

TURALIO™ (pexidartinib)
Risk Evaluation and Mitigation Strategy (REMS)

Prescriber Training



Welcome to the TURALIO™ REMS Prescriber Training

To prescribe TURALIO, you must become certified in the TURALIO REMS, which includes reviewing this training.

After reviewing this training, you must complete and submit a *Prescriber Knowledge Assessment* and a *Prescriber Enrollment Form* before you can prescribe TURALIO. You can complete these via fax (1-833-TRL-REMS), email (Enroll@TURALIOREMS.com), or online at www.TURALIOREMS.com.

For more information or to obtain any REMS materials visit www.TURALIOREMS.com

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TURALIO Overview

What is TURALIO?

TURALIO™ (pexidartinib) is indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

Risk of Liver Injury

It is important to be aware of the risk of serious and potentially fatal liver injury associated with TURALIO (see *Prescribing Information for full details*).

- Hepatotoxicity with ductopenia and cholestasis has occurred in patients treated with TURALIO.
 - Across 768 patients who received TURALIO in clinical trials, there were two irreversible cases of cholestatic liver injury.
 - One patient died with advanced cancer and ongoing liver toxicity and one patient required a liver transplant.
 - The mechanism of cholestatic hepatotoxicity is unknown and its occurrence cannot be predicted. It is unknown whether liver injury occurs in the absence of increased transaminases.

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TURALIO REMS Overview

What is the TURALIO REMS?

The TURALIO REMS (Risk Evaluation and Mitigation Strategy) is a safety program that manages the serious risks of TURALIO. The TURALIO REMS is required by the Food and Drug Administration (FDA) because of the serious, and potentially fatal liver injury.

- Only prescribers and pharmacies certified by the TURALIO REMS can prescribe and dispense TURALIO to patients.
- Patients must be enrolled in the TURALIO REMS patient registry and follow all the safety rules in the REMS to receive TURALIO.

What Do I Need to Do Before Prescribing TURALIO?

To prescribe TURALIO, you must become certified in the TURALIO REMS

Complete the following 4 steps to become certified:

1	Review the <i>TURALIO Prescribing Information</i>
2	Review the <i>Program Overview</i> and the <i>Prescriber Training</i> (this document)
3	Complete and submit the <i>Prescriber Knowledge Assessment</i> to the TURALIO REMS
4	Complete and submit the <i>Prescriber Enrollment Form</i> to the TURALIO REMS

What Do I Need to Do Prior to Initiating TURALIO?

To receive TURALIO, patients must be counseled and enrolled in the TURALIO REMS

Prior to initiating treatment, counsel patients on:

1	The risk of serious and potentially fatal liver injury
2	Liver test monitoring prior to and during treatment with TURALIO
3	Immediately reporting any signs and/or symptoms of liver injury during therapy

What Do I Need to Do Prior to Initiating TURALIO?

Prior to initiating treatment:

- Enroll the patient into the TURALIO REMS and patient registry by completing and submitting the *Patient Enrollment Form* to the REMS
- Provide the *Patient Guide* to educate and communicate these messages with each new or refill TURALIO prescription
- Assess the patient by obtaining liver tests

Prescriptions should be limited to a 30 days' supply
for each of the first 3 months of treatment

How Will My Patient Get TURALIO?

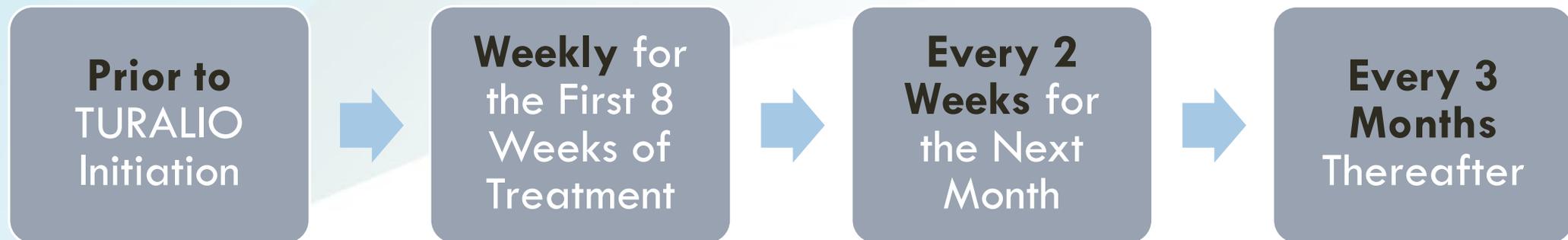
TURALIO will only be dispensed by certified pharmacies.

