

**TURALIO- pexidartinib capsule**  
**Daiichi Sankyo Inc.**

**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. (2.3, 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, Concomitant Use of Moderate or Strong CYP3A Inhibitors or UGT Inhibitors (2.4) 04/2020  
Warnings and Precautions, Embryo-Fetal Toxicity (5.3) 04/2020

**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**

- Important Administration Instructions: Administer TURALIO on an empty stomach, at least 1 hour before or 2 hours after a meal or snack. (2.1)
- Recommended Dosage: 400 mg orally twice daily (2.2)

**DOSAGE FORMS AND STRENGTHS**

Capsules: 200 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)

**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](http://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. (2.4, 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. (2.4, 7.2)
- Acid-Reducing Agents: Avoid concomitant use of proton pump inhibitors. Use histamine-2 receptor antagonists or

antacids if needed. (2.5, 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 dose for patients with mild to severe renal impairment. (2.6, 8.6)

See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**.

Revised: 4/2020

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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 (2.3), 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 Important Administration Instructions**

Administer TURALIO on an empty stomach, at least one hour before or two hours after a meal or snack [see Warnings and Precautions (5.1), Clinical Pharmacology (12.2, 12.3)].

**2.2 Recommended Dosage**

The recommended dosage of TURALIO is 400 mg taken twice daily on an empty stomach until disease progression or unacceptable toxicity [see Dosage and Administration (2.1), Clinical Pharmacology (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.

**2.3 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**

| <b>Dose Reduction</b> | <b>Total Daily Dose</b> | <b>Administration of Total Daily Dose</b>       |
|-----------------------|-------------------------|---|
| First                 | 600 mg                  | 200 mg in the morning and 400 mg in the evening |
| Second                | 400 mg                  | 200 mg twice daily                              |

Permanently discontinue TURALIO in patients who are unable to tolerate 200 mg orally twice daily. 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  |
|--|---|---|
| <i>Hepatotoxicity [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"> <li>• Withhold and monitor liver tests <u>weekly</u>.</li> <li>• If AST and ALT are less than or equal to 3 times ULN within 4 weeks, resume at reduced dose.</li> <li>• If AST or ALT is <u>not</u> less than or equal to 3 times ULN in 4 weeks, permanently discontinue TURALIO.</li> </ul>                       |
|  | Greater than 5 to 10 times ULN  | <ul style="list-style-type: none"> <li>• Withhold and monitor liver tests <u>twice weekly</u>.</li> <li>• If AST and ALT are less than or equal to 3 times ULN within 4 weeks, resume at reduced dose.</li> <li>• If AST or ALT is <u>not</u> less than or equal to 3 times ULN in 4 weeks, permanently discontinue TURALIO.</li> </ul>                 |
|  | Greater than 10 times ULN   | <ul style="list-style-type: none"> <li>• Permanently discontinue TURALIO.</li> <li>• 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.</li> </ul>  |
| Increased ALP* and GGT                                     | ALP greater than 2 times ULN with GGT greater than 2 times ULN                                  | <ul style="list-style-type: none"> <li>• 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.</li> </ul>  |
| 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"> <li>• Withhold and monitor liver tests <u>twice weekly</u>.</li> <li>• If an alternate cause for increased bilirubin is confirmed and bilirubin is less than ULN within 4 weeks, resume at reduced dose.</li> <li>• If bilirubin is <u>not</u> less than ULN in 4 weeks, permanently discontinue TURALIO.</li> </ul> |
|  | TB greater or equal to 2 times ULN or DB greater than 1.5 times ULN                             | <ul style="list-style-type: none"> <li>• Permanently discontinue TURALIO.</li> <li>• Monitor liver tests <u>twice weekly</u> until bilirubin is less than or equal to ULN.</li> </ul>   |

| Adverse Reactions or Other Laboratory Abnormalities [see Adverse Reactions (6.1)] |                       |   |
|---|-----------------------|---|
| Any   | Severe or intolerable | <ul style="list-style-type: none"> <li>• Withhold until improvement or resolution.</li> <li>• Resume at a reduced dose upon improvement or resolution.</li> </ul> |

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; DB = direct bilirubin; GGT = gamma-glutamyl transferase; TB = total bilirubin; ULN = upper limit of normal

\* Confirm ALP elevations as liver isozyme fraction.

