CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215559Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	215559
PDUFA Goal Date	August 16, 2023
Nexus TTT #	2022-586
Reviewer Name(s)	Cristen Lambert, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD
Review Completion Date	August 15, 2023
Subject	Evaluation of Need for a REMS
Established Name	palovarotene
Trade Name	Sohonos
Name of Applicant	Ipsen Biopharmaceuticals, Inc.
Therapeutic Class	Retinoic Acid Derivatives
Formulation(s)	1 mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg capsules for oral (PO) administration
Dosing Regimen	Adult and pediatric patients 14 years and older Chronic: 5 mg daily Flare: 20 mg daily (weeks 1 to 4); 10 mg daily (weeks 5 to 12). Flare up regiment may be initiated for flare up or high-risk traumatic event likely to cause flare-up. Weight-adjusted dosing proposed for children < 14 years of age

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Sohonos (palovarotene) is necessary to ensure the benefits outweigh its risks. Ipsen Biopharmaceuticals, Inc. resubmitted a New Drug Application NDA 215559 for Sohonos on February 16, 2023 with the proposed indication for prevention of heterotopic ossifications in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP). The serious risks associated with palovarotene under consideration for a REMS include the following: teratogenicity, premature physeal closure and reduced bone growth.

During the previous review cycle (submitted on April 29, 2022), DRM was unable to make a final determination if a REMS is needed to ensure the benefits of Sohonos outweigh the risks as the full benefit risk assessment could not be completed at that time.[1] DRM and the Division of General Endocrinology presented our recommendation that a REMS is not necessary to mitigate the serious risks of teratogenicity and premature epiphyseal closure (PPC) at the REMS Oversight Committee (ROC) on August 29, 2022. The ROC agreed with the review team's recommendation at that time. Ipsen resubmitted NDA 2155559 on February 16, 2023 to address major deficiencies regarding efficacy of Sohonos in FOP.

DRM maintains that a REMS is not needed to ensure the benefits of Sohonos (palovarotene) outweigh its risks. FOP is a progressive and debilitating disease which can become life-threatening, and the FOP population is extremely small and has low reproductive fitness. Pregnancy is high risk for an FOP mother and fetus and FOP consensus guidelines emphasize this risk and appropriate family planning. Regarding the risk of PPC, growing children at risk of PPC are a subpopulation of this small patient population. Patients with FOP are followed closely by specialists who are expected to have comprehensive and individualized risk-benefit discussions with FOP patients and caregivers upon diagnosis and throughout the course of the disease. The risks of embryo-fetal toxicity and PPC will be communicated to healthcare providers and patients in labeling as a *Boxed Warning*, in *Warnings and Precautions*, in *Use in Specific Populations,* as well as in a Medication Guide.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Sohonos (palovarotene) is necessary to ensure the benefits outweigh its risks. Ipsen Biopharmaceuticals, Inc. submitted a New Drug Application NDA 215559 for Sohonos with a proposed indication for the prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP). This application is under review in the Division of General Endocrinology (DGE).

2. Background

2.1. Product Information

Sohonos (palovarotene), a new molecular entity (NME) [a], is a retinoic acid receptor gamma (RARγ) selective agonist (retinoid) proposed for prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva. Sohonos is proposed as an oral capsule. The proposed dosing regimen consists of chronic dosing at 5 mg daily and flare up dosing at 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks. The expected duration of chronic treatment is indefinitely[b] and use is expected in the outpatient community and institutional settings. Sohonos was granted orphan drug, fast track, breakthrough therapy, and rare pediatric disease designations and was approved in Canada in January 2022. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) gave an initial opinion to refuse marketing authorization for Sohonos on January 26, 2023 and after re-examination requested by Ipsen, confirmed refusal on May 25, 2023.[2] The EMA "considered that no firm conclusions could be drawn on the benefits of the medicine," "results from other studies and limited long-term clinical data available did not support efficacy," and "the risk of premature physeal closure could not adequately be mitigated with the risk minimization measures proposed by the company."[2] The concerns did not change after re-examination and the EMA considered the benefits of Sohonos did not outweigh its risks and it recommended refusing marketing authorization.[2] On July 19, 2023, the European Commission announced that they have determined not to grant marketing authorization approval for palovarotene as a treatment for FOP.[3]

Sohonos is part of the retinoic acid derivatives class which has a broad risk management landscape for teratogenicity. Some medications in this class, like tretinoin and bexarotene, utilize labeling to manage the risk, whereas acitretin has a non-REMS risk management plan, and isotretinoin has a REMS with elements to assure safe use (ETASU). All systemic medications in the retinoic acid derivatives and retinoid-like compounds class of medications contain a Boxed Warning for embryofetal toxicity risk in pregnancy.

