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Turalio® pexidartinib 125 mg capsules

SAFETY MONITORING & MANAGEMENT

The first FDA-approved systemic therapy for symptomatic TGCT (also known as PVNS or GCT-TS) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.[1,2]

INDICATION

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.

IMPORTANT SAFETY INFORMATION

WARNING: HEPATOTOXICITY

- **TURALIO can cause serious and potentially fatal liver injury, including vanishing bile duct syndrome.**
- **Monitor liver tests prior to initiation of TURALIO and at specified intervals during treatment. Withhold and dose reduce or permanently discontinue TURALIO based on severity of hepatotoxicity. Monitoring and prompt cessation of TURALIO may not eliminate the risk of serious and potentially fatal liver injury.**
- **TURALIO is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program.**

Please see additional Important Safety Information and full Prescribing Information, including Boxed WARNING, and Medication Guide.

Indication and Important Safety Information

INDICATION

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.

IMPORTANT SAFETY INFORMATION

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- **TURALIO can cause serious and potentially fatal liver injury, including vanishing bile duct syndrome.**
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- **TURALIO is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program.**

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity

- Hepatotoxicity, including liver failure and life-threatening vanishing bile duct syndrome (VBDS), ductopenia, and symptomatic cholestasis (including severe pruritus) can occur in patients treated with TURALIO and can occur despite monitoring and prompt drug cessation.
- The mechanism of cholestatic hepatotoxicity is unknown and its occurrence cannot be predicted. It is unknown whether liver injury can also occur in the absence of increased transaminases.
- Of the first 609 patients who received TURALIO under the REMS program, 32 (5.3%) developed a liver injury event of concern, defined as any serious liver-related outcome or any liver abnormality that triggers drug discontinuation per the US Prescribing Information. These 32 patients developed liver toxicity within 71 days of the first dose of TURALIO; ten required hospitalization and two developed VBDS. Sixteen of the 32 patients had not fully recovered at the time of the analysis, including 6 patients followed for at least 6 months after discontinuation.
- Among 768 patients who received TURALIO in clinical trials, there were two irreversible cases of cholestatic liver injury. One patient with advanced cancer and ongoing liver toxicity died and one patient with a confirmed case of VBDS required a liver transplant.
- In ENLIVEN, 3 of 61 (5%) patients who received TURALIO developed signs of serious liver injury, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 × upper limit of normal (ULN) with total bilirubin ≥2 × ULN. In these patients, peak ALT ranged from 6 to 9 × ULN, peak total bilirubin ranged from 2.5 to 15 × ULN, and alkaline phosphatase (ALP) was ≥2 × ULN. ALT, AST, and total bilirubin improved to <2 × ULN in these three patients 1 to 7 months after discontinuing TURALIO.
- Avoid TURALIO in patients with preexisting increased serum transaminases, total bilirubin, or direct bilirubin (>ULN); or active liver or biliary tract disease, including increased ALP.
- Monitor liver tests, including AST, ALT, total bilirubin, direct bilirubin, ALP, and gamma-glutamyl transferase (GGT), prior to initiation of TURALIO, weekly for the first 8 weeks, every 2 weeks for the next month and every 3 months thereafter.
- Withhold and dose reduce, or permanently discontinue TURALIO based on the severity of the hepatotoxicity. Refer patients to a hepatologist if liver tests do not return to normal. Rechallenge with a reduced dose of TURALIO may result in a recurrence of increased serum transaminases, bilirubin, ALP or other signs of liver injury. Monitor liver tests weekly for the first month after rechallenge.

TURALIO REMS

- Requirements include: 1) prescribers must be certified by enrolling and completing training, 2) patients must complete and sign an enrollment form for inclusion in a patient registry, and 3) pharmacies must be certified and must dispense only to patients who are authorized (enrolled in the REMS patient registry).
- Further information is available at www.TURALIOREMS.com or 1-833-887-2546.

Embryo-Fetal Toxicity

- TURALIO may cause fetal harm when administered to a pregnant woman. Advise patients of reproductive potential of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to the initiation of TURALIO.

