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New Drug Evaluation: Palovarotene, oral capsules

Date of Review: December 2025
Generic Name: palovarotene

End Date of Literature Search: 10/01/25
Brand Name (Manufacturer): SOHONOS (Ipsen Biopharmaceuticals, Inc)

Dossier Received: yes

Plain Language Summary:

- Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease where muscles and connective tissue gradually turn into bone.
- Early signs of FOP include malformed big toes, painful "flare-ups" after minor injuries, and loss of mobility.
- There is no cure for FOP; care focuses on avoiding injury and using short steroid courses, such as prednisone, to ease flare-ups.
- Palovarotene (SOHONOS) is a medicine the Food and Drug Administration (FDA) approved to treat FOP in girls at least 8 years old and boys at least 10 years old. It is a medicine that may help slow new bone growth to allow normal repair of muscles and tissues.
- Common side effects of palovarotene are skin dryness and joint aches; serious risks include stunted growth in children and birth defects.
- Providers must explain to the Oregon Health Authority (OHA) why someone needs palovarotene before OHA will pay for it. This process is called prior authorization.

Research Questions:

1. What is the efficacy of palovarotene compared to placebo or currently available treatments for FOP?
2. What is the safety of palovarotene compared to placebo or currently available treatments for FOP?
3. Are there any subgroups (based on age, gender, race, ethnicity, socioeconomic status, comorbidities, disease duration or severity) that would particularly benefit or be harmed by treatment with a specific agent for FOP?

Conclusions:

- Data from one pivotal phase 3, multi-center, open-label, single arm study indicate that at 18 months, patients treated with palovarotene had a statistically significant reduction in new heterotopic ossification (HO) formation compared to the untreated natural history study (NHS) cohort used as a historical control (Mean new HO volume: -10.9 cm^3/year (95% confidence interval [CI] -21.2 to -0.6; p=0.039; quality of evidence (QoE): insufficient).[1] It is unclear whether a 10.9 cm^3/year reduction in new HO volume is clinically meaningful to patients with FOP as the outcome has not been associated with improvements in functional status.
- There is insufficient evidence comparing palovarotene to surgical interventions or agents used in the treatment of FOP such as glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX2) inhibitors as no head-to-head trials have been conducted.

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- Roughly 97% of participants experienced at least one retinoid-associated mucocutaneous adverse event; the most common adverse events (≥10%) were dry skin, lip dryness, arthralgia, pruritis, rash, alopecia, erythema, and headache.[1-3]
- Palovarotene has FDA warnings for increased risk of metabolic bone disorders, psychiatric disorders, and night blindness.[3]
- Palovarotene is contraindicated in pregnancy and has an FDA black-box warning for embryo-fetal toxicity.[3] For females of reproductive potential, prescribers should obtain a negative pregnancy test within one week prior to initiating and periodically during therapy.[3]
- Palovarotene has a boxed warning for premature epiphyseal closure.[3] In growing pediatric patients, assessment of skeletal maturity, hand and wrist bone age, and knee x-rays, is recommended at baseline and then every 6 to 12 months until skeletal maturity or final adult height is reached.[3]

Recommendations:
- Designate palovarotene as non-preferred on the preferred-drug list (PDL).
- Implement prior authorization (PA) criteria for palovarotene to ensure safe and appropriate use for children and adults with FOP (**Appendix 3**).

Background:
Fibrodysplasia ossificans progressiva is a rare genetic disorder where unrestrained, atypical growth of bone takes place in soft tissues (e.g. muscles, ligaments, tendons, etc.) which eventually become ossified.[4] FOP causes significant joint inflammation and pain that eventually results in permanent immobility and greatly reduces patient survival.[4-6] The disease is caused by a gain-of-function mutation in the activin receptor IA (ACVR1) gene that occurs randomly in reproductive cells or during early embryonic development.[7] FOP affects about 1 in 1.6 million newborns worldwide and is not of higher prevalence in any particular race, gender, or geographic region.[8]

Diagnosis of FOP is challenging as clinical presentation is heterogeneous which often leads to a missed or delayed diagnosis.[9,10] Malformed great toes at birth occur in roughly 90% of people with FOP which can be an early sign that further genetic testing is necessary.[9,10] The progressive, postnatal formation of extra-skeletal bone in muscle and soft tissues, or heterotopic ossification (HO), is the hallmark of FOP.[9] Flare-up episodes often occur in the first decade of life following trigger events such as trauma, intramuscular injections, surgery, or viral illness.[9,10] HO degeneration destabilizes joints which affect posture, gait, and mobility.[10] Over half the patients with FOP report progressive mobility constraints regardless of flare-ups.[9,10] Mobility restrictions are one of many complications that lead to a poor prognosis in patients with FOP.[9] FOP may also result in cardiopulmonary issues such as right-side heart failure, respiratory compromise, and pneumonia.[10] HO in the temporomandibular joint region may hamper eating and lead to malnutrition and weight loss.[10] By the age of 30, many patients with FOP are wheelchair bound and require lifelong assistance and rehabilitation with activities of daily living (ADLs).[9,10] The median life expectancy of patients with FOP is around 56 years of age with respiratory complications identified as the most common cause of death.[9,10] The accumulation of HO in patients with FOP is considered to be irreversible.[9,10]