2.2. Regulatory History

- 7/21/2014: Orphan Drug designation granted
- 11/25/2014: Fast Track designation granted
- 7/11/2017: Breakthrough Therapy designation granted
- 2/7/2019: Rare Pediatric Disease designation granted

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

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

- 3/31/2021: NDA 215559 submission for prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibro-dysplasia (myositis) ossificans progressiva (FOP) received
- 8/12/2021: Ipsen withdrew submission for internal review of efficacy data
- 4/29/2022: NDA 215559 resubmission for prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibro-dysplasia (myositis) ossificans progressiva (FOP) received
- 8/9/2022: A Mid-Cycle meeting was held between the Agency and the Applicant via teleconference.
- 10/19/2022: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for palovarotene.
- 10/21/2022: The Agency informed the applicant via teleconference that the Endocrinologic and Metabolic Drugs Advisory Committee (EDMAC) meeting scheduled for October 31, 2022 was postponed. The Agency requested additional efficacy data and analyses.
- 12/23/2022: Complete Response (CR) letter sent to the applicant due to major review issues that remain unresolved including, but not limited to, appropriateness of reliance on post-hoc analyses to support efficacy, acceptability of the external control group for evaluation of efficacy of the chronic/flare-up dosing regimen, and uncertain implications of the observed negative new HO volume data.[4]
- 2/16/2023: Complete Response received
- 6/28/2023: Endocrinologic and Metabolic Drugs Advisory Committee (EDMAC) meeting for Sohonos (palovarotene) NDA 215559

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

FOP is a progressive, debilitating, lethal disease due to heterotopic ossification (HO). HO consists of heterotopic bone formation in muscles, tendons, and ligaments. Extension of HO across joints leads to progressive and irreversible immobility. Onset begins in childhood in “flare-ups” with localized pain, swelling, and inflammation resulting in new extraskeletal bone at that location. HO can also develop insidiously, without flare-up symptoms. Those afflicted experience cardio-respiratory complications and are often wheelchair-bound by the third decade of life. FOP has a median survival in the mid-50s and

has no cure. [c] FOP is an autosomal dominant genetic disease, ultra-rare with only 800-900 cases reported worldwide and 200-300 cases in the US in 2020. The population likely to use palovarotene is very small (less than 1000 patients globally) [d] and includes initiation in children upon diagnosis and adults for chronic and flare-up therapy.

3.2. Description of Current Treatment Options

There are currently no approved treatments for this disease, so there is an unmet medical need. Supportive treatments recommended in consensus guidelines include glucocorticoids, oral and topical non-steroidal anti-inflammatory medications, cyclo-oxygenase-2 inhibitors, mast cell stabilizers, leukotriene inhibitors, and occasionally intravenous bisphosphonates.

4. Benefit Assessment

In support of this application, the Applicant conducted a phase 2, randomized, double-blind, placebo-controlled study in patients with FOP (Study 201; National Clinical Trial (NCT) 02190747), with a phase 2 open-label single arm extension study (Study 202; NCT 02279095), as well as a single arm, open-label, externally controlled phase 3 study (Study 301; NCT 03312634). The external control group for Study 301 was a 36-month Natural History Study (NHS), also conducted by the Applicant, in pediatric and adult patients with FOP.

The proposed dosing regimen includes chronic daily treatment (5 mg), with higher-dose treatment (20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks) during symptomatic "flare-up" episodes. This flare-up treatment cycle is continued for persisting symptoms or restarted for new flare events. All proposed doses are adjusted based on body weight in patients under 14 years of age. This dosing regimen was used in Study 301 and in Study 202 Part C.

The primary endpoint for Study 201 was the incidence of new HO at the flare-up site 6 weeks after flare-up initiation; secondary endpoints included the volume of new HO at the flare-up site by CT scan at 12 weeks. The primary endpoint for Study 301 was annualized change in new whole-body HO volume, and the key secondary endpoint was proportion of subjects with any new HO. Studies 201 and 301 failed their respective prespecified primary efficacy analyses, and none of the secondary or exploratory endpoints in Study 301 showed statistically significant differences between palovarotene-treated and untreated/control subjects and thus did not provide supportive evidence of the efficacy of palovarotene in the treatment of FOP.[5]

[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.*

It was determined that substantial evidence of the effectiveness of palovarotene in the treatment of FOP was provided by data from the phase 3 Study 301, using the NHS as an external control, and by supportive efficacy data, primarily from Study 202C, which used the same dosing regimen and protocol design as Study 301. Additional, but not as robust, supportive evidence was provided by data from Studies 201 and 202A/B, as well as by non-clinical data in a FOP mouse model that supports the mechanism of action of palovarotene to inhibit over-activation of the ALK2 receptor and thereby reduce HO formation.[5]

Overall, the Agency concluded that the Applicant demonstrated substantial evidence of the effectiveness of palovarotene to reduce new volume HO in pediatric and adult patients with FOP, but has not provided substantial evidence to support an indication for the prevention of HO in patients with FOP.[5] Based on these efficacy data, the approved indication will be for reduction in volume of new heterotopic ossification (HO) in adults and pediatric patients (aged 8 years and above for females and 10 years and above for males) with FOP.[5] Further, efficacy of palovarotene treatment in patients with FOP appears to be present only when chronic daily dosing is combined with flare-based dosing, when needed, for flare-up episodes.

5. Risk Assessment & Safe-Use Conditions

The primary safety population includes 139 FOP subjects (aged 8 years and above for females, and aged 10 years and above for males) on the 5 mg chronic non-flare dose (n=131) or the 20/10 mg flare-up regimen (n=105) in Studies 202 B and C (NCT 02279095), and 301 (NCT 03312634).[6] In this pooled safety population, serious adverse events were reported in 50 (36%) subjects. The most common serious adverse events reported include premature epiphyseal closure in 9 (6%) subjects, coronavirus infection in 4 (3%) subjects, pneumonia in 4 (3%) subjects, condition aggravated in 3 (2%) subjects, and cellulitis in 3 (2%) subjects.[6] Four (3%) subjects discontinued palovarotene studies due to adverse events, all from Study 301.[6] Two subjects were withdrawn for premature epiphyseal closure, one for intentional self-injury and one for malnutrition.

