

SAFETY MONITORING & MANAGEMENT



Indication and Important Safety Information

Indication and Usage

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.

WARNING: HEPATOTOXICITY

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

Contraindications

None.

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

ENLIVEN: The only phase 3, placebo-controlled trial evaluating an oral systemic therapy for TGCT^{1,2}

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) 1000 mg daily for 2 weeks followed by 400 mg twice daily. The 2019 FDA-approved dose of TURALIO was 400 mg twice daily on an empty stomach.¹

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.^{1,2}

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.

Indication and Important Safety Information (continued)

Warnings and Precautions

Hepatotoxicity

TURALIO can cause serious and potentially fatal liver injury and is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.



As part of post-marketing requirements from the FDA, pharmacokinetic studies were conducted to further evaluate the effects of food when taking TURALIO

Pharmacokinetic data indicated that taking the 250 mg dose of TURALIO with a low-fat meal has no clinically significant difference compared to taking 400 mg on an empty stomach¹

- Lowering the dose of TURALIO and taking it with a low-fat meal (approximately 11 to 14 grams of total fat) helps to minimize the potential for drug overexposure in the event a patient did not carefully follow the dietary recommendations when taking the 400 mg dose of TURALIO
 - When TURALIO 400 mg is taken with a high-fat meal^a instead of on an empty stomach, TURALIO exposure doubles
 - When TURALIO 400 mg is taken with a low-fat meal^b instead of on an empty stomach, TURALIO exposure increases by almost 60%
- The current FDA-approved dose of TURALIO is 250 mg twice daily with a low-fat meal (approximately 11 to 14 grams of total fat)

^a The high-fat meal comprised 800 to 1000 calories with approximately 50% from fat (approximately 55 to 65 grams of total fat).¹
^b The low-fat meal comprised approximately 400 calories with 25% from fat (approximately 11 to 14 grams of total fat).¹

Indication and Important Safety Information (continued)

Warnings and Precautions Hepatotoxicity

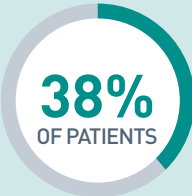
Hepatotoxicity with ductopenia and cholestasis occurred in patients treated with TURALIO. Across 768 patients who received TURALIO in clinical trials, there were two irreversible cases of cholestatic liver injury. One patient with advanced cancer and ongoing liver toxicity died and one patient required 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.

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.



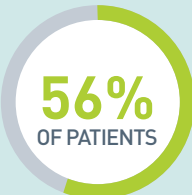
TURALIO reduced tumor size and increased ROM^{1,2,5,a}

Overall response^b by RECIST v1.1 at week 25¹



23 of 61 [95% CI: 27%, 50%] achieved ORR vs 0% [0 of 59] for placebo [95% CI: 0%, 6%], $P < 0.0001$.^c Of these, 23% (n=14) had a PR and 15% (n=9) had a CR.
CR is 100% total reduction; PR is 30% reduction^{3,4}

Overall response by TVS at week 25^{1,2}



34 of 61 [95% CI: 43%, 67] achieved ORR vs 0% [0 of 59] for placebo [95% CI: 0%, 6%], $P < 0.0001$.^c Of these, 51% (n=31) had a PR and 5% (n=3) had a CR.
CR is 100% total reduction; PR is 50% reduction.^{3,4}

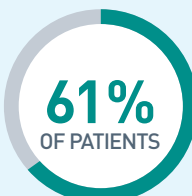
Significant improvement in ROM at week 25^{1,2}



Mean improvement with TURALIO vs placebo (15.1% vs 6.2%) [95% CI: 2.9%, 14.9%], $P = 0.004$.

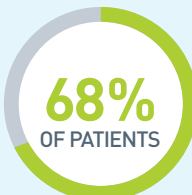
More patients responded over time in the final analysis at ~5.5 years^{1,5,d}

Overall response by RECIST v1.1 at ~5.5 years^{1,5}



37 of 61 [95% CI: 48%, 72%]

Overall response by TVS at ~5.5 years⁵



62 of 91 [95% CI: 58.0%, 76.8%]

PR is defined as 30% tumor reduction for RECIST v1.1 and as 50% tumor reduction for TVS, CR is defined as 100% reduction in tumor length or volume.^{3,4}

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; ROM, range of motion; TVS, tumor volume score.
^aThe efficacy 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
^bORR was determined by BICR.¹
^cFisher's exact test.^{1,2}
^dA median follow-up of 31.2 [range: 2, 66] months (final database lock June 1, 2021).⁵

Indication and Important Safety Information (continued)

Warnings and Precautions

Hepatotoxicity

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

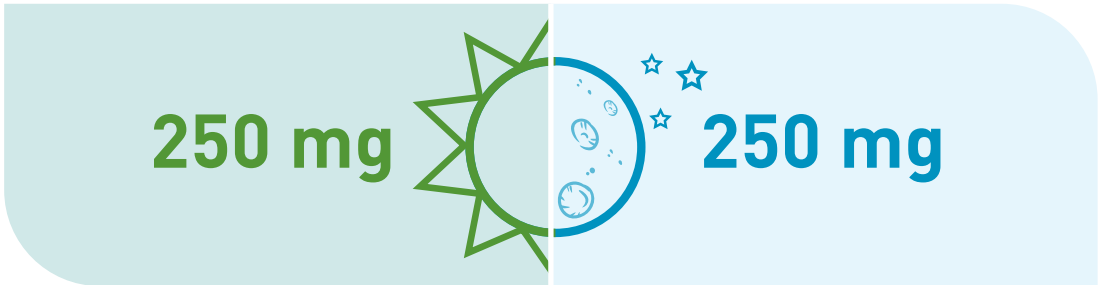
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TURALIO safety and dosing were evaluated in the ENLIVEN phase 3 trial^{1,a}

Straightforward, twice-daily, oral dosing for TGCT¹

- The recommended dosage of TURALIO is 250 mg taken orally twice daily



- TURALIO must be taken with a low-fat meal (approximately 11 to 14 grams of total fat). Taking TURALIO with a high-fat meal (approximately 55 to 65 grams of total fat) increases pexidartinib concentrations and may increase the risk of adverse reactions, including hepatotoxicity
- Avoid TURALIO in patients with preexisting increased serum transaminases, total bilirubin, or direct bilirubin (>ULN) or patients with active liver or biliary tract disease including increased ALP

TURALIO MUST BE TAKEN WITH A LOW-FAT MEAL
~11 TO 14 GRAMS OF TOTAL FAT



TURALIO dosage and administration

- 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

ALP, alkaline phosphatase; ULN, upper limit of normal.

^aThe 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

Indication and Important Safety Information (continued)

Warnings and Precautions

Hepatotoxicity

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. Rechallenge 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.

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

TURALIO Risk Evaluation and Mitigation Strategy (REMS)¹

TURALIO can cause serious and potentially fatal liver injury and is available only through a restricted program called the Risk Evaluation and Mitigation Strategy (REMS) Program

The TURALIO REMS Program is designed to **PROACTIVELY MONITOR FOR AND HELP MITIGATE** the risk of hepatotoxicity in patients receiving TURALIO. TURALIO is only available through the REMS Program.



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)

ALP, alkaline phosphatase; ULN, upper limit of normal.

Indication and Important Safety Information (continued)

Warnings and Precautions

TURALIO REMS

TURALIO is available only through a restricted program under a REMS, because of the risk of hepatotoxicity. Notable requirements of the TURALIO REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Patients must complete and sign an enrollment form for inclusion in a patient registry.
- Pharmacies must be certified with the program and must dispense only to patients who are authorized (enrolled in the REMS patient registry) to receive TURALIO.

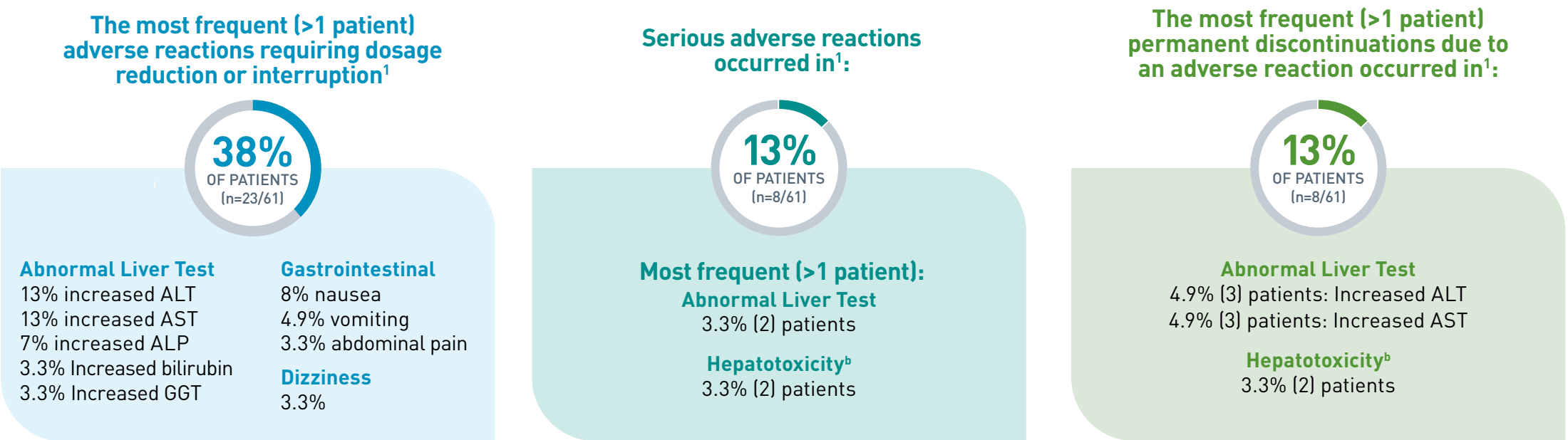
Further information is available at turalioREMS.com or by calling 1-833-887-2546.