Please see additional Important Safety Information and full Prescribing Information, including Boxed WARNING, and Medication Guide.

Turalio® pexidartinib 125 mg capsules

Indication and Important Safety Information (CONT.)

- Advise females of reproductive potential to use an effective nonhormonal method of contraception. TURALIO can render hormonal contraceptives ineffective during treatment with TURALIO and for 1 month after the final dose.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with TURALIO and for 1 week after the final dose.

Potential Risks Associated with a High-Fat Meal

- Taking TURALIO with a high-fat meal increases pexidartinib concentrations, which may increase the incidence and severity of adverse reactions, including hepatotoxicity.
- Instruct patients to take TURALIO with a low-fat meal (approximately 11 to 14 grams of total fat) and to avoid taking TURALIO with a high-fat meal (approximately 55 to 65 grams of total fat).

ADVERSE REACTIONS

- The most common adverse reactions (>20%) were increased lactate dehydrogenase (92%), increased AST (88%), hair color changes (67%), fatigue (64%), increased ALT (64%), decreased neutrophils (44%), increased cholesterol (44%), increased ALP (39%), decreased lymphocytes (38%), eye edema (30%), decreased hemoglobin (30%), rash (28%), dysgeusia (26%), and decreased phosphate (25%).

DRUG INTERACTIONS

- Hepatotoxic products: Avoid coadministration in patients with increased serum transaminases, total bilirubin, or direct bilirubin (>ULN) or active liver or biliary tract disease.
- Moderate or strong CYP3A inhibitors and UGT inhibitors: Concomitant use may increase pexidartinib concentrations. Reduce TURALIO dosage if concomitant use cannot be avoided.
- Strong CYP3A inducers: Avoid concomitant use due to decreased pexidartinib concentrations.
- Acid-reducing agents: Avoid concomitant use of proton pump inhibitors due to decreased pexidartinib concentrations. Use histamine-2 receptor antagonists or antacids if needed.
- CYP3A substrates: Avoid concomitant use where minimal concentration changes may lead to serious therapeutic failure (e.g., hormonal contraceptives) due to decreased concentrations of CYP3A substrates.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed and for at least 1 week after the final dose.
- Renal impairment: Reduce the dosage for patients with mild to severe renal impairment.
- Hepatic impairment: Reduce the dosage for patients with moderate hepatic impairment. TURALIO has not been studied in patients with severe hepatic impairment.

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see full Prescribing Information, including Boxed WARNING, and Medication Guide.

National Comprehensive Cancer Network® (NCCN®) Recommendation

TURALIO is the first FDA-approved systemic therapy for symptomatic TGCT (also known as PVNS or GCT-TS) associated with severe morbidity or functional limitations and not amenable to improvement with surgery

Pexidartinib is an NCCN Category 1 recommended therapy option for TGCT/PVNS in the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma[3]

IMPORTANT SAFETY INFORMATION (CONT.)

WARNING: HEPATOTOXICITY

- **TURALIO can cause serious and potentially fatal liver injury, including vanishing bile duct syndrome.**
- **Monitor liver tests prior to initiation of TURALIO and at specified intervals during treatment. Withhold and dose reduce or permanently discontinue TURALIO based on severity of hepatotoxicity. Monitoring and prompt cessation of TURALIO may not eliminate the risk of serious and potentially fatal liver injury.**
- **TURALIO is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program.**

PREV NEXT

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ENLIVEN: The first phase 3, placebo-controlled trial evaluating an oral systemic therapy for TGCT[1,2,4]

How TURALIO works

TURALIO is an oral small-molecule TKI that works by blocking CSF-1R, a receptor involved in signaling between tumor cells and infiltrating inflammatory cells in the synovium. TURALIO also inhibits tyrosine kinase activity of c-KIT and mutant FMS-like tyrosine kinase (FLT3).[1]

Study design

TURALIO was investigated in ENLIVEN, a phase 3, double-blind, placebo-controlled, randomized clinical trial of 120 patients with advanced TGCT for whom surgery was not recommended. Patients were randomized to placebo (n=59) or TURALIO (n=61).[1,4]