## 2.4 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**

| Planned Total Daily Dose | Modified Total Daily Dose | Administration of Modified Total Daily Dose |
|--------------------------|---------------------------|---|
| 800 mg                   | 400 mg                    | 200 mg twice daily                          |
| 600 mg*                  | 400 mg                    | 200 mg twice daily                          |
| 400 mg*                  | 200 mg                    | 200 mg once daily                           |

\* Planned total daily dose refers to recommended dose reductions for TURALIO for adverse reactions based on dosing recommendations in Table 2.

## 2.5 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 (H<sub>2</sub>)-receptor antagonist, administer TURALIO at least 2 hours before or 10 hours after taking an H<sub>2</sub>-receptor antagonist [see Clinical Pharmacology (12.3)].

## 2.6 Dosage Modification for Renal Impairment

The recommended dosage of TURALIO for patients with mild to severe renal impairment (creatinine clearance [CL<sub>cr</sub>] 15 to 89 mL/min estimated by Cockcroft-Gault using actual body weight) is 200 mg in the morning and 400 mg in the evening [see Clinical Pharmacology (12.3)].

## 3 DOSAGE FORMS AND STRENGTHS

Capsules: 200 mg, size 0 with white opaque body and dark green opaque cap with white print "T10"

## 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 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. Taking TURALIO with food increases drug exposure by 100% and may increase the risk of hepatotoxicity. Administer TURALIO on an empty stomach, either 1 hour before or 2 hours after a meal or snack [see *Dosage and Administration (2.1)*, *Clinical Pharmacology (12.2, 12.3)*]. 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](http://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 of 800 mg 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)*].

## 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 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  $\geq 3$ ) in Patients Receiving TURALIO with a Difference Between Arms of  $>5\%$  Compared to Placebo Through Week 25 in ENLIVEN**

| Adverse Reaction                    | TURALIO<br>N=61   |                       | Placebo<br>N=59   |                       |
|-------------------------------------|-------------------|-----------------------|-------------------|-----------------------|
|                                     | All Grades<br>(%) | Grade $\geq 3$<br>(%) | All Grades<br>(%) | Grade $\geq 3$<br>(%) |
| <b>Skin and subcutaneous tissue</b> |                   |                       |                   |                       |
| Hair color changes                  | 67                | 0                     | 3.4               | 0                     |
| Rash*                               | 28                | 1.6                   | 7                 | 0                     |
| Pruritus <sup>†</sup>               | 18                | 0                     | 3.4               | 0                     |
| <b>General</b>                      |                   |                       |                   |                       |
| Fatigue <sup>‡</sup>                | 64                | 0                     | 41                | 0                     |
| Peripheral edema <sup>§</sup>       | 20                | 0                     | 7                 | 0                     |

| <b>Eye</b>                      |    |     |     |   |
|---------------------------------|----|-----|-----|---|
| Eye edema <sup>¶</sup>          | 30 | 1.6 | 5   | 0 |
| <b>Nervous system</b>           |    |     |     |   |
| Dysgeusia <sup>#</sup>          | 26 | 0   | 1.7 | 0 |
| Neuropathy <sup>ᵀ</sup>         | 10 | 0   | 5   | 0 |
| <b>Gastrointestinal</b>         |    |     |     |   |
| Vomiting                        | 20 | 1.6 | 5   | 0 |
| Constipation                    | 12 | 0   | 5   | 0 |
| <b>Metabolism and nutrition</b> |    |     |     |   |
| Decreased appetite              | 16 | 0   | 10  | 0 |
| <b>Vascular</b>                 |    |     |     |   |
| Hypertension                    | 15 | 4.9 | 10  | 0 |

\* Rash includes rash, maculo-papular rash, rash pruritic, urticaria, erythema, dermatitis acneiform, dermatitis allergic.

† Pruritis includes pruritus, pruritus generalized.

‡ Fatigue includes fatigue, asthenia, malaise.

§ Peripheral edema includes face edema, localized edema, edema peripheral, peripheral swelling.

