CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211810Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211810
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Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	August 1, 2019
Subject	Evaluation of the Need for a REMS
Established Name	Pexidartinib
Trade Name	Turalio
Name of Applicant	Daichii Sankyo, Inc
Therapeutic class	Colony Stimulating Factor-1 Receptor (CSF1R), tyrosine kinase inhibitor (TKI)
Formulation	200 mg oral tablets
Dosing Regimen	400 mg by mouth twice daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Turalio (pexidartinib) is necessary to ensure the benefits outweigh its risks. Daiichi Sankyo submitted a New Drug Application (NDA) 211810 for pexidartinib with the proposed indication 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. The risks associated with pexidartinib include serious and potentially fatal liver injury. The Applicant's proposed REMS is comprised of a communication plan (CP) and elements to assure safe use (ETASU) that consists of prescriber and pharmacy certification, an implementation system, and a timetable for submission of assessments.

Pexidartinib is a new molecular entity; there is no prior clinical experience with this drug class. The most concerning risk associated with pexidartinib is hepatoxicity. It occurs frequently and can be serious and potentially fatal. In the clinical trial program, treatment with pexidartinib resulted in acute increases in hepatic transaminases in nearly all of the patients within the first 8 weeks of therapy; most resolving or returning to baseline with dose interruption, reductions or discontinuation. Some patients had a prolonged time to recovery despite these interventions, and there were cases of irreversible liver injury. Less is known about the long-term hepatotoxic effects of pexidartinib, specifically the development of ductopenia and the progression to irreversible liver failure.

While it is expected that oncologists are familiar with managing hepatotoxicity and the importance of monitoring, due to the degree and severity of the elevations of hepatic transaminases and bilirubin reported in the clinical trial and the need to dose adjust, withhold, or discontinue therapy, additional risk mitigation measures beyond labeling are required to ensure that prescribers are made aware of the degree of monitoring that is required while the patient is receiving pexidartinib. Because less is known about the long-term hepatotoxic effects of pexidartinib, the review team determined that a patient registry would be included in the REMS to further assess the safe use and acute, chronic and irreversible hepatotoxicity. DRISK and the Division of Oncology Products (DOP) 2 agree that a REMS is needed to ensure the benefits of pexidartinib outweigh its risk of serious and potentially fatal liver injury.

The goal of the TURALIO REMS is to mitigate the risk of serious and potentially fatal liver injury by:

1. Ensuring that prescribers are educated on the following:
    a. the approved indication for Turalio
    b. the risk of serious and potentially fatal liver injury associated with the use of Turalio
    c. the need for liver monitoring at baseline and periodically during treatment with dose modifications as described in the Prescribing Information
    d. the need to counsel patients about the risk of serious and potentially fatal liver injury, liver monitoring at baseline and periodically during treatment with TURALIO as described in the Patient Guide and to report signs and/or symptoms of liver injury to the prescriber during therapy
2. Ensuring that prescribers adhere to the requirement of baseline and periodic monitoring as described in the Prescribing Information.

3. Enrollment of all patients in a registry to further assess the safe use and acute, chronic and irreversible hepatotoxicity of Turalio.

The REMS for pexidartinib will include the following elements: a communication and ETASU that requires that healthcare providers have particular experience or training, or are specially certified, pharmacies, practitioners, or health care settings that dispense the drug are specially certified, each patient using Turalio will be subject to certain monitoring and each patient using the drug is enrolled in a registry. The REMS will also include an implementation system, and a timetable for submission of assessments.

Depending on the assessment findings FDA may modify the REMS or consider other regulatory actions particularly if reports of severe hepatotoxicity or deaths occur beyond what was observed in the clinical trial, and if there is evidence of insufficient monitoring. If the REMS assessments or other data indicate that prescribers have gained familiarity with the drug and data supports that prescribers are taking appropriate actions to reduce the risk of hepatotoxicity, FDA may, in the future, determine that the REMS is no longer necessary.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Turalio (pexidartinib) is necessary to ensure the benefits outweigh its risks. Daiichi Sankyo submitted a New Drug Application (NDA) 211810 for Turalio (pexidartinib) with the proposed indication: 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. This application is under review in the Division on Oncology Products (DOP) 2. The applicant's proposed REMS consists of a communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of pexidartinib outweigh the risk of serious and potentially fatal liver injury.

2 Background

2.1 Product Information

Pexidartinib is a small molecule tyrosine kinase inhibitor that targets colony stimulating factor-1 receptor (CSF1R), proto-oncogene receptor tyrosine kinase (KIT), and feline McDonough sarcoma (FMS)-like tyrosine kinase 3 (FLT3) harboring an internal tandem mutation (ITD).[1] Overexpression of the CSF1R ligand is a driver of cell proliferation and the accumulation in the synovium that causes TGCT. In vitro, pexidartinib inhibited the proliferation of cell lines dependent on CSF1R and ligand-induced autophosphorylation of CSF1R.[2]

The proposed indication of pexidartinib is 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. Pexidartinib is supplied as 200 mg capsules, with a

recommended dose of 400 mg orally twice daily. Treatment with pexidartinib is expected to be long term, or until unacceptable disease toxicity.[a]

Oncology surgeons specializing in sarcoma treatment are expected to be the primary prescribers of pexidartinib, given in an outpatient/ambulatory care center. It is expected that patients receiving pexidartinib will likely be managed by prescribers who are in tertiary care centers, as the patients in the clinical trial were most often treated by practitioners in these sites.

Pexidartinib is an NME,[b] and is a first in class molecule; granted Orphan Drug Designation on February 14, 2014, as well as Breakthrough Therapy Designation on October 28, 2015. It is currently not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211810 relevant to this review:

- 03/08/2013: Investigational New Drug (IND) 117332 filed
- 02/14/2014: Orphan Drug Designation granted
- 10/28/2015: Breakthrough Therapy Designation granted
- 10/12/2016: Partial clinical hold due to 2 reported serious adverse events of mixed or cholestatic hepatotoxicity in PLX10810 and other cases across the program (removed 04/10/2017)
- 11/24/2017: Partial clinical hold requiring risk mitigation strategies for mixed or cholestatic hepatotoxicity for all pexidartinib studies (removed 01/12/2018)
- 03/20/2018: Applicant informed the FDA at pre-NDA meeting that their submission would include a REMS with ETASU for the risk of hepatotoxicity
- 08/30/2018: Rolling review granted
- 09/18/2018: Part 1 of 3 Modules submitted (nonclinical)
- 09/21/2018: Part 2 of 3 Modules submitted (CMC)
- 12/03/2018: Part 3 of 3 Modules submitted (clinical) for the proposed indication for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amendable to improvement with surgery.
- 03/15/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that their REMS is currently under review by the Agency.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

- 05/14/2019: The Oncologic Drugs Advisory Committee (ODAC) Meeting was convened to discuss whether the benefits of pexidartinib, as characterized by a clinically meaningful reduction in tumor burden and an improvement in range of motion, outweigh its risk of hepatotoxicity. The AC members voted 9 in favor and 3 against approval for pexidartinib. In general, committee members who voted against approval expressed concern about whether the clinical endpoint was beneficial in a disease state that can be severely debilitating but is not life threatening and considered the risks of serious and potentially fatal hepatotoxicity. The committee thought that the proposed REMS was appropriate, given the severity of the adverse events, lack of long-term use and the need to further access adverse events.
- 05/24/2019: An information request (IR) was sent to the Applicant informing them of the need to submit all of their REMS materials in Microsoft word format so that DRISK may provide comments.
- 05/28/2019: Applicant responded to Agency IR of May 24, 2019.
- 06/26/2019: The Agency sent general comments on the Applicant's REMS materials.
- 07/08/2019: Applicant resubmitted materials in response to Agency IR of June 26, 2018
- 07/19/: The Agency sent comments on the REMS, REMS materials, and REMS assessment plan
- 07/23/2019: The Applicant submitted the full REMS and appended materials
- 07/25/2019: The Agency sent comments on some REMS materials
- 07/26/2019: The Applicant submitted the required changes to the REMS materials
- 07/30/2019: The Agency sent the revised REMS Assessment Plan to the Applicant
- 07/31/2019: The Agency sent further revisions of the REMS Assessment Plan to the Applicant
- 08/01/2019: The Applicant submitted the full REMS and appended materials and REMS Supporting Document

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

TGCT is a rare, non-malignant tumor associated with pain, stiffness and functional impairment of the joints and limbs. There are two major variants of this disease that include giant cell tumor of the tendon sheath (GCT-TS), which is the more localized type and is common in upper extremities, notably in the wrist and finger. The annual incidence of GCT-TS is 1.8 cases per million in the United States. The other variant of TGCT is pigmented villonodular synovitis (PVNS), which is a more diffuse type and common in the lower extremities, mainly the knee. The annual incidence of PVNS is 9.2 cases per million in the

United States.[3,c,d] Patients are usually diagnosed between the ages of 20 and 60 years old, and most often presents with pain and swelling at the affected joint.[4] Due to the slow growing nature of the tumor, symptoms are minimal at first. The tumors often expand in the intra-articular space of the joints and surrounding tissues, which can lead to severe pain, swelling, and reduced range of motion of the affected limb(s). The growth of these tumors appears to be governed by a mutation in chromosome 1p13 that induces overexpression of CSF-1 on the tumor cells.[4] The bulk of the tumor mass seen in these patients appears to consist of these inflammatory cells.

3.2 Description of Current Treatment Options

There are currently no systemic therapies approved for the treatment of patients with TGCT. The current standard of care is surgical resection of the tumor to lessen the pain, stiffness, and joint destruction for patients with localized disease.[4,5] The outcomes following surgery largely depend on the location and extent of the disease. For patients with diffuse forms of TGCT, surgery can be difficult, and recurrence rates can range from as low as 8%-15% to as high as 20-40%.[4,5] In addition, patients with extensive disease may also have poorer outcomes with surgery. There remains an unmet medical need for treatment of patients with severe TGCT disease that is not amenable with surgery.