Study endpoints

The primary efficacy outcome measured at week 25 was ORR per RECIST v1.1. The secondary endpoints included ORR per Tumor Volume Score (TVS), mean change from baseline in ROM of the affected joint, DOR, mean change from baseline in PROMIS-PF, mean change from baseline in worst stiffness, and proportion of responders based on BPI worst pain.[1,4,a]

BPI, Brief Pain Inventory; CSF-1R, colony stimulating factor 1 receptor; DOR, duration of response; ORR, overall response rate; PROMIS-PF, Patient-Reported Outcomes Measurement Information System-Physical Function; RECIST, Response Evaluation Criteria In Solid Tumors; ROM, range of motion; TGCT; tenosynovial giant cell tumor, TKI, tyrosine kinase inhibitor.

[a]TVS was defined in ENLIVEN as the estimated volume of the maximally distended synovial cavity or tendon sheath involved, measured in 10% increments.[1]

IMPORTANT SAFETY INFORMATION (CONT.)

Embryo-Fetal Toxicity

- TURALIO may cause fetal harm when administered to a pregnant woman. Advise patients of reproductive potential of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to the initiation of TURALIO.
- Advise females of reproductive potential to use an effective nonhormonal method of contraception. TURALIO can render hormonal contraceptives ineffective during treatment with TURALIO and for 1 month after the final dose.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with TURALIO and for 1 week after the final dose.

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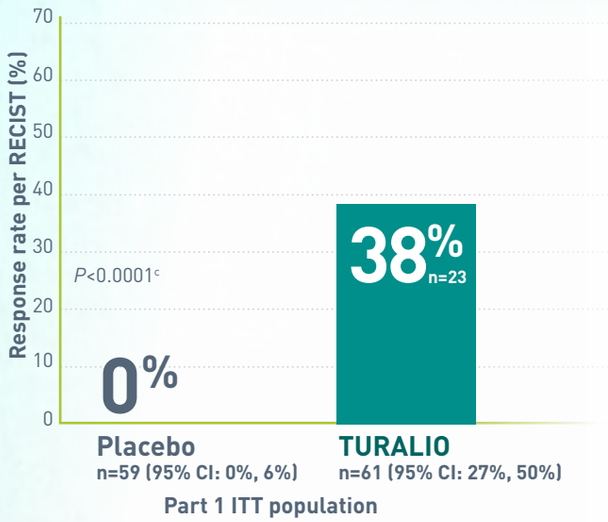
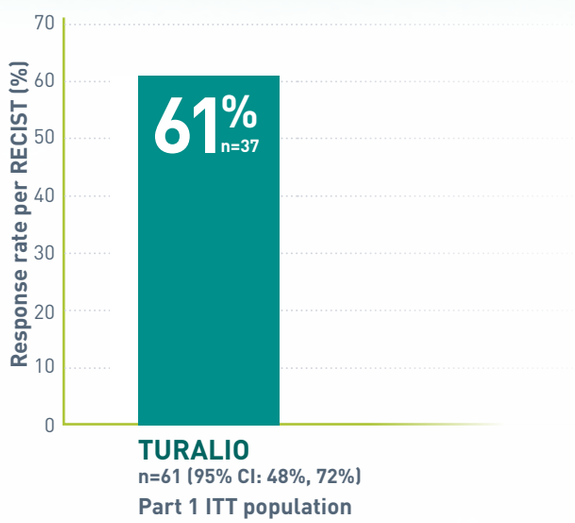
TURALIO demonstrated durable tumor responses[4,5]

Overall response rate (ORR) by RECIST v1.1[1,5,6]

Primary Endpoint: ORR at 25 weeks[a]



ORR at final analysis (31-month median follow-up)[b]



Of the patients taking TURALIO at 6 months[1,4]

23% (14 out of 61) had their tumors reduced in length by 30% or more (partial response)[d]

15% (9 out of 61) had their tumors disappear completely (complete response)[e]

Secondary endpoint: duration of response

TURALIO helped patients achieve lasting reduction in tumor size

At primary endpoint analysis

More than half of responders had an on-going response. Median duration of response was not reached with a median follow-up of 22 months (response range: 6.9+ to 24.9+ months)[1,4,f]

At final analysis

The median duration of response was not reached (range: 4.6+, 63.4+ months) in the 37 responders.[1,g]

Duration of response is defined as the time when the patient experiences first response to the time of progression, regardless of whether the patient has discontinued treatment.[4]

CI, confidence interval; ITT, intent-to-treat; ORR, overall response rate; RECIST, Response Evaluation Criteria In Solid Tumors.