¶ Eye edema includes periorbital edema, eye edema, eyelid edema, papilledema.

# Dysgeusia includes dysgeusia, ageusia.

ᵀ Neuropathy includes neuropathy peripheral, paresthesia, hypoesthesia, burning sensation.

**Table 5: Hepatic Laboratory Abnormalities (≥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 <sup>†</sup> | TURALIO*    |             |               | Placebo*    |             |               |
|-------------------------------------|-------------|-------------|---------------|-------------|-------------|---------------|
|                                     | Grade 1 (%) | Grade 2 (%) | Grade ≥ 3 (%) | Grade 1 (%) | Grade 2 (%) | Grade ≥ 3 (%) |
| <b>Liver Tests</b>                  |             |             |               |             |             |               |
| 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

\* 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).

† 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 <sup>†</sup> | TURALIO*       |              | Placebo*       |              |
|-------------------------------------|----------------|--------------|----------------|--------------|
|                                     | All Grades (%) | Grade ≥3 (%) | All Grades (%) | Grade ≥3 (%) |
| <b>Chemistry</b>                    |                |              |                |              |
| Increased LDH <sup>‡</sup>          | 92             | 0            | 5              | 0            |
| Increased cholesterol               | 44             | 4.9          | 25             | 0            |
| Decreased phosphate                 | 25             | 3.3          | 5              | 0            |

| <b>Hematology</b>     |    |     |     |     |
|-----------------------|----|-----|-----|-----|
| 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

\* 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).

† Graded per NCI CTCAE v 4.03 except for LDH

‡ LDH: Grade 1 >ULN to ≤2.5 × ULN; Grade 2 >2.5 to ≤5 × ULN; Grade 3 >5 to ≤20 × ULN; Grade 4 >20 × 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)

## 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 on TURALIO

**Table 7: Effect of Other Drugs on TURALIO**

| <b>Moderate or Strong CYP3A Inhibitors</b> |  |
|--|--|
| <b>Clinical Impact</b>                     | <ul style="list-style-type: none"> <li>Concomitant use of a moderate or strong CYP3A inhibitor may increase pexidartinib concentrations [see <i>Clinical Pharmacology (12.3)</i>], which may increase the incidence and severity of adverse reactions of TURALIO.</li> </ul> |
| <b>Management</b>                          | <ul style="list-style-type: none"> <li>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 (2.4)</i>].</li> </ul>                                 |
| <b>Strong CYP3A Inducers</b>               |  |
| <b>Clinical Impact</b>                     | <ul style="list-style-type: none"> <li>Concomitant use of a strong CYP3A inducer decreases pexidartinib concentrations [see <i>Clinical Pharmacology (12.3)</i>], which may decrease the efficacy of TURALIO.</li> </ul>   |

|                             |  |
|-----------------------------|--|
| <b>Management</b>           | <ul style="list-style-type: none"> <li>• Avoid concomitant use of strong CYP3A inducers, including St John's wort.</li> </ul>  |
| <b>UGT Inhibitors</b>       |  |
| <b>Clinical Impact</b>      | <ul style="list-style-type: none"> <li>• Concomitant use of a UGT inhibitor increases pexidartinib concentrations [see <i>Clinical Pharmacology (12.3)</i>], which may increase the incidence and severity of adverse reactions of TURALIO.</li> </ul> |
| <b>Management</b>           | <ul style="list-style-type: none"> <li>• Reduce TURALIO dosage if concomitant use of UGT inhibitors cannot be avoided [see <i>Dosage and Administration (2.4)</i>].</li> </ul>   |
| <b>Acid-Reducing Agents</b> |  |
| <b>Clinical Impact</b>      | <ul style="list-style-type: none"> <li>• Concomitant use of a PPI decreases pexidartinib concentrations [see <i>Clinical Pharmacology (12.3)</i>], which may decrease the efficacy of TURALIO.</li> </ul>  |
| <b>Management</b>           | <ul style="list-style-type: none"> <li>• Avoid concomitant use of PPIs with TURALIO. As an alternative to PPIs, use locally-acting antacids or H<sub>2</sub>-receptor antagonists [see <i>Dosage and Administration (2.5)</i>].</li> </ul>             |