Overall, 50 (36%) subjects had adverse events leading to palovarotene dose modification, 37 (27%) subjects had adverse events leading to palovarotene dose interruption and 11 (8%) subjects had adverse events leading to palovarotene discontinuation.[6] In Study 301, 9 subjects discontinued study drug. Four subjects stopped study drug due to premature epiphyseal closure and one each for pruritis, furuncle, mobility decreased, dry skin and intentional self-harm.

Adverse events were reported in 100% of study subjects receiving palovarotene. The most common adverse events were dry skin (81%), dry lip (57%), arthralgia (49%), pain in extremity (42%), alopecia (42%) pruritis (42%), erythema (34%), rash (33%), headache (29%), and dry eye (27%).[6] All of these events have been seen with other retinoids and are considered known adverse reactions to the drug.

No deaths occurred in the palovarotene treatment studies. One death occurred in a 13-year-old subject with a history of restrictive lung disease who died 2.5 months after discontinuing palovarotene treatment. Additionally, a 38-year-old subject in the NHS with substantial disease burden, based on the

CAJIS[e] (Cumulative Analogue Joint Involvement Scale), died of a cardiac arrest. This subject never received treatment with palovarotene.

Safety risks associated with palovarotene include those associated with the retinoid drug class of medications, as well as risks seen specifically in patients with FOP. Boxed Warnings and Warnings and Precautions contained in the retinoid class product labels include teratogenicity; psychiatric disorders; pseudotumor cerebri; serious skin reactions; pancreatitis; lipid abnormalities (hypertriglyceridemia); hearing impairment; hepatotoxicity; inflammatory bowel disease; skeletal abnormalities, including decreased bone mineral density; hyperostosis and premature epiphyseal closure; and vision impairment, including corneal opacities and decreased night vision.[6]

The serious risks associated with palovarotene use in patients with FOP are embryo-fetal toxicity, premature epiphyseal closure (PPC) in growing children, increased rate of reported flare-ups during treatment with potential for retinoid-induced myositis, and apparent adverse effects on vertebral bone mineral density, bone mineral content, and fractures.

5.1. Embryo-Fetal Toxicity

Embryo-fetal toxicity consistent with retinoid effects was observed in fetal rat studies of palovarotene.[7] As a precaution, clinical studies of palovarotene included a pregnancy testing protocol for females of child-bearing potential with baseline and monthly pregnancy testing as well as contraception requirements. The studies also excluded pregnant and breastfeeding females. To date, there are no reports of pregnancy or in utero exposure to palovarotene. A Phase 1 study found administration to a male patient is considered unlikely to affect development of an embryo or fetus carried by a pregnant female sexual partner.

The risk of teratogenicity will be communicated in a Medication Guide and in the label as a *Boxed Warning*, in *Warnings and Precautions*, and in *Use in Specific Populations* to inform healthcare professionals of this serious risk. The label advises that palovarotene, as a member of the retinoid class of drugs, is associated with birth defects in humans, as such, palovarotene should be administered only if conditions for pregnancy prevention are met. The label describes the contraindication in pregnancy and advises providers to discontinue treatment immediately in patients who become pregnant and to refer the patient to an obstetrician/ gynecologist or other specialist experienced in reproductive toxicity for further evaluation and counseling.

[e] CAJIS is a functional mobility assessment of FOP patients which can provide a rapid and accurate snapshot of total body and regional mobility burden of FOP

5.1. Premature Epiphyseal Closure (PPC)[f]

Systemic retinoids have long been associated with adverse musculoskeletal effects. Growth plate abnormalities and premature closure were observed in juvenile rats exposed to palovarotene and were consistent with retinoid class effects.[7] Because of the potential risk, palovarotene FOP studies included a Bone Safety Management Plan (BSMP) in pediatric subjects less than 18 years of age. Based on hand/wrist x-rays at screening to assess growth plates, subjects with <90% skeletal maturity (i.e., had achieved <90% of adult height), defined as bone age <12 years (girls) or <14 years (boys), received weight-adjusted dosing. In those with open growth plates, continued monitoring occurred.

Study 301 began enrollment in November 2017. In 2019, multiple instances of PPC among pediatric subjects in this study were reported based on scheduled radiographs. In December 2019, a partial clinical hold was imposed for the dosing of any children under age 14 years; dosing was never resumed except for children who subsequently reached age 14. Protocol amendment 5 added an extended 2-year safety follow-up for pediatric subjects, including annual assessment of growth, hand/wrist radiograph and whole-body computed tomography (WBCT).[7]

Premature epiphyseal closure development was most apparent at the active growth plates of the knee (distal femur and proximal tibia), which is consistent with literature reports involving other retinoids. Premature epiphyseal closure was not generally associated with rapid advances in bone age as assessed by x-rays of the hand/wrist. All patients with open growth plates are likely to be at risk of PPC. The Applicant could not identify specific risk factors or a safe level of palovarotene exposure. The review team concluded that because PPC involved the knee and appeared to be irreversible, reduced height is expected to result. In addition to reduced stature, and potentially disproportionate growth (e.g., short legs relative to trunk), the review team concluded that PPC of growth plates at the knee poses a potential risk of leg length discrepancy or abnormal knee angulation.

The risk of PPC and impaired growth will be communicated in the Medication Guide and in the label as a *Boxed Warning* and in *Warnings and Precautions* with recommendations for patient monitoring, including height measurements and imaging of growth plates. A planned postmarketing safety study will further investigate PPC and impaired growth in children with FOP and open growth plates treated with palovarotene.