[a]ORR was determined by blinded independent central review (BICR)[1]; [b]A median follow-up of 31.2 (range: 2, 66) months (final database lock June 1, 2021)[5]; [c]Fisher's exact test[4]; [d]Partial response was defined as 30% or more reduction in tumor length[6]; [e]Complete response was defined as 100% reduction in tumor length[6]; [f]Data cutoff January 31, 2018[1]; [g]At completion of the ENLIVEN study.[1]

IMPORTANT SAFETY INFORMATION (CONT.)

WARNINGS AND PRECAUTIONS

Hepatotoxicity

- Hepatotoxicity, including liver failure and life-threatening vanishing bile duct syndrome (VBDS), ductopenia, and symptomatic cholestasis (including severe pruritus) can occur in patients treated with TURALIO and can occur despite monitoring and prompt drug cessation.
- The mechanism of cholestatic hepatotoxicity is unknown and its occurrence cannot be predicted. It is unknown whether liver injury can also occur in the absence of increased transaminases.

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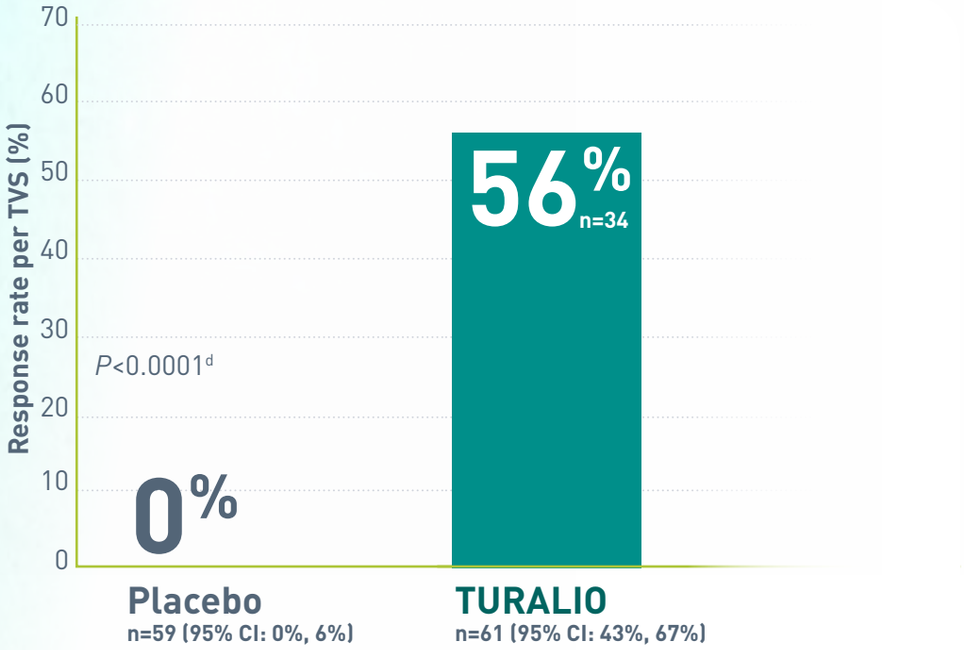
The majority of TURALIO patients showed a reduction in tumor volume of 50% or more—at 25 weeks and at final analysis (median 31-month follow-up)[4,5,7]

ORR by Tumor Volume Score (TVS)[1,4,5,7,a]

Secondary Endpoint: ORR by TVS at 25 weeks[1,4,b]