### 7.3 Effect of TURALIO on Other Drugs

**Table 8: Effect of TURALIO on Other Drugs**

|                         |   |
|-------------------------|---|
| <b>CYP3A Substrates</b> |   |
| <b>Clinical Impact</b>  | <ul style="list-style-type: none"> <li>• TURALIO is a moderate CYP3A inducer. Concomitant use of TURALIO decreases the concentration of CYP3A substrates [see <i>Clinical Pharmacology (12.3)</i>], which may reduce the efficacy of these substrates.</li> </ul>   |
| <b>Management</b>       | <ul style="list-style-type: none"> <li>• Avoid coadministration of TURALIO with hormonal contraceptives [see <i>Warnings and Precautions (5.3)</i>, <i>Use in Specific Populations (8.3)</i>].</li> <li>• 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.</li> </ul> |

## 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 of 800 mg (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 of 800 mg). 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 of 800 mg).

## **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)*].

### 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 dose when administering TURALIO to patients with mild to severe renal impairment (CL<sub>cr</sub> 15 to 89 mL/min, estimated by Cockcroft-Gault [C-G]) [see *Dosage and Administration (2.6)*, *Clinical Pharmacology (12.3)*].

## 8.7 Hepatic Impairment

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

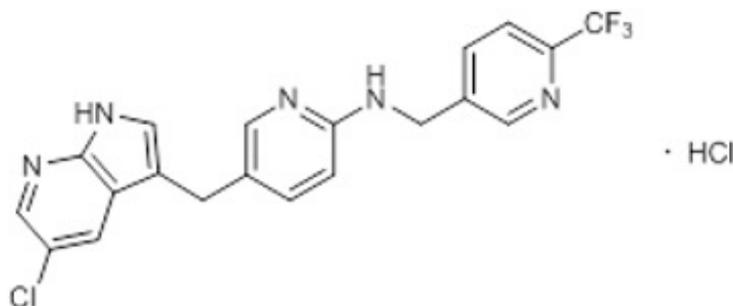
The recommended dose of TURALIO has not been established for patients with moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) to severe (total bilirubin greater than 3 to 10 times ULN and any AST) hepatic impairment [see *Warnings and Precautions (5.1)*].

## 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<sub>20</sub>H<sub>15</sub>ClF<sub>3</sub>N<sub>5</sub>·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 pK<sub>a1</sub> and pK<sub>a2</sub> 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 200 mg pexidartinib which is equivalent to 217.5 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, black iron oxide and yellow iron oxide.

## 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 (200 to 1200 mg per day).

### Cardiac Electrophysiology

At two times the mean maximum exposure of the 400 mg twice daily dose, 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**

| <b>General Information</b>  |  |                       |
|---|--|-----------------------|
| Steady state exposure [Mean (SD)]*  | C <sub>max</sub>   | 8625 (2746) ng/mL     |
|   | AUC <sub>0-12h</sub>   | 77465 (24975) ng·h/mL |
| Dose proportionality  | Pexidartinib exposure (C <sub>max</sub> and AUC <sub>0-INF</sub> ) increased linearly over the single oral dose range of 200 to 2400 mg (0.5 to 6 times the recommended dose). |                       |
| Time to steady state <sup>†</sup>   | Approximately 7 days   |                       |
| Accumulation ratio (AUC) [Median] <sup>†</sup>                                | 3.6  |                       |
| <b>Absorption</b>   |  |                       |
| T <sub>max</sub> [Median]   | 2.5 hours  |                       |
| <b>Effect of food</b>   |  |                       |
| Administration with high-fat meal <sup>‡</sup>                                | <ul style="list-style-type: none"> <li>Increased pexidartinib C<sub>max</sub> and AUC<sub>0-INF</sub> by 100%</li> <li>Delayed T<sub>max</sub> by 2.5 hours</li> </ul>         |                       |
| Administration with low-fat meal <sup>§</sup>                                 | <ul style="list-style-type: none"> <li>Increased C<sub>max</sub> by 56% and AUC<sub>0-INF</sub> by 59%</li> <li>Delayed T<sub>max</sub> by 1.5 hours</li> </ul>                |                       |
| <b>Distribution</b>   |  |                       |
| In vitro plasma protein binding   | <ul style="list-style-type: none"> <li>Greater than 99%</li> <li>Human serum albumin: 99.9%</li> <li>α-1 acid glycoprotein: 89.9%</li> </ul>                                   |                       |
| Apparent volume of distribution (V <sub>z/F</sub> ) [Mean (CV%)] <sup>¶</sup> | <ul style="list-style-type: none"> <li>187 L (27%)</li> </ul>  |                       |
| <b>Elimination</b>  |  |                       |

