Press Release

TURALIO® New Dosing Regimen Now Available in the U.S. for Certain Patients with Tenosynovial Giant Cell Tumor

Basking Ridge, NJ – (February 1, 2023) – Daiichi Sankyo (TSE: 4568) today announced that the new dosing regimen for TURALIO® (pexidartinib) is now available in the U.S. 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. A new 125 mg capsule of TURALIO is now available and the 200 mg capsule has been discontinued.

TGCT is a rare, typically non-malignant tumor that affects small and large joints. The disease can cause debilitating symptoms, can be locally aggressive and can significantly impact everyday activities in a relatively young patient population.[1,2,3]

The new recommended dose of TURALIO is 250 mg orally twice daily (taken as two 125 mg capsules) with a low-fat meal of approximately 11 to 14 grams of total fat until disease progression or unacceptable toxicity. The previous dose was 400 mg orally twice daily on an empty stomach. Patients currently taking TURALIO 200 mg capsules can take the 125 mg capsules as the next scheduled dose once the 200 mg capsules have been finished. Patients should consult with their physicians to answer any questions they may have as they transition to the new dose.

As part of post-marketing requirements with the U.S. Food and Drug Administration (FDA), Daiichi Sankyo conducted pharmacokinetic studies to evaluate the effects of food when taking TURALIO. Taking TURALIO with a high-fat meal (approximately 55 to 65 grams of total fat) was found to increase the concentration of TURALIO in the body and may increase the risk of adverse reactions, including hepatotoxicity. These studies demonstrated that lowering the dose of TURALIO and taking it with a low-fat meal helps to minimize the potential for drug overexposure in the event a patient did not carefully follow the dietary recommendations when taking the 200 mg capsule of TURALIO. Studies also showed that taking TURALIO 250 mg with a low-fat meal (11 to 14 grams of total fat) has no clinically significant difference in efficacy to taking TURALIO 400 mg on an empty stomach.

“The new dose reflects study data that evaluated the impact of food on TURALIO exposure should patients not follow the previous recommended dietary requirements when taking the medication,” said Dan Switzer, Head of U.S. Oncology Business, Daiichi Sankyo, Inc. “As patient safety is our primary goal, we will continue to inform healthcare professionals about the new dosing regimen of TURALIO so that they can continue to treat appropriate patients with tenosynovial giant cell tumor with the only FDA-approved therapy.”

TURALIO is approved with a Boxed WARNING for hepatotoxicity due to the risk of serious and potentially fatal liver injury. Hepatotoxicity with ductopenia and cholestasis has occurred in patients treated with TURALIO. Across 768 patients who received TURALIO in clinical trials, there were two irreversible cases of cholestatic liver injury. One patient died with advanced cancer and ongoing liver toxicity and one patient required a liver transplant. The mechanism of cholestatic hepatotoxicity is unknown and its occurrence cannot be predicted. It is unknown whether liver injury occurs in the absence of increased transaminases. Because of the risk of hepatotoxicity, TURALIO is available by prescription in the U.S. only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program where only certified healthcare providers may prescribe TURALIO. Patients must complete and sign an enrollment form for inclusion in a patient registry to receive treatment. Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive TURALIO.

Daiichi Sankyo is committed to ensuring that patients in the U.S. who are prescribed TURALIO can access the medication and receive necessary financial support. Provider and patient support related to access, reimbursement and distribution for TURALIO in the U.S. will be accessible through Daiichi Sankyo Access Central by visiting www.DSIAccessCentral.com or calling 1-866-4-DSI-NOW (1-866-437-4669). Further information is available at www.TURALIOREMS.com. For more information, please visit www.TURALIO.com for full Prescribing Information, including Boxed WARNING, and for additional Important Safety Information.

About TGCT (PVNS/GCT-TS)

TGCT, also referred to as pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (GCT-TS), is a rare, typically non-malignant tumor that can be locally aggressive. TGCT affects the synovium-lined joints, bursae and tendon sheaths, resulting in reduced mobility in the affected joint or limb.[1,2,3]

While the exact incidence of TGCT is not known, it is estimated that the worldwide incidence of TGCT is 43 patients per million person-years.[4,5,6] TGCT is subcategorized into two types: localized, which is more common and accounts for 80% to 90% of cases, and diffuse, which accounts for 10% to 20% of cases.[5,6] The current standard of care for TGCT is surgical resection.[1,7] However, in patients with recurrent, difficult-to-treat, or the diffuse form of TGCT, the tumor may wrap around bone, tendons, ligaments and other parts of the joint. In these cases, the tumor may be difficult to remove and/or may not be amenable to improvement with surgery. Multiple surgeries for more severe cases can lead to significant joint damage, debilitating functional impairments and reduced quality of life, and amputation may be considered.[7,8,9]

Recurrence rates for localized TGCT are estimated to be up to 15% following complete resection.[3,6,10,11,12] Diffuse TGCT recurrence rates are estimated to be up to 55% following complete resection.[3,6,10,13] TGCT affects all age groups with the diffuse type on average occurring most often in people below the age of 40, and the localized type typically occurring in people between 30 and 50 years old.[1,4,5,6]

About TURALIO

TURALIO (pexidartinib) is an oral small molecule 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.

TURALIO is approved in the U.S. for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. The medicine was granted Priority Review, Breakthrough Therapy and Orphan Drug Designation by the U.S. FDA prior to FDA approval in August 2019.

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.

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 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%).

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.

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

About Daiichi Sankyo

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit www.daiichisankyo.com.

Media Contacts:

US:
Don Murphy
Daiichi Sankyo, Inc.
domurphy@dsi.com
+1 917 817 2649 (mobile)

Investor Relations:
DaiichiSankyoIR@daiichisankyo.co.jp

References:

[1] de Saint Aubain, et al. WHO. 2013;100-103.
[2] Rao AS, et al. *J Bone Joint Surg AM*. 1984;66(1):76-94.
[3] Ravi V, et al. *Curr Opin Oncol*. 2011;23:361-366.
[4] Myers BW, et al. *Medicine* (Baltimore). 1980;59(3):223-238.
[5] Mastboom MJL, et al. *Acta Orthopaedica*. 2017;88(6):688-694.
[6] Ehrenstein V, et al. *J Rheumatol.* 2017; 44(10):1476-1483.
[7] Verspoor FGM, et al. *Future Oncol.* 2013;10:1515-1531.
[8] Verspoor FGM, et al. *Rheumatol.* 2014;53(11):2063-2070.
[9] Brahmi M, et al. *Curr Treat Options Oncol.* 2016;17(2):10.

[10] Gouin F, Noailles T. *Orthop Traumatol Surg Res.* 2017;103(1S):S91-S97.
[11] Palmerini E, Staals EL, Maki RG, et al. *Eur J Cancer.* 2015;51(2):210-217.
[12] Dines JS, et al. *Arthroscopy.* 2007;23(9):930-937.
[13] Xie GP, et al. *PLOS One.* 2015;10(3):e0121451.