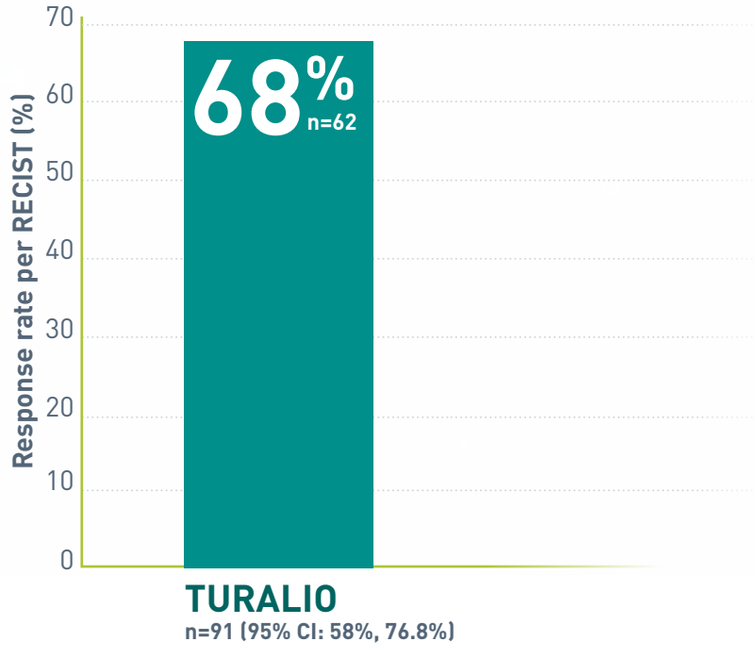


Part 1 ITT population

Of the patients taking TURALIO at 6 months[4,7]:

- 51% (31 out of 61) had their tumors reduce in volume by 50% or more (partial response)[e]
- 5% (3 out of 61) had their tumors disappear completely (complete response)[f]

ORR by TVS (31-month median follow-up)[5,c]



Part 1 ITT population and placebo crossover patients

Significant improvement in ROM at week 25[4]

>2X Mean improvement with TURALIO vs placebo (15.1% vs 6.2%) (95% CI: 2.9%, 14.9%), *P*=0.004.

CI, confidence interval; ITT, intent-to-treat; ORR, overall response rate; RECIST, Response Evaluation Criteria In Solid Tumors; ROM, Range of Motion.

[a]TVS was defined in ENLIVEN as the estimated volume of the maximally distended synovial cavity or tendon sheath involved, measured in 10% increments.[1]

[b]ORR was determined by blinded independent central review (BICR).[1]

[c]A median follow-up of 31.2 (range: 2, 66) months (final database lock June 1, 2021).[5]

[d]Fisher's exact test.[4]

[e]Partial response was defined as 50% or more reduction in tumor volume.[6]

[f]Complete response was defined as 100% reduction in tumor volume.[6]

IMPORTANT SAFETY INFORMATION (CONT.)

WARNINGS AND PRECAUTIONS (CONT.)

Hepatotoxicity (CONT.)

- Of the first 609 patients who received TURALIO under the REMS program, 32 (5.3%) developed a liver injury event of concern, defined as any serious liver-related outcome or any liver abnormality that triggers drug discontinuation per the US Prescribing Information. These 32 patients developed liver toxicity within 71 days of the first dose of TURALIO; ten required hospitalization and two developed VBDS. Sixteen of the 32 patients had not fully recovered at the time of the analysis, including 6 patients followed for at least 6 months after discontinuation.
- Among 768 patients who received TURALIO in clinical trials, there were two irreversible cases of cholestatic liver injury. One patient with advanced cancer and ongoing liver toxicity died and one patient with a confirmed case of VBDS required a liver transplant.

Please see additional Important Safety Information and full Prescribing Information, including Boxed WARNING, and Medication Guide.

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Serious Adverse Reactions in ENLIVEN[1]

- **TURALIO can cause serious and potentially fatal liver injury, including vanishing bile duct syndrome**
- **Monitor liver tests; however, monitoring and prompt cessation of TURALIO may not eliminate the risk of serious and potentially fatal liver injury**

Please see full Indication and Important Safety Information below, including Boxed WARNING, and Medication Guide.

