JYNARQUE REMS (Risk Evaluation and Mitigation Strategy)

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

Acute liver failure requiring liver transplantation has been reported in the post-marketing autosomal dominant polycystic kidney disease (ADPKD) experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity.

PRESCRIBERS

Click here to learn how to prescribe JYNARQUE

To prescribe JYNARQUE:

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

PHARMACIES (OUTPATIENT & INPATIENT)

Click here to learn how to dispense JYNARQUE

To dispense JYNARQUE:

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

PATIENTS

Click here to learn how to receive JYNARQUE

To receive JYNARQUE:

1. **Understand the risks** associated with JYNARQUE.
2. **Enroll** in the REMS by completing the ***Patient Enrollment Form*** with your healthcare provider.
3. **Complete** baseline liver testing before your first dose, 2 weeks and 4 weeks after your first dose and monthly for the first 18 months of treatment and every 3 months thereafter.

PDFs for Download

Resources for Healthcare Providers

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

Resources for Pharmacies

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

Resources for Patients

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

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

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

Indication

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

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

[Month Year of Approval] XXXXXXXXXXXXX

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

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

Manufactured by Otsuka Pharmaceutical Co., Ltd. Tokyo 101-8535 Japan.
Marketed and distributed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA.
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Reference ID: 4707327

Prescribers

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

1. Ensuring that healthcare providers are educated on the following:
   a. the risk of serious and potentially fatal liver injury associated with the use of JYNARQUE
   b. the requirement for monitoring at baseline and periodic monitoring as described in the *Prescribing Information*
   c. the need to counsel patients about the risk of serious and potentially fatal liver injury and the need for monitoring at baseline and periodic monitoring as described in the *Prescribing Information*
2. Ensuring that healthcare providers adhere to:
   a. the requirement for monitoring at baseline and periodic monitoring as described in the *Prescribing Information*
3. Ensuring that patients are informed about:
   a. the risk of serious and potentially fatal liver injury associated with the use of JYNARQUE
   b. the requirement for monitoring at baseline and periodic monitoring as described in the *Prescribing Information*
4. Enrollment of all patients in a registry to further support long term safety and safe use of JYNARQUE

Prescriber Requirements

How do I become certified in the JYNARQUE REMS?

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

How do I enroll a patient in the JYNARQUE REMS?

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

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

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

How should I report liver adverse events?

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

PDFs for Download

Resources for Prescribers

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

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Patients

What is JYNARQUE?

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

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

Who should not take JYNARQUE?

Do not take JYNARQUE if you:

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

How do I become enrolled in the JYNARQUE REMS?

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

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

What do I need to do while taking JYNARQUE?

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

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

How will I get my JYNARQUE medicine?

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

PDFs for Download

Resources for Patients

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

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

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Pharmacies

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

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

JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity.

To become certified, pharmacies must:

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

To Ensure Compliance with REMS requirements, pharmacies must:

1. Before dispensing JYNARQUE,

   Outpatient: Obtain authorization to dispense each prescription by contacting the REMS online or by phone to verify prescriber is certified, and the patient is enrolled and authorized to receive the drug.
   - Dispense no more than a 30-day supply.

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

Login is available for certified pharmacies.

PDFs for Download

Resources for Pharmacies

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

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

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Contact us

Phone

1-866-244-9446

Fax

1-866-750-6820

Hours of Operation

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

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

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Login

Please enter your User Name

Login

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

User Name

LOGIN

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Resources

Resources for Prescribers

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

Resources for Patients

JYNARQUE REMS Patient Guide	English	Español	Chinese
JYNARQUE REMS Patient Enrollment Form	English	Español	Chinese

Resources for Pharmacies

JYNARQUE REMS Program Overview	English
JYNARQUE REMS Inpatient Pharmacy Enrollment Form	English
JYNARQUE REMS Outpatient Pharmacy Enrollment Form	English

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Prescriber Certification

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

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

* NPI Number:

* Email

CONTINUE

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Prescriber Certification

JYNARQUE® (tolvaptan) tablets

JYNARQUE REMS (RISK EVALUATION AND MITIGATION STRATEGY) PRESCRIBER TRAINING

This training includes information about:

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

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Prescriber Certification

JYNARQUE® (tolvaptan) tablets

WHAT IS JYNARQUE?

- JYNARQUE is a selective vasopressin V_2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)
- Please see Prescribing Information, including BOXED WARNING, for additional safety information

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Prescriber Certification

JYNARQUE® (tolvaptan) tablets

JYNARQUE HAS A **BOXED** WARNING

WARNING: RISK OF SERIOUS LIVER INJURY

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

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

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

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Prescriber Certification

JYNARQUE® (tolvaptan) tablets

RISK ASSOCIATED WITH JYNARQUE: SERIOUS AND POTENTIALLY FATAL LIVER INJURY

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

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JYNARQUE® (tolvaptan) tablets

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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Prescriber Certification

JYNARQUE® (tolvaptan) tablets

ADDITIONAL RISKS AND SAFETY INFORMATION

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

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Prescriber Certification

JYNARQUE® (tolvaptan) tablets

WHAT IS THE JYNARQUE REMS?

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

JYNARQUE can cause serious and potentially fatal liver injury.

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

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

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JYNARQUE® (tolvaptan) tablets

WHAT IS THE GOAL OF THE JYNARQUE REMS?