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.


Serious adverse reactions in patients receiving TURALIO in ENLIVEN^{1,a}

Patients received TURALIO orally without food at a dose of 400 mg in the morning and 600 mg in the evening for 2 weeks, followed by 400 mg orally twice daily until disease progression or unacceptable toxicity. The FDA-approved dose is 250 mg orally twice daily with a low-fat meal.

The following safety profile is a partial presentation of the risks associated with TURALIO.



^aThe 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
^bThe same 2 patients with hepatotoxicity who experienced investigator-reported serious adverse reactions also discontinued the study.^{1,2}

 These are not all of the possible side effects of TURALIO

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Indication and Important Safety Information (continued)

Warnings and Precautions

Embryo-fetal toxicity

Based on animal studies and its mechanism of action, TURALIO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective nonhormonal method of contraception, since 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.

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

Hepatotoxicity and dose adjustments in patients receiving TURALIO^{1,a}

In ENLIVEN, 3 of 61 (5%) patients who received TURALIO developed signs of serious liver injury^{1,b}

In ENLIVEN, liver enzyme elevations were reversible upon temporary or permanent TURALIO discontinuation^{1,2}

- In 2 individuals, hyperbilirubinemia recovered within 1 to 2 months of pexidartinib discontinuation²
- In another individual (a 75-year-old woman), hyperbilirubinemia lasted approximately 7 months and required 2 liver dialysis procedures; a liver biopsy revealed substantial ductopenia and severe cholestasis²
- No additional cases of mixed or cholestatic hepatotoxicity were reported through the January 31, 2018 data cutoff²
- Compared with TURALIO-treated patients in part 1 (n=61), fewer liver enzyme elevations were observed with the part 2 crossover population (n=30), and no bilirubin increases or signs of drug-induced cholestatic hepatotoxicity were observed. The part 2 crossover population received 800 mg of TURALIO per day²



Monitor liver tests as outlined in the PI. In ENLIVEN, all cases of hepatotoxicity occurred during the first 8 weeks of treatment. Liver function testing is more frequent during the first 2 months

^aThe 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

^bDefined as ALT or AST $\geq 3 \times$ ULN with total bilirubin $\geq 2 \times$ ULN. In these patients, peak ALT ranged from 6 to 9 \times ULN, peak total bilirubin ranged from 2.5 to 15 \times ULN, and alkaline phosphatase (ALP) was $\geq 2 \times$ ULN. ALT, AST and total bilirubin improved to $< 2 \times$ ULN in these patients 1 to 7 months after discontinuing TURALIO.¹

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Indication and Important Safety Information (continued)

Adverse Reactions

The safety of TURALIO was evaluated in ENLIVEN, in which patients received TURALIO without food at a dose of 400 mg in the morning and 600 mg in the evening orally for 2 weeks followed by 400 mg orally twice daily until disease progression or unacceptable toxicity.

Serious adverse reactions were reported in 13% of patients who received TURALIO. The most frequent serious adverse reactions (occurring in >1 patient) included abnormal liver tests (3.3%) and hepatotoxicity (3.3%).

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.



Hepatotoxicity and dose adjustments in patients receiving TURALIO^{1,a}



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.
^aThe 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

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Indication and Important Safety Information (continued)

Adverse Reactions

Permanent discontinuation due to adverse reactions occurred in 13% of patients who received TURALIO. The most frequent adverse reactions (occurring in >1 patient) requiring permanent discontinuation included increased ALT (4.9%), increased AST (4.9%), and hepatotoxicity (3.3%).

Dose reductions or interruptions occurred in 38% of patients who received TURALIO. The most frequent adverse reactions (occurring in >1 patient) requiring a dosage reduction or interruption were increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), vomiting (4.9%), increased bilirubin (3.3%), increased GGT (3.3%), dizziness (3.3%), and abdominal pain (3.3%).

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

Recommended dosage modifications for TURALIO for hepatic adverse reactions^{1,a}

In ENLIVEN, liver enzyme elevations improved upon TURALIO discontinuation.¹

Adverse Reactions	Severity	TURALIO Dosage Modifications
Increased ALT and/or AST	>3 to 5 × ULN	<ul style="list-style-type: none">Withhold and monitor liver tests weeklyIf AST and ALT are ≤3 × ULN within 4 weeks, resume at reduced doseIf AST or ALT is not ≤3 × ULN in 4 weeks, permanently discontinue TURALIO
	>5 to 10 × ULN	<ul style="list-style-type: none">Withhold and monitor liver tests twice weeklyIf AST and ALT are ≤3 × ULN within 4 weeks, resume at reduced doseIf AST or ALT is not ≤3 × ULN in 4 weeks, permanently discontinue TURALIO
	>10 × ULN	<ul style="list-style-type: none">Permanently discontinue TURALIOMonitor liver tests twice weekly until AST or ALT is ≤5 × ULN, then weekly until ≤3 × ULN
Increased ALP ^b and GGT	ALP >2 × ULN with GGT >2 × ULN	<ul style="list-style-type: none">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	<ul style="list-style-type: none">Withhold and monitor liver tests twice weeklyIf an alternate cause for increased bilirubin is confirmed and bilirubin is less than ULN within 4 weeks, resume at reduced doseIf bilirubin is not less than ULN in 4 weeks, permanently discontinue TURALIO
	TB ≥2 × ULN or DB >1.5 × ULN	<ul style="list-style-type: none">Permanently discontinue TURALIOMonitor liver tests twice weekly until bilirubin is ≤ULN

Note: There are alternate causes for increased bilirubin levels. If an alternate cause is confirmed and the issue is resolved within a 4-week period, TURALIO can be resumed at a reduced dose. If the issue does not resolve, permanently discontinue TURALIO.¹

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

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Indication and Important Safety Information (continued)

Adverse Reactions

The most common adverse reactions for all grades (>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%).

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

Common adverse reactions in patients receiving TURALIO in ENLIVEN^{1,a}

Most common adverse reactions occurring in >20% of patients¹



- 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%)

Managing skin and subcutaneous tissue adverse reactions



Hair color changes:

- The mechanism of hair color changes is thought to be due to the disruption of melanogenesis through c-KIT signaling⁷
- In most cases, hair depigmentation due to c-KIT inhibition is reversible after treatment discontinuation. During treatment, hair color changes may be addressed cosmetically⁷



Rash, maculopapular rash, pruritic rash, urticaria, erythema, dermatitis acneiform, and dermatitis allergic:^{1,8,9}

Grade 3:

- Topical antibiotic: clindamycin 1% lotion or emulsion 1 to 2 times daily; moderately to highly potent topical corticosteroids 1 to 2 times daily (e.g., hydrocortisone 1%-2.5% face, triamcinolone acetonide 0.1% body)^{8,9}
- Consider addition of doxycycline or minocycline 100 mg every 12 hours, and oral antihistamines^{8,9}
- Consider addition of oral corticosteroids (10-30 mg/day), consider oral isotretinoin in recalcitrant cases⁸

Grade 4:

- Refer to hospital dermatology consultant⁸



These are not all of the possible side effects of TURALIO

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

^aThe 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

Indication and Important Safety Information (continued)

Warnings and Precautions

Clinically relevant adverse reactions occurring in <10% of patients were blurred vision, photophobia, diplopia, reduced visual acuity, dry mouth, stomatitis, mouth ulceration, pyrexia, cholangitis, hepatotoxicity, liver disorder, cognitive disorders (memory impairment, amnesia, confusional state, disturbance in attention, and attention deficit/hyperactivity disorder), alopecia, and skin pigment changes (hypopigmentation, depigmentation, discoloration, and hyperpigmentation).

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

Turalio
pexidartinib
125 mg capsules

Dose adjustments^a

Recommended dose reductions for TURALIO for adverse reactions¹

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 inhibitors¹

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

^aThe 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

^bThe 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.

Indication and Important Safety Information (continued)

Drug Interactions

- Use with hepatotoxic products: TURALIO can cause hepatotoxicity. In patients with increased serum transaminases, total bilirubin, or direct bilirubin (>ULN) or active liver or biliary tract disease, avoid coadministration of TURALIO with other products known to cause hepatotoxicity.