Serious adverse reactions occurred in[1]:

13% OF PATIENTS (N=8/61)

Most frequent (>1 patient):

Abnormal Liver Test
3.3% (2) patients

Hepatotoxicity[a]
3.3% (2) patients

The most frequent (>1 patient) permanent discontinuations due to an adverse reaction occurred in[1]:

13% OF PATIENTS (N=8/61)

Abnormal Liver Test
4.9% (3) patients: Increased ALT

4.9% (3) patients: Increased AST

Hepatotoxicity[a]
3.3% (2) patients

[a]The same 2 patients with hepatotoxicity who reported serious adverse reactions also discontinued the study.[1,4]

IMPORTANT SAFETY INFORMATION (CONT.)

WARNINGS AND PRECAUTIONS (CONT.)
Hepatotoxicity (CONT.)

- In ENLIVEN, 3 of 61 (5%) patients who received TURALIO developed signs of serious liver injury, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 × upper limit of normal (ULN) with total bilirubin ≥2 × ULN. In these patients, peak ALT ranged from 6 to 9 × ULN, peak total bilirubin ranged from 2.5 to 15 × ULN, and alkaline phosphatase (ALP) was ≥2 × ULN. ALT, AST, and total bilirubin improved to <2 × ULN in these three patients 1 to 7 months after discontinuing TURALIO.

Please see information on Monitoring for Hepatotoxicity and Dosage Modifications in this presentation.

Please see additional Important Safety Information and full Prescribing Information, including Boxed WARNING, and Medication Guide.

Turalio® pexidartinib 125 mg capsules

Most common adverse reactions in patients receiving TURALIO in ENLIVEN[1]

The following is a summary of the most common adverse reactions in the ENLIVEN study. **Please see the complete Important Safety Information, including Boxed WARNING in tab.**
Adverse reactions led to dose reductions or interruptions in 38% of patients; 13% discontinued treatment.[1]

Most common adverse reactions occurring in >20% of patients[1]

- Increased LDH (92%)
- Increased AST (88%)
- Increased ALT (64%)
- Increased cholesterol (44%)
- Increased ALP (39%)

- Decreased neutrophils (44%)
- Decreased lymphocytes (38%)
- Decreased hemoglobin (30%)
- Decreased phosphate (25%)

- Hair color changes (67%)
- Fatigue (64%)
- Eye edema (30%)
- Rash (28%)
- Dysgeusia (26%)

Hair color changes:
- The mechanism of hair color changes is thought to be due to the disruption of melanogenesis through c-KIT signaling[9,10]
- In most cases, hair depigmentation due to c-KIT inhibition is reversible after treatment discontinuation. During treatment, hair color changes may be addressed cosmetically[9,10]

These are not all of the possible side effects of TURALIO

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; LDH, lactate dehydrogenase.

Please see additional Important Safety Information and full Prescribing Information, including Boxed WARNING, and Medication Guide.

TURALIO Risk Evaluation and Mitigation Strategy (REMS)[1]

WARNING: HEPATOTOXICITY

- **TURALIO can cause serious and potentially fatal liver injury, including vanishing bile duct syndrome.**
- **Monitor liver tests prior to initiation of TURALIO and at specified intervals during treatment. Withhold and dose reduce or permanently discontinue TURALIO based on severity of hepatotoxicity. Monitoring and prompt cessation of TURALIO may not eliminate the risk of serious and potentially fatal liver injury.**
- **TURALIO is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program.**

Because of the risk of hepatotoxicity, TURALIO is available only through a Risk Evaluation and Mitigation Strategy (REMS) Program.[1]

Prescribers must be certified and enrolled in the program in order to prescribe TURALIO

Patients must complete and sign an enrollment form for inclusion in a patient registry