Osteogenesis, or bone formation, is a complex process of progenitor cell differentiation into mineralized bone.[6,9-10] The ACVR1 gene codes for a bone morphogenic protein (BMP) type 1 receptor within the transforming growth factor beta (TGF-β) superfamily.[6,9-10] BMP ligands initiate a signaling cascade to promote tissue growth and repair as well as cell differentiation (e.g. myoblasts to osteoblasts) and proliferation.[6,9-10] However, variants of the ACVR1 gene can disrupt normal BMP signaling and lead to abnormal ACVR1 protein production.[6,9-10] Approximately 97% of the patients with FOS have the ACVR1 gene mutation identified as c.617G>A;R206H.[6,9-10] This mutation causes hyper responsiveness to Activin A and excessive signaling through the SMAD1/5/8 over activation of HO pathways.[6,9-10] Disproportionate receptor activity produces an overgrowth of bone and cartilage observed in patients with FOP.[6,9-10]

Although HO as a result of FOP follows a fairly consistent pattern, comprehensive data concerning the natural disease progression and its morbidity/mortality rates are insufficient.[11] There are specific regions of the body that tend to be early targets for HO.[6,9,10] HO typically begins in the axial/cranial and proximal areas of the body (e.g. neck, spine, shoulders) then radiates to the appendicular/caudal and distal bodily regions (e.g. hips, elbows, knees, wrists, and ankles).[6,9-10] There are no blood tests available to monitor disease activity, however, certain imaging techniques may be employed to assist.[5] Computed tomography (CT) imaging supports the initial diagnosis of FOP and helps monitor changes in fully formed bone.[5] Changes in HO volume may be estimated using low-dose whole body computed tomography (WBCT) and, when performed sequentially, may help detect heterotopic bone volume increases over time.[5] Some studies have converted WBCT observations into an analog scoring scale to assess outcomes of drug interventions.[1,2,4] While HO gradually accumulates over time and generally leads to worsening mobility, it remains unclear whether negative HO volumes are indicative of improvements in function and/or quality of life.[2]

Clinical staging of FOP is important because it allows clinicians to develop appropriate care plans as well as monitor and adjust interventions based on effectiveness.[10,12,13] There are 5 major stages of FOP identified with common features that help distinguish each stage.[10,12,13] The features of each clinical stage include affected body region and flare-up activity, thoracic insufficiency syndrome, functional assessments (ADLs, ambulation, and cumulative analog joint involvement scale CAJIS score), and other complications.[10,12,13] Some patients may present with additional atypical features such as mild cognitive impairment but this phenomenon is rare.[10,12,13] The staging and clinical features of each stage are summarized in **Table 1.**

Table 1. Clinical Stages of FOP (modified)[10,13]

	Clinical Stages				
Features	**Early/Mild**	**Moderate**	**Late/Severe**	**Profound**	**End-Stage**
Body regions affected	Neck, back, upper limbs	Neck, back, upper and lower limbs	Neck, back, upper and lower limbs; jaw	Neck, back, upper and lower limbs; jaw and distal limbs (wrists and ankles)	Ankyloses of most or all joints
Flare-ups	None or limited to scalp, neck or back	Limited to axial regions and upper limbs	Any location	Any location	Any location
Thoracic insufficiency	N/A	Limited chest expansion	Rigid chest wall; no chest expansion; diaphragmatic breathing	Symptomatic thoracic insufficiency syndrome	Symptomatic thoracic insufficiency syndrome
ADLs	No or minimal assistance required due to mild joint limitations or physical delay in developmental milestones	Some assistance required	Assistance needed for most activities	Dependent for all ADLs	Dependent for all ADLs
Ambulation	Unaffected or cannot evaluate due to very young age	Walks; Use wheelchair in extenuating circumstances (e.g. long distances)	Walks with assistive device and/or uses wheelchair	Wheelchair-bound	Mostly bed-bound

Other complications	N/A	N/A	N/A	Pneumonia; pressure ulcers	Recurrent respiratory infections
CAJIS score (range 0 to 30)	≤4	5–18	19–24	≥24	≥28
Abbreviations: ADLs=activities of daily living; CAJIS=cumulative analog joint involvement scale					