Enrolled patients will be contacted by a certified pharmacy to set up shipment of TURALIO.

Liver Monitoring During Treatment

Monitor aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT).

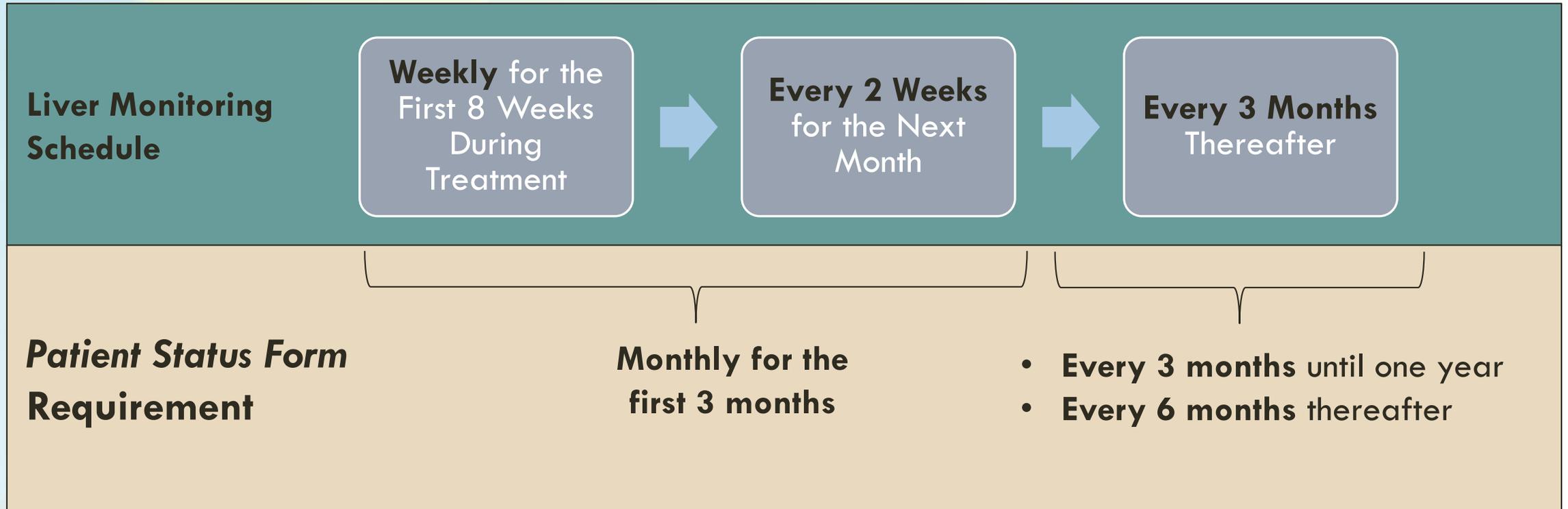
Liver Monitoring Schedule*



*More frequent monitoring is required for severe liver adverse reactions or TURALIO re-challenge.

