form and submitting it to the REMS Program if the authorized representative changes.

At all times	<ol style="list-style-type: none">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.
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5. Wholesalers that distribute JYNARQUE must:

To be able to distribute	<ol style="list-style-type: none">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	<ol style="list-style-type: none">3. Distribute only to certified pharmacies.4. Maintain and submit records of drug distribution to the REMS Program.5. Comply with audits carried out by Otsuka Pharmaceutical Company, Ltd or third party acting on behalf of the applicant to ensure that all processes and procedures are in place and are being followed.

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

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

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

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

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

Target Audience**Communication Materials & Dissemination Plans**

Healthcare providers who are likely to prescribe JYNARQUE

REMS Letter: [Letter for Healthcare Providers](#)

1. Email within 60 calendar days of the date JYNARQUE is first commercially distributed and again 12 months later.
 - a. Send by mail within 30 calendar days of the date the first email was sent if a healthcare provider's email address is not available or the email is undeliverable.
 - b. Send a second email within 30 calendar days of the date the first email was sent if the first email is marked as unopened.
 2. Make available via a link from the JYNARQUE REMS Program Website.
 3. Disseminate through field-based sales and medical representatives.
 4. Disseminate through professional societies and request the letter or content be provided to their members.
 5. Disseminate at Professional Meetings for 12 months from the date JYNARQUE is first commercially distributed.
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To support REMS Program operations, Otsuka Pharmaceutical Company, Ltd must:

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

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

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

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

IV. REMS Assessment Timetable

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

V. REMS Materials

The following materials are part of the JYNARQUE REMS:

Enrollment Forms

Prescriber:

1. [Prescriber Enrollment Form](#)

Patient:

2. [Patient Enrollment Form](#)

Pharmacy:

3. [Outpatient Pharmacy Enrollment Form](#)
4. [Inpatient Pharmacy Enrollment Form](#)

Training and Educational Materials

Prescriber:

5. [Program Overview](#)
6. [Prescriber Training](#)
7. [Prescriber Knowledge Assessment](#)

Patient:

8. [Patient Guide](#)

Pharmacy:

9. [Program Overview](#)

Patient Care Form

10. [Patient Status Form](#)
11. [Liver Adverse Events Reporting Form](#)

Communication Materials

12. [Letter for Healthcare Providers](#)

Other Materials

13. [Program website](#)