The cumulative analog joint involvement scale (CAJIS) and patient-reported mobility assessment (PRMA) are two scales commonly used to evaluate functional status and mobility in patients with FOP.[12,14] The CAJIS is a physician-derived scale that assesses limitation at 15 different body locations such as the jaw, neck, thoracic and lumbar spine, bilateral shoulders, elbows, wrists, hip, knees, and ankles.[12] Patients are given a score of 1 point for each affected location and receive an additional point if the site is functionally ankylosed.[12] The CAJIS scale has a maximum score of 30 points.[12] There is research to suggest that the CAJIS score increases by about 0.5 points per year in the typical patient with FOP.[12] The other common scale used to assess function is the patient-reported mobility assessment (PRMA).[13,14] The anatomical areas assessed with the PRMA are the same as CAJIS in which the patient evaluates whether movement is normal (0 points), partially impaired (1 point), or completely restricted (2 points).[13,14] The scoring for the PRMA ranges from 0 (no limitation) to 30 (severe limitation).[13,14]

Management of FOP is largely supportive as there are no available agents to cure the underlying cause.[13,15] Physical rehabilitation may be employed but must be carefully considered as excessive stress to joints may exacerbate lesions and potentially worsen disease.[13,15] Surgical intervention and invasive biopsies may also cause flare-ups and worsen ossification.[13,15] Flare-ups are usually managed by a short course of high-dose corticosteroids (e.g. prednisone) to provide temporary relief, but it does not completely resolve symptoms.[4,6,13] The anti-inflammatory effects of corticosteroids, specifically glucocorticoids, are most effective within 24 hours of a flare-up.[4,6,13] Non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX2) inhibitors may be used when prednisone is discontinued, but evidence of long-term efficacy in treating the symptoms of patients with FOP is limited.[4,6,13] Imatinib, a tyrosine kinase inhibitor, has been studied for its immunomodulatory and anti-proliferative effects in mast cells with the goal of decreasing flare-up intensity in patients with HO related to FOP.[6,13] With no cure for FOP, guidelines recommend prevention of injury as the most reasonable treatment.[13]

In 2023, the FDA approved palovarotene, a selective gamma retinoic acid receptor (RARγ) agonist, for patients with FOP.[3] Retinoids are derivatives of vitamin A and function in the regulation of tissue and organ development.[16] Progenitor cell differentiation into cartilage is greatly influenced by retinoid signaling.[16] Studies have shown that exogenous active retinoids may inhibit chondrogenesis.[17] Retinoic acid receptor gamma (RARγ) is a nuclear hormone receptor found in chondrogenic cells that regulates ectopic bone development and skeletal formation.[17] RARγ agonists are being explored in the treatment of various diseases such as FOP due to their anti-inflammatory and inhibitory effects on bone/cartilage production.[17,18] By binding to RARγ, it is believed that BMP/ACVR1 signaling may be decreased by blocking SMAD1/5/8, resulting in reduced chondrogenesis and osteocyte differentiation.[6,9,19] Whether RARγ agonists have a significant role in reducing HO volume or lesion activity remains unclear.[2] It is uncertain whether reductions in HO volume, lesions, or inflammation is of clinical benefit since these factors have not been associated with improvements in the functional status of patients with FOP.[2]

Beginning in January 2026, the Oregon Health Authority is proposing that high cost, rarely used medications be carved out of Coordinated Care Organization (CCO) payments and billed directly to fee-for-service (FFS). Medications can be included in this carve-out if they meet the following criteria:

1. Estimated acquisition cost of more than $500,000 per member over a 12-month period
2. Are indicated for rare conditions, and
3. Have few alternatives, as determined by the Oregon Health Authority

Palovarotene (SOHONOS) is a medication proposed to be carved-out of CCO budgets. Over a 1 year period from 10/1/24 to 9/30/25, one member had a diagnosis of fibrodysplasia ossificans progressiva in their medical claims.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

Clinical Efficacy:
SOHONOS (palovarotene) was approved for the treatment of FOP in females at least 8 years old and in males at least 10 years old.[2,3] Approval by the United States FDA was granted on the basis of one pivotal trial (MOVE) which was a global, open label, single arm, phase 3 trial over 18 months in 97 patients at least 4 years of age with FOP (Study PVO-1A-301; NCT03312634; **Table 3**).[2,3]