5.2. Increased Rate of Reported Flare-Ups During Treatment; Potential for Retinoid-Induced Myositis

Flare-up incidence and rate were designated in phase 3 as secondary efficacy endpoints to assess whether chronic palovarotene treatment may suppress the initiation of new flare-ups, in addition to potentially suppressing formation of new HO. However, retinoids, and vitamin A in toxic doses, have

[f] The Review Team refers to Premature Physeal Closure (PPC), wording proposed by the Applicant, as Premature Epiphyseal Closure.

been associated with hyperostosis and calcification of ligaments and tendons; musculoskeletal adverse effects including back pain, arthralgia, myalgia; and rare reports of severe myositis, sometimes associated with strenuous physical activity. Because FOP flare-ups are frequently triggered by local inflammation or trauma and are characterized by ossification of muscle and other soft tissues, there is a theoretical concern for induction or exacerbation of flare-ups by palovarotene.

In the early phase 2 Studies 201/202A/B, flare-ups were treated if they met certain criteria including number of pre-defined symptoms, timing of onset, and consistency with previous symptoms; however, in the later phase 2 Study 202C and phase 3 Study 301, the criteria for initiating flare-up treatment were expanded such that only one symptom (or a traumatic event likely to lead to a flare-up) was required if consistent with previous flare-ups.

During the 12-week period of treatment/follow-up of the index flare-up in Study 201, new symptoms consistent with a flare-up (i.e., condition aggravated AEs) were reported by more subjects randomized to the palovarotene 10/5 mg regimen (13/21, 62%) in comparison to the 5/2.5 mg regimen (2/9, 22%) or placebo (3/10, 30%).[5] In addition, some of the subjects treated with the 10/5 mg regimen experienced more than one new flare-up event within the 12-week observation period, therefore the rate of new events was highest in this treatment group. However, it should be noted that subjects in this 10/5 mg arm reported a greater number of flare-ups in the year prior to enrollment (4.6) compared to the placebo and 5/2.5 mg arms (2.3, 2.0).[5] In subjects receiving the chronic/flare-up regimen in Study 202 Parts B and C, new flare-ups (or condition aggravated AEs) occurred at a higher rate during treatment with the 20/10 mg flare-up regimen compared to treatment with the chronic 5 mg daily dosing.

Flare-ups were reported by a slightly greater proportion of palovarotene-treated versus untreated subjects in Study 301 vs NHS through month 12: 67% in Study 301 and 56% in the NHS, based on at least one relevant symptom.[5] The clinical reviewer agreed with the Applicant that these differences in flare-up rate may be explained, at least in part, by differences in reporting related to study design and conduct. The clinical significance of the number of flare-ups in these studies with regard to disease progression remains unclear, even after additional Applicant analyses per FDA request.

The review team concluded that the rate of flare-ups and the extent of palovarotene dosing were not strong predictors of new HO in these studies. Given these uncertainties, the review team concluded the issue should be further evaluated in the post-marketing setting. A PMR to assess long term safety of palovarotene in pediatric and adult patients enrolled into an observational safety study will be implemented to further asses the risk of HO flares and other risks associated with palovarotene, including PPC, bone fractures, and any pregnancy data available.[5]

5.3. Adverse Effects on Vertebral Bone Mineral Density (BMD), Bone Mineral Content (BMC), and Fractures

Literature reports indicate that retinoids and vitamin A toxicity may cause bone demineralization, osteoporosis, or “slender long bones” in children. Labeling for isotretinoin for the treatment of acne

includes a Warning for negative effects on BMD seen in clinical trials. There is no definitive evidence of an increase in fractures related to retinoid use.

Assessments of BMD and BMC by dual x-ray absorptiometry (DXA) were not included in the palovarotene FOP studies because of the likely confounding effects of extensive HO in overlying soft tissues. However, DXA was conducted on subjects ages 2-14 years with multiple osteochondromas in study PVO-2A-201 under another program. Although treatment duration was limited in most subjects due to early termination of the trial, there were discernable trends of reduced BMC accrual in the palovarotene 5 mg treatment group compared to the 2.5 mg and placebo groups.

The review team concluded that the results of the Biomechanical CT (BCT) analysis suggest that palovarotene treatment may be associated with decreases in vertebral bone strength, BMC and BMD. Prior vertebral fractures appeared to be highly prevalent at baseline in FOP studies given the young age of the population, which may be disease related, and new abnormalities occurred at a higher rate in palovarotene-treated versus untreated patients over 12 months. These effects are consistent with some data involving other retinoids, but do not establish a definitive causal association due to the post hoc nature of the analyses, use of non-validated measures, and differences between the populations of the two non-randomized studies. This issue will be further explored in the planned post-marketing study. The risk of metabolic bone disorders, including that decreased vertebral bone mineral content and decreased bone density may occur, will be communicated in *Warnings and Precautions* to inform healthcare professionals of the risk and to recommend assessing for spinal fractures periodically using radiologic methods.

6. Expected Postmarket Use

The Applicant proposes palovarotene to be distributed via an exclusive United States (U.S.) Specialty Pharmacy to patients or institutions that may also purchase and dispense palovarotene. The expected prescribing population includes endocrinologists, FOP experts, primary care physicians and pediatric specialists. FOP experts and specialists work closely with their patients and caregivers in managing FOP, a rare and debilitating disease. The prescribers are experienced in identifying and managing the risk of teratogenicity associated with other medications; however, they may have variable experience in bone safety monitoring. Off-label use of palovarotene is not expected.

