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Pexidartinib Risk Evaluation and Mitigation Strategy Program: 3-year Safety Data Assessment

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Objective

- Pexidartinib is a first-in-class colony-stimulating factor-1 (CSF1) receptor blocker indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations not amenable to improvement with surgery
- Due to the potential risk of hepatotoxicity, pexidartinib (400 mg orally dosed twice daily) was granted approval by the US Food and Drug Administration (FDA) on the condition of establishing a Risk Evaluation and Mitigation Strategy (REMS) program
- The 3-year (August 2019-June 2022) cumulative safety data collected from patients enrolled in the pexidartinib REMS (pREMS) program are described here

Conclusions

- The safety profile of pexidartinib remains consistent with the data from the ENLIVEN trial. Furthermore, no new hepatic safety signals were identified
- Based on data collected from the pREMS program, careful monitoring of liver enzyme levels combined with early intervention using dose modification, interruption, and discontinuation is being actively conducted to mitigate the risk of potential hepatotoxicity
- Overall, the results of this cumulative safety data assessment suggest the pREMS program is ensuring the safe use of pexidartinib in patients with TGCT

Introduction

- TGCTs are a rare group of cancers forming in the synovium, bursae, and tendon sheath in or outside joints.[1] The primary mechanistic driver of TGCT is the overexpression of CSF1, resulting in downstream recruitment of macrophages expressing CSF1 receptors, which are the primary cellular components of TGCTs[2]
- TGCT can be classified as either localized or diffuse. Although the 2 classifications differ in their prognosis, they share typical clinical presentations of pain, stiffness, and decreased mobility that can range from only a few symptoms to potentially debilitating[3]
- Pexidartinib (Turalio®) is a first-in-class, oral, tyrosine kinase inhibitor developed by Daiichi Sankyo for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations not amenable to surgical improvement[4]
- Prior to the approval of pexidartinib, there was a significant unmet medical need for systemic agents to treat patients with TGCT

Methods

- The pREMS program consists of elements to ensure safe use, a communication plan, an implementation system, and a timetable for REMS assessments
- Health care providers (HCPs) prescribing pexidartinib must be educated and certified in the pREMS program and should educate patients with TGCT who are receiving the drug
- Dispensing pharmacies and distributors of pexidartinib must also be certified in the program. Scheduled safety assessments were collected on patient access forms (PAFs)

Results

- During the 3-year period, 451 TGCT patients were enrolled in the pREMS program (**Table 1**)
- The majority (94.2%) of adverse events (AEs), including hepatic and non-hepatic, were nonserious
- Hair color change was the most frequently reported nonserious AE (4.4%; **Table 2**), and increased aspartate aminotransferase (AST; 0.5%) was the most frequently reported serious AE
- Of the 451 TGCT patients, only 51 (2.4%) lab tests had alanine aminotransferase (ALT) or AST liver enzymes >3 × upper limit of normal (ULN) and total bilirubin (TBIL) >2 × ULN; 17 (0.8%) had ALT or AST >10 × ULN with/without TBIL elevation, and 12 (0.6%) had no changes in ALT or AST with TBIL ≥2 × ULN (**Table 3**)
- Twenty-one cases (4.7%) met the criteria for a liver AE and indicated that the reported hepatic injury was consistent with the ENLIVEN trial results
- There were no events of irreversible liver injury
- Following initiation of pexidartinib, treatment interruption (n = 106) was seen in 98 (21.7%) patients, which were primarily due to hepatic AEs (n = 24; 22.6%), nonhepatic AEs (n = 15; 14.2%), disease progression (n = 2; 1.9%), and death (n = 1; 0.9%). Among patients resuming treatment, all received a lower dose
- Treatment discontinuation was reported in 132 patients (29.3%; 137 events), due to hepatic AEs (n = 26; 19.0%), nonhepatic AEs (n = 23; 16.8%), disease progression (n = 13; 9.5%), confirmed pregnancy (n = 2; 1.5%), and death (n = 1; 0.7%; not related to hepatotoxicity)
- Based on liver AE report forms (LAERFs; 65 patients, 95 LAERFs), 12 (12.6%) cases required hepatology referral, 14 (14.7%) liver ultrasound, 12 (12.6%) other liver imaging, and 5 (5.3%) endoscopic retrograde cholangiopancreatography. Of these, 14 (14.7%) cases required hospitalization, 1 (1.1%) liver dialysis, 6 (6.3%) medication prescribed to treat liver injury, and 7 (7.4%) other. Liver AEs resolved in 33 (34.7%) cases, 51 (53.7%) cases were ongoing, and 1 (1.1%) case resolved with sequelae. No liver transplant or hepatotoxicity-related death was reported

Table 1. Characteristics of the Pexidartinib REMS Enrollees

Enrollees	Enrolled	Active[a]
All patients (N)	451	426
Male, n (%)	184 (40.8)	174 (40.8)
Female, n (%)	267 (59.2)	252 (59.2)
Mean (SD) age, years	45.1 (15.8)	45.1 (15.6)

REMS, Risk Evaluation and Mitigation Strategy; SD, standard deviation.
[a]Patients on treatment at data cut-off.

Table 2. Distribution of Most Frequently Reported Nonhepatic AEs

AE, n (%)	Nonserious	Serious
Hair color changes	223 (4.37)	0 (0)
Fatigue	210 (4.12)	1 (0)
Nausea	132 (2.59)	1 (0)
Pruritus	102 (2.00)	0 (0)
Rash	90 (1.77)	1 (0)

AE, adverse event.

Table 3. Frequency of Hepatic AEs

Hepatic AE	n (%)
AST increased	26 (0.51)
ALT increased	25 (0.49)
GGT increased	20 (0.39)
ALP increased	17 (0.33)
Bilirubin increased	16 (0.31)

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

References

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Disclosures

CD, MK, MW, and MS are employees of Daiichi Sankyo, Inc. OF is a postdoctoral fellow employed by Rutgers University and has no financial disclosures to report. MF is an employee of Daiichi Sankyo UK, Ltd. All Daiichi Sankyo employees own restricted stock units of Daiichi Sankyo.

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