4 Benefit Assessment

The efficacy of pexidartinib was evaluated in the ENLIVEN trial (NCT02371369), which was a double-blind, randomized 1:1, placebo-controlled, multicenter trial in patients with symptomatic TGCT for whom surgical removal of the tumor would be associated with worsening functional limitation or severe morbidity.[2] Patients were randomized to receive pexidartinib 400 mg orally in the morning and 600 mg in the evening for 2 weeks, followed by twice daily or placebo. Randomization was also stratified by geographic region (United States versus ex-United States) and disease location (upper extremity versus lower extremity). The patients remained on treatment until unacceptable toxicity or disease progression. One hundred and twenty patients were randomized; 61 to the pexidartinib arm and 59 to the placebo arm. The median age was 44 years (18-79), 59% were female, 88% were white, and 53% had a prior surgery.[2] The primary efficacy outcome was overall response rate (ORR) at the 25th week of the clinical trial using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Additional efficacy measures were mean change from baseline in range of motion of the affected joint at week 25 and ORR as assessed by the RECIST criteria using tumor volume score (TVS). Patients in the placebo arm were offered pexidartinib at week 25 beginning with a 400 mg twice daily dose.

The table below reflects the efficacy results assessed at week 25 for the Enliven trial:

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Table 1: Efficacy Results Assessed at Week 25 for Enliven[2]

Efficacy Parameter	Pexidartinib (n = 61)	Placebo (n = 59)
Overall Response Rate (ORR)		
ORR	38%	0
Complete Response	15%	0
Partial Response	23%	0
P-value	<0.0001	
Duration of Response (DOR)		
Range (months)	6.9+, 24.9+	NA

In addition, an analysis of mean change from baseline in range of motion at week 25 demonstrated a statistically significant improvement in patients who received pexidartinib. ORR by TVS was also statistically significant in patients who received pexidartinib.

Based on the clinical data available, and discussion at the ODAC meeting on May 14, 2019, the review division has concluded that pexidartinib is approvable in patients with TGCT disease for whom surgery is not an option.[e] Please see the clinical review written by Drs Osgood and Fiero for more information.

5 Risk Assessment & Safe-Use Conditions

The most common adverse reactions of pexidartinib that occurred in at least 20% or more of patients in the clinical trial program were changes in hair color, fatigue, increased aspartate aminotransferase (AST), eye/facial edema, increased alanine aminotransferase (ALT), rash, dysgeusia, and vomiting.[2]

5.1 HEPATOTOXICITY

Hepatotoxicity was a serious risk identified in in the clinical development trial program. In the overall development program of pexidartinib, 768 patients received pexidartinib. There were 2 cases of irreversible cholestatic liver injury.[2,f] One patient died with advanced cancer and ongoing liver toxicity, and one patient required a liver transplant. In ENLIVEN, the registrational trial for pexidartinib, 3 of 61 (5%) of patients receiving pexidartinib developed signs of serious liver injury that was defined as ALT or AST $\geq$3 times the upper limit of normal (ULN), with total bilirubin $\geq$ 2 times the ULN. The peak ALT range was 6 to 9 times the ULN, peak total bilirubin ranged from 2.5 to 15 the ULN, and alkaline phosphatase

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

(ALP) was ≥2 the ULN.[2] In all three cases the hepatic transaminases and total bilirubin returned to the patient's baseline between one and seven months after discontinuing pexidartinib.

The liver injury was mostly cholestatic, however mixed and hepatocellular forms of injury, including ductopenia were also identified in some patients. Increases in hepatic transaminases commonly appeared in the first 8 weeks of therapy with pexidartinib, and the majority resolved to baseline values with dose interruption or reduction. In the Applicant's registrational trial, ENLIVEN, 22 patients had been treated for more than 18 months, 17 patients had been treated for more than 24 months, and one patient had been treated for more than 48 months at the time of the data cut off.[4]

The risk of hepatoxicity was identified as a serious risk in clinical trials and was mitigated in some patients receiving pexidartinib by dose reductions and dose interruptions. Labeling will recommend monitoring of ALT, AST, ALP, total bilirubin, direct bilirubin, and gamma-glutamyl transferase (GGT) weekly for the first 8 weeks, every 2 weeks for the next month, and every 3 months thereafter to assess hepatic function, and to withhold, reduce the dose, or permanently discontinue pexidartinib if necessary. Recommendations will also include to avoid the use of pexidartinib in patients with pre-existing increased hepatic transaminases, or active liver or biliary tract disease. It is also recommended that pexidartinib be taken on an empty stomach, either one hour before or two hours after a meal or snack, because food increases drug exposure by 100% and may increase the risk of hepatotoxicity.[2]

Because of the serious risk of hepatotoxicity, a REMS is necessary to ensure the benefits of pexidartinib outweigh this risk.

6 Expected Postmarket Use

Pexidartinib is likely to be prescribed in an ambulatory care setting, by medical and orthopedic oncologists who treat sarcomas or diagnose symptomatic TGCT. In the current paradigm of treatment, patients with inoperable, progressive TGCT disease with increasing pain and stiffness are usually referred to a tertiary oncology center for workup and management.[6]

7 Risk Management Activities Proposed by the Applicant

To mitigate the risk of hepatoxicity, the Applicant submitted prescribing information that contained a boxed warning, a Medication Guide as part of labeling, and a REMS.

The Medication Guide, which will be part of labeling, is not a required element of the REMS but contains information for the patient that is beyond the risks the REMS is intended to mitigate. The Medication Guide will be available on the Turalio product website or Turalio REMS website.

The Applicant submitted a REMS proposal that included a REMS document, REMS materials and REMS Supporting Document with Part 3 of 3 Modules (clinical) on December 3, 2018 of their rolling submission. The proposed REMS submitted on December 3, 2018, included a communication plan and elements to assure safe use (ETASU) that included prescriber certification (A), and pharmacy certification (B), an implementation system, and a timetable for submission of the assessment of the

REMS. The Applicant did not propose any other risk management activities outside of the prescribing information and the proposed REMS with ETASU.

The Applicant's proposed REMS was in part based on the protocol that was used for monitoring during the clinical development program and the reported adverse everts. In response to comments sent by the Agency on May 24, June 26, and July 19, 2019, the proposed REMS was amended on July 23, 2019. The final REMS document, REMS materials and REMS Supporting document was submitted on August 1, 2019. Below is the overview of the Applicant's proposed REMS, submitted on December 3, 2018 and the changes made during the review of the application.

7.1 REVIEW OF APPLICANT'S PROPOSED REMS

7.1.1 REMS Goals

The Applicant's proposed goals for the REMS as submitted on December 3,2018, were as follows:

The goal of the TURALIO REMS is to mitigate the risk of serious and potentially fatal liver injury by:

1. Ensuring that healthcare providers are educated on the following:

    a. approved indication for TURALIO

    b. the risk of serious and potentially fatal liver injury associated with the use of TURALIO

    c. liver monitoring at baseline and periodically during treatment with dose modifications as described in the Prescribing Information

    d. the need to counsel patients about the risk of serious and potentially fatal liver injury, liver monitoring at baseline and periodically during treatment with TURALIO as described in the Patient Guide and to report signs and/or symptoms of liver injury to the (b) (4) during therapy

(b) (4)

Reviewer comments: *The Applicant amended the goals to the proposed Turalio REMS on July 23, 2019, based on feedback from the Advisory Committee and comments from the Agency.*

The goal of the TURALIO REMS is to mitigate the risk of serious and potentially fatal liver injury by:

1. Ensuring that prescribers providers are educated on the following:

a. the approved indication for Turalio

b. the risk of serious and potentially fatal liver injury associated with the use of Turalio

c. the need for liver monitoring at baseline and periodically during treatment with dose modifications as described in the Prescribing Information

d. the need to counsel patients about the risk of serious and potentially fatal liver injury, liver monitoring at baseline and periodically during treatment with TURALIO as described in the Patient Guide and to report signs and/or symptoms of liver injury to the prescriber during therapy

2. Ensuring that prescribers adhere to the requirement of baseline and periodic monitoring as described in the Prescribing Information

3. Enrollment of all patients in a registry to further assess the safe use and acute, chronic and irreversible hepatotoxicity of Turalio.

Reviewer comments: *The REMS goal and objectives are acceptable and align with the REMS requirements.*

7.1.2 Communication Plan

The Applicant proposes to send REMS letters to healthcare providers (including medical and orthopedic oncologists who may treat sarcoma or diagnose symptomatic TGCT), and REMS Letters to Professional Societies: Sarcoma Alliance for Research through Collaboration (SARC) and Connective Tissue Oncology Society (CTOS), to communicate the risk of serious and potentially fatal liver injury and the need to certify in the REMS program to prescribe Turalio. The Applicant proposes to send these communication pieces within 60 calendar days of product launch and then again 12 months later.

Reviewer comments: *We agree with the Applicant's proposal that is it necessary to communicate the serious risks of Turalio, the requirement that prescribers must certify in the REMS program prior to prescribing Turalio, the need for monitoring and that patients must be enrolled in the registry prior to receiving Turalio. The Applicant's proposed timelines for the communications are acceptable. Comments on the letters were shared with the Applicant on July 19, 2019 and July 25, 2019. The letters submitted on July 26, 2019 are acceptable.*

7.1.3 Elements to Assure Safe Use (ETASU)

The Sponsor proposed the following ETASU as part of the REMS requirements: prescriber and pharmacy certification. As the review of the application progressed, the FDA identified the need for additional ETASU which are also described below.

ETASU A: Prescriber Certification: Prior to prescribing, the healthcare provider must certify in the Turalio REMS. To become a certified prescriber, the prescriber must review the prescribing information, the REMS Overview and Prescriber Training, successfully complete the Knowledge Assessment, complete the (b) (4) form, and submit these to the REMS program. Prior to initiating treatment with pexidartinib, the prescriber must; counsel the patient on the risk of serious and potentially fatal hepatotoxicity and the need for liver monitoring at baseline and periodically throughout treatment, assess the patient's baseline liver tests, and provide a copy of the Patient Guide that outlines the hepatotoxic risk of pexidartinib to the patient.