7. Risk Management Activities Proposed by the Applicant

Ipsen proposed labeling with a *Boxed Warning*, contraindication in pregnancy, and precautions for the risks of PPC and teratogenicity and recommended monitoring. Ipsen also proposed a non-REMS risk management plan focused on educating on the risks and pregnancy prevention as well as limited distribution through one exclusive Specialty Pharmacy.[8] Ipsen proposes the Specialty Pharmacy staff will educate (b) (4) about the risk of embryo-fetal toxicity and PPC associated with palovarotene as well as the importance of counseling patients and caregivers on the risks. Ipsen also proposes to (b) (4)

(b) (4)

Ipsen states "in light of the nature, severity, and incidence of PPC, the Applicant has proposed routine labeling as well as additional pharmacovigilance and risk minimization measures."[9] Ipsen states that the "indication statement also contributes to the management of the risk of PPC" and that "the proposed target population was chosen based on the average ages at which pediatric female and male patients achieve approximately 80% of their adult height."[9]

7.1. Other Proposed Risk Management Activities

The Applicant proposed the following risk management activities:

- Voluntary (non-REMS) Risk Management Plan [8]
    - Proposed goal is to educate prescribers, pharmacists, and patients about the benefits and risks of PPC and teratogenicity associated with the use of palovarotene
    - Proposed educational materials consist of a medication guide, a guide for prescribers and pharmacists, a guide for patients and their caregivers, a guide on the importance of avoiding pregnancy, and a caregiver guide for growing pediatric patients
    - Proposed one exclusive Specialty Pharmacy for prescriber education and limited distribution of palovarotene
    - (b) (4)
- Enhanced Pharmacovigilance
    - A voluntary post-approval FOP patient registry to provide further characterization on the risks of PPC and teratogenicity

Reviewer's Comments: *The proposed risk management plan consists of training and limited distribution and dispensing. We do not object to the Applicant providing additional training to stakeholders or using*

restricted distribution for palovarotene. FOP patients are expected to be closely monitored in inpatient institutional settings with consultation of FOP specialist teams. FOP patients in long term care facilities and outpatient settings are followed by FOP experts and specialized teams. We note that the enhanced pharmacovigilance activities proposed by the Applicant are outside of the scope of a REMS program and defer to Division of Pharmacovigilance and/or Epidemiology for review and input.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of palovarotene on the basis of the efficacy and safety information currently available.

Embryo-fetal toxicity and premature epiphyseal closure (PPC) are serious safety concerns for palovarotene.

Embryo-fetal toxicity is a class-wide risk for retinoids with outcomes including irreversible fetal malformations, adverse pregnancy outcomes, and stillbirths. *Boxed Warnings* for pregnancy and teratogenicity are included in the labeling of all approved retinoids (isotretinoin, acitretin, tretinoin, bexarotene). FDA has required a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU) for isotretinoin to ensure the benefits of isotretinoin outweighs the risk of embryo-fetal toxicity that can lead to life-threatening birth defects. Isotretinoin is approved for the treatment severe recalcitrant nodular acne, a condition, that while severe, is not life-threatening. There is significant use of isotretinoin in individuals that can become pregnant. These and other factors have led the FDA to require a REMS for isotretinoin that is designed to ensure that safe use conditions, including pregnancy testing and appropriate contraception, be documented prior to dispensing the drug to the patient. Acitretin, tretinoin, and bexarotene are other systemic retinoids approved without a REMS due to their differences from isotretinoin in various factors considered when determining whether a REMS is necessary. Tretinoin and bexarotene are approved for conditions that may become life-threatening. Acitretin, tretinoin, and bexarotene each have smaller treatment populations with lesser use in individuals that can become pregnant compared to isotretinoin.

Embryo-fetal toxicity consistent with retinoid effects was observed in fetal rat studies of palovarotene. To date, there are no reports of pregnancy or in utero exposure to palovarotene. Pregnancy in patients with FOP is rare due to disease burden resulting in low reproductive fitness. Pregnancy in FOP poses life-threatening risks for both the mother and fetus, including cardio-respiratory complications, thromboembolism, delivery complications, fetal distress, and premature birth. Consensus guidelines[10] for FOP advise of these life-threatening risks and urge serious consideration and family planning before attempting to get pregnant. As a result of the high-risk nature of pregnancy to both mother and fetus, reports of miscarriage are fairly common amongst the small number of FOP pregnancies documented in case reports[11].

Regarding PPC, in general, timing of epiphyseal closure in the pediatric population is extremely variable and premature epiphyseal closure can occur for a variety of reasons including trauma/fracture, septic arthritis, ischemia, malnutrition and use of certain medications. Skeletal abnormalities are a known risk

of the retinoid class; however, the PPC risk for palovarotene occurred sooner and more frequently than expected for the class.

The Applicant proposed enhanced labeling (a boxed warning, contraindication in pregnancy, and precautions) including these risks and recommended monitoring. The Applicant also proposed a non-REMS risk management plan with the goal of educating prescribers, pharmacists, and patients about the benefits and risks associated with the use of palovarotene. The risks of PPC and teratogenicity are the focus of the educational program. The Applicant proposed restricting distribution through one exclusive Specialty Pharmacy for dispensing of palovarotene to patients and the requirement for institutions to receive educational materials prior to receiving a palovarotene shipment. The proposed materials package consists of a medication guide, a guide for prescribers and pharmacists, a guide for patients and their caregivers, a guide on the importance of avoiding pregnancy, and a caregiver guide for growing pediatric patients. [8]

DRM and DGE discussed risk management for Sohonos during the previous review cycle and agreed that a REMS for palovarotene was not necessary to mitigate the risks of embryo-fetal toxicity and premature physeal closure in patients treated for FOP for reasons noted above including the rarity of pregnancy in FOP and that these patients are followed closely by specialists. Although the Applicant, OSE, and OND did not recommend a REMS, Sohonos was discussed at the REMS Oversight Committee (ROC) on August 29, 2022 given that other products in the retinoic acid derivative class are approved with a REMS with Elements to Ensure Safe Use (ETASU) to mitigate the risk of embryo-fetal toxicity. The ROC was in agreement that based on the information available, a REMS for palovarotene is not necessary to mitigate the risks of teratogenicity and premature epiphyseal closure in patients treated for FOP.[12] Additional details are discussed in the DRM review from December 2022.