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

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

[Month Year of Approval] XXXXXXXXXXXXX

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

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

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

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

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HOW DOES THE JYNARQUE REMS WORK?

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

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WHAT ARE THE REQUIREMENTS OF THE JYNARQUE REMS?

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

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

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

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PRESCRIBER REQUIREMENTS

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

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HOW DOES A PRESCRIBER BECOME CERTIFIED?

Before prescribing JYNARQUE:

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

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HOW DOES A PRESCRIBER ENROLL PATIENTS?

Before starting each patient on JYNARQUE:

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

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HOW DOES A PRESCRIBER MONITOR PATIENTS?

Once your patient is on JYNARQUE:

1. **Monitor** your JYNARQUE patients on an ongoing basis
   - Assess the patient's liver function and appropriateness of initiating and continuing treatment
2. **Submit** a completed ***Patient Status Form*** to the REMS for each patient:
   - Every 3 months for the first 18 months of treatment
   - Every 6 months thereafter
3. **Report** any Adverse Events suggestive of serious and potentially fatal liver injury to the REMS by doing any one of the following:
   - Contact the JYNARQUE REMS Program at 1-866-244-9446
   - Submit a completed ***Liver Adverse Events Reporting Form*** (via fax or online at www.JYNARQUEREMS.com)
   - Submit a completed ***Patient Status Form*** (via fax or online at www.JYNARQUEREMS.com)
4. Inform the REMS if a patient is no longer under your care or has discontinued JYNARQUE

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JYNARQUE REMS PATIENT STATUS FORM

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

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PRESCRIBER DELEGATE

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

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DEFINITION OF SERIOUS AND POTENTIALLY FATAL LIVER INJURY

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

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

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

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

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

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

Reporting Procedures:

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

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

Report treatment discontinuation or transfer of care to the REMS

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

The ***Liver Adverse Event Reporting Form*** and ***Patient Status Form*** are available at www. JYNARQUEREMS.com

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

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

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PATIENT REGISTRY

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

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NEXT STEPS

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

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

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

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

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PRESCRIBERS WHO SUCCESSFULLY COMPLETE THE KNOWLEDGE ASSESSMENT WILL RECEIVE:

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

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

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

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

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

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

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

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

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

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Question 1:

Before treating each patient with JYNARQUE, I should.

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

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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

[Month Year of Approval] XXXXXXXXXXXXX

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

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

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

[Month Year of Approval] XXXXXXXXXXXXX

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Question 4:

The primary counseling message I should tell my patients is:

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

[Month Year of Approval] XXXXXXXXXXXXX

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Question 5:

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

- ○ True
- ○ False

[Month Year of Approval] XXXXXXXXXXXXX

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Question 6:

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

- ○ True
- ○ False

[Month Year of Approval] XXXXXXXXXXXXX

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Question 7:

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

- ○ True
- ○ False

[Month Year of Approval] XXXXXXXXXXXX

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Question 8:

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

- ○ True
- ○ False

[Month Year of Approval] XXXXXXXXXXXXX

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SUBMIT

Reference ID: 4707327

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

[Month Year of Approval] XXXXXXXXXXXX

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Prescriber Knowledge Assessment

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

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

REVIEW TRAINING SLIDES

RETAKE KNOWLEDGE ASSESSMENT

[Month Year of Approval] XXXXXXXXXXXXX

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Reference ID: 4707327

Prescriber Enrollment

NPI Validation ••• Review Materials ••• Knowledge Assessment ••• 4 Online 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.JYNARQUErems.com, or fax them to the REMS at 1-866-750-6820.
3. **Complete** all mandatory fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the REMS will notify you upon successful certification.

Prescriber Information

*NPI Number:

*State License #:

*First Name

Middle Initial

*Last Name

Preferred Method of Contact:
○ Phone ○ Email ○ Fax

Preferred Time of Contact:
○ AM ○ PM

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

*Specialty
☐ Nephrology
☐ Other

Practice/Facility Name

*Address Line 1

Address Line 2

*City

*State
-- Please Select --

*Zip

*Phone

*Fax

*Email

Office Liaison First Name

Office Liaison Last Name

Office Liaison Email

Prescriber Agreement

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

I have:

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

Before treatment initiation with the first dose I must:

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

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

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

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

At all times, I must:

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

I understand and acknowledge that:

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

☐ *Signature

RESET SUBMIT

[Month Year of Approval] XXXXXXXXXXXXX

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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.

Inpatient Pharmacy Information

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

SUBMIT

[Month Year of Approval] XXXXXXXXXXXXX

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Inpatient Pharmacy Enrollment Form

Instructions

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

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

Instructions for Authorized Representative:

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

Inpatient Pharmacy Information

*Pharmacy National Provider Information No. (NPI)

RESET

*Inpatient Pharmacy Name

*Type

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

*Pharmacy Address Line 1

Pharmacy Address Line 2

*City

*State

-- Please Select --

*Zip

Inpatient Pharmacy Ship to Address, if different from above

Pharmacy Address

City

State

-- Please Select --

Zip Code

Inpatient Pharmacy Authorized Representative Information

*First Name

Middle Initial

*Last Name

*Telephone Number

Alternate Telephone Number

*Office Fax

*Email

Preferred Method of Contact

Authorized Representative Responsibilities

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

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

Before dispensing I will ensure that all pharmacy staff must:

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

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

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

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

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

*Signature

SUBMIT

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

/s/

MARY R SOUTHWORTH
11/25/2020 07:29:03 AM