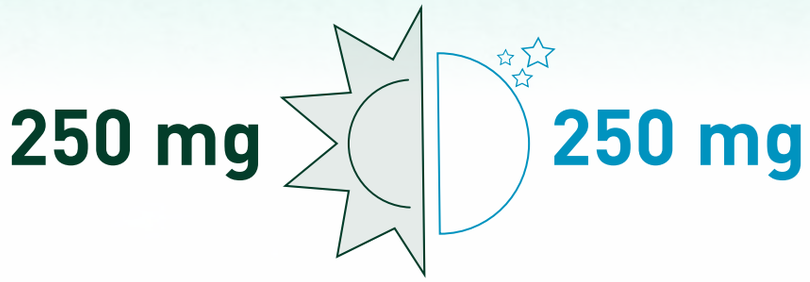
Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive TURALIO

Further information is available at www.TURALIOREMS.com or 1-833-TURALIO (1-833-887-2546)

TURALIO Dosing Information

Twice-daily, oral dosing for TGCT[1]

- The recommended dosage of TURALIO is 250 mg taken orally twice daily for a total of 500 mg per day. TURALIO must be taken with a low-fat meal (approximately 11 to 14 grams of total fat)
- It's important to swallow TURALIO capsules whole and **DO NOT** open, break, or chew them
- If patients vomit or miss a dose of TURALIO, they should take the next dose at its scheduled time



AVOID TAKING TURALIO WITH A HIGH-FAT MEAL
(APPROXIMATELY 55 TO 65 GRAMS OF TOTAL FAT)
due to increased pexidartinib concentrations which may increase the risk of adverse reactions, including hepatotoxicity.[1]

IMPORTANT SAFETY INFORMATION (CONT.)

Potential Risks Associated with a High-Fat Meal

- Taking TURALIO with a high-fat meal increases pexidartinib concentrations, which may increase the incidence and severity of adverse reactions, including hepatotoxicity.
- Instruct patients to take TURALIO with a low-fat meal (approximately 11 to 14 grams of total fat) and to avoid taking TURALIO with a high-fat meal (approximately 55 to 65 grams of total fat).

Please see information about Dosage Modifications for Adverse Reactions (including hepatotoxicity), Drug Interactions, and Specific Populations (renal and hepatic impairment) on following slides.

Please see additional Important Safety Information and full Prescribing Information, including Boxed WARNING, and Medication Guide.

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Hepatotoxicity Monitoring and Managing with TURALIO[1]

Avoid TURALIO in patients with preexisting increased serum transaminases; increased total bilirubin or direct bilirubin (>ULN); or active liver or biliary tract disease, including increased ALP

Monitor liver tests, including AST, ALT, total bilirubin, direct bilirubin, ALP, and GGT:

- before starting treatment with TURALIO
- every week for the first 8 weeks of treatment
- every 2 weeks for the next month
- every 3 months after that

Withhold and dose reduce, or permanently discontinue TURALIO based on the severity of the hepatotoxicity (see table on the following page)

- Rechallenging with a reduced dose of TURALIO may result in a recurrence of increased serum transaminases, bilirubin, or ALP
- Monitor liver tests weekly for the first month after rechallenge

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

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Recommended dosage modifications for adverse reactions[1]

Adverse Reactions	Severity	TURALIO Dosage Modifications
Hepatotoxicity		
Increased ALT and/or AST	>3 to 5 × ULN	• Withhold and monitor liver tests ***weekly*** • If AST and ALT are ≤3 × ULN within 4 weeks, resume at reduced dose • If AST or ALT is ***not*** ≤3 × ULN in 4 weeks, permanently discontinue TURALIO
	>5 to 10 × ULN	• Withhold and monitor liver tests ***twice weekly*** • If AST and ALT are ≤3 × ULN within 4 weeks, resume at reduced dose • If AST or ALT is ***not*** ≤3 × ULN in 4 weeks, permanently discontinue TURALIO
	>10 × ULN	• Permanently discontinue TURALIO • Monitor liver tests ***twice weekly*** until AST or ALT is ≤5 × ULN, then ***weekly*** until ≤3 × ULN
Increased ALP[a] and GGT	ALP >2 × ULN with GGT >2 × ULN	• Permanently discontinue TURALIO. Monitor liver tests ***twice weekly*** until ALP is ≤5 × ULN, then ***weekly*** until ≤ 2 × ULN
Increased bilirubin	TB >ULN to <2 × ULN or DB >ULN and <1.5 × ULN	• Withhold and monitor liver tests ***twice weekly*** • 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 ***not*** less than ULN in 4 weeks, permanently discontinue TURALIO
	TB ≥2 × ULN or DB >1.5 × ULN	• Permanently discontinue TURALIO • Monitor liver tests ***twice weekly*** until bilirubin is ≤ULN
Adverse Reactions or Other Laboratory Abnormalities		
Any	Severe or intolerable	• Withhold until improvement or resolution • Resume at a reduced dose upon improvement or resolution