Reviewers comments: *We agree with the Applicant's proposal that it is necessary to require prescriber training and certification as part of the REMS; it ensures that prescribers are educated on the approved indication, risks of serious and potentially fatal liver injury associated with the use of Turalio, the need for monitoring and dosage adjustment if necessary, and the need to counsel patients on the risk before prescribing Turalio. We also agree with the requirements for certification as listed above.*

We conveyed to the Applicant on July 19, 2019 that prescribers need to enroll in the program to become certified, the (b) (4) *Form was subsequently changed to the Prescriber Enrollment Form. Changes were also made to the prescriber attestations in the Prescriber Enrollment Form. As a condition of certification, prescribers must attest on the Prescriber Enrollment Form that they agree to comply with the Turalio REMS requirements which includes that they should counsel patients on the risk of hepatotoxicity, assess patient liver function prior to and during treatment as described in the Prescribing Information and enroll each patient into the Turalio REMS Registry, and prescribe no more than a 30-day supply of Turalio for the first 3 months of treatment.*

The FDA also determined to support safe use, that a patient registry was a necessary requirement of the REMS (see details on the Patient Registry below). In order to support a patient registry, when enrolling in the REMS the prescriber also agrees to complete and submit the Patient Enrollment Form, Patient Status Form, as well as the Liver Adverse Event Reporting Forms if a case of serious and potentially fatal liver injury occurs in a treated patient.

ETASU B: Pharmacy Certification: The sponsor proposed to restrict pexidartinib to a limited number of pharmacies and wholesalers. Pharmacies must become certified by designating a representative who will ensure that all relevant staff are trained in the REMS program, obtain authorization to dispense the prescription by verifying the prescriber is certified in the REMS program, and dispense no more than a 30-day supply of pexidartinib for each of the first 3 months of treatment.

Reviewer comments: *FDA agrees with the Applicant's proposal for pharmacy certification to ensure that prescribers are certified in the REMS program prior to dispensing. The Pharmacy Enrollment Form is used to support this ETASU. On July 19, 2019 we provided feedback on the attestations included in the Pharmacy Enrollment Form. For the authorized pharmacy representative these attestations include complying with reviewing the REMS Program Overview, completing the Pharmacy Enrollment Form and submitting it to the Turalio REMS Program, and agreeing to use the REMS Program Overview to train all relevant staff involved in dispensing of Turalio. As a condition of certification, the authorized pharmacy representatives must oversee the implementation and compliance with Turalio REMS requirements at their pharmacy, including that before dispensing Turalio, the pharmacy staff must obtain authorization to dispense each prescription by contacting the Turalio REMS Center to verify that the REMS program requirements have been met (i.e. the prescriber is certified, the patient is enrolled in the REMS program and the Patient Status Forms are received as appropriate). No more than a 30-days' supply for each of the first 3 months of treatment will be dispensed. In addition, the authorized pharmacy representative will comply with the following REMS requirements:*

- *Report adverse events of serious and potentially fatal liver injury by submitting the Liver Adverse Event Reporting Form.*
- *Agree not to distribute, transfer, loan or sell Turalio, except to certified dispensers.*
- *Maintain records documenting the staff's completion of training.*
- *Maintain records that all Turalio REMS processes and procedures are in place and being followed.*
- *Maintain and submit dispensing information for all patients.*
- *Obtain authorization to dispense each prescription by contacting the REMS Program to verify the prescriber is certified and the patient is enrolled and authorized to receive the drug.*

We do not agree that it is necessary to limit the number of pharmacies to be certified in the REMS, the REMS requirement is that only pharmacies that can meet the REMS requirements can become certified in this REMS.

ETASU F: Patient Registry: Although not part of the Applicant's initial proposal, prior to the Advisory Committee the FDA determined that a registry was a necessary REMS requirement and the Applicant agreed to add a patient registry to the REMS to further characterize the acute and long-term risk of pexidartinib. The Applicant amended their submission on May 28, 2019 to include a Patient Enrollment Form, Patient Status Form and a Liver Adverse Event Form.

Reviewer comments: *Patients are required to enroll in the registry prior to receiving pexidartinib. The data that will be collected include: baseline liver function tests, concomitant medications, past history of liver dysfunction, number of patients, length of time patients receive pexidartinib, type and numbers of acute or long term effects (which may include the point in time a patient received an intervention, frequency of monitoring, what type of work-up and intervention was done in relationship to the adverse event), and outcomes of any adverse events such as deaths, liver transplants, or drug discontinuation. For hepatotoxic events that occur at any time during drug therapy, the Applicant will be required to report these events in an expedited manner and will be required to gather further information on the outcomes of these events. The components of the registry include:*

- *Patient Enrollment Form – to be completed prior to treatment initiation with baseline liver function and medical history.*
- *Patient Status Form – to be completed during treatment; monthly for the first 3 months, then at month 6, 9 and 12 and every 6 months thereafter while the patient is receiving Turalio. To authorize subsequent dispensing the form must be received within 20 calendars after the date the last Patient Status Form was due.*
- *Liver Adverse Event Reporting Form – this form is to be completed for all hepatic adverse events suggestive of serious or potentially fatal liver injury at any time the patient is receiving Turalio.*

ETASU E: Monitoring: The FDA determined that monitoring was a necessary REMS requirement and communicated this to the Applicant on July 19, 2019. In the amendment received on July 23, 2019 the Applicant agreed and updated the REMS accordingly.

Reviewer comments: *Prescribers are required to assess the patient's liver function prior to starting a patient on Turalio and during treatment. The Prescriber Enrollment Form supports this ETASU. In signing the form prescribers agree to comply with assessing the patient the liver function at baseline and weekly for the first 8 weeks of treatment, then every 2 weeks for 1 month, then every 3 months, and modify the dose of Turalio as needed in accordance with the Prescribing Information.*

7.1.4 Implementation System

For successful implementation of the REMS, the Applicant proposes to maintain a REMS Call Center to support patients, prescribers, pharmacies and wholesalers in interfacing with the REMS. The Applicant will ensure that pexidartinib is only distributed to certified pharmacies, by wholesalers who are compliant with distributing pexidartinib as per outlined in the REMS program. To ensure compliance with the REMS, the Applicant will maintain processes and procedures to maintain adequate records to demonstrate that REMS requirements are met (including but not limited to records of: drug distribution and dispensing; certification of prescribers and pharmacies; and audits of certified pharmacies). These records must be readily available for Food and Drug Administration (FDA) inspections. The Applicant will establish monitoring and audit procedures on an ongoing basis to ensure that the requirements of the REMS are being met and take corrective measures if non-compliance is identified.

Reviewer's comment*: We agree with the Applicant's proposal to include an implementation system. We provided comments on July 19, 2019, that added additional actions that the Applicant must include in their implementation system. This includes establishing and maintaining a registry which includes a reporting and collection system for all patients to provide information on acute, chronic, and irreversible hepatotoxicity, ensuring that the Applicant follows up with the healthcare provider to obtain all data required for complete adverse event reporting related to serious or potentially fatal liver injury is received under the REMS, and that these reports are received no later than 15 calendar days from the initial receipt of the information by the Applicant.*

Additional requirements include ensuring that the Patient Status Form is received for each patient within 20 days from the date the last Patient Status Form was due. Auditing of pharmacies and wholesales are to be done no later than 90 calendar days after they become certified, versus (b) (4) *as the Applicant previously proposed.*

The Applicant agreed with these changes to the Implementation System; we have no further comments.

7.1.5 Timetable for Submission of Assessments of the REMS

The Applicant proposed to submit REMS Assessments to the FDA at (b) (4) (b) (4) from the date of the approval of the REMS.

Reviewer's comment*: We did not agree with the Applicant's proposal of submitting REMS Assessments at* (b) (4) *Due to the severity of the hepatoxicity reported in the clinical trial there is a need to assess this program more frequently to determine if it is meeting the goal and objectives. We communicated with the Applicant on July 19, 2019, that they will be required to*

submit REMS assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS. The Applicant updated their timetable on July 23, 2019, to reflect this change.

7.2 REMS Materials & Key Risk Messages

The Applicant included the following materials as part of the original submission of the REMS:

- REMS Letter to Healthcare Providers
- REMS Letter to Professional Societies
- REMS Program Overview
- Prescriber Training, including Knowledge Assessment
- (b) (4) Form (subsequently revised to the Prescriber Enrollment Form)
- Pharmacy Enrollment Form
- Patient Guide
- REMS website

Reviewer's Comments: *We agree with the Applicant's proposed REMS materials, but also communicated on May 23rd, 2019, June 26th, 2019, July 19, and July 25, 2019 that changes were needed to the proposed materials and three new materials were necessary to support the various requirements of the REMS. The new materials include a Patient Enrollment Form, a Patient Status Form and a Liver Adverse Event Reporting Form. Throughout the review of this application, we advised the Applicant of the need to include a patient registry as part of the REMS, in which they agreed. The following additional REMS communications pieces were later developed by the Applicant:*

- *Patient Enrollment Form*
- *Patient Status Form*
- *Liver Adverse Event Reporting Form*

The Applicant did not include key risk messages with their submissions of the REMS materials. See section 8 of this review for our proposed key risk messages.

7.3 REMS Assessment Plan

The Applicant included a REMS assessment plan for the proposed REMS in their Supporting Document in their initial submission on December 3, 2018.

Reviewer's Comments: *We provided a revised REMS assessment plan to the Applicant on July 30, 2019 and on August 1, 2019 the Applicant provided an updated assessment plan that was acceptable. The final and agreed upon REMS Assessment Plan is included in Section the Appendix 10.2 of this review.*

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of pexidartinib on the basis of the efficacy and safety information that is currently available.[3,7] TGCT is associated with severe morbidity and/or functional limitations in patients, however, this disease is not imminently life-threatening.

The most concerning risk associated with pexidartinib is hepatoxicity. It occurs frequently, and it can be serious and potentially fatal. In the clinical trial program, treatment with pexidartinib resulted in acute

increases in hepatic transaminases in the majority of patients within the first 8 weeks of therapy; most resolving or returning to baseline with dose reductions, interruptions or discontinuation. Some patients had a prolonged time to recovery despite these interventions and there were cases of irreversible liver injury. Less is known about the long-term hepatotoxic effects of pexidartinib, specifically the development of ductopenia and the progression to irreversible liver failure.

