

Risk Evaluation and Mitigation Strategy (REMS) Document

TURALIO™ (pexidartinib) REMS Program

I. Administrative Information

Application Number: NDA 211810
Application Holder: Daiichi Sankyo, Inc.
Initial REMS Approval: 08/2019
Most Recent REMS Update: 08/2020

II. REMS Goal

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

1. Ensuring that prescribers are educated on the following:
 - a. approved indication for TURALIO
 - b. the risk of serious and potentially fatal liver injury associated with the use of TURALIO
 - c. the need for liver monitoring at baseline and periodically during treatment with dose modifications as described in the Prescribing Information
 - d. the need to counsel patients about the risk of serious and potentially fatal liver injury, liver monitoring at baseline and periodically during treatment with TURALIO as described in the Patient Guide and to report signs and/or symptoms of liver injury to the prescriber during therapy
2. Ensuring that prescribers adhere to the requirement of baseline and periodic monitoring as described in the Prescribing Information
3. Enrollment of all patients in a registry to further assess the safe use and acute, chronic and irreversible hepatotoxicity of TURALIO.

III. REMS Requirements

Daiichi Sankyo, Inc. must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare Providers who prescribe TURALIO 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 [Prescriber Knowledge Assessment](#) and submit it to the REMS.
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. Provide the patient with the Patient Guide. 6. Assess the patient's baseline liver function. Document and submit the results to the REMS Program using the Patient Enrollment Form. 7. Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS Program.
During treatment, at least weekly for the first 8 weeks, then every 2 weeks for 1 month, then every 3 months	<ol style="list-style-type: none"> 8. Assess the patient's liver function and modify the dose of TURALIO as needed as described in the Prescribing Information.
During treatment, monthly for the first 3 months	<ol style="list-style-type: none"> 9. Prescribe no more than a 30 days' supply.
During treatment, monthly for the first 3 months, then month 6, 9, and 12, and every 6 months thereafter	<ol style="list-style-type: none"> 10. Assess the patient by performing liver tests. Document and submit to the REMS Program using the Patient Status Form.
At all times	<ol style="list-style-type: none"> 11. Report adverse events suggestive of serious and potentially fatal liver injury to the REMS Program using the Liver Adverse Event Reporting Form.

2. Patients who are prescribed TURALIO:

Before treatment initiation	<ol style="list-style-type: none"> 1. Review the Patient Guide. 2. Get blood tests to check your liver. 3. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program.
During treatment, weekly for the first 8 weeks, then every 2 weeks for 1 month, then every 3 months or more often as directed by your prescriber	<ol style="list-style-type: none"> 4. Get blood tests to check your liver so your prescriber can modify your TURALIO treatment, if needed.
At all times	<ol style="list-style-type: none"> 5. Inform the prescriber of signs and/or symptoms of liver injury.

3. Pharmacies that dispense TURALIO 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 by completing the Pharmacy Enrollment Form and submitting it to the REMS Program. 4. Train all relevant staff involved in dispensing TURALIO using the Program Overview.
Before dispensing	<ol style="list-style-type: none"> 5. 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.
Before dispensing; for the first 3 months	<ol style="list-style-type: none"> 6. Dispense no more than a 30 days supply.
To maintain certification to dispense	<ol style="list-style-type: none"> 7. Have the new authorized representative enroll in the REMS by completing the Pharmacy Enrollment Form and submitting it to the REMS if the authorized representative changes.
At all times	<ol style="list-style-type: none"> 8. Report adverse events suggestive of serious and potentially fatal liver injury to the REMS Program using the Liver Adverse Event Reporting Form. 9. Do not distribute, transfer, loan, or sell TURALIO, except to certified dispensers. 10. Maintain records documenting the staff's completion of REMS training. 11. Maintain records that all processes and procedures are in place and being followed. 12. Comply with audits carried out by Daiichi Sankyo, Inc. or a third party acting on behalf of the applicant, to ensure that all processes and procedures are in place and are being followed.

4. Wholesalers-Distributors that distribute TURALIO 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 relevant staff involved in TURALIO distribution on the REMS requirements.
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- At all times
3. Distribute only to certified pharmacies.
 4. Maintain records of all drug distributions.
 5. Comply with audits carried out by Daiichi Sankyo, Inc. or a 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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Daiichi Sankyo, Inc. must provide training to healthcare providers who prescribe TURALIO.

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

Daiichi Sankyo, Inc. must provide training to pharmacies that dispense TURALIO.