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

Recommended dosage modifications for TURALIO for adverse reactions or laboratory abnormalities other than hepatotoxicity¹

Adverse Reaction	Severity	TURALIO Dosage Modifications
Any	Severe or intolerable	<ul style="list-style-type: none">Withhold until improvement or resolutionResume at a reduced dose upon improvement or resolution

- 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

Dose modification for renal impairment¹

- 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 impairment¹

- 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)

SAFETY MONITORING & MANAGEMENT

Person depicted is not an actual patient.

Pexidartinib is a category 1 recommendation for TGCT/PVNS in the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma¹¹

NCCN, National Comprehensive Cancer Network.

Indication and Important Safety Information

Indication and Usage

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.

WARNING: HEPATOTOXICITY

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

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Contraindications

None.

Warnings and Precautions

Hepatotoxicity

TURALIO can cause serious and potentially fatal liver injury and is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

Hepatotoxicity with ductopenia and cholestasis 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 with advanced cancer and ongoing liver toxicity died 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.

In ENLIVEN, 3 of 61 (5%) patients who received TURALIO developed signs of serious liver injury, defined as ALT or AST $\geq 3 \times$ upper limit of normal (ULN)

with total bilirubin $\geq 2 \times$ ULN. In these patients, peak ALT ranged from 6 to 9 \times ULN, peak total bilirubin ranged from 2.5 to 15 \times ULN, and alkaline phosphatase (ALP) was $\geq 2 \times$ ULN. ALT, AST and total bilirubin improved to $< 2 \times$ ULN in these patients 1 to 7 months after discontinuing TURALIO.

Avoid TURALIO in patients with preexisting increased serum transaminases, total bilirubin, or direct bilirubin ($> \text{ULN}$); 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. Rechallenge 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.

TURALIO REMS

TURALIO is available only through a restricted program under a REMS, because of the risk of hepatotoxicity.

Notable requirements of the TURALIO REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Patients must complete and sign an enrollment form for inclusion in a patient registry.
- Pharmacies must be certified with the program and must dispense only to patients who are authorized (enrolled in the REMS patient registry) to receive TURALIO.

Further information is available at turalioREMS.com or by calling 1-833-887-2546.

Embryo-fetal toxicity

Based on animal studies and its mechanism of action, TURALIO may cause fetal harm when administered to pregnant women. Advise pregnant women of the

potential risk to a fetus. Advise females of reproductive potential to use an effective nonhormonal method of contraception, since 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.

Adverse Reactions

The safety of TURALIO was evaluated in ENLIVEN, in which patients received TURALIO without food at a dose of 400 mg in the morning and 600 mg in the evening orally for 2 weeks followed by 400 mg orally twice daily until disease progression or unacceptable toxicity.

Serious adverse reactions were reported in 13% of patients who received TURALIO. The most frequent serious adverse reactions (occurring in > 1 patient) included abnormal liver tests (3.3%) and hepatotoxicity (3.3%).

Permanent discontinuation due to adverse reactions occurred in 13% of patients who received TURALIO. The most frequent adverse reactions (occurring in > 1 patient) requiring permanent discontinuation included increased ALT (4.9%), increased AST (4.9%), and hepatotoxicity (3.3%).

Dose reductions or interruptions occurred in 38% of patients who received TURALIO. The most frequent adverse reactions (occurring in > 1 patient) requiring a dosage reduction or interruption were increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), vomiting (4.9%), increased bilirubin (3.3%), increased GGT (3.3%), dizziness (3.3%), and abdominal pain (3.3%).

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Indication and Important Safety Information (continued)

Adverse Reactions (continued)

The most common adverse reactions for all grades (>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%).

Clinically relevant adverse reactions occurring in <10% of patients were blurred vision, photophobia, diplopia, reduced visual acuity, dry mouth, stomatitis, mouth ulceration, pyrexia, cholangitis, hepatotoxicity, liver disorder, cognitive disorders (memory impairment, amnesia, confusional state, disturbance in attention, and attention deficit/hyperactivity disorder), alopecia, and skin pigment changes (hypopigmentation, depigmentation, discoloration, and hyperpigmentation).

Drug Interactions

- Use with hepatotoxic products: TURALIO can cause hepatotoxicity. In patients with increased serum transaminases, total bilirubin, or direct bilirubin (>ULN) or active liver or biliary tract disease, avoid coadministration of TURALIO with other products known to cause hepatotoxicity.
- Moderate or strong CYP3A inhibitors: Concomitant use of a moderate or strong CYP3A inhibitor may increase pexidartinib concentrations. Reduce TURALIO dosage if concomitant use of moderate or strong CYP3A inhibitors cannot be avoided.
- Strong CYP3A inducers: Concomitant use of a strong CYP3A inducer decreases pexidartinib concentrations. Avoid concomitant use of strong CYP3A inducers.

- Uridine diphosphate glucuronosyltransferase (UGT) inhibitors: Concomitant use of a UGT inhibitor increases pexidartinib concentrations. Reduce TURALIO dosage if concomitant use of UGT inhibitors cannot be avoided.
- Acid-reducing agents: Concomitant use of a proton pump inhibitor (PPI) decreases pexidartinib concentrations. Avoid concomitant use of PPIs. Use histamine-2 receptor antagonists or antacids if needed.
- CYP3A substrates: TURALIO is a moderate CYP3A inducer. Concomitant use of TURALIO decreases concentrations of CYP3A substrates. Avoid coadministration of TURALIO with hormonal contraceptives and other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failure. Increase the CYP3A substrate dosage in accordance with approved product labeling if concomitant use is unavoidable.

Use in Specific Populations

- **Pregnancy:** TURALIO may cause embryo-fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus.
- **Lactation:** Because of the potential for serious adverse reactions in the breastfed child, advise women to not breastfeed during treatment with TURALIO and for at least 1 week after the final dose.
- **Females and males of reproductive potential:** 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, since TURALIO can render hormonal contraceptives ineffective, during treatment with TURALIO and for

1 month after the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TURALIO and for 1 week after the final dose.

- **Renal impairment:** Reduce the dose when administering TURALIO to patients with mild to severe renal impairment (CLcr 15 to 89 mL/min, estimated by Cockcroft-Gault [C-G] using actual body weight).
- **Hepatic impairment:** Reduce the 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). TURALIO has not been studied in patients with severe hepatic impairment (total bilirubin greater than 3 to 10 times ULN and any AST).

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](https://www.fda.gov/medwatch).

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

References: 1. Turalio® [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2022. 2. Tap WD et al; ENLIVEN investigators. *Lancet*. 2019;394(10197):478-487. 3. Tap WD et al. *N Engl J Med*. 2015;373(5)(suppl):1-39. 4. Eisenhauer EA et al. *Eur J Cancer*. 2009;45(2):228-247. 5. Wagner AJ. Slides presented at: CTOS Connective Tissue Oncology Society; November 16-19, 2022; Vancouver, BC, Canada. 6. Data on file. Daiichi Sankyo. 7. Data on file. Daiichi Sankyo. 8. Ricci F, De Simone C, Del Regno L, et al. *Eur J Dermatol*. 2016;26(6):531-536. 9. Gravalos C et al. *Clin Transl Oncol*. 2019;21:556-571. 10. Lynch JT Jr et al. *Oncologist*. 2007;12:610-621. 11. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.2.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed November 21, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TURALIO safely and effectively. See full prescribing information for TURALIO.

TURALIO® (pexidartinib) capsules, for oral use
Initial U.S. Approval: 2019

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning.

- **TURALIO can cause serious and potentially fatal liver injury. (5.1)**
- **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. (2.2, 5.1)**
- **TURALIO is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program. (5.2)**

RECENT MAJOR CHANGES	
Dosage and Administration (2.1, 2.2, 2.3, 2.5, 2.6)	10/2022
Warnings and Precautions (5.4)	10/2022

INDICATIONS AND USAGE

TURALIO is a kinase inhibitor 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. (1)

- DOSAGE AND ADMINISTRATION**
- **Recommended Dosage:** 250 mg orally twice daily with a low-fat meal (approximately 11 to 14 grams of total fat). (2.1)
 - See full prescribing information for dosage modifications due to adverse reactions, renal impairment and hepatic impairment. (2.2, 2.5, 2.6)

DOSAGE FORMS AND STRENGTHS

Capsules: 125 mg (3)

CONTRAINDICATIONS

None. (4)

- WARNINGS AND PRECAUTIONS**
- **Embryo-Fetal Toxicity:** May cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use an effective non-hormonal method of contraception. (5.3, 7.3, 8.1, 8.3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- WARNING: HEPATOTOXICITY**
- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
- 2.1 Recommended Dosage
- 2.2 Dosage Modifications for Adverse Reactions
- 2.3 Concomitant Use of Moderate or Strong CYP3A Inhibitors or UGT Inhibitors
- 2.4 Concomitant Use of Acid-Reducing Agents
- 2.5 Dosage Modification for Renal Impairment
- 2.6 Dosage Modification for Hepatic Impairment
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
- 5.1 Hepatotoxicity
- 5.2 TURALIO REMS Program
- 5.3 Embryo-Fetal Toxicity
- 5.4 Potential Risks Associated with a High-Fat Meal
- 6 ADVERSE REACTIONS**
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience
- 7 DRUG INTERACTIONS**
- 7.1 Use with Hepatotoxic Products
- 7.2 Effect of Other Drugs or Food on TURALIO
- 7.3 Effect of TURALIO on Other Drugs