The risk of serious and potentially fatal hepatoxicity, the need to monitor liver tests prior to initiation of treatment and at specified intervals, and to withhold, dose reduce or permanently discontinue pexidartinib due to hepatoxicity, will be included in a box warning. Despite the potential benefits of pexidartinib for patients with TGCT, DRISK and DOP-2 determined that labeling is not sufficient to mitigate these risks and a REMS is necessary to ensure the benefits outweigh the risks, particularly in a patient population where the disease is not imminently life threatening.

Pexidartinib is a new molecular entity with a novel mechanism of action and toxicity profile compared to other oncology drugs. There is no prior experience with this drug class and it is the first systemic therapy approved for TGCT. The severity of the risk as seen in the clinical trial and the proposed mitigation strategies such as the monitoring and dosage adjustments or discontinuation, must be well known to the prescribers. While it is expected that oncologists are familiar with managing hepatotoxicity and the importance of monitoring, it is necessary to ensure that prescribers are educated on the approved indication for Turalio, the risk of serious and potentially fatal liver injury, the need to counsel patients about this risk and the need for liver monitoring. It is also necessary to educate prescribers about the need for liver monitoring and dose modifications as described in the Prescribing Information and the importance of adhering to the liver monitoring as described in the Prescribing Information. Because less is known about the long-term hepatotoxic effects of pexidartinib, enrollment of all patients in a registry is necessary to assess the safe use and acute, chronic and irreversible hepatotoxicity of Turalio.

On March 28, 2019 this Application was discussed at the REMS Oversight Committee Meeting and on May 14, 2019 at the Oncologic Drugs Advisory Committee. Both concurred that a REMS with elements to assure safe use that included prescriber certification (ETASU A), pharmacy certification (ETASU B) and a patient registry (F) is necessary to ensure the benefits of Turalio outweigh the risks of risk of serious and potentially fatal hepatotoxicity. Upon further review in the Agency, it was determined that monitoring (ETASU E) is also a necessary requirement of the REMS. The REMS will also include a targeted communication plan to inform prescribers of the risks and that Turalio is approved with a REMS that includes restricted distribution.

We believe that the proposed REMS received on August 1, 2019, will support actions that will mitigate the risk of serious and potentially fatal liver injury and further assess the safe use and acute, chronic and irreversible hepatotoxicity of Turalio.

Depending on the assessment findings, FDA may modify the REMS or consider other regulatory actions, particularly if reports of severe hepatotoxicity or deaths occur beyond what was observed in the clinical trial, and if there is evidence of insufficient monitoring. If the REMS assessments or other data indicate

that prescribers have gained familiarity with the drug and data supports that prescribers are taking appropriate actions to reduce the risk of hepatotoxicity, FDA may, in the future, determine that the REMS is no longer necessary.

8.1 REMS MATERIALS AND KEY RISK MESSAGES

The following REMS materials will provide education and support the risks messages of the REMS:

- REMS Letter to Healthcare Providers
- REMS Letter to Professional Societies
- REMS Program Overview
- Prescriber Training, including Knowledge Assessment
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Patient Guide
- REMS website
- Patient Enrollment Form
- Patient Status Form
- Liver Adverse Event Reporting Form

The key risk messages for healthcare providers are:

1. Turalio is a kinase inhibitor indicated for adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.
2. There is a risk of serious and potentially fatal liver injury associated with the use of Turalio.
3. Per the prescribing information, monitor liver baseline and periodically during treatment with dose modifications.
4. Counsel patient about the risks of serious and potentially fatal liver injury, liver monitoring at baseline and periodically and report signs and symptoms of liver injury to the physician during therapy.
5. Prescribe no more than a 30-day supply for each month of the first 3 months of treatment.
6. Enroll patient into the registry by completing the Patient Enrollment Form prior to initiating therapy with Turalio, completing the Patient Status Forms monthly for the first 3 months, then at months 6, 9 and 12 and every 6 months thereafter while the patient is receiving Turalio. This form must be received within 20 calendars after the date the last Patient Status Form was due; if not, the patient is not authorized to receive subsequent drug shipments. Additionally, the Liver Adverse Event Reporting Form must be completed for all hepatic adverse events suggestive of serious or potentially fatal liver injury at any time the patient is receiving Turalio.

The key risk message for pharmacies is:

1) Dispense no more than a 30-day treatment for the first 3 months of treatment.

The key risk messages for patients are:

TURALIO can cause serious side effects, including serious liver problems, which may be severe and can lead to death.

1. Your healthcare provider will do blood tests to check for liver problems:
2. Stop taking TURALIO and contact your doctor right away if you have:

- Jaundice (yellowing of the skin and whites of the eye)
- Dark urine

3. 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 pain or tenderness
   - Feeling overly tired
   - Nausea
   - Vomiting
   - Fever
   - Rash
   - Itching

8.2 REMS Assessment Plan

The REMS Assessment Plan is included in the Appendix of this review. There are four primary areas that will be assessed based on the goals of the Turalio REMS and the program requirements. They include the following:

Program Outreach and Communication—Measures the extent to which the REMS materials reached the intended stakeholders. This includes but is not limited to the number of healthcare providers and professional societies targeted, number of field-based sales and medical representative visits to healthcare providers professional and number of meetings where Turalio REMS martials were disseminated.

Program Implementation and Operations—Measures the extent to which the intended stakeholders are participating in the program, including the number of newly certified and active prescribers, stratified by medical credentials and geographic region; the number newly certified and active pharmacies, stratified by geographic region; the number of newly enrolled patients stratified by age, gender, race, hepatic medical history, and geographic region; and the number of newly enrolled and active wholesaler/distributors; how effectively the REMS program is being implemented, including the extent of use of REMS materials and compliance with REMS requirements; and any unintended consequences that could affect patient access or potential burden to the healthcare system related to the program operations. In summary, this refers to when the Turalio REMS became live and fully operational, date of the first commercial distribution of Turalio, as well as REMS certification and enrollment statistics for healthcare providers, pharmacies, patients, and wholesalers. The number of new and refilled prescriptions for Turalio will be reported, as well as visits to the REMS website and call center support. There will be reporting on the compliance of the overall REMS program, in addition to compliance of the submission of Patient Status Forms and Liver Adverse Event Reporting Forms.

Knowledge—Measures the extent of stakeholders' (e.g., prescriber, pharmacist) knowledge about the REMS-related risk of serious and potentially fatal liver toxicity or knowledge of any safe use conditions that are needed in order to mitigate this risk. This will include the number of prescriber post-training knowledge assessments completed, including the method of completion and number of attempts to complete, a summary of the most frequently missed knowledge assessment questions, and a summary

of potential comprehension or perception issues identified with the knowledge assessment. There will also be stakeholder knowledge surveys (beginning with the 1-year REMS assessment) of healthcare providers to evaluate the knowledge of the approved indication for Turalio, the risk of serious and potentially fatal liver injury associated with the use of Turalio, the liver monitoring described in the product label, number of dose interruptions and discontinuations, and the need to counsel patients about the risk of serious and potentially fatal liver injury. In Section 8.1 of this review, there are a list of key risk messages related to the risk of this REMS as well as operational procedures significant in the implementation of this REMS that will inform whether survey participants are adequately knowledgeable about the goals of the Turalio REMS.

Health Outcomes and/or Surrogates of Health Outcomes—Measures the safety-related health outcome of any known or suspected adverse events related to serious and potentially fatal liver injury. The sources of these reports will come from adverse events reported in the REMS registry by way of the periodic Patient Status Form and the Liver Adverse Event Form. This information can also be reported from spontaneous adverse events reports, literature searches and social media. The Applicant will provide an analysis and discussion of these cases identified with each assessment report, including patient-level data sets with all variables collective.

9 Conclusion & Recommendations

The severity of the risk of serious and potentially fatal hepatotoxicity associated with pexidartinib is such that it is necessary for prescribers to understand the risk, the importance of monitoring for it, appropriate patient selection based on the approved indication, and the need to counsel patients on the risk prior to prescribing pexidartinib. Based on the severity of hepatotoxicity, and the uncertainty of the long-term hepatotoxic effects that may occur with chronic pexidartinib therapy, we agree that requiring a REMS consisting of a communication plan, prescriber certification, pharmacy certification, monitoring of patients, and enrollment of all patients receiving pexidartinib in a registry is necessary to ensure that the benefits outweigh the risks.

10 Appendices

10.1 REFERENCES

[1] NDA 211810 Pexidartinib Clinical Overview, Daiichi Sankyo, submitted December 3, 2018

[2] Pexidartinib draft US Prescribing Information, June 12, 2019

[3] Midcycle meeting clinical slides, March 4, 2019

[4] Turalio (pexidartinib) ODAC FDA Briefing Document, May 14, 2019

[5] Ravi V, Wang WL, Lewis V. Treatment of tenosynovial giant cell tumor and pigmented villonodular synovitis. *Curr Opin Oncol.* 2011 Jul;23(4):361-6

[6] Pexidartinib NDA 211810 REMS Oversight Committee Presentation, March 28, 2019

[7] Fashoyin-Aje, I. NDA 211810 Cross Discipline Team Leader Memorandum, submitted in DARRTS July 22, 2019.