The review team recommended a complete response (CR) for Sohonos in December 2022 on the basis of incomplete evidence of efficacy of palovarotene for FOP. Deficiencies included reliance on post-hoc analyses to support efficacy, use of an external control group for evaluation of efficacy of the chronic/flare-up dosing regimens, uncertain implications of negative new HO volume data, efficacy of flare-up-only dosing not established in the phase 2 studies, and the chronic/flare-up dosing efficacy was generally not consistent between phase 2 and phase 3 data.[13] Due to a lack of conclusion on the efficacy of palovarotene in FOP patients, a final REMS determination could not be made during the previous review cycle.

The Applicant submitted a Complete Response in February 2023. This submission included additional analyses of efficacy data but did not include additional safety data or new proposals for labeling or the Applicant's non-REMS risk management plan. Due to remaining key efficacy concerns, an Endocrinologic and Metabolic Drugs Advisory Committee meeting was held on June 28, 2023. Issues discussed included appropriateness of reliance on post hoc analyses to support efficacy, use of an external control group (NHS) for evaluation of efficacy of the chronic/flare-up regimen, uncertain clinical implications of negative new HO volume data, and consistency of Phase 2 and Phase 3 whole-body HO data. The Advisory Committee provided a wide range of input regarding evidence of effectiveness of palovarotene in Study 301. Overall, the members agreed that the pre-specified analyses were flawed and

acknowledged the limitations of post-hoc analyses. The Committee also highlighted the lack of correlation between flare-ups and HO development as reassuring and a majority of members agreed the flareup events were less concerning than other safety issues such as PPC in patients under 14 years of age, as well as reduced vertebral bone mineral density and subsequent vertebral fractures. The majority of Committee members voted, "Yes", that the evidence from Study 301 demonstrates that palovarotene is effective in patients with FOP and "Yes", that the benefits of palovarotene outweigh its risks for the treatment of patients diagnosed with FOP. Members that voted "Yes" acknowledged the effectiveness shown by palovarotene was small, but that these benefits can positively impact the quality of life of those affected by FOP. Those members recommended that patient criteria be carefully specified to mitigate palovarotene's safety risks as well as patient/family-provider discussions. They also recommended monitoring bone mineral density, screening for PPC in pediatric patients, and creation of a patient registry to better understand the patient population and HO volumes.

The Agency concluded that the Applicant has demonstrated substantial evidence of the effectiveness of palovarotene to reduce new volume HO in pediatric and adult patients with FOP, but not for the prevention of HO.[14] Given the progressive and debilitating nature of FOP, the Agency has further concluded that the potential benefits of palovarotene in reducing accumulation of new HO in patients with FOP outweighs the known and potential risks associated with palovarotene.[14] The review team maintains that a REMS is not necessary to ensure the benefits outweigh the risks of palovarotene for FOP and recommended labeling including a Boxed Warning, Contraindications, and Warnings and Precautions in the Prescribing Information as well as a Medication Guide to communicate the risks of teratogenicity and PPC and recommended monitoring.

9. Conclusion & Recommendations

Based on the clinical review, the potential benefits outweigh the known and potential risks given the progressive and debilitating nature of FOP and the unmet medical need in this patient population. A REMS is not necessary for palovarotene to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] Lambert, C. Division of Risk Management. Determination and Evaluation of Proposed REMS for Sohonos (palovarotene) NDA 215559. December 21, 2022.

[2] European Medicines Agency. Refusal of the marketing authorization for Sohonos (palovarotene), last updated May 25, 2023. Available from: https://www.ema.europa.eu/en/documents/smop-initial/questions-answers-refusal-marketing-authorisation-sohonos-palovarotene_en.pdf

[3] International Fibrodysplasia Ossificans Progressiva Association (IFOPA). European Commission Does Not Grand Marketing Authorization Approval for Palovarotene as a Treatment for FOP. July 20, 2023. Accessed at: https://www.ifopa.org/european_commission_issues_palovarotene_decision

[4] Cabellon, N. Division of General Endocrinology. Complete Response Letter for Sohonos (palovarotene) NDA 215559. December 23, 2022.

[5] Division of General Endocrinology. DRAFT Integrated Review for Sohonos (palovarotene) NDA 215559, July 24, 2023.

[6] Division of General Endocrinology. FDA Briefing Document for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting for Sohonos (palovarotene) NDA 215559, June 28, 2023.

[7] Division of General Endocrinology. DRAFT Integrated Review for Sohonos (palovarotene) NDA 215559, July 14, 2023.

[8] Ipsen Biopharmaceuticals Inc. Proposed Non-REMS Risk Management Plan for Sohonos (palovarotene) NDA 215559, April 29, 2022.

[9] Ipsen Biopharmaceuticals, Inc. Clinical Overview for Sohonos (palovarotene) NDA 215559, April 29, 2022.