- **Potential Risks Associated with a High-Fat Meal:** May increase incidence and severity of adverse reactions, including hepatotoxicity. Avoid taking TURALIO with a high-fat meal (approximately 55 to 65 grams of total fat). (2.1, 5.4)

ADVERSE REACTIONS

Most common adverse reactions (>20%) were increased lactate dehydrogenase, increased aspartate aminotransferase, hair color changes, fatigue, increased alanine aminotransferase, decreased neutrophils, increased cholesterol, increased alkaline phosphatase, decreased lymphocytes, eye edema, decreased hemoglobin, rash, dysgeusia, and decreased phosphate. (6.1)

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

- DRUG INTERACTIONS**
- **Use with Hepatotoxic Products:** Avoid coadministration of TURALIO with other products known to cause hepatotoxicity. (7.1)
 - **Moderate or Strong CYP3A Inhibitors:** Reduce the dose of TURALIO if concomitant use of moderate or strong CYP3A inhibitors cannot be avoided. (2.3, 7.2)
 - **Strong CYP3A Inducers:** Avoid concomitant use of strong CYP3A inducers. (7.2)
 - **UGT Inhibitors:** Reduce the dose of TURALIO if concomitant use of UGT inhibitors cannot be avoided. (2.3, 7.2)
 - **Acid-Reducing Agents:** Avoid concomitant use of proton pump inhibitors. Use histamine-2 receptor antagonists or antacids if needed. (2.4, 7.2)
 - **High-Fat Meal:** Avoid taking TURALIO with a high-fat meal. (2.1, 5.4, 7.2).
 - **CYP3A Substrates:** Avoid concomitant use with CYP3A substrates where minimal concentration changes may lead to serious therapeutic failure. (7.3)

- USE IN SPECIFIC POPULATIONS**
- **Lactation:** Advise not to breastfeed. (8.2)
 - **Renal Impairment:** Reduce the dosage for patients with mild to severe renal impairment. (2.5, 8.6)
 - **Hepatic Impairment:** Reduce the dosage for patients with moderate hepatic impairment. (2.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 10/2022

- 8 USE IN SPECIFIC POPULATIONS**
- 8.1 Pregnancy
- 8.2 Lactation
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FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

- TURALIO can cause serious and potentially fatal liver injury *[see Warnings and Precautions (5.1)]*.
- 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 *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.
- TURALIO is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

TURALIO 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of TURALIO is 250 mg taken orally twice daily with a low-fat meal (approximately 11 to 14 grams of total fat) until disease progression or unacceptable toxicity *[see Clinical Pharmacology (12.3)]*. Taking TURALIO with a high-fat meal (approximately 55 to 65 grams of total fat) increases pexidartinib concentrations and may increase the risk of adverse reactions, including hepatotoxicity *[see Warnings and Precautions (5.1, 5.4), Drug Interactions (7.2), Clinical Pharmacology (12.2, 12.3)]*.

Swallow TURALIO capsules whole. Do not open, break, or chew the capsules.

If a patient vomits or misses a dose of TURALIO, instruct the patient to take the next dose at its scheduled time.

2.2 Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 1.

Table 1: Recommended Dose Reductions for TURALIO for Adverse Reactions

Dose Reduction	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

Permanently discontinue TURALIO in patients who are unable to tolerate 125 mg orally twice daily.

The recommended dosage modifications for adverse reactions are summarized in Table 2.

Table 2: Recommended Dosage Modifications for TURALIO for Adverse Reactions

Adverse Reaction	Severity	TURALIO Dosage Modifications
Hepatotoxicity <i>[see Warnings and Precautions (5.1)]</i>		
Increased ALT and/or AST	Greater than 3 to 5 times 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.
	Greater than 5 to 10 times 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.
	Greater than 10 times 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.
Increased ALP ^a and GGT	ALP greater than 2 times ULN with GGT greater than 2 times 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.

(continued)

Table 2: Recommended Dosage Modifications for TURALIO for Adverse Reactions

Adverse Reaction	Severity	TURALIO Dosage Modifications
Increased bilirubin	TB greater than ULN to less than 2 times ULN or DB greater than ULN and less than 1.5 times 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.
	TB greater or equal to 2 times ULN or DB greater than 1.5 times 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.
Adverse Reactions or Other Laboratory Abnormalities <i>[see Adverse Reactions (6.1)]</i>		
Any	Severe or intolerable	<ul style="list-style-type: none">Withhold until improvement or resolution.Resume at a reduced dose upon improvement or resolution.

ALT = alanine aminotransferase; ALP = alkaline phosphatase; 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.

2.3 Concomitant Use of Moderate or Strong CYP3A Inhibitors or UGT Inhibitors

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 in Table 3.

If concomitant use of a moderate or strong CYP3A inhibitor or UGT inhibitor is discontinued, increase the TURALIO dose (after 3 plasma half-lives of the moderate or strong CYP3A inhibitor or UGT inhibitor) to the dose that was used before starting the inhibitor *[see Clinical Pharmacology (12.3)]*.

Table 3: Recommended Dosage Reductions for TURALIO for Concomitant Use of Moderate or Strong CYP3A Inhibitors or UGT Inhibitors

Total Daily Dose*	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

* 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) *[see Dosage and Administration (2.2, 2.5, 2.6)]*.

2.4 Concomitant Use of Acid-Reducing Agents

Avoid the concomitant use of proton pump inhibitors (PPI) 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 a histamine 2 (H₂)-receptor antagonist, administer TURALIO at least 2 hours before or 10 hours after taking an H₂-receptor antagonist *[see Clinical Pharmacology (12.3)]*.

2.5 Dosage Modification for Renal Impairment

The recommended dosage of TURALIO for patients with mild to severe renal impairment (creatinine clearance [CL_{cr}] 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 *[see Clinical Pharmacology (12.3)]*.

2.6 Dosage Modification for Hepatic Impairment

The recommended dosage of TURALIO for patients with moderate hepatic impairment (total bilirubin >1.5 to 3 × upper limit of normal [ULN], not due to Gilbert's syndrome, with any AST) is 125 mg twice daily with a low-fat meal *[see Clinical Pharmacology (12.3)]*. TURALIO has not been studied in patients with severe hepatic impairment (total bilirubin >3 to 10 × ULN and any AST).

3 DOSAGE FORMS AND STRENGTHS

Capsules: 125 mg, size 1 with white opaque body and powder blue opaque cap with black print "DSC521"

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

TURALIO can cause serious and potentially fatal liver injury and is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity with ductopenia and cholestasis occurred in patients treated with TURALIO. Across 768 patients who received TURALIO in clinical trials, there were

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.



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.

In ENLIVEN, 3 of 61 (5%) patients who received TURALIO developed signs of serious liver injury, defined as ALT or AST $\geq 3 \times$ ULN with total bilirubin $\geq 2 \times$ ULN. In these patients, peak ALT ranged from 6 to 9 \times ULN, peak total bilirubin ranged from 2.5 to 15 \times ULN, and alkaline phosphatase (ALP) was $\geq 2 \times$ ULN. ALT, AST and total bilirubin improved to $< 2 \times$ ULN in these patients 1 to 7 months after discontinuing TURALIO.

Avoid TURALIO in patients with pre-existing increased serum transaminases; total bilirubin or direct bilirubin ($> \text{ULN}$); 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 [see *Dosage and Administration (2.2)*]. Rechallenge 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.

5.2 TURALIO REMS Program
TURALIO is only available through a restricted program under a REMS, because of the risk of hepatotoxicity [see *Warnings and Precautions (5.1)*].

Notable requirements of the TURALIO REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- 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 1-833-887-2546.

5.3 Embryo-Fetal Toxicity
Based on animal studies and its mechanism of action, TURALIO may cause fetal harm when administered to a pregnant woman. Oral administration of pexidartinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations, increased post-implantation loss, and abortion at exposures approximately equal to the human exposure at the recommended dose based on area under the curve (AUC).

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception, since 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 [see *Drug Interactions (7.3)*, *Use in Specific Populations (8.1, 8.3)*].

5.4 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 [see *Clinical Pharmacology (12.2, 12.3)*].

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). Consider referring patients to a dietician as deemed necessary [see *Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)*, *Drug Interactions (7.2)*].

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity [see *Warnings and Precautions (5.1)*].

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TURALIO 250 mg orally twice daily administered with a low-fat meal has been established based on adequate and well-controlled studies of TURALIO 400 mg orally twice daily administered on an empty stomach and additional pharmacokinetic data that indicate there is no clinically significant difference in the relative exposure between the two dosages [see *Clinical Pharmacology (12.3)*].

The safety of TURALIO was evaluated in ENLIVEN [see *Clinical Studies (14.1)*]. ENLIVEN excluded patients with ALT, AST, or total bilirubin $> 1.5 \times$ ULN; and known active or chronic infection with hepatitis B or C virus, or human immunodeficiency virus. Patients received TURALIO without food at a dose of 400 mg in the morning and 600 mg in the evening orally for 2 weeks followed by 400 mg orally twice daily until disease progression or unacceptable toxicity. Seventy-nine percent of patients received TURALIO for 6 months or longer and 66% for greater than one year.