10.2 REMS ASSESSMENT PLAN

The Turalio REMS assessment plan must include but is not limited to the following:

Program Outreach and Communication

1. Communication Plan (6-month, 1-year, and 2-year assessments only)
    a. Sources of the distribution lists for healthcare providers
    b. Number of healthcare providers targeted
    c. The date(s), number and medical specialty of healthcare providers who were sent the Letter for Healthcare Providers by the methods of distribution
    d. The date(s), number and names of Professional Societies that were sent the Letter for Professional Societies by the methods of distribution
    e. The number of mailings returned or undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients
    f. Professional meetings where Turalio REMS materials were disseminated

Program Implementation and Operations

2. REMS Program Implementation (6-month and 1-year assessments only)
    a. Date of first commercial distribution of Turalio
    b. Date when the Turalio REMS website became live and fully operational
    c. Date prescribers could become certified
    d. Date when pharmacies could become certified
    e. Date when patients could become enrolled
    f. Date when the REMS call center was established and fully operational
3. REMS Certification and Enrollment Statistics (provide previous, current, and cumulative reporting periods)
    a. Healthcare Providers
        i. Number of newly certified and active (i.e. who have prescribed at least once during the reporting period) healthcare providers stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), specialty (e.g., Oncology, Orthopedics, Other) and geographic region
        ii. Method of healthcare provider certification (online, fax or email)

    b. Pharmacies
        i. Number of newly certified and active (i.e. have received Turalio) pharmacies stratified by geographic region.
        ii. Number of pharmacies that dispensed Turalio stratified by geographic region
        iii. Number of pharmacies that were unable to become certified and reason why
    c. Patients
        i. Number of newly enrolled patients stratified by age, gender, race, hepatic medical history, and geographic region
        ii. Number of patients who have discontinued therapy and the reason for

discontinuation

d. Wholesalers/Distributors
    i. Number of newly enrolled and active (i.e., have shipped Turalio) wholesalers/distributors

4. Turalio Utilization Data (provide previous, current, and cumulative reporting periods)
    a. Number of prescriptions (new and refills) dispensed stratified by:
        i. Prescriber specialty, provider degree/credentials, geographic region
        ii. Patient demographics (age, gender, race, and geographic region)
    b. Number of unique patients receiving Turalio, stratified by age, gender, race, and geographic region,
5. REMS Infrastructure and Performance (provide previous, current, and cumulative reporting periods)
    a. REMS Website
        i. Number of visits and unique visits to the REMS websites
        ii. Number of REMS materials downloaded or printed for each material
    b. Call Center Report
        i. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, pharmacy, wholesalers/distributors, other)
        ii. Summary of reasons for calls (e.g., enrollment question) and by reporter (authorized representative, patient/caregiver, healthcare provider, other)
        iii. If the summary reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
        iv. Summary of frequently asked questions (FAQ) by stakeholder type
        v. A summary report of corrective actions resulting from issues identified
    c. Report on Patient Status Forms
        i. Number of Patient Enrollment Forms expected, received and outstanding as of the report cut-off date
        ii. Number of first patient shipments sent prior to receipt of a Patient Enrollment Form. Include outreach activities performed to collect the forms.
        iii. Number of Patient Status Forms not received within 20 calendar days of the receipt of the last Patient Status Form for subsequent prescription refill shipments. Include outreach activities performed to collect the forms.
        iv. Number of Patient Status Forms outstanding from previous reporting periods (if applicable)
        v. Number of unique patients that experienced a treatment interruption, duration of the treatment interruption and reason for treatment interruption (e.g. liver toxicity, no status form received)
        vi. Number of unique patients whose Turalio was discontinued and the reason treatment was discontinued (e.g. liver toxicity, non-response to therapy, no status form received)
    d. Report on Liver Adverse Event Reporting Form
        i. Number of Liver Adverse Event Reporting Forms expected due to a “yes” response on the Patient Status Form indicating that a form is required, received, and outstanding as of the report cut-off date.
        ii. Number of unique patients who had a Liver Adverse Event Reporting Form

submitted

6. REMS Compliance (provide previous, current, and cumulative reporting periods))
    a. Provide a summary of non-compliance identified, including but not limited to:
        i. Provide a copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event lead to de-certification from the REMS.
        ii. Provide a copy of the audit plan for each stakeholder
        iii. Report of audit findings for each stakeholder (REMS contact center, pharmacies and wholesalers/distributors).
            1. The number of audits expected, and the number of audits performed.
            2. The number and types of deficiencies noted for each group of audited stakeholders.
            3. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
            4. For any that did not complete the CAPA within one month of the audit, describe actions taken.
            5. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
            6. Documentation of completion of training for relevant staff.
            7. The existence of documented processes and procedures for complying with the REMS
            8. Verification that each audited stakeholder's site that the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification.
    b. Healthcare Providers (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
        i. The number of healthcare providers who were non-compliant with the Turalio REMS program requirements.
        ii. Number of prescriptions written by non-certified healthcare providers.
        iii. Number of healthcare providers that were de-certified and reasons for decertification. Include if any healthcare providers were re-certified.
    c. Patients
        i. Number of patients not enrolled in the REMS program or registry who were dispensed Turalio.
    d. Pharmacies (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
        i. The number and type of pharmacy for which non-compliance with the REMS is detected.
        ii. The number and type of non-certified pharmacies that dispensed Turalio and the number of incidents for each
        iii. Number of Turalio prescriptions dispensed that were written by non- certified prescribers and the actions taken to prevent future occurrences
        iv. Number of Turalio prescriptions dispensed by non-certified pharmacies and the

actions taken to prevent future occurrences

v. Number of Turalio prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences.
vi. Number of times a Turalio prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken
vii. Number of Turalio prescriptions dispensed for more than a 30 days' supply for each of the first three months of treatment
viii. Number of pharmacies decertified, reasons for decertification, and actions to address non-compliance

e. Wholesalers/distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
    i. The number of authorized wholesalers/distributors for which non-compliance with the REMS is detected
    ii. Number of wholesalers de-enrolled, reasons for de-enrollment, and actions to address non-compliance
    iii. Number of times Turalio was distributed to a non-certified pharmacy or directly to patients.

Health Outcomes and/or Surrogates of Health Outcomes

7. Safety Surveillance (provide previous, current, and cumulative reporting periods)

    a. Known, or suspected adverse events related to serious and potentially fatal liver injury are to be reported regardless of outcome. Root cause analyses of whether periodic monitoring of liver function was followed per the prescribing information are to be included. Provide an overall analysis and discussion of all cases identified from all sources (i-vi) including but not limited to the following for each case: , drug discontinued due to liver toxicity, drug withheld due to liver toxicity, pertinent clinical data (i.e. liver biochemical tests, liver biopsy, etc), ALT or AST >3x ULN and TBIL >2x ULN, ALT or AST > 10x ULN with or without TBIL elevation, TBIL >2x ULN without changes in ALT or AST, relevant comorbidities, prior and concomitant medications with hepatotoxic potential, treatment required, and clinical outcome. Sources of the reports are to include but not be limited to:

        i. Patient Status Form

            1. Number of cases of serious and potentially fatal liver injury adverse events reported on the Patient Status Form, including a calculation of the event incidence.
            2. Number of patients who experienced more than one event.
            3. Trend analysis of whether adverse events decrease or increase over time

        ii. Liver Adverse Event Form

        iii. Spontaneous adverse event reports

1. Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest
2. Include a line listing of all cases that includes: manufacturer control number, narrative, assessment of causality, and source of the report

iv. Literature searches

1. Include the search strategy used to identify literature search cases
2. Include a line listing of all literature search cases that includes: reference, narrative, and assessment of causality

v. Social Media

b. Include an overall analysis and discussion of information collected on the Patient Status Form and Adverse Event Liver Forms which further assesses the registry data with respect to the safe use and acute, chronic, and irreversible hepatotoxicity of Turalio.. Provide data in tabular format where applicable. Submit patient-level datasets with all variables collected and analytical programs compliant with current FDA standards, including appropriate define files and reviewer guides.

c. Include whether the data warrant further detailed assessment, labeling changes, and/or communication.

Evaluation of Knowledge

8. Post-Training Knowledge Assessments (provide previous, current, and cumulative reporting periods)
    a. Number of completed post-training Knowledge Assessments for healthcare providers including method of completion and number of attempts to complete
    b. Summary of the most frequently missed Knowledge Assessment questions
    c. A summary of potential comprehension or perception issues identified with the Knowledge Assessment

9. Stakeholder Surveys (beginning with the 1-year assessment report and annually thereafter with each assessment report)
    a. Healthcare Provider surveys to assess if healthcare providers are educated on the following:
        i. the approved indication for Turalio
        ii. the risk of serious and potentially fatal liver injury associated with the use of Turalio
        iii. liver monitoring and dose modifications as described in the Prescribing Information
        iv. the need to counsel patients about the risk of serious and potentially fatal liver injury, liver monitoring at baseline and periodically during treatment with Turalio as described in the Patient Guide and to report signs and/or symptoms of liver injury to the physician during therapy.

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

57 Pages of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

NAOMI S BOSTON
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ELIZABETH E EVERHART
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I concur.

SHELLY L HARRIS
08/01/2019 05:24:41 PM

CYNTHIA L LACIVITA
08/01/2019 05:29:02 PM
Concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OHOP
DOP2

NDA:	211810
Products:	Turalio (pexidartinib)
APPLICANT:	Daiichi Sankyo Inc
FROM:	Jeff Summers
DATE:	see DARRTS date stamp

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Turalio (pexidartinib) to ensure that the benefits of the drug outweigh the risks of serious and potentially fatal liver injury. In reaching this determination, we considered the following:

A. The estimated number of patients in the United States with Giant cell tumor of the tendon sheath (GCT-TS), usually manifesting as extra-articular disease, is approximately 9.2 cases per 1 million population, while Pigmented villonodular synovitis (PVNS), manifesting as intra-articular disease, is 1.8 cases per 1 million population. A subset of these patients would have disease that is not amenable to effective surgical correction or palliation. This estimate is based on Steinmetz S; Rougemont AL; Peter R. Pigmented villonodular synovitis of the hip. EFORT Open Rev. 2016; 1(6):260-266) and Elumogo CO; Kochenderfer JN; Civelek AC; Bluemke DA. Pigmented villonodular synovitis mimics metastases on fluorine 18 fluorodeoxyglucose position emission tomography-computed tomography. Quant Imaging Med Surg. 2016; 6(2):218-23

B. Patients with diffuse disease can have joint involvement that is not amenable to surgery or they may experience multiple recurrences after surgery. Diffuse disease can manifest with morbid cosmetic

disfigurement and extreme functional limitations greatly impacting activities of daily living and quality of life. Rarely malignant transformation can occur.

C. Treatment with Turalio resulted in a 39% overall response rate, 95% CI (28%, 52%), compared to a 0% response rate in patients treated with placebo. Fifty percent of patients with a response had a duration of response of at least 6 months. Patients randomized to the pexidartinib arm had statistically significant improvements in the secondary endpoints of mean change in range of motion, mean change in physical function per PROMIS®, and mean change in worst stiffness. Some patients experienced marked improvement in cosmetic joint deformities.