|  |   |
|--|---|
| Apparent clearance [Mean (CV%)] <sup>¶</sup> | <ul style="list-style-type: none"> <li>• 5.1 L/h (36%)</li> </ul>   |
| t <sub>1/2</sub> [Mean (SD)]                 | <ul style="list-style-type: none"> <li>• 26.6 (6.5) hours</li> </ul>  |
| <b>Metabolism</b>                            |   |
| Primary pathway                              | <ul style="list-style-type: none"> <li>• Oxidation: CYP3A4</li> <li>• Glucuronidation: UGT1A4</li> </ul>  |
| N-glucuronide metabolite                     | <ul style="list-style-type: none"> <li>• Major inactive metabolite formed by UGT1A4</li> <li>• Approximately 10% higher exposure than pexidartinib after a single dose</li> </ul> |
| <b>Excretion<sup>#</sup></b>                 |   |
|  | <ul style="list-style-type: none"> <li>• Feces: 65% (44% as unchanged)</li> <li>• Urine: 27% as metabolites (≥10% as N-glucuronide)</li> </ul>                                    |

\* Pexidartinib 400 mg twice daily

† Estimated based on half life

‡ The high-fat meal comprised 800 to 1000 calories with fat being 50% of total caloric content; approximately 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat.

§ The low-fat meal comprised 387 calories with fat being approximately 25% of total caloric content.

¶ After a single oral dose of pexidartinib 400 mg

# After a single oral dose of radiolabeled pexidartinib 400 mg

### 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 ≤ ULN with AST > ULN or total bilirubin > 1 to 1.5 × ULN with any AST).

#### *Patients with Renal Impairment*

Mild (CL<sub>cr</sub> 60 to 89 mL/min), moderate (CL<sub>cr</sub> 30 to 59 mL/min) and severe (CL<sub>cr</sub> 15 to 29 mL/min) renal impairment increased pexidartinib exposure (AUC) by approximately 30%, relative to that in patients with normal renal function (CL<sub>cr</sub> ≥90 mL/min).

#### *Patients with Hepatic Impairment*

The pharmacokinetics of pexidartinib has not been adequately characterized in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3 × ULN and any AST) or studied in patients with severe hepatic impairment (total bilirubin > 3 to 10 × ULN and any AST).

### Drug Interaction Studies

#### *Clinical Studies and Model-Informed Approaches*

##### *Effects of Other Drugs on Pexidartinib*

**Strong CYP3A Inducers:** Coadministration of rifampicin (strong CYP3A inducer) decreased pexidartinib C<sub>max</sub> by 33% and AUC<sub>0-INF</sub> by 65%.

**Moderate CYP3A Inducers:** Coadministration of efavirenz (moderate CYP3A inducer) is predicted to decrease pexidartinib C<sub>max</sub> by 27% and AUC by 38% at steady state.

**Strong CYP3A Inhibitors:** Coadministration of itraconazole (strong CYP3A inhibitor) increased pexidartinib C<sub>max</sub> by 48% and AUC<sub>0-INF</sub> by 70%.

*Moderate CYP3A Inhibitors:* 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  $C_{\max}$  by 5% and  $AUC_{0-1NF}$  by 60%.

*Acid-Reducing Agents:* Coadministration of esomeprazole (proton pump inhibitor) decreased pexidartinib  $C_{\max}$  by 55% and  $AUC_{0-1NF}$  by 50%. The effects of H<sub>2</sub>-receptor antagonists and locally-acting antacids on pexidartinib pharmacokinetics have not been studied.