The median age of TURALIO-treated patients was 44 years (range: 22-75), 57% were females, and 85% were White.

Serious adverse reactions were reported in 13% of patients who received TURALIO. Most frequent (occurring in > 1 patient) serious adverse reactions included abnormal liver tests (3.3%) and hepatotoxicity (3.3%).

Permanent discontinuation due to an adverse reaction occurred in 13% of patients who received TURALIO. Most frequent adverse reactions (occurring in > 1 patient) requiring permanent discontinuation included increased ALT (4.9%), increased AST (4.9%) and hepatotoxicity (3.3%).

Dose reductions or interruptions occurred in 38% of patients who received TURALIO. Most frequent adverse reactions (occurring in > 1 patient) requiring a dosage reduction or interruption were increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), vomiting (4.9%), increased bilirubin (3.3%), increased GGT (3.3%), dizziness (3.3%), and abdominal pain (3.3%).

The most common ($> 20\%$) adverse reactions, including laboratory abnormalities, in patients who received TURALIO were: increased lactate dehydrogenase (LDH), increased AST, hair color changes, fatigue, increased ALT, decreased neutrophils, increased cholesterol, increased ALP, decreased lymphocytes, eye edema, decreased hemoglobin, rash, dysgeusia and decreased phosphate.

Tables 4, 5 and 6 summarize the adverse reactions and laboratory abnormalities in ENLIVEN during the randomized phase (Week 25).

Table 4: Adverse Reactions ($\geq 10\%$ All Grades or $> 2\%$ Grade ≥ 3) in Patients Receiving TURALIO with a Difference Between Arms of $> 5\%$ Compared to Placebo Through Week 25 in ENLIVEN

Adverse Reaction	TURALIO N=61		Placebo N=59	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Skin and subcutaneous tissue				
Hair color changes	67	0	3.4	0
Rash ^a	28	1.6	7	0
Pruritus ^b	18	0	3.4	0
General				
Fatigue ^c	64	0	41	0
Peripheral edema ^d	20	0	7	0
Eye				
Eye edema ^e	30	1.6	5	0
Nervous system				
Dysgeusia ^f	26	0	1.7	0
Neuropathy ^g	10	0	5	0
Gastrointestinal				
Vomiting	20	1.6	5	0
Constipation	12	0	5	0
Metabolism and nutrition				
Decreased appetite	16	0	10	0
Vascular				
Hypertension	15	4.9	10	0

^a Rash includes rash, maculo-papular rash, rash pruritic, urticaria, erythema, dermatitis acneiform, dermatitis allergic.

^b Pruritis includes pruritus, pruritus generalized.

^c Fatigue includes fatigue, asthenia, malaise.

^d Peripheral edema includes face edema, localized edema, edema peripheral, peripheral swelling.

^e Eye edema includes periorbital edema, eye edema, eyelid edema, papilledema.

^f Dysgeusia includes dysgeusia, ageusia.

^g Neuropathy includes neuropathy peripheral, paresthesia, hypoesthesia, burning sensation.

Table 5: Hepatic Laboratory Abnormalities ($\geq 10\%$ All Grades or $> 2\%$ Grade ≥ 3) Worsening from Baseline in Patients Receiving TURALIO with a Difference Between Arms of $> 5\%$ Compared to Placebo Through Week 25 in ENLIVEN

Laboratory Abnormality ^b	TURALIO ^a			Placebo ^a		
	Grade 1 (%)	Grade 2 (%)	Grade ≥ 3 (%)	Grade 1 (%)	Grade 2 (%)	Grade ≥ 3 (%)
Liver Tests						
Increased AST	61	15	12	15	0	0
Increased ALT	31	13	20	22	0	0
Increased ALP	31	3.3	4.9	1.7	0	0
Increased bilirubin	3.3	3.3	3.3	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

^a Each test incidence is based on the number of patients who had both a baseline and at least one on-study measurement TURALIO (n=61) and placebo (n=59).
^b Graded per NCI CTCAE v 4.03

Table 6: Other Laboratory Abnormalities Worsening from Baseline (≥10% All Grades or >2% of Grade ≥ 3) in Patients Receiving TURALIO with a Difference Between Arms of >5% Compared to Placebo Through Week 25 in ENLIVEN

Laboratory Abnormality ^b	TURALIO ^a		Placebo ^a	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Chemistry				
Increased LDH ^c	92	0	5	0
Increased cholesterol	44	4.9	25	0
Decreased phosphate	25	3.3	5	0
Hematology				
Decreased neutrophils	44	3.3	9	0
Decreased lymphocytes	38	1.6	3.4	0
Decreased hemoglobin	30	0	14	1.7
Decreased platelets	15	0	5	0

LDH=Lactate Dehydrogenase
^a Each test incidence is based on the number of patients who had both a baseline and at least one on-study measurement TURALIO (n = 61) and placebo (n = 58-59).
^b Graded per NCI CTCAE v 4.03 except for LDH
^c LDH: Grade 1 >ULN to ≤2.5 x ULN; Grade 2 >2.5 to ≤5 x ULN; Grade 3 >5 to ≤20 x ULN; Grade 4 >20 x ULN

Clinically relevant adverse reactions occurring in <10% of patients were:

Eye: blurred vision, photophobia, diplopia, reduced visual acuity

Gastrointestinal: dry mouth, stomatitis, mouth ulceration

General: pyrexia

Hepatobiliary: cholangitis, hepatotoxicity, liver disorder

Neurological: cognitive disorders (memory impairment, amnesia, confusional state, disturbance in attention, attention deficit/hyperactivity disorder)

Skin and subcutaneous tissue: alopecia, skin pigment changes (hypopigmentation, depigmentation, discoloration, hyperpigmentation)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TURALIO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Investigations: Blood creatine phosphokinase increased

7 DRUG INTERACTIONS

7.1 Use with Hepatotoxic Products

TURALIO can cause hepatotoxicity. In patients with increased serum transaminases, total bilirubin, or direct bilirubin (>ULN) or active liver or biliary tract disease, avoid coadministration of TURALIO with other products known to cause hepatotoxicity [see *Warnings and Precautions* (5.1)].

7.2 Effect of Other Drugs or Food on TURALIO

Table 7: Effect of Other Drugs or Food on TURALIO

Moderate or Strong CYP3A Inhibitors	
Clinical Impact	• Concomitant use of a moderate or strong CYP3A inhibitor may increase pexidartinib concentrations [see <i>Clinical Pharmacology</i> (12.3)], which may increase the incidence and severity of adverse reactions of TURALIO.
Management	• Reduce TURALIO dosage if concomitant use of moderate or strong CYP3A inhibitors, including grapefruit or grapefruit juice, cannot be avoided [see <i>Dosage and Administration</i> (2.3)].
Strong CYP3A Inducers	
Clinical Impact	• Concomitant use of a strong CYP3A inducer decreases pexidartinib concentrations [see <i>Clinical Pharmacology</i> (12.3)], which may decrease the efficacy of TURALIO.
Management	• Avoid concomitant use of strong CYP3A inducers, including St John's wort.
UGT Inhibitors	
Clinical Impact	• Concomitant use of a UGT inhibitor increases pexidartinib concentrations [see <i>Clinical Pharmacology</i> (12.3)], which may increase the incidence and severity of adverse reactions of TURALIO.
Management	• Reduce TURALIO dosage if concomitant use of UGT inhibitors cannot be avoided [see <i>Dosage and Administration</i> (2.3)].

(continued)

Table 7: Effect of Other Drugs or Food on TURALIO

Acid-Reducing Agents	
Clinical Impact	• Concomitant use of a PPI decreases pexidartinib concentrations [see <i>Clinical Pharmacology</i> (12.3)], which may decrease the efficacy of TURALIO.
Management	• Avoid concomitant use of PPIs with TURALIO. As an alternative to PPIs, use locally-acting antacids or H ₂ -receptor antagonists [see <i>Dosage and Administration</i> (2.4)].
High-Fat Meal	
Clinical Impact	• Taking TURALIO with a high-fat meal increased pexidartinib concentrations [see <i>Clinical Pharmacology</i> (12.3)], which may increase the incidence and severity of TURALIO adverse reactions, including hepatotoxicity [see <i>Warnings and Precautions</i> (5.1, 5.4)].
Management	• Take TURALIO with a low-fat meal (approximately 11 to 14 grams of total fat). Avoid taking TURALIO with a high-fat meal (approximately 55 to 65 grams of total fat) [see <i>Dosage and Administration</i> (2.1)].

