Considerations for Your Peer-to-Peer Review

Turalio® pexidartinib 125 mg capsules

If coverage of TURALIO is denied for your patient, the following checklist can serve as a guide for your peer-to-peer review, allowing you to explain why your preferred course of treatment is medically necessary.

NOTE: It is recommended that peer-to-peer attestation be completed by the prescribing clinician (eg, physician, PA, NP) who is treating the patient for TGCT. Additionally, this prescribing clinician may request that the insurer's peer reviewer be of the same specialty (eg, oncology).

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.**

Use of the resource does not guarantee that the insurance company will provide reimbursement for TURALIO, and is not intended to be a substitute for or an influence on the independent medical judgment of the health care provider. This is a guide and is not to be taken as a specific recommendation.

Information to gather ahead of time

Patient and policy information

- Name and date of birth of:
  - Patient
  - Primary insurance policy holder
- Insurance policy and group number

Explanation of why the first request was denied

Have you already initiated an appeal? If so, be prepared with the details of the appeal.

Clinical documentation

- Summary of patient's TGCT diagnosis
- Details as to why TURALIO is medically necessary for your patient (eg, patient is not amenable for surgery)
- Prior treatments and frequency (surgeries or other non-medical strategies, eg, physical therapy)
- Current laboratory reports (liver function tests including AST, ALT, total bilirubin, direct bilirubin, ALP, GGT)
- Any additional patient-specific characteristics or medical records supporting the diagnosis and/or TURALIO treatment (patient reported outcomes such as range of motion, worsening pain, and worsening stiffness)

Focus on specifics beyond severity, and provide supportive clinical data.

Please see Important Safety Information on pages 3-4, and click here for full Prescribing Information, including **Boxed WARNING**, and Medication Guide.

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Information to gather ahead of time (*cont'd*)

Drug information

- Indication statement
  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.
- Prescribing Information (please click here)

Click here for product, billing, and administration codes associated with TURALIO use.

Additional resources to consider

Relevant publications/data

- Peer-reviewed clinical trials
- National Comprehensive Cancer Network (NCCN) guidelines

Supporting letters of medical necessity

Visit DSIAccessCentral.com for template letters.

For case-specific questions or additional information, please contact your local Field Reimbursement Manager, visit DSIAccessCentral.com, or call 1-866-4-DSI-NOW (1-866-437-4669).

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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 ≥3 × upper limit of normal (ULN) with total bilirubin ≥2 × ULN. In these patients, peak ALT ranged from 6 to 9 × ULN, peak total bilirubin ranged from 2.5 to 15 × ULN, and alkaline phosphatase (ALP) was ≥2 × ULN. ALT, AST and total bilirubin improved to <2 × ULN in these patients 1 to 7 months after discontinuing TURALIO.

Avoid TURALIO in patients with preexisting increased serum transaminases, total bilirubin, or direct bilirubin (>ULN); or active liver or biliary tract disease, including increased ALP. Monitor liver tests, including AST, ALT, total bilirubin, direct bilirubin, ALP, and gamma-glutamyl transferase (GGT), prior to initiation of TURALIO, weekly for the first 8 weeks, every 2 weeks for the next month and every 3 months thereafter. Withhold and dose reduce, or permanently discontinue TURALIO based on the severity of the hepatotoxicity. 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 www.TURALIOREMS.com or 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.

Potential Risks Associated with a High-Fat Meal

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

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%).

Important Safety Information

Adverse Reactions *(cont'd)*

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%).

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, attention deficit/hyperactivity disorder), alopecia, skin pigment changes (hypopigmentation, depigmentation, discoloration, hyperpigmentation), and photosensitivity reactions.

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.

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

Abbreviations: AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; NP, nurse practitioner; PA, physician assistant.

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