#### *Effects of Pexidartinib on Other Drugs*

*CYP2C19 Substrates:* Coadministration of a single oral dose of TURALIO 1800 mg (4.5 times the approved recommended dose of 400 mg) decreased omeprazole (CYP2C19 substrate)  $C_{\max}$  by 37% and  $AUC_{0-1NF}$  by 17%.

*CYP3A Substrates:* Coadministration of TURALIO 400 mg twice daily decreased midazolam (CYP3A substrate)  $C_{\max}$  by 28% and  $AUC_{0-1NF}$  by 59%.

*CYP2C9 Substrates:* Coadministration of TURALIO 400 mg twice daily increased tolbutamide (CYP2C9 substrate)  $AUC_{0-1NF}$  by 28%. The effect of pexidartinib on CYP2C9 substrates is not considered clinically relevant.

*P-gp Substrates:* Coadministration of a single oral dose of TURALIO 1800 mg (4.5 times the approved recommended dose of 400 mg) increased digoxin (P-gp substrate)  $C_{\max}$  by 30% and  $AUC_{0-1NF}$  by 9%.

*CYP2C8 Substrates:* The effect of pexidartinib on CYP2C8 substrates is predicted not to be clinically relevant.

#### *In Vitro Studies*

*CYP/UGT Enzymes:* Pexidartinib is likely to inhibit CYP2B6 and induce CYP2B6 at clinically relevant concentrations. Pexidartinib is likely to inhibit UGT1A1 at clinically relevant concentrations.

*Transporter Systems:* 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 of 800 mg 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 of 800 mg). 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  $\geq 10$  mg/kg/day (approximately 0.3 times the human exposure at the recommended dose of 800 mg). 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 of 800 mg). 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 of 800 mg).

In female rats, necrosis of corpora lutea occurred at doses  $\geq 0.5$  mg/kg/day (approximately 0.01 times the human exposure at the recommended dose of 800 mg) 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 of 800 mg). 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 of 800 mg).

### **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 of 800 mg). 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 of 800 mg). 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  $\geq 60$  mg/kg.

## **14 CLINICAL STUDIES**

### **14.1 Tenosynovial Giant Cell Tumor**

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 400 mg in the morning and 600 mg in the evening for 2 weeks followed by 400 mg twice daily. Treatment continued 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).

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**

| <b>Efficacy Parameter</b>                        | <b>TURALIO<br/>N=61</b> | <b>Placebo<br/>N=59</b> |
|--|-------------------------|-------------------------|
| <b>Overall Response Rate (ORR)<sup>*,†</sup></b> |                         |                         |
| ORR<br>(95% CI)                                  | 38%<br>(27%, 50%)       | 0<br>(0, 6%)            |
| Complete Response                                | 15%                     | 0                       |
| Partial Response                                 | 23%                     | 0                       |
| P-value <sup>‡</sup>                             | <0.0001                 |                         |
| <b>Duration of Response (DOR)<sup>†</sup></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