Monitoring and prompt cessation of TURALIO may not eliminate the risk of serious and potentially fatal liver injury.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, direct bilirubin; GGT, gamma-glutamyl transferase; TB, total bilirubin; ULN, upper limit of normal.
[a]Confirm ALP elevations as liver isozyme fraction.[1]

Please see information about Dosage Modifications for Drug Interactions, and Specific Populations (renal and hepatic impairment) on following slide.

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Turalio® pexidartinib 125 mg capsules

Dose Modifications[a]

Recommended dose reductions for TURALIO for adverse reactions[1]

Dose Adjustment	Total Daily Dose	Administration of Total Daily Dose with Low-Fat Meal
First	375 mg	125 mg in the morning and 250 mg in the evening
Second	250 mg	125 mg twice daily

The total recommended starting dose is 500 mg daily. Permanently discontinue TURALIO in patients who are unable to tolerate 125 mg orally twice daily.[1]

Recommended dosage reductions for TURALIO for unavoidable concomitant use of moderate or strong CYP3A inhibitors or UGT inhibitors[1]

Total Daily Dose[b]	Modified Total Daily Dose for Concomitant Use with Moderate or Strong CYP3A Inhibitors or UGT Inhibitors	Dosing Schedule for Modified Total Daily Dose for Use with Moderate or Strong CYP3A Inhibitors or UGT Inhibitors Administer with Low-Fat Meal
500 mg	250 mg	125 mg twice daily
375 mg	250 mg	125 mg twice daily
250 mg	125 mg	125 mg once daily

- Avoid concomitant use of TURALIO with moderate or strong CYP3A inhibitors or UGT inhibitors during treatment with TURALIO
  - If concomitant use with a moderate or strong CYP3A inhibitor or UGT inhibitor cannot be avoided, reduce the TURALIO dose according to the recommendations
- Avoid the concomitant use of PPIs while taking TURALIO. As an alternative to a PPI:
  - Administer TURALIO 2 hours before or 2 hours after taking a locally acting antacid, or
  - If using an H2RA, administer TURALIO at least 2 hours before or 10 hours after taking an H2RA

Dosage Modifications for Specific Populations

Dose modification for renal impairment[1]

- The recommended dosage of TURALIO for patients with mild to severe renal impairment (CLcr 15 to 89 mL/min estimated by Cockcroft-Gault using actual body weight) is 125 mg in the morning and 250 mg in the evening with a low-fat meal

Dose modification for hepatic impairment[1]

- The recommended dosage of TURALIO for patients with moderate hepatic impairment (total bilirubin greater than 1.5 and up to 3 times ULN, not due to Gilbert's syndrome with any AST) is 125 mg twice daily with a low-fat meal. TURALIO has not been studied in patients with severe hepatic impairment (total bilirubin greater than 3 to 10 times ULN and any AST)

[a]The safety of TURALIO 250 mg orally twice daily administered with a low-fat meal has been established based on additional pharmacokinetic data and adequate and well-controlled studies of TURALIO 400 mg orally twice daily administered on an empty stomach.[1]
[b]The Total Daily Dose represents the recommended dose (row one) and the recommended dose after modifications due to adverse reactions, renal impairment, or moderate hepatic impairment (rows two and three).[1]
CLcr, creatinine clearance; H2RA, histamine2-receptor antagonist; PPIs, proton pump inhibitors; UGT, uridine diphosphate glucuronosyltransferase.

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References

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