D. It is expected that patients with severe forms of PVVS or GCT-TS, who are not candidates for surgical resection, would receive chronic treatment with Turalio.

E. Turalio poses risks of serious and potentially fatal liver injury. A majority of patients who received this drug experienced elevations in transaminase values. A smaller percentage of patients (approximately 5%) incurred unequivocal drug induced liver injury as defined by a total bilirubin of greater than or equal to 2 times the upper limit of normal [ULN] and an AST or ALT greater than or equal to 3 x ULN. Most patients in the TGCT population who experienced transaminase elevations and total bilirubin increase had improvement to baseline levels with appropriate dose reduction, dose interruption, and/or discontinuation of pexidartinib. Limited biopsy evaluation across the pexidartinib development program for hepatic toxicity provided evidence of bile duct injury and ductopenia, raising concerns of possible subclinical, smoldering, chronic hepatic injury.

   Acute liver failure (fulminant or subfulminant) in the healthy patient population without underlying liver disease is a rare occurrence, affecting two to three thousand patients in the US each year.

F. Turalio contains pexidartinib, which is a new molecular entity.

The elements of the REMS will be ETASU A (healthcare providers who prescribe Turalio are specially certified), ETASU B (pharmacies and practitioners that dispense Turalio are specially certified), ETASU E (each patient using Turalio will be subject to certain monitoring), ETASU F (each patient using Turalio will be enrolled in a registry), a communication plan, an implementation system, and a timetable for submission of assessments.

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/s/

NATALIYA N FESENKO
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JEFFERY L SUMMERS
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Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211810
PDUFA Goal Date	August 3, 2019
OSE RCM #	2018-2053
Reviewer Name(s)	Naomi Boston, Pharm.D., Senior Risk Management Analyst
Team Leader	Elizabeth Everhart, MSN, RN, ACNP, Risk Management Team Leader
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 30, 2019
Subject	REMS Assessment Plan
Established Name	Pexidartinib
Trade Name	Turalio
Name of Applicant	Daichii Sankyo, Inc
Therapeutic class	Colony Stimulating Factor-1 Receptor (CSF1R), tyrosine kinase inhibitor (TKI)
Formulation	200 mg oral tablets
Dosing Regimen	400 mg by mouth twice daily

Background:

Daiichi Sankyo submitted a proposed REMS for NDA 211810, Turalio (pexidartinib) on December 3, 2018. They also submitted additional materials on May 28, June 17, and June 24, 2019. The Agency provided comments on the materials on June 26, 2019 and the sponsor resubmitted on July 8, 2019. FDA provided comments on July 19, 2019 and the sponsor resubmitted on July 23, 2019 and July 26, 2019.

Attached to this document is our revised REMS Assessment Plan that aligns with the agreed upon REMS Document the Applicant submitted on July 23, 2019.

Comments for Sponsor:

Please review the revised REMS Assessment Plan that aligns with the agreed upon REMS Document you submitted on July 23, 2019. Submit the final versions of the REMS document, REMS Materials, and the REMS Supporting Document with the updated REMS Assessment Plan that is attached to this correspondence by close of business, July 31, 2019. Submit these documents in MS Word, and .PDF or PowerPoint files.

TURALIO REMS Assessment Plan

The Turalio REMS assessment plan must include but is not limited to the following:

Program Outreach and Communication

1. Communication Plan (6-month, 1-year, and 2-year assessments only)
    a. Sources of the distribution lists for healthcare providers
    b. Number of healthcare providers targeted
    c. The date(s), number and medical specialty of healthcare providers who were sent the Letter for Healthcare Providers by the methods of distribution
    d. The date(s), number and names of Professional Societies that were sent the Letter for Professional Societies by the methods of distribution
    e. The number of mailings returned or undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients
    f. Professional meetings where Turalio REMS materials were disseminated

Program Implementation and Operations

2. REMS Program Implementation (6-month and 1-year assessments only)
    a. Date of first commercial distribution of Turalio
    b. Date when the Turalio REMS website became live and fully operational
    c. Date prescribers could become certified
    d. Date when pharmacies could become certified
    e. Date when patients could become enrolled
    f. Date when the REMS call center was established and fully operational

3. REMS Certification and Enrollment Statistics (provide previous, current, and cumulative reporting periods)
    a. Healthcare Providers
        i. Number of newly certified and active (i.e. who have prescribed at least once during the reporting period) healthcare providers stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), specialty (e.g., Oncology, Orthopedics, Other) and geographic region.
        ii. Method of healthcare provider certification (online, fax or email).

    b. Pharmacies
        i. Number of newly certified and active (i.e. have received Turalio) pharmacies stratified by geographic region.
        ii. Number of pharmacies that dispensed Turalio stratified by geographic region.
        iii. Number of pharmacies that were unable to become certified and reason why.
    c. Patients

i. Number of newly enrolled patients stratified by age, gender, race, hepatic medical history, and geographic region.
ii. Number of patients who have discontinued therapy and the reason for discontinuation.

d. Wholesalers/Distributors
i. Number of newly enrolled and active (i.e., have shipped Turalio) wholesalers/distributors.

4. Turalio Utilization Data (provide previous, current, and cumulative reporting periods)

a. Number of prescriptions (new and refills) dispensed stratified by:
i. Prescriber specialty, provider degree/credentials, geographic region.
ii. Patient demographics (age, gender, race, and geographic region).
b. Number of unique patients receiving Turalio, stratified by age, gender, race, and geographic region.

5. REMS Infrastructure and Performance (provide previous, current, and cumulative reporting periods)
a. REMS Website
i. Number of visits and unique visits to the REMS websites.
ii. Number of REMS materials downloaded or printed for each material.
b. Call Center Report
i. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, pharmacy, wholesalers/distributors, other).
ii. Summary of reasons for calls (e.g., enrollment question) and by reporter (authorized representative, patient/caregiver, healthcare provider, other).
iii. If the summary reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues.
iv. Summary of frequently asked questions (FAQ) by stakeholder type.
v. A summary report of corrective actions resulting from issues identified.
c. Report on Patient Status Forms
i. Number of Patient Status Forms expected, received and outstanding as of the report cut-off date.
ii. Number of first patient shipments sent prior to receipt of a Patient Status Form. Include outreach activities performed to collect the forms.
iii. Number of Patient Status Forms not received within 20 calendar days of the receipt of the last Patient Status Form for subsequent prescription refill shipments. Include outreach activities performed to collect the forms.
iv. Number of Patient Status Forms outstanding from previous reporting periods (if applicable).
v. Number of unique patients that experienced a treatment interruption, duration of the treatment interruption and reason for treatment interruption (e.g. liver toxicity, no status form received).
vi. Number of unique patients whose Turalio was discontinued and the reason treatment was discontinued (e.g. liver toxicity, non-response to therapy, no status form received).
d. Report on Liver Adverse Event Reporting Form

i. Number of Liver Adverse Event Reporting Forms expected due to a "yes" response on the Patient Status Form indicating that a form is required, received, and outstanding as of the report cut-off date.
ii. Number of unique patients who had a Liver Adverse Event Reporting Form submitted.

6. REMS Compliance (provide previous, current, and cumulative reporting periods))
    a. Provide a summary of non-compliance identified, including but not limited to:
        i. Provide a copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event lead to de-certification from the REMS.
        ii. Provide a copy of the audit plan for each stakeholder.
        iii. Report of audit findings for each stakeholder (REMS contact center, pharmacies and wholesalers/distributors).
            1. The number of audits expected, and the number of audits performed.
            2. The number and types of deficiencies noted for each group of audited stakeholders.
            3. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
            4. For any that did not complete the CAPA within one month of the audit, describe actions taken.
            5. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
            6. Documentation of completion of training for relevant staff.
            7. The existence of documented processes and procedures for complying with the REMS.
            8. Verification that each audited stakeholder's site that the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification.
    b. Healthcare Providers (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
        i. The number of healthcare providers who were non-compliant with the Turalio REMS program requirements.
        ii. Number of prescriptions written by non-certified healthcare providers.
        iii. Number of healthcare providers that were de-certified and reasons for decertification. Include if any healthcare providers were re-certified.
    c. Patients
        i. Number of patients not enrolled in the REMS program or registry who were dispensed Turalio.
    d. Pharmacies (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
        i. The number and type of pharmacy for which non-compliance with the REMS is detected.
        ii. The number and type of non-certified pharmacies that dispensed Turalio and the number of incidents for each.

iii. Number of Turalio prescriptions dispensed that were written by non- certified prescribers and the actions taken to prevent future occurrences.
iv. Number of Turalio prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.
v. Number of Turalio prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences.
vi. Number of times a Turalio prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken.
vii. Number of Turalio prescriptions dispensed for more than a 30 days' supply for each of the first three months of treatment.
viii. Number of pharmacies decertified, reasons for decertification, and actions to address non-compliance.

e. Wholesalers/distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
    i. The number of authorized wholesalers/distributors for which non-compliance with the REMS is detected.
    ii. Number of wholesalers de-enrolled, reasons for de-enrollment, and actions to address non-compliance.
    iii. Number of times Turalio was distributed to a non-certified pharmacy or directly to patients.

Health Outcomes and/or Surrogates of Health Outcomes

7. Safety Surveillance (provide previous, current, and cumulative reporting periods)

    a. Known, or suspected adverse events related to serious and potentially fatal liver injury are to be reported regardless of outcome. Root cause analyses of whether periodic monitoring of liver function was followed per the prescribing information are to be included. Provide an overall analysis and discussion of all cases identified from all sources (i-vi) including but not limited to the following for each case: time to onset, dose modifications, pertinent clinical data (i.e. liver biochemical tests, liver biopsy, etc), grade of toxicity, relevant comorbidities, prior and concomitant medications with hepatotoxic potential, treatment required, and clinical outcome. Sources of the reports are to include but not be limited to:

        i. Patient Status Form

            1. Number of cases of serious and potentially fatal liver injury adverse events reported on the Patient Status Form, including a calculation of the event incidence.
            2. Number of patients who experienced more than one event.
            3. Trend analysis of whether adverse events decrease or increase over time.

        ii. Liver Adverse Event Form

        iii. Adverse events reported in the REMS registry

        iv. Spontaneous adverse event reports

1. Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest.
2. Include a line listing of all cases that includes: manufacturer control number, narrative, assessment of causality, and source of the report.

v. Literature searches

1. Include the search strategy used to identify literature search cases.
2. Include a line listing of all literature search cases that includes: reference, narrative, and assessment of causality.

vi. Social Media

b. Include an overall analysis and discussion of information collected on the Patient Status Form and Adverse Event Liver Forms which further assesses the registry data with respect to the safe use and acute, chronic, and irreversible hepatotoxicity of Turalio. Provide data in tabular format where applicable. Submit patient-level datasets with all variables collected and analytical programs compliant with current FDA standards, including appropriate define files and reviewer guides.

c. Include whether the data warrant further detailed assessment, labeling changes, and/or communication.