7.3 Effect of TURALIO on Other Drugs

Table 8: Effect of TURALIO on Other Drugs

CYP3A Substrates	
Clinical Impact	• TURALIO is a moderate CYP3A inducer. Concomitant use of TURALIO decreases the concentration of CYP3A substrates [see <i>Clinical Pharmacology</i> (12.3)], which may reduce the efficacy of these substrates.
Management	• Avoid coadministration of TURALIO with hormonal contraceptives [see <i>Warnings and Precautions</i> (5.3), <i>Use in Specific Populations</i> (8.3)]. • Avoid concomitant use of TURALIO with other CYP3A substrates, where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with approved product labeling.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology* (12.1)], TURALIO may cause embryo-fetal harm when administered to a pregnant woman. The available human data do not establish the presence or absence of major birth defects or miscarriage related to the use of TURALIO. Oral administration of pexidartinib to pregnant animals during the period of organogenesis resulted in malformations, post-implantation loss, and abortion at maternal exposures that were approximately equal to the human exposure at the recommended dose (see *Data*). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Embryo-fetal development studies investigating the administration of pexidartinib during the period of organogenesis were conducted in rats and rabbits. In rats, pexidartinib resulted in increased post-implantation loss and fetal malformations including localized fetal edema, absence of kidney and ureter, abnormalities of the reproductive tract, and developmental variations including misshapen kidney, decreased skeletal ossification and higher mean litter proportions of slightly or moderately malaligned sternebrae at doses of 40 mg/kg (approximately equal to the human exposure at the recommended dose). In rabbits, administration of pexidartinib resulted in increased post-implantation loss, abortion, and fetal malformations including absence of kidney or ureter, rudimentary, misshapen or malpositioned kidney, rib abnormalities, and skeletal variations of accessory skull bones at doses of 60 mg/kg (approximately equal to the human exposure at the recommended dose).

8.2 Lactation

Risk Summary

There are no data on the presence of pexidartinib or its metabolites in either human or animal milk or its effects on a breastfed child or on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with TURALIO and for at least 1 week after the final dose.

8.3 Females and Males of Reproductive Potential

TURALIO may cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations* (8.1)].

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to the initiation of TURALIO [see *Use in Specific Populations* (8.1)].

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Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TURALIO and for 1 month after the final dose. Counsel patients to use non-hormonal method(s) of contraception, since TURALIO can render hormonal contraceptives ineffective [see *Drug Interactions* (7.3), *Nonclinical Toxicology* (13.1)].

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TURALIO and for 1 week after the final dose [see *Nonclinical Toxicology* (13.1)].

Infertility

Based on findings from animal studies, TURALIO may impair both male and female fertility [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

The safety and effectiveness of TURALIO in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of TURALIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

Reduce the dosage when administering TURALIO to patients with mild to severe renal impairment (CLcr 15 to 89 mL/min, estimated by Cockcroft-Gault [C-G]) [see *Dosage and Administration* (2.5), *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No dosage adjustment is recommended for patients with mild hepatic impairment (total bilirubin \leq upper limit of normal [ULN] with AST $>$ ULN or total bilirubin >1 to $1.5 \times$ ULN with any AST) [see *Clinical Pharmacology* (12.3)].

Reduce the dosage of TURALIO for patients with moderate hepatic impairment (total bilirubin >1.5 to $3 \times$ ULN, not due to Gilbert's syndrome, with any AST) [see *Dosage and Administration* (2.6), *Clinical Pharmacology* (12.3)].

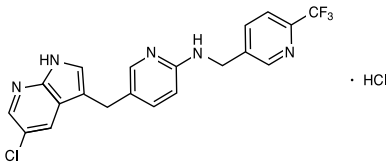
TURALIO has not been studied in patients with severe hepatic impairment (total bilirubin >3 to $10 \times$ ULN and any AST).

10 OVERDOSAGE

Due to the high plasma protein binding, TURALIO is not expected to be dialyzable [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Pexidartinib is a kinase inhibitor. The chemical name of pexidartinib hydrochloride is 5-[(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-N-[(6-(trifluoromethyl)pyridin-3-yl)methyl]pyridin-2-amine monohydrochloride. Pexidartinib hydrochloride is an off-white to white solid. The molecular formula for pexidartinib hydrochloride is $C_{20}H_{15}ClF_3N_5 \cdot HCl$. The molecular weight is 454.28 for the hydrochloride salt and 417.81 for the free base. The chemical structure is:



The solubility of pexidartinib hydrochloride in aqueous solutions decreases with increasing pH. The pKa1 and pKa2 were determined to be 2.6 and 5.4 respectively for the conjugate acids. Pexidartinib hydrochloride is soluble in methanol, slightly soluble in water and ethanol, and practically insoluble in heptane.

TURALIO (pexidartinib) capsules are for oral use. Each capsule contains 125 mg pexidartinib which is equivalent to 135.9 mg pexidartinib hydrochloride. The capsule contains the following inactive ingredients: poloxamer 407, mannitol, crospovidone, and magnesium stearate. The hypromellose capsule shell contains hypromellose, titanium dioxide and FD&C Blue No. 1.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pexidartinib is a small molecule tyrosine kinase inhibitor that targets colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD) mutation. Overexpression of the CSF1R ligand promotes cell proliferation and accumulation in the synovium. In vitro, pexidartinib inhibited proliferation of cell lines dependent on CSF1R and ligand-induced autophosphorylation of CSF1R. Pexidartinib also inhibited the proliferation of a CSF1R dependent cell line in vivo.

12.2 Pharmacodynamics

Exposure-Response Relationships

There is an exposure response relationship between pexidartinib steady state exposure and serum transaminase levels (ALT and AST) with a higher risk of increased serum transaminases at higher exposure. Additionally, increased transaminases occurred more frequently with higher pexidartinib doses between 200 to 1200 mg per day administered on an empty stomach (0.25 to 1.5 times the exposure from the recommended dose).

Cardiac Electrophysiology

At two times the mean maximum exposure of the recommended dosage, TURALIO does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of TURALIO was evaluated following single doses in healthy subjects and following multiple doses in patients as summarized in Table 9.

Table 9: TURALIO Exposure and Pharmacokinetic Parameters

General Information		
Steady state exposure [Mean (SD)] ^a	C _{max}	8625 (2746) ng/mL
	AUC _{0-12h}	77465 (24975) ng•h/mL
Dose proportionality	Pexidartinib exposure (C _{max} and AUC _{0-INF}) increased linearly over the single oral dose range of 200 to 2400 mg administered on an empty stomach (0.5 to 6 times the exposure from the recommended dose).	
Time to steady state ^b	Approximately 7 days	
Accumulation ratio (AUC) [Median] ^b	3.6	
Absorption		
T _{max} [Median] ^a	2.5 hours	
Effect of food		
TURALIO 400 mg with a high-fat meal ^c	Compared to an empty stomach: • Increased pexidartinib C _{max} and AUC _{0-INF} by 100% • Delayed T _{max} by 2.5 hours	
TURALIO 400 mg with a low-fat meal ^d	Compared to an empty stomach: • Increased pexidartinib C _{max} by 56% and AUC _{0-INF} by 59% • Delayed T _{max} by 1.5 hours	
Predicted relative AUC _{0-24h} of TURALIO 250 mg with a low-fat meal to that of TURALIO 400 mg on an empty stomach	• No clinically significant difference	
Distribution		
In vitro plasma protein binding	• Greater than 99% • Human serum albumin: 99.9% • α-1 acid glycoprotein: 89.9%	
Apparent volume of distribution (V _{z/F}) [Mean (CV%)] ^e	• 187 L (27%)	
Elimination		
Apparent clearance [Mean (CV%)] ^e	• 5.1 L/h (36%)	
t _{1/2} [Mean (SD)]	• 26.6 (6.5) hours	
Metabolism		
Primary pathway	• Oxidation: CYP3A4 • Glucuronidation: UGT1A4	
N-glucuronide metabolite	• Major inactive metabolite formed by UGT1A4 • Approximately 10% higher exposure than pexidartinib after a single dose	
Excretion ^f		
	• Feces: 65% (44% as unchanged) • Urine: 27% as metabolites (≥10% as N-glucuronide)	

^a Pexidartinib 400 mg twice daily on an empty stomach (similar exposure to that of the recommended dosage)

^b Estimated based on half life

^c The high-fat meal comprised 800 to 1000 calories with approximately 50% from fat (approximately 55 to 65 grams of total fat).

^d The low-fat meal comprised approximately 400 calories with 25% from fat (approximately 11 to 14 grams of total fat).

^e After a single oral dose of pexidartinib

^f After a single oral dose of radiolabeled pexidartinib

Specific Populations

No clinically meaningful differences in the pharmacokinetics of pexidartinib were observed based on age (18 to 84 years), sex, race (White and Black), or mild hepatic impairment (total bilirubin \leq ULN with AST $>$ ULN or total bilirubin >1 to $1.5 \times$ ULN with any AST).

Patients with Renal Impairment

Mild (CLcr 60 to 89 mL/min), moderate (CLcr 30 to 59 mL/min) and severe (CLcr 15 to 29 mL/min) renal impairment increased pexidartinib exposure (AUC)

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by approximately 30%, relative to that in patients with normal renal function (CL_{Cr} ≥90 mL/min).

Patients with Hepatic Impairment
Moderate hepatic impairment (total bilirubin > 1.5 to 3 × ULN, not due to Gilbert's syndrome, with any AST) increased pexidartinib exposure (AUC) by 43% relative to exposure in patients with normal hepatic function (total bilirubin and AST ≤ ULN). The pharmacokinetics of pexidartinib have not been studied in patients with severe hepatic impairment (total bilirubin > 3 to 10 × ULN with any AST).