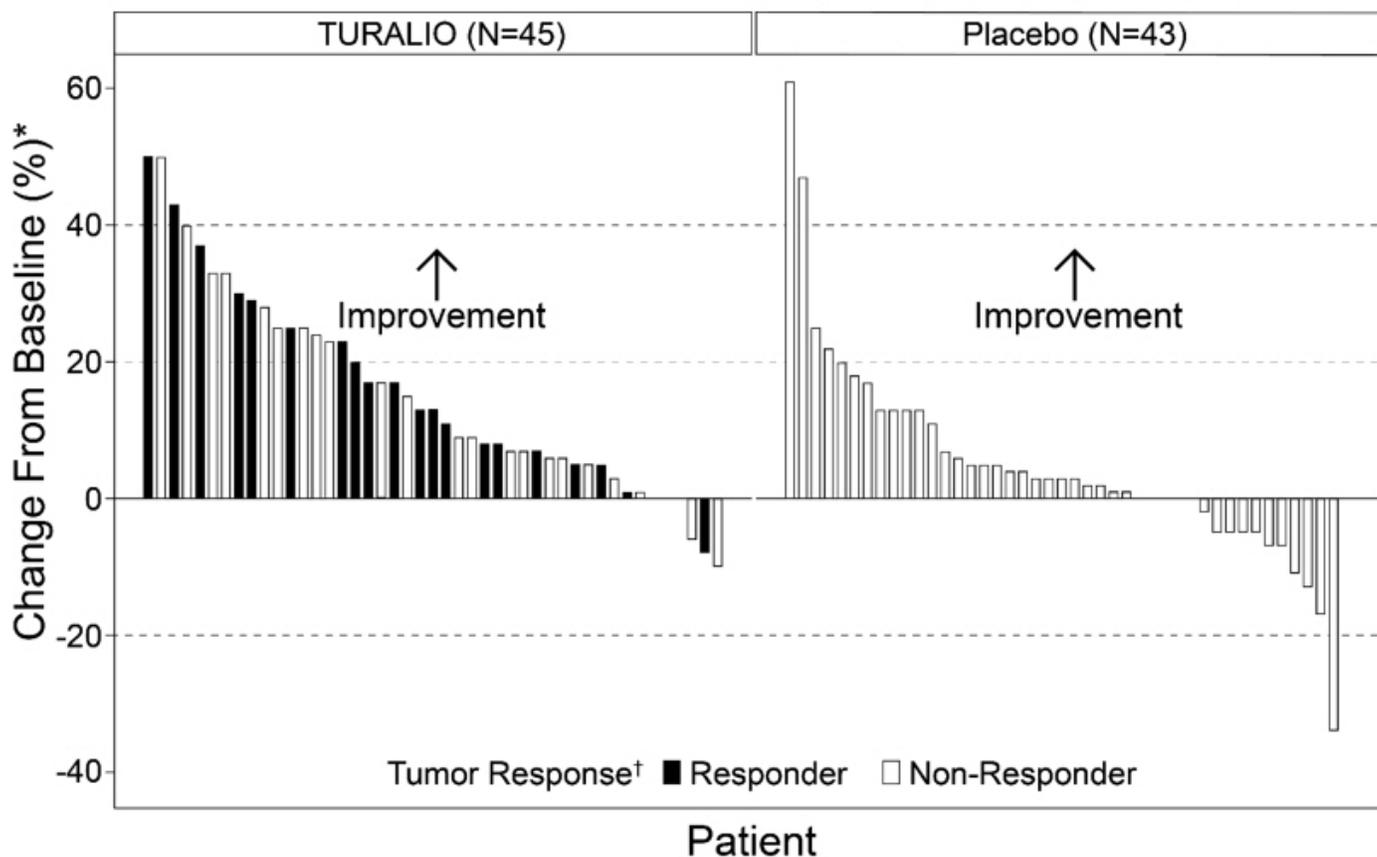
\* Blinded independent central review

† Data cut-off date January 31, 2018

‡ Fisher's exact test

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**



\*Percent of normal reference range for the affected joint.

†Tumor Response by RECIST v1.1.

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;  $p < 0.0001$ .

## 16 HOW SUPPLIED/STORAGE AND HANDLING

TURALIO 200 mg capsules are supplied as size 0 with white opaque body and dark green opaque cap with white print "T10", available in:

- 28 count bottle                   NDC#: 65597-402-28
- 120 count bottle                NDC#: 65597-402-20

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)].

### 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)].

### Administration

Instruct patients to take TURALIO on an empty stomach (at least 1 hour before or 2 hours after a meal or snack). Instruct patients to swallow capsules whole (do not open, break, or chew) [see Dosage and Administration (2.1, 2.2)].

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

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USPI-TUR-C2-0420-r002

|   |
|---|
| <p><b>Medication Guide</b><br/>TURALIO<sup>®</sup> (tur-a-lee-oh)<br/>(pexidartinib)<br/>Capsules</p>   |
| <p><b>What is the most important information I should know about TURALIO?</b><br/><b>TURALIO can cause serious side effects, including:</b><br/><b>Serious Liver Problems which may be severe and can lead to death.</b><br/>Your healthcare provider will do blood tests to check for liver problems:</p> <ul style="list-style-type: none"> <li>• before starting treatment with TURALIO,</li> <li>• every week for the first 8 weeks during treatment,</li> <li>• every 2 weeks for the next month,</li> <li>• then, every 3 months after that.</li> </ul> |

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

**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.

#### **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.
- are pregnant or plan to become pregnant. TURALIO may harm your unborn baby.