Patient Status Form

During treatment, prescribers must complete and submit a *Patient Status Form* to the REMS



Liver Adverse Event Reporting Form

During treatment, use the *Liver Adverse Event Reporting Form* to report adverse events or laboratory abnormalities suggestive of serious and potentially fatal liver injury

Adverse events or laboratory abnormalities suggestive of serious and potentially fatal liver injury are:

- ALT or AST $> 3 \times$ ULN and TBIL $> 2 \times$ ULN
- ALT or AST $> 10 \times$ ULN with or without TBIL elevation
- TBIL $> 2 \times$ ULN without changes in ALT or AST
- Liver Transplantation
- Death

Dose Reductions For Adverse Reactions

To manage adverse reactions, interruption of treatment, dose reduction, or dose discontinuation may be needed.

Adverse Reactions	Severity	Required Modification
Increased ALT/AST	> 3-5 x ULN	<ul style="list-style-type: none">Withhold and monitor liver tests <u>weekly</u>.If AST and ALT are less than or equal to 3 times ULN within 4 weeks, resume at reduced dose.If AST or ALT is <u>not</u> less than or equal to 3 times ULN in 4 weeks, permanently discontinue TURALIO.
	> 5-10 x ULN	<ul style="list-style-type: none">Withhold and monitor liver tests <u>twice weekly</u>.If AST and ALT are less than or equal to 3 times ULN within 4 weeks, resume at reduced dose.If AST or ALT is <u>not</u> less than or equal to 3 times ULN in 4 weeks, permanently discontinue TURALIO.
	> 10 x ULN	<ul style="list-style-type: none">Permanently discontinue TURALIO.Monitor liver tests <u>twice weekly</u> until AST or ALT is less than or equal to 5 times ULN, then <u>weekly</u> until less than or equal to 3 times ULN.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

Dose reductions should be in increments of 200 mg (1 capsule)

Dose Reductions For Adverse Reactions Continued

To manage adverse reactions, interruption of treatment, dose reduction, or dose discontinuation may be needed.

Adverse Reactions	Severity	Required Modification
Increased ALP ¹ and GGT	ALP > 2 x ULN with GGT > 2 x ULN	<ul style="list-style-type: none"> Permanently discontinue TURALIO. Monitor liver tests <u>twice weekly</u> until ALP is less than or equal to 5 times ULN, then <u>weekly</u> until less than or equal to 2 times ULN.
Increased Bilirubin	TBIL > ULN to < 2 x ULN or DBIL > ULN and < 1.5 x ULN	<ul style="list-style-type: none"> Withhold and monitor liver tests <u>twice weekly</u>. If an alternate cause for increased bilirubin is confirmed and bilirubin is less than ULN within 4 weeks, resume at reduced dose. If bilirubin is <u>not</u> less than ULN in 4 weeks, permanently discontinue TURALIO.
	TBIL ≥ to 2 x ULN or DBIL > 1.5 x ULN	<ul style="list-style-type: none"> Permanently discontinue TURALIO. Monitor liver tests <u>twice weekly</u> until bilirubin is less than or equal to ULN.

ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; TBIL = total bilirubin; DBIL = direct bilirubin; ULN = upper limit of normal

¹ Confirm ALP elevations as liver isozyme fraction.

Dose reductions should be in increments of 200 mg (1 capsule)

Dose Reductions For Adverse Reactions Continued

To manage adverse reactions, interruption of treatment, dose reduction, or dose discontinuation may be needed.

Adverse Reactions	Severity	Required Modification
Adverse Reactions or Other Laboratory Abnormalities	Severe or intolerable	<ul style="list-style-type: none">• Withhold until improvement or resolution.• Resume at a reduced dose upon improvement or resolution.

Dose reductions should be in increments of 200 mg (1 capsule)

Dose Reductions

To manage adverse reactions, interruption of treatment, dose reduction, or dose discontinuation may be needed.

Dose Reductions

Dose Reduction	Total Daily Dose	Administration of Total Daily Dose
First	600 mg	200 mg in the morning and 400 mg in the evening
Second	400 mg	200 mg twice daily

Permanently discontinue TURALIO in patients who are unable to tolerate 200 mg orally twice daily.

Dose reductions should be in increments of 200 mg (1 capsule)

This concludes the Prescriber Training.