[10] The International Clinical Council on FOP (ICC) & Consultants. The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations, April 2021 updated May 2022.

[11] Muglu et al. Pregnancy in fibrodysplasia ossificans progressiva. Obstet Med. 5: 35-38, March 2012.

[12] Guan, N. CDER Office of the Center Director (OCD). REMS Oversight Committee (ROC) Sohonos (palovarotene) Meeting Minutes, August 29, 2022.

[13] Cabellon, N. Division of General Endocrinology. DRAFT Complete Response Letter, December 14, 2022.

[14] Division of General Endocrinology. DRAFT Integrated Review for Sohonos (palovarotene) NDA 215559, July 17, 2023.

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Division of Risk Management (DRM)
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	215559
PDUFA Goal Date	December 29, 2022
OSE TTT#	2022-586
Reviewer Name(s)	Cristen Lambert, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD
Review Completion Date	December 21, 2022
Subject	Evaluation of Need for a REMS
Established Name	palovarotene
Trade Name	Sohonos
Name of Applicant	Ipsen Biopharmaceuticals, Inc.
Therapeutic Class	Retinoic Acid Derivatives
Formulation(s)	1 mg, 1.5 mg, 2.5 mg, 5 mg, and 10 mg capsules for oral (PO) administration
Dosing Regimen	Adult and pediatric patients 14 years and older Chronic: 5 mg daily Flare: 20 mg daily (weeks 1 to 4); 10 mg daily (weeks 5 to 12). Flare up regiment may be initiated for flare up or high-risk traumatic event likely to cause flare-up. Weight-adjusted dosing proposed for children < 14 years of age

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Sohonos (palovarotene) is necessary to ensure the benefits outweigh its risks. Ipsen Biopharmaceuticals, Inc. submitted a New Drug Application NDA 215559 for Sohonos with the proposed indication for prevention of heterotopic ossifications in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP). The serious risks associated with palovarotene under consideration for a REMS include the following: teratogenicity, premature physeal closure and reduced bone growth. The Applicant did not submit a REMS with this application but proposed a voluntary education program.

DRM is unable to make a final determination if a REMS is needed to ensure the benefits of Sohonos outweigh its risks. DRM and the Division of General Endocrinology presented our recommendation that a REMS is not necessary to mitigate the serious risks of teratogenicity and premature physeal closure at the REMS Oversight Committee (ROC) on August 29, 2022. The ROC agreed with the review team's recommendation at that time; however, the full benefit risk assessment cannot be completed until Ipsen addresses major deficiencies regarding efficacy of Sohonos in FOP by providing additional data and data analyses requested by the Agency.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Sohonos (palovarotene) is necessary to ensure the benefits outweigh its risks. Ipsen Biopharmaceuticals, Inc. submitted a New Drug Application NDA 215559 for Sohonos with a proposed indication for the prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP). This application is under review in the Division of General Endocrinology (DGE). The Applicant did not submit a REMS with this application but proposed a non-REMS voluntary education program[1].

2. Background

2.1. Product Information

Sohonos (palovarotene), a new molecular entity (NME) [a], is a retinoic acid receptor gamma (RARγ) selective agonist (retinoid) proposed for prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva. Sohonos is proposed as an oral capsule. The proposed dosing regimen consists of chronic dosing at 5 mg daily and flare up dosing at 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks.

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

The expected duration of chronic treatment is indefinitely[b] and use is expected in the outpatient community and institutional settings. Sohonos was granted orphan drug, fast track, breakthrough therapy, and rare pediatric disease designations and was approved in Canada in January 2022. It is currently under review by the European Medicines Agency and Swissmedic.

Sohonos is part of the retinoic acid derivatives class which has a broad risk management landscape for teratogenicity. Some medications in this class, like tretinoin and bexarotene, utilize labeling to manage the risk, whereas acitretin has a non-REMS risk management plan, and isotretinoin has a REMS with elements to assure safe use (ETASU). All systemic medications in the retinoic acid derivatives and retinoid-like compounds class of medications contain a Boxed Warning for embryofetal toxicity risk in pregnancy.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 215559 relevant to this review:

- 7/21/2014: Orphan Drug designation granted
- 11/25/2014: Fast Track designation granted
- 7/11/2017: Breakthrough Therapy designation granted
- 2/7/2019: Rare Pediatric Disease designation granted
- 3/31/2021: NDA 215559 submission for prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibro-dysplasia (myositis) ossificans progressiva (FOP) received
- 8/12/2021: Ipsen withdrew submission for internal review of efficacy data
- 4/29/2022: NDA 215559 resubmission for prevention of heterotopic ossification in adults and children (aged 8 years and above for females and 10 years and above for males) with fibro-dysplasia (myositis) ossificans progressiva (FOP) received
- 8/9/2022: A Mid-Cycle meeting was held between the Agency and the Applicant via teleconference.
- 10/19/2022: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for palovarotene.
- 10/21/2022: The Agency informed the applicant via teleconference that the Endocrinologic and Metabolic Drugs Advisory Committee (EDMAC) meeting scheduled for October 31, 2022 was postponed. The Agency requested additional efficacy data and analyses.

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

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

FOP is a progressive, debilitating, lethal disease due to heterotopic ossification (HO). HO consists of heterotopic bone formation in muscles, tendons, and ligaments. Extension of HO across joints leads to progressive and irreversible immobility. Onset begins in childhood in "flare-ups" with localized pain, swelling, and inflammation resulting in new extraskeletal bone at that location. HO can also develop insidiously, without flare-up symptoms. Those afflicted experience cardio-respiratory complications and are often wheelchair-bound by the third decade of life. FOP has a median survival in the mid-50s and has no cure. [c] FOP is an autosomal dominant genetic disease, ultra-rare with only 800-900 cases reported worldwide and 200-300 cases in the US in 2020. The population likely to use palovarotene is very small (less than 1000 patients globally) [d] and includes initiation in children upon diagnosis and adults for chronic and flare-up therapy.