#### **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 can increase the amount of TURALIO in your blood. This may make it more likely for**

**you to have 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.
- **TURALIO must be taken on an empty stomach, at least 1 hour before or 2 hours after eating a meal or snack.**
- 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. **See "What should I avoid while taking TURALIO?"**
  - Antacid medicines: Take TURALIO either **2 hours before or 2 hours after** taking an antacid medicine.
  - H<sub>2</sub> receptor blocker medicines. Take TURALIO **at least 2 hours before or 10 hours after** taking an H<sub>2</sub> receptor blocker medicine.
- 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?"**

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
- loss of taste or changes in the way things taste

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, black iron oxide and yellow iron oxide

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

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USMG-TUR-C2-0420-r002

For more information, call 1-877-437-7763 or go to [www.turalio.com](http://www.turalio.com).

This Medication Guide has been approved by the  
U.S. Food and Drug Administration.

Revised: 04/2020

**PRINCIPAL DISPLAY PANEL - 120 Capsule Bottle Carton**

NDC 65597-402-20

Rx only

Turalio®

(pexidartinib)

capsules

200 mg

120 capsules

for oral use

Dispense the accompanying  
Medication Guide to each patient.

Daiichi-Sankyo



## PRINCIPAL DISPLAY PANEL - 28 Capsule Bottle Carton

NDC 65597-402-28

Rx only

Turalio®  
(pexidartinib)  
capsules

200 mg

28 capsules

for oral use

Dispense the accompanying  
Medication Guide to each patient.

Daiichi-Sankyo



## TURALIO

pexidartinib capsule

### Product Information

|                                |                         |                           |               |
|--------------------------------|-------------------------|---------------------------|---------------|
| <b>Product Type</b>            | HUMAN PRESCRIPTION DRUG | <b>Item Code (Source)</b> | NDC:65597-402 |
| <b>Route of Administration</b> | ORAL                    |                           |               |

### Active Ingredient/Active Moiety

| Ingredient Name   | Basis of Strength | Strength |
|---|-------------------|----------|
| PEXIDARTINIB HYDRO CHLORIDE (UNII: YS6WAI3XN7) (PEXIDARTINIB - UNII:6783M2LV5X) | PEXIDARTINIB      | 200 mg   |

## Inactive Ingredients

| Ingredient Name                              | Strength |
|--|----------|
| POLOXAMER 407 (UNII: TUF2IVW3M2)             |          |
| MANNITOL (UNII: 3OWL53L36A)                  |          |
| CROSPVIDONE, UNSPECIFIED (UNII: 2S7830E561)  |          |
| MAGNESIUM STEARATE (UNII: 70097M6I30)        |          |
| HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO) |          |
| TITANIUM DIOXIDE (UNII: 15FIX9V2JP)          |          |
| FERROSO FERRIC OXIDE (UNII: XM0M87F357)      |          |
| FERRIC OXIDE YELLOW (UNII: EX438O2MRT)       |          |

## Product Characteristics

|          |   |              |          |
|----------|---|--------------|----------|
| Color    | WHITE (white opaque body) , GREEN (Dark green opaque cap) | Score        | no score |
| Shape    | CAPSULE   | Size         | 21mm     |
| Flavor   |   | Imprint Code | T10      |
| Contains |   |              |          |

## Packaging

| # | Item Code        | Package Description                                | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:65597-402-20 | 1 in 1 CARTON                                      | 08/02/2019           |                    |
| 1 |                  | 120 in 1 BOTTLE; Type 0: Not a Combination Product |                      |                    |
| 2 | NDC:65597-402-28 | 1 in 1 CARTON                                      | 08/02/2019           |                    |
| 2 |                  | 28 in 1 BOTTLE; Type 0: Not a Combination Product  |                      |                    |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| NDA                | NDA211810                                | 08/02/2019           |                    |

**Labeler** - Daiichi Sankyo Inc. (068605067)