Drug Interaction Studies
Clinical Studies
Effects of Other Drugs on Pexidartinib
Strong or Moderate CYP3A Inducers: Coadministration of rifampicin (strong CYP3A inducer) decreased pexidartinib C_{max} by 33% and AUC_{0-1NF} by 65%. Coadministration of efavirenz (moderate CYP3A inducer) is predicted to have no clinically significant differences in pexidartinib pharmacokinetics.
Strong or Moderate CYP3A Inhibitors: Coadministration of itraconazole (strong CYP3A inhibitor) increased pexidartinib C_{max} by 48% and AUC_{0-1NF} by 70%. Coadministration of fluconazole (moderate CYP3A inhibitor) is predicted to increase pexidartinib C_{max} by 41% and AUC by 67% at steady state.
UGT Inhibitors: Coadministration of probenecid (UGT inhibitor) increased pexidartinib AUC_{0-1NF} by 60% with no effect on C_{max}.
Acid-Reducing Agents: Coadministration of esomeprazole (proton pump inhibitor) decreased pexidartinib C_{max} by 55% and AUC_{0-1NF} by 50%. The effects of H₂-receptor antagonists and locally-acting antacids on pexidartinib pharmacokinetics have not been studied.

Effects of Pexidartinib on Other Drugs
CYP3A Substrates: Coadministration of TURALIO at the approved recommended dosage decreased midazolam (CYP3A substrate) C_{max} by 28% and AUC_{0-1NF} by 59%.
Other Drugs: When coadministered with omeprazole (CYP2C19 substrate), tolbutamide (CYP2C9 substrate), digoxin (P-gp substrate), or CYP2C8 substrate with TURALIO, no clinically significant differences in their pharmacokinetics were observed or predicted.

In Vitro Studies
CYP/UGT Enzymes: Pexidartinib inhibited and induced CYP2B6 at clinically relevant concentrations. Pexidartinib inhibited UGT1A1 at clinically relevant concentrations.
Transporters: Pexidartinib is not a substrate for P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, OATP2B1, and BSEP.

Pexidartinib is an inhibitor of MATE1, MATE2-K, OATP1B1, OATP1B3 and OATP2B1.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies were performed in mice and rats. Both studies were negative for carcinogenic findings at exposures up to 9 times the human exposure at the recommended daily dose based on AUC.

Pexidartinib was not mutagenic in an in vitro bacterial reverse mutation (AMES) assay or clastogenic in either an in vitro human peripheral blood lymphocyte chromosomal aberrations assay or in an in vivo mouse bone marrow micronucleus assay.

Based on nonclinical findings, TURALIO may impair male and female fertility. In a fertility study in which pexidartinib was administered orally to male and female rats, there were reductions in pregnancy, as well as increases in pre- and post-implantation loss with a corresponding reduction in viable embryos at 40 mg/kg (approximately 1.3 times the human exposure at the recommended dose). Males at this dose level displayed reductions in spermatogenic parameters and adverse effects on sperm concentration, production, motility, and morphology. Lower testicular and epididymal weights occurred in this study at doses of ≥10 mg/kg/day (approximately 0.3 times the human exposure at the recommended dose). This is consistent with findings in chronic toxicology studies of germ cell depletion of the testes and hypospermia and cellular debris in the epididymis in male reproductive tissues of both rats and dogs at respective doses as low as 20 and 30 mg/kg/day (approximately 0.6 and 0.1 times the human exposure at the recommended dose). In rats, these changes persisted following a 16-week recovery period at the 60 mg/kg/day dose level (approximately 1.5 times the human exposure at the recommended dose).

In female rats, necrosis of corpora lutea occurred at doses ≥0.5 mg/kg/day (approximately 0.01 times the human exposure at the recommended dose) with pigment deposition within the interstitium of the ovaries, an increased incidence of luteal cysts and incidence/severity of hemorrhage of corpora lutea, and a decreased incidence of retained antral follicles and decreased corpora lutea at 60 mg/kg (approximately 1.8 times the human exposure at the recommended dose). In female dogs there were decreased follicle numbers and moderate atrophy of the oviduct, uterus, and cervix at doses as low as 1 mg/kg (approximately 0.01 times the human exposure at the recommended dose).

13.2 Animal Toxicology and/or Pharmacology
In repeat dose toxicity studies of up to 26 weeks in rats, there were findings of myxomatous change in the skin, tongue, and gastrointestinal tract, lymphoid depletion of the bone marrow and thymus, and chronic progressive nephropathy of the kidney at 20 mg/kg/day (approximately 0.6 times the human exposure at the recommended dose). Similar changes occurred in the rat carcinogenicity study along with alterations in the tunica intima of the aorta. Vascular inflammation consistent with polyarteritis nodosa occurred in male rats at 60 mg/kg/day (approximately 1.5 times the human exposure at the recommended dose). There were also dose-dependent findings of minimal to moderate subphyseal or cortical hyperostosis and physeal hypertrophy in the femur that correlated with decreased systemic phosphate levels at doses ≥ 60 mg/kg.

14 CLINICAL STUDIES
14.1 Tenosynovial Giant Cell Tumor
The efficacy of TURALIO 250 mg orally twice daily administered with a low-fat meal has been established based on adequate and well-controlled studies of TURALIO 400 mg orally twice daily administered on an empty stomach and additional pharmacokinetic data that indicate there is no clinically significant difference in the relative exposure between the two dosages.

The efficacy of TURALIO was evaluated in ENLIVEN (NCT02371369), a double-blind, randomized (1:1), placebo-controlled, multicenter trial in patients with symptomatic TGCT [also referred to as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS)] for whom surgical removal of the tumor would be associated with worsening functional limitation or severe morbidity. Eligible patients were required to have measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients were randomized to placebo or TURALIO administered on an empty stomach: 400 mg in the morning and 600 mg in the evening for 2 weeks followed by 400 mg twice daily until unacceptable toxicity or disease progression. Randomization was stratified by geographic region (US vs. non-US countries) and disease location (upper extremity vs. lower extremity involvement). Patients who completed treatment in the double-blind, randomized part of the trial were eligible to advance to an open-label extension part in which all patients were given the option to receive pexidartinib.

The major efficacy outcome measure was overall response rate (ORR) as assessed by blinded independent central review (BICR) at Week 25 using RECIST v1.1. Additional efficacy outcome measures were mean change from baseline in range of motion of the affected joint at Week 25 and ORR as assessed by BICR at Week 25 using tumor volume score (TVS). Range of motion was measured as a percent of normal reference range for the affected joint. Range of motion assessments were performed by a third-party clinical assessor using a goniometer. TVS was defined in ENLIVEN as the estimated volume of the maximally distended synovial cavity or tendon sheath involved, measured in 10% increments. Patients in the placebo arm were offered TURALIO at Week 25 beginning with a 400 mg twice daily dose, as permitted by the study protocol.

A total of 120 patients were randomized, 61 to the TURALIO arm and 59 to the placebo arm. The median age was 44 years (range: 18-79); 59% were females; 88% were White; 53% had prior surgery; 88% were diagnosed with diffuse TGCT; and 9% had previously been treated with systemic therapy. Disease locations were knee (61%), ankle (18%), hip (11%), wrist (3%), foot (3%) and other (5%).

ENLIVEN demonstrated a statistically significant improvement in ORR in patients randomized to TURALIO compared with placebo. Efficacy results are summarized in Table 10.

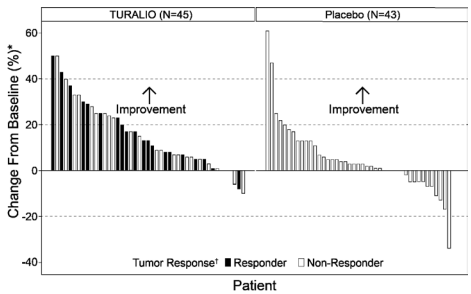
Table 10: Efficacy Results Assessed at Week 25 for ENLIVEN		
Efficacy Parameter	TURALIO N=61	Placebo N=59
Overall Response Rate (ORR) ^{a,b}		
ORR (95% CI)	38% (27%, 50%)	0 (0, 6%)
Complete Response	15%	0
Partial Response	23%	0
P-value ^c	<0.0001	
Duration of Response (DOR) ^b		
Range (months)	6.9+, 24.9+	NA

CI: confidence interval; NA: not applicable; SD: standard deviation; LS: least squares;
+: denotes ongoing at last assessment
^a Blinded independent central review
^b Data cut-off date January 31, 2018
^c Fisher's exact test

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The analysis of mean change from baseline in range of motion at Week 25 demonstrated a statistically significant improvement in patients randomized to TURALIO compared to placebo. Figure 1 shows the change from baseline in range of motion for each patient at Week 25 (TURALIO N=45, placebo N=43). Results were excluded for 1 patient with missing baseline and 31 patients with a missing range of motion assessment at Week 25.