3.2. Description of Current Treatment Options

There are currently no approved treatments for this disease, so there is an unmet medical need. Supportive treatments recommended in consensus guidelines include glucocorticoids, oral and topical non-steroidal anti-inflammatory medications, cyclo-oxygenase-2 inhibitors, mast cell stabilizers, leukotriene inhibitors, and occasionally intravenous bisphosphonates.

4. Discussion of Need for a REMS

Embryo-fetal toxicity and premature physeal closure (PPC) are serious safety concerns for palovarotene.

Embryo-fetal toxicity is a class-wide risk for retinoids with outcomes including irreversible fetal malformations, adverse pregnancy outcomes, and stillbirths. Non-clinical evidence of this risk with palovarotene exposure is apparent in animal model studies. Pregnancy in patients with FOP is rare due to disease burden resulting in low reproductive fitness. Pregnancy in FOP poses life-threatening risks for both the mother and fetus, including cardio-respiratory complications, thromboembolism, delivery complications, fetal distress, and premature birth. Consensus guidelines[2] for FOP advise of these life-threatening risks and urge serious consideration and family planning before attempting to get pregnant. As a result of the high-risk nature of pregnancy to both mother and fetus, reports of miscarriage are fairly common amongst the small number of FOP pregnancies documented in case reports[3].

[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.*

Regarding PPC, in general, timing of physeal closure in the pediatric population is extremely variable and premature physeal closure can occur for a variety of reasons including trauma/fracture, septic arthritis, ischemia, malnutrition and use of certain medications. Skeletal abnormalities are a known risk of the retinoid class; however, the PPC risk for palovarotene occurred sooner and more frequently than expected for the class.

The Applicant proposed a non-REMS risk management plan with the goal of educating prescribers, pharmacists, and patients about the benefits and risks associated with the use of palovarotene. The risks of PPC and teratogenicity are the focus of the educational program. The Applicant also proposed enhanced labeling (a boxed warning, contraindication in pregnancy, and precautions) including these risks and recommended monitoring. The proposed materials package consists of a medication guide, a guide for prescribers and pharmacists, a guide for patients and their caregivers, a guide on the importance of avoiding pregnancy, and a caregiver guide for growing pediatric patients.[1]

DRM and DGE discussed risk management for Sohonos and agreed that a REMS for palovarotene was not necessary to mitigate the risks of embryo-fetal toxicity and premature physeal closure in patients treated for FOP for the following reasons. The FOP population is extremely small and has low reproductive fitness. Pregnancy is high risk for an FOP mother and fetus and FOP consensus guidelines emphasize this risk and appropriate family planning. Regarding the risk of PPC, growing children is a subpopulation of this small patient population. Patients with FOP are followed closely by specialists familiar with the severity of their individual disease and progression. Specialists are expected to have comprehensive and individualized risk-benefit discussions with FOP patients and caregivers upon diagnosis and throughout the course of the disease. DRM and DGE agreed that a REMS is not necessary regardless of the implementation status of the Applicant's voluntary non-REMS risk management plan. During the course of the review, the review team recommended labeling including a Boxed Warning, Contraindications, and Warnings and Precautions in the Prescribing Information as well as a Medication Guide to communicate the risks of teratogenicity and PPC and appropriate monitoring.

Although OSE and OND did not recommend a REMS, Sohonos was discussed at the REMS Oversight Committee (ROC) on August 29, 2022 given that other products in the retinoic acid derivative class are approved with a REMS with Elements to Ensure Safe Use (ETASU) to mitigate the risk of embryofetal toxicity. The ROC was in agreement that based on the information available, a REMS for palovarotene is not necessary to mitigate the risks of teratogenicity and premature physeal closure in patients treated for FOP.[4]

The review team is recommending a complete response (CR) for Sohonos on the basis of incomplete evidence of efficacy of palovarotene for FOP. Deficiencies to be resolved include reliance on post-hoc analyses to support efficacy, use of an external control group for evaluation of efficacy of the chronic/flare-up dosing regimens, uncertain implications of negative new HO volume data, efficacy of flare-up-only dosing not established in the phase 2 studies, and the chronic/flare-up dosing efficacy was generally not consistent between phase 2 and phase 3 data.[5]

5. Conclusion & Recommendations

The review division recommends a complete response on the basis of several efficacy deficiencies. Because efficacy cannot be determined at this time, we are unable to complete the risk-benefit analysis or finalize recommendations for risk management, specifically REMS.

6. Appendices

6.1. References

[1] Ipsen Biopharmaceuticals Inc. Proposed Non-REMS Risk Management Plan, April 29, 2022.

[2] The International Clinical Council on FOP (ICC) & Consultants. The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations, April 2021 updated May 2022.

[3] Muglu et al. Pregnancy in fibrodysplasia ossificans progressiva. Obstet Med. 5: 35-38, March 2012.

[4] Guan, N. CDER Office of the Center Director (OCD). REMS Oversight Committee (ROC) Sohonos (palovarotene) Meeting Minutes, August 29, 2022.

[5] Cabellon, N. Division of General Endocrinology. DRAFT Complete Response Letter, December 14, 2022.

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