Evaluation of Knowledge

8. Post-Training Knowledge Assessments (provide previous, current, and cumulative reporting periods)
    a. Number of completed post-training Knowledge Assessments for healthcare providers including method of completion and number of attempts to complete.
    b. Summary of the most frequently missed Knowledge Assessment questions.
    c. A summary of potential comprehension or perception issues identified with the Knowledge Assessment.

9. Stakeholder Surveys (beginning with the 1-year assessment report and annually thereafter with each assessment report).
    a. Healthcare Provider surveys to assess if healthcare providers are educated on the following:
        i. the approved indication for Turalio.
        ii. the risk of serious and potentially fatal liver injury associated with the use of Turalio.
        iii. liver monitoring and dose modifications as described in the Prescribing Information.
        iv. the need to counsel patients about the risk of serious and potentially fatal liver injury, liver monitoring at baseline and periodically during treatment with Turalio as described in the Patient Guide and to report signs and/or symptoms of liver injury to the physician during therapy.

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAOMI S BOSTON
07/30/2019 11:12:08 AM

ELIZABETH E EVERHART
07/30/2019 11:13:47 AM
I concur.

CYNTHIA L LACIVITA
07/30/2019 11:44:29 AM

Date of Memo:	July 24, 2019
NDA #:	211810
Drug:	Turalio (pexidartinib)
Date of Submission:	July 23, 2019
RMA:	Naomi Boston
Re:	HCA Comments (Kate Oswell)
Review Division:	DOP 2
Comment set:	# 3

Background:

Daiichi Sankyo submitted, a proposed REMS for NDA 211810, Turalio (pexidartinib) on December 3, 2018. They also submitted additional materials on May 28, June 17, and June 24, 2019. The Agency provided comments on the materials on June 26, 2019 and the sponsor resubmitted on July 8, 2019. FDA provided comments on July 19, 2019 and the sponsor resubmitted on July 23, 2019.

Materials reviewed

- REMS Letter to Healthcare Providers
- REMS Letter to Professional Societies
- Program Overview
- Prescriber Training, including Knowledge Assessment
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Patient Guide
- Patient Enrollment Form
- Patient Status Form
- Liver Adverse Event Reporting Form
- REMS website
- Wholesale Distributor Form (In Supporting Document)

The Office of Prescription Drug Promotion (OPDP) was consulted and sent materials on July 8th and July 10th. This review incorporates OPDPs comments. Please acknowledge OPDPs comments in the next review.

Comments for Sponsor:

General comment:

Remove the phrasing (b) (4)

REMS Letter for Healthcare Providers

We have made minor edits to your letter to reinforce the monitoring requirement and better aligning with the label. See redlined track changes of the REMS Letter for Healthcare Providers.

REMS Letter for Professional Societies
We have made some formatting changes to reinforce the monitoring requirement and better aligning with the label. See redlined track changes of the REMS Letter for Professional Societies.

Program Overview
We have made the risk information more prominent and concise using content from the Boxed Warning in the highlights section of the Prescribing Information. We have also clarified that the monitoring should be done according to the Prescribing Information.
Remove the phrase [redacted] (b) (4) See redlined track changes of the Program Overview.

Patient Guide:
Remove the phrase [redacted] (b) (4) See redlined track changes of the Patient Guide.

Training Program:
We improved the presentation of risk information on slide 16. We also revised the monitoring of liver tests to better align with the label. See comments and edits to the Training Program.

REMS Website:
Remove the phrasing [redacted] (b) (4) throughout the website. See edits to the REMS website.

We have no further edits on these materials at this time:
Knowledge Assessment Form
Prescriber Enrollment Form
Pharmacy Enrollment Form
Patient Enrollment Form
Patient Status Form
Liver Adverse Event Reporting Form
Wholesale Distributor Form

Resubmit only documents that you have modified with tracked changes. Additionally, submit REMS communications materials as clean .PDF or PowerPoint files. Submit one complete file containing the REMS Document and all REMS materials. Resubmit by 12:00 Friday July 26, 2019.

35 Pages of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAOMI S BOSTON
07/25/2019 02:49:25 PM

KATE H OSWELL
07/25/2019 03:00:10 PM

ELIZABETH E EVERHART
07/25/2019 03:05:44 PM
I concur.

Office of Prescription Drug Promotion

Internal Consults

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Kate Heinrich Oswell, Health Communications Analyst,
Division of Risk Management (DRISK),
Office of Surveillance and Epidemiology (OSE)

From: Emily Dvorsky, Regulatory Review Officer, OPDP

CC: Susannah O'Donnell, Team Leader, OPDP
Latonia Ford, Safety Regulatory Project Manager, OSE
Elizabeth Everhart, Team Leader, DRISK
Naomi Boston, Risk Management Analyst, DRISK
Doris Auth, Associate Director, DRISK
Carole Broadnax, OPDP
Jina Kwak, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: July 22, 2019

Re: NDA 211810
TURALIO™ (pexidartinib) capsules, for oral use
Comments on draft Risk Evaluation and Mitigation Strategies (REMS) Materials (Submission date: July 8, 2019)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for TURALIO™ (pexidartinib) capsules, for oral use (Turalio):

- Healthcare Provider (HCP) REMS Materials:
  - REMS Letter for Healthcare Provider
  - REMS Letter for Professional Society
  - REMS Overview
  - Prescriber Training and Knowledge Assessment
  - Prescriber Enrollment Form
  - Pharmacy Enrollment Form
  - Liver (b) (4) Adverse Event Reporting Form
  - Patient Status Form

- Direct-to-Consumer (Patient) REMS Materials:
  - Patient Enrollment Form
  - Patient Guide

- REMS Website

The version of the draft REMS materials used in this review were sent from DRISK (Kate Heinrich Oswell) via email on July 10, 2019. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Turalio.

General Comments

Please remind Daiichi Sankyo that REMS materials are not appropriate for use in a promotional manner.

OPDP notes that the Turalio PI and Medication Guide are still being reviewed and modified. OPDP's review is based on the current draft PI and draft Medication Guide. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved label.

The proposed REMS materials include references to www.TURALIOREMS.com and the phone number 1-833-TURALIO (1-833-887-2546). OPDP recommends that these items represent a direct link to only REMS-related information and not be promotional in tone. Furthermore, we remind Daiichi Sankyo that the REMS-specific website should not be the sole source of approved REMS materials.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Healthcare Provider (HCP) REMS Materials:
  - REMS Letter for Healthcare Provider
  - REMS Letter for Professional Society
  - REMS Overview
  - Prescriber Training and Knowledge Assessment
  - Prescriber Enrollment Form
  - Pharmacy Enrollment Form
  - Liver (b) (4) Adverse Event Reporting Form
  - Patient Status Form

- Direct-to-Consumer (Patient) REMS Materials:
  - Patient Enrollment Form
  - Patient Guide

- REMS Website

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them in the REMS piece:

- REMS Letter for Healthcare Provider

  - Page one of the proposed REMS Letter for Healthcare Provider includes the following statement in the "Serious Risk of TURALIO" section:

    - (b) (4)

      Risk

      We note that this statement omits material information from the draft PI regarding the schedule of liver testing. Specifically, Section 5.1 of the draft PI states (emphasis added):

      > 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.

The omission of this material information may minimize the mitigation of the REMS risk. We recommend revising the Turalio REMS Letter for Healthcare Provider to include this material information.

- Page one of the proposed REMS Letter for Healthcare Provider presents dosing information for Turalio in the "Serious Risk of TURALIO" section and includes the following claim:

  - (b) (4)

    Risk

    This claim omits material information regarding the REMS risk. Specifically, according to section 5.1 of the draft PI:

    > Withhold and dose reduce, or permanently discontinue TURALIO based on severity of the hepatotoxicity.

    The omission of this material information may minimize the mitigation of the REMS risk. We recommend revising the Turalio REMS Letter for Healthcare Provider to include this material information.

- The REMS Letter for Healthcare Providers, "As part of the TURALIO REMS" section, includes the following statement:

  - (b) (4)

    General Comment

    We are concerned that this statement is vague and promotional in tone. OPDP recommends more descriptive language be added to this statement for clarification. For example, please consider a statement such as, "Visit www.TURALIOREMS.com to access the prescriber training and enrollment forms" or similar language.

- The REMS Letter for Healthcare Provider includes the following statement in the "As part of the TURALIO REMS" section (emphasis added):

  - "During treatment monitor patient's liver tests and <u>modify the TURALIO dose as needed</u>"

    General Comment

We note this statement is inconsistent with the Turalio draft PI. The draft PI details dosage modifications for hepatotoxicity in Table 2. Section 5.1 also states, "Withhold and dose reduce, or permanently discontinue TURALIO based on the severity of the hepatotoxicity." Please consider revising this statement to clearly indicate that Turalio has specific dose modifications associated with the level of the severity of the hepatotoxicity.

- REMS Letter for Professional Society

  - Page one of the proposed REMS Letter for Professional Society presents dosing information for Turalio including the following claim:

    - (b) (4)

      Risk

      This claim omits material information regarding the REMS risk. Specifically, according to section 5.1 of the draft PI:

      > Withhold and dose reduce, or permanently discontinue TURALIO based on severity of the hepatotoxicity.

      The omission of this material information may minimize the mitigation of the REMS risk. We recommend revising the Turalio REMS Letter for Professional Society to include this material information.