Figure 1: Change from Baseline in Range of Motion at Week 25 for ENLIVEN



ORR by TVS was 56% (95% CI: 43%, 67%) in patients randomized to the TURALIO arm and 0% in patients randomized to the placebo arm; $p < 0.0001$. At completion of the open-label extension part of the study in which all patients received TURALIO, the ORR using RECIST v1.1 was 61% (95% CI: 48%, 72%) in the 61 patients originally randomized to the TURALIO arm. The median duration of response was not reached (range: 4.6+, 63.4+ months) in the 37 responders.

16 HOW SUPPLIED/STORAGE AND HANDLING

TURALIO 125 mg capsules are supplied as size 1 with white opaque body and powder blue opaque cap with black print "DSC521", available in:

- 28 count bottle NDC#: 65597-407-28
- 120 count bottle NDC#: 65597-407-20

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Keep containers closed and do not remove desiccant from bottles.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Hepatotoxicity

Advise patients of the risk of hepatotoxicity that could be fatal and that they will need to undergo monitoring for liver injury and to report immediately any signs or symptoms of severe liver injury to their healthcare provider [see *Warnings and Precautions* (5.1)].

TURALIO REMS Program

- TURALIO is available only through a restricted program called TURALIO REMS Program and patients are required to be part of the patient registry [see *Warnings and Precautions* (5.2)].
- TURALIO is available only from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.3), *Use in Specific Populations* (8.1, 8.3)].
- Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TURALIO and for 1 month after the final dose [see *Drug Interactions* (7.3), *Use in Specific Populations* (8.3)].
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the final dose [see *Use in Specific Populations* (8.3), *Nonclinical Toxicology* (13.1)].

Lactation

Advise females not to breastfeed during treatment with TURALIO and for 1 week after the final dose [see *Use in Specific Populations* (8.2)].

Infertility

Advise females and males of reproductive potential that TURALIO may impair fertility [see *Use in Specific Populations* (8.3), *Nonclinical Toxicology* (13.1)].

Administration

- 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). Consider referring patients to a dietician as deemed necessary [see *Dosage and Administration* (2.1), *Warnings and Precautions* (5.4), *Drug Interactions* (7.2)].
- Instruct patients to swallow capsules whole (do not open, break, or chew) [see *Dosage and Administration* (2.1)].

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant products, including over-the-counter products and supplements [see *Dosage and Administration* (2), *Drug Interactions* (7)].

Manufactured for: Daiichi Sankyo, Inc.
Basking Ridge, NJ 07920

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USPI-TUR125-C6-1022-r100

Medication Guide

TURALIO® (tur-a-lee-oh)
(pexidartinib)
capsules

What is the most important information I should know about TURALIO?

TURALIO can cause serious side effects, including:

Serious Liver Problems which may be severe and can lead to death.

Your healthcare provider will do blood tests to check for liver problems:

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

If you develop liver problems during treatment with TURALIO, your healthcare provider may do blood tests more often to monitor you. It is important to stay under the care of your healthcare provider during treatment with TURALIO.

Stop taking TURALIO and call your healthcare provider right away if you develop:

- yellowing of your skin and whites of your eyes
- dark urine

Tell your healthcare provider right away if you have any of these symptoms of liver problems while taking TURALIO:

- lack or loss of appetite
- vomiting
- right upper stomach-area (abdomen)
- fever
- pain or tenderness
- rash
- feeling overly tired
- itching
- nausea

TURALIO Risk Evaluation and Mitigation Strategy (REMS): Because of the risk of serious liver problems, TURALIO is available only through a restricted program called the TURALIO REMS Program. Your healthcare provider must be enrolled in the program in order for you to be prescribed TURALIO. There is a registry that collects information about the effects of taking TURALIO over time. You must complete and sign an enrollment form for the TURALIO REMS Program and the registry. Ask your healthcare provider for more information.

See "What are the possible side effects of TURALIO?" for more information about side effects.

What is TURALIO?

TURALIO is a prescription medicine used to treat certain adults who have tenosynovial giant cell tumor (TGCT) that is not likely to improve with surgery. TGCT is also known as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS).

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

Before taking TURALIO, tell your healthcare provider about all of your medical conditions, including if you:

- have or had liver problems.
- have kidney problems.
- are pregnant or plan to become pregnant. TURALIO may harm your unborn baby.

Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.

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If you are a female who is able to become pregnant:

- Your healthcare provider will do a pregnancy test before you start treatment with TURALIO.
- Females who are able to become pregnant should use effective non-hormonal birth control (contraception) during treatment with TURALIO and for 1 month after your final dose of TURALIO. Birth control pills (oral contraceptives) and other hormonal forms of birth control may not be effective if used during treatment with TURALIO. Talk with your healthcare provider about birth control methods you can use during this time.
- Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with TURALIO.

If you are a male with a female partner who is able to become pregnant:

- Use effective birth control (contraception) during treatment and for 1 week after your final dose of TURALIO.
- Tell your healthcare provider right away if your female partner becomes pregnant or thinks she is pregnant during your treatment with TURALIO.

- are breastfeeding or plan to breastfeed. **Do not** breastfeed during treatment with TURALIO and for at least 1 week after your final dose of TURALIO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Certain medicines may affect the way TURALIO works and TURALIO may affect how other medicines work. **Taking TURALIO with certain medicines may increase the amount of TURALIO in your blood. This may make it more likely for you to develop side effects and may cause more severe side effects.**

- Avoid taking the following medicines or supplements during treatment with TURALIO because they can affect how TURALIO works:
 - Proton Pump Inhibitor medicines (PPIs)
 - St. John's wort

How should I take TURALIO?

- **Your healthcare provider will explain to you how you will receive your TURALIO.**
- Take TURALIO exactly as your healthcare provider tells you to.
- TURALIO is usually taken 2 times a day. Your healthcare provider will tell you how much TURALIO to take and when to take it.
- **Take TURALIO with a low-fat meal (about 11 to 14 grams of total fat). Taking TURALIO with a high-fat meal increases the amount of TURALIO in your blood. This may make it more likely for you to develop side effects and may cause more severe side effects, including serious liver problems. See "What are the possible side effects of TURALIO?"**
 - **Talk with your healthcare provider about examples of foods that you can eat for a low-fat meal that contains about 11 to 14 grams of total fat.**
 - Your healthcare provider may refer you to a dietician, if needed.
- Swallow TURALIO capsules whole.
- **Do not** open, break, or chew TURALIO capsules.
- If you need to take an acid-reducing medicine, follow your healthcare provider's instructions for which medicine to take and when to take it.
 - If you take an antacid medicine: Take TURALIO either **2 hours before or 2 hours after** taking an antacid medicine.
 - If you take an H₂ receptor blocker medicine: Take TURALIO at **least 2 hours before or 10 hours after** taking an H₂ receptor blocker medicine.
- **Tell your healthcare provider about all the medicines you take. See the section "Before taking TURALIO, tell your healthcare provider about all of your medical conditions, including if you."**
- If you vomit after taking a dose, or if you miss a dose of TURALIO, take your next dose at your regular time.

What should I avoid while taking TURALIO?

- Avoid grapefruit or drinking grapefruit juice during treatment with TURALIO. Grapefruit or grapefruit juice can cause you to have too much TURALIO in your blood and may lead to increased side effects and more severe side effects.

What are the possible side effects of TURALIO?

TURALIO can cause serious side effects.

- See "What is the most important information I should know about TURALIO?"
- **There are possible risks if TURALIO is taken with a high-fat meal. Avoid taking TURALIO with a high-fat meal (about 55 to 65 grams of total fat). Taking TURALIO with a high-fat meal increases the amount of medicine in your blood. This may make it more likely for you to develop side effects and may cause more severe side effects, including serious liver problems. Take TURALIO with a low-fat meal (about 11 to 14 grams of total fat). See "How should I take TURALIO?"**

The most common side effects of TURALIO include:

- changes in blood liver tests
- hair color changes
- tiredness
- increased cholesterol level in your blood
- decreased white blood cells and red blood cells
- swelling in or around your eyes
- rash, itching, hives, skin redness, and acne
- loss of taste or changes in the way things taste
- decreased phosphate in your blood

TURALIO may affect fertility in females and males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of TURALIO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TURALIO?

- Store TURALIO at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the TURALIO container closed tightly.
- TURALIO comes with a drying agent (desiccant) in the container. Keep the desiccant in the container.

Keep TURALIO and all medicines out of the reach of children.

General information about the safe and effective use of TURALIO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TURALIO for a condition for which it was not prescribed. Do not give TURALIO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TURALIO that is written for health professionals.

What are the ingredients in TURALIO?

Active Ingredient: pexidartinib

Inactive Ingredients: poloxamer 407, mannitol, crospovidone, and magnesium stearate. Capsule shell: hypromellose, titanium dioxide, and FD&C Blue No. 1

Manufactured for: Daiichi Sankyo, Inc., Basking Ridge, NJ 07920

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For more information, call 1-877-437-7763 or go to <https://www.turalio.com/>.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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Please see [Important Safety Information](#) and accompanying full [Prescribing Information](#), including **Boxed WARNING**, and Medication Guide.