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

To inform healthcare providers about the REMS and the risks and safe use of TURALIO, Daiichi Sankyo, Inc. must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials-& Dissemination Plans
Healthcare providers who are likely to prescribe TURALIO	<p>REMS Letter: Letter for Healthcare Providers, Letter for Professional Societies</p> <ol style="list-style-type: none">1. Email within 60 calendar days of the date TURALIO is first commercially distributed and again 12 months later.<ol style="list-style-type: none">a. Send by mail within 30 calendar days of approval of the REMS 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.c. Send by mail within 30 calendar days of the date the second email was sent if the second email is marked as unopened.2. Disseminate through field-based sales and medical representatives.3. Disseminate through professional societies and request the letter or content be provided to their members.<ol style="list-style-type: none">a. Sarcoma Alliance for Research through Collaboration; Connective Tissue Oncology Society; American Society of Clinical Oncology; and National Comprehensive Cancer Network4. Disseminate at professional meetings for 12 months from the date TURALIO is first commercially distributed.

To support REMS operations, Daiichi Sankyo, Inc. must:

1. Authorize dispensing for each patient based on receipt of the [Patient Enrollment Form](#) and [Patient Status Form](#) on the following schedule: Authorize the first patient shipment upon receipt of the [Patient Enrollment Form](#). If a completed [Patient Enrollment Form](#) is not received, the patient is not

authorized to receive drug. For subsequent dispensing, if the [Patient Status Form](#) is not received within 20 calendar days after the date the last [Patient Status Form](#) was due, the patient is not authorized to receive subsequent drug shipments.

2. Establish and maintain a REMS Website, www.TURALIOREMS.com. The REMS website must include the capability to complete prescriber certification and enrollment online, the capability to enroll and manage patients online including patient authorization and reporting liver injury, and the option to print the Prescribing Information and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS website. The REMS website must not link back to the promotional product website(s).
3. Make the REMS website fully operational and all REMS materials available through website and call center by the date TURALIO is first commercially distributed.
4. Establish and maintain a REMS call center for REMS participants at [1-833-887-2546].
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the TURALIO REMS Program.
6. Ensure prescribers are able to enroll online, by fax, and by email.
7. Ensure pharmacies are able to enroll by fax and email.
8. Ensure prescribers and pharmacies are able to report serious and potentially fatal liver injury by phone and online.
9. Ensure pharmacies are able to obtain authorization to dispense by phone and online.
10. Provide [Program Overview](#), [Prescriber Training](#), [Prescriber Knowledge Assessment](#), [Patient Enrollment Form](#), [Patient Guide](#) and the Prescribing Information to prescribers who (1) attempt to prescribe and are not yet certified or (2) inquire about how to become certified.
11. Provide [Program Overview](#), [Pharmacy Enrollment Form](#) to pharmacies that (1) attempt to order/dispense 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.
13. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.
14. Provide certified prescribers access to the database of certified pharmacies and their enrolled patients.
15. Provide authorized wholesalers-distributors access to the database of certified pharmacies.
16. Establish and maintain a registry which includes a reporting and collection system for all patients to provide information on acute, chronic and irreversible hepatotoxicity.
17. Ensure that once a report suggestive of serious or potentially fatal liver injury is received, Daiichi Sankyo, Inc. follows up with the healthcare provider to obtain all data required for complete adverse event reporting related to serious and potentially fatal liver injury under the REMS.
18. Report serious and potentially fatal liver injury as soon as possible to the FDA but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under applicable FDA regulations.

To ensure REMS participants' compliance with the REMS, Daiichi Sankyo, Inc. must:

19. Ensure the [Patient Status Form](#) is received for each patient on the following schedule: If the form is not received within 20 calendar days of the date the last [Patient Status Form](#) was due, Daiichi Sankyo, Inc. must contact the prescriber for the form. The patient is not authorized to receive the drug until the form is received.
20. Verify annually that the designated authorized representative for the pharmacy is the same. If different, the pharmacy must re-certify with a newly authorized representative.
21. 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; enrollment and status of patients; and audits of pharmacies and wholesalers-distributors. These records must be readily available for FDA inspections.

22. Establish a plan for addressing noncompliance with REMS requirements.
23. 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.
24. Audit pharmacies no later than 90 calendar days after they become certified, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.
25. Audit all wholesalers-distributors no later than 90 calendar days after they become authorized to distribute the drug and annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.
26. Take reasonable steps to improve operations of and compliance with the requirements in the TURALIO REMS based on monitoring and evaluation of the TURALIO REMS.

IV. REMS Assessment Timetable

Daiichi Sankyo, Inc. must submit REMS Assessments at 6 months, 12 months and annually thereafter from the date of the initial approval of the REMS (08/02/2019). 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. Daiichi Sankyo, Inc. 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 TURALIO REMS:

Enrollment Forms

Prescriber:

1. [Prescriber Enrollment Form](#)

Patient:

2. [Patient Enrollment Form](#)

Pharmacy:

3. [Pharmacy Enrollment Form](#)

Training and Educational Materials

Prescriber:

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

Patient:

7. [Patient Guide](#)

Pharmacy:

8. [Program Overview](#)

Patient Care Forms

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

Communication Materials

11. [Letter for Healthcare Providers](#)
12. [Letter for Professional Societies](#)

Other Materials

13. [REMS Website](#)