  - Page one of the proposed REMS Letter for Professional Society presents the following statement (emphasis added):

    - (b) (4)

      General Comment

      We note that the DRISK Health Communications Analyst has indicated on the REMS Letter for Healthcare Provider that the REMS program for Turalio does not make liver testing a requirement and language was modified to reflect this. Please consider revising this statement and similar statements across all materials to be consistent with the Letter for Healthcare Provider.

In addition, we note that the phrase [redacted] omits material information from the draft PI regarding the schedule of liver testing. Specifically, Section 5.1 of the draft PI states (emphasis added):

> 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.

The omission of this material information may minimize the mitigation of the REMS risk. We recommend revising the Turalio REMS Letter for Healthcare Provider to include this material information.

- The proposed REMS Letter for Professional Society includes the following statement (emphasis added):
  - "During treatment monitor patient's liver tests and modify the TURALIO dose as needed"

General Comment

We note this statement is inconsistent with the Turalio draft PI. The draft PI details dosage modifications for hepatotoxicity in Table 2. Section 5.1 also states, "Withhold and dose reduce, or permanently discontinue TURALIO based on the severity of the hepatotoxicity." Please consider revising this statement to clearly indicate that Turalio has specific dose modifications associated with the level of the severity of hepatotoxicity.

- REMS Overview
  - Page two of the proposed REMS Overview contains the following claim:
    - [redacted]

Risk

This claim omits material information regarding the REMS risk. Specifically, according to section 5.1 of the draft PI, "Withhold and dose reduce, or permanently discontinue TURALIO based on severity of the hepatotoxicity." We recommend revising to include this information.

- Page two of the proposed REMS Overview includes the following statement (emphasis added):

  - "Prior to initiating treatment…liver test monitoring prior to and during treatment with TURALIO"

    Risk

    We note that this statement omits material information from the draft PI regarding the schedule of liver testing. Specifically, Section 5.1 of the draft PI states (emphasis added):

    > 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.

    The omission of this material information may minimize the mitigation of the REMS risk. We recommend revising the Turalio REMS Overview to include this material information.

- Page two of the proposed REMS Overview includes the following statement (emphasis added):

  - (b) (4)

    General Comment

    We note this statement is inconsistent with the Turalio draft PI. The draft PI details dosage modifications for hepatotoxicity in Table 2. Section 5.1 also states, "Withhold and dose reduce, or permanently discontinue TURALIO based on the severity of the hepatotoxicity." Please consider revising this statement to clearly indicate that Turalio has specific dosage modifications associated with the level of the severity of hepatotoxicity.

- Page two of the proposed REMS Overview includes the following statement (emphasis added):

  - (b) (4)

General Comment

We note that this statement is inconsistent with the draft PI. The draft PI does not include (b) (4) (b) (4) Please consider revising this statement to be consistent with the final PI.

- Prescriber Training and Knowledge Assessment
  - Pages five and twelve of the proposed Prescriber Training include the following statement (emphasis added):
    - (b) (4)

General Comment

We note that this statement is inconsistent with the draft PI. The draft PI does not include (b) (4) (b) (4) Please consider revising this statement to be consistent with the final PI.

  - Question five of the proposed Knowledge Assessment is correctly answered with the following selection (emphasis added):
    - "There is a risk of liver injury associated with TURALIO and liver monitoring is required prior to treatment initiation and periodically while taking TURALIO"

General Comment

We note that the DRISK Health Communications Analyst has indicated on the REMS Letter for Healthcare Provider that the REMS program for Turalio does not make liver testing a requirement and language was modified to reflect this. Please consider revising this statement to be consistent with the Letter for Healthcare Provider.

- Prescriber Enrollment Form
  - The proposed Prescriber Enrollment Form includes the following statement as part of the attestations (emphasis added):

- (b) (4)

Risk

This statement is inconsistent with the draft PI for Turalio and may minimize the REMS risk associated with Turalio. According to section 5.1 of the draft PI, "TURALIO can cause serious and potentially fatal liver injury" (emphasis added). We recommend revising this statement to be consistent with the draft PI and to avoid minimizing the risk associated with Turalio.

- Patient Status Form
  - The proposed Patient Status Form includes the following statement (as currently edited; underlined emphasis added):
    - (b) (4)

General Comment

Please consider deleting (b) (4) to increase reader comprehension.

- Patient Enrollment Form
  - The proposed Patient Enrollment Form includes the following statement as part of the attestations (emphasis added):
    - (b) (4)

Risk

This statement is inconsistent with the draft Medication Guide for Turalio and may minimize the REMS risk. According to the "What is the most important information that I should know about TURALIO?" section, "TURALIO can cause serious side effects, including serious liver problems which may be severe and can lead to death" (emphasis added). We recommend revising this statement to be consistent with the draft PI and to avoid minimizing the risk associated with Turalio.

- Patient Guide
  - Page one of the proposed Patient Guide includes the following statement (emphasis added):
    - (b) (4)

      Risk

      This statement is inconsistent with the draft Medication Guide for Turalio and may minimize the REMS risk. According to the "What is the most important information that I should know about TURALIO?" section, "TURALIO can cause serious side effects, including serious liver problems which may be severe and can lead to death" (emphasis added). We recommend revising this statement to be consistent with the draft PI and to avoid minimizing the risk associated with Turalio.
  - Page two of the proposed Patient Guide includes the following statement (emphasis added):
    - "You must have blood tests to test for liver problems as part of the TURALIO REMS"

      General Comment

      We note that the DRISK team has modified the REMS program to no longer require liver testing. As this is no longer a requirement, please consider revising this statement to reflect this modification.
- REMS Website
  - Page 11 of the proposed website (Prescriber Portal) includes the answer key for the Knowledge Assessment for the Turalio REMS. Question five is correctly answered with the following selection (emphasis added):
    - "There is a risk of liver injury associated with TURALIO and liver monitoring is required prior to treatment initiation and periodically while taking TURALIO"

      General Comment

      We note that the DRISK reviewer has indicated on the REMS Letter for Healthcare Provider that the REMS program for Turalio does not make liver testing a requirement and language was modified to

reflect this. Please consider revising this statement to be consistent with the Letter for Healthcare Provider.

- Page 16 of the proposed website (Prescriber Portal) contains the proposed Prescriber Enrollment Form. This form includes the following statement as part of the attestations (emphasis added):
  - (b) (4)

Risk

This statement is inconsistent with the draft PI for Turalio and may minimize the REMS risk. According to section 5.1 of the draft PI, "TURALIO can cause serious and potentially fatal liver injury" (emphasis added). We recommend revising this statement to be consistent with the draft PI and to avoid minimizing the risk associated with Turalio.

- The proposed REMS Website includes the following statement on pages 24 and 33 of the Prescriber Portal:
  - (b) (4)

General Comment

We note that this statement is inconsistent with the draft PI. The draft PI does not include (b) (4) (b) (4) Please consider revising this statement to be consistent with the final PI.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

86 Pages of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY M DVORSKY
07/22/2019 12:17:50 PM

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211810
PDUFA Goal Date	August 3, 2019
OSE RCM #	2018-2053
Reviewer Name(s)	Naomi Boston, Pharm.D., Senior Risk Management Analyst Kate Oswell, Senior Health Communications Analyst
Team Leader	Elizabeth Everhart, RN, MSN, ACNP, Risk Management Team Leader
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 18, 2019
Subject	Evaluation of the REMS and REMS materials
Established Name	Pexidartinib
Trade Name	Turalio
Name of Applicant	Daichii Sankyo, Inc
Therapeutic class	Colony Stimulating Factor-1 Receptor (CSF1R), tyrosine kinase inhibitor (TKI)
Formulation	200mg oral tablets
Dosing Regimen	400mg by mouth twice daily

INTRODUCTION

This review provides comments and changes to the proposed risk evaluation and mitigation strategy (REMS) and the REMS materials for the new molecular entity (NME) Turalio (pexidartinib).

On December 3, 2018, Daiichi Sankyo submitted a New Drug Application (NDA) 211810 for pexidartinib with the proposed indication 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. This application is under review in the Division on Oncology Products (DOP) 2. The risk of pexidartinib is serious and potentially fatal liver injury. Daiichi Sankyo's proposed REMS consists of a communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Additional review of the REMS for this application by DRISK will be provided in the final review. Comments on the REMS assessment plan will be provided at a later date.

MATERIALS REVIEWED

General comments on the Applicant's REMS materials were provided on June 26th, 2019. On July 8, 2019, the Applicant provided responses to the Agency's comments. In addition to the review by the Division of Risk Management, the REMS document and attestations for the prescriber, pharmacy and patient enrollment forms have been reviewed by the Office of Chief Counsel (OCC). The revisions to these materials include OCC's comments.

The following materials have been reviewed and comments on these materials are appended to this review:

- REMS Document
- REMS Letter to Healthcare Providers
- REMS Letter to Professional Societies
- REMS Program Overview
- Prescriber Training, including Knowledge Assessment
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Patient Guide
  REMS website
- Patient Enrollment Form
- Patient Status Form
- Liver Adverse Event Reporting Form
- Attestations for the prescriber, pharmacy, and patient enrollment forms

COMMENTS FOR THE APPLICANT

The Agency has reviewed your REMS document submitted on December 3, 2018 and have provided changes and a comment to the REMS Document which is appended to this communication; the REMS

document you submitted has had significant revisions and you should use this version going forward. The REMS materials submitted on July 8, 2019 have additional changes and comments and are also appended to this communication. Note that the attestations have been revised are provided at the beginning of the PDF file of the compiled materials. Replace the attestations in your Prescriber, Pharmacy, and Patient Enrollment forms with these. Please note that the REMS Supporting Document must be updated to include changes in the aforementioned materials. Resubmit these documents with tracked changes and a clean version in MS Word format by Wednesday, July 23, 2019. Additionally, submit REMS communications materials as clean .PDF or PowerPoint files. A revised REMS assessment plan will be shared with you early next week.

95 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAOMI S BOSTON
07/19/2019 10:19:04 AM

KATE H OSWELL
07/19/2019 11:20:45 AM

ELIZABETH E EVERHART
07/19/2019 11:26:49 AM
I concur.

CYNTHIA L LACIVITA
07/19/2019 11:32:44 AM
Concur