Enrolled subjects received palovarotene 5 mg once daily for 24 months.[1,2] For flare-ups, palovarotene 20 mg was given once daily for 4 weeks followed by 10 mg once daily for 8 weeks.[1,2] The palovarotene dose was adjusted for skeletally immature patients, defined as patients less than 18 years of age with less than 90% skeletal maturity on hand/wrist x-rays at the time of screening.[1,2] The primary endpoint was the annualized change in new HO volume in nine body regions (chest, neck, shoulder, mid-torso, arms, hips, and legs) as assessed by whole body commuted tomography (WBCT) at months 12, 24, 36 and overall.[1,2] WBCT-imaging observations/measurements were converted into an analog scoring scale.[1,2] Clinicians measured the quantity and diameter of HO spicules or coalescing island/reticular complexes of bone and score accordingly with a 0 up to 6 (higher score = more severe).[2] A score of NE was used if the HO lesion was not evaluable.[2] The key secondary endpoint was the proportion of patients with new HO at month 12.[1,2] Results from the MOVE trial were compared to an external historical control of untreated participants with FOP who were enrolled in the 3-year global, observational, prospective, Natural History Study (NHS Study PVO-1A-001; NCT02322255).[1,2,20] In the NHS, patients used standard treatments such as NSAIDs and corticosteroids.[1,2] Disease progression was tracked via WBCT and other clinical assessments performed at different intervals in the two studies (scheduled every 6 months in study 301 and every 12 months in the NHS).[1,2,20] Study subjects had some notable differences between cohorts at baseline.[1,2] There were a higher proportion of adult (>18 years old) patients in the NHS group than the palovarotene group (roughly 50% vs 30%, respectively), a higher frequency of flare-ups in the past year (2.5 vs 1.4, respectively), and less time since their last flare-up (about 19 vs 25 months, respectively).[1,2,20] The study called for two prespecified formal interim analyses at 12 months and 18 months to assess both efficacy and futility.[1,2]

To measure changes from baseline in HO volume, a square root transformation of HO volume was used to account for the high variability in HO volume observed in the NHS.[1,2] With this method, the rate of growth in HO volume was to be estimated for each incremental change by body region between scans.[1,2] The prespecified futility analysis revealed that the trial was unlikely to meet its primary efficacy endpoints at 12 months.[2] After a study pause to reassess the trial design, endpoint definitions, and statistical methods, the manufacturer proposed that the study endpoint be modified to use annualized absolute change in HO volume rather than percent change in HO volume. This change was deemed necessary to better reflect reductions in HO volume by providing an ability to accommodate negative HO values.[2] The new post-hoc analysis at 18 months demonstrated a statistically significant reduction in new HO formation in patients treated with palovarotene compared to the untreated NHS cohort (Mean new HO volume: -10.9 cm^3/year (95% CI -21.2 to -0.6; p=0.039).[1-3] It is unclear whether a 10.9 cm^3/year reduction in new HO volume across 9 body regions is clinically meaningful to patients with FOP as the measurement has not been conclusively associated with improvements in functional status, health-related quality of life, or frequency of flare ups.[2]

There were limitations noted in the MOVE study. The study was not randomized so there were limits in the ability to control for unknown or undocumented confounding factors such as undocumented disease severity, incidence of injury, undocumented interventions, or changes in standard of care over time. In addition, there were no data on relevant clinical outcomes such as disease progression, function, symptom change, survival, or quality of life. Lastly, the method of analysis was changed post-hoc so there is a significant risk of reporting bias. Palovarotene was approved by Health Canada in January 2022, but was denied authorization for marketing after review by the European Medicines Agency (EMU) in May 2023.[21,22] The EMU cited concerns with post-hoc analysis of data, the clinical relevance of the study's main endpoint, and a lack of efficacy in functional areas.[22]

Clinical Safety:

Palovarotene safety was evaluated in 164 subjects with FOP, including 139 subjects in the indicated population of ages 8 years and above for females and 10 years and above for males.[2,3] Most of the palovarotene safety data comes from patients exposed to the 5 mg chronic dose or the 20/10 mg flare-up for 12 weeks regimen.[2,3] Doses were reduced according to weight in subjects who displayed <90% skeletal maturity.[1-3] Safety was evaluated over part A (24 months) and part B (24-month extension).[1-3] The mean duration of palovarotene exposure was 79 weeks for chronic dosing (N=131 subjects) and 35 weeks for flare-up dosing (N=105 subjects).[2] All patients treated with palovarotene experienced at least 1 adverse event, with the most frequent events summarized in **Table 2**.[3] About 97% of participants experienced at least one retinoid-associated mucocutaneous adverse event such as dry skin, arthralgia, pruritis, rash, and alopecia.[1-3] Serious adverse events occurred in approximately 29% of subjects treated with palovarotene with the most serious being premature epiphyseal closure in patients under 14 years of age (37%).[1-3] Other metabolic bone disorders associated with palovarotene use are decreased bone mineral density and increased fracture risk.[2,3]

Table 2. Summary of Adverse Reactions Reported at greater than 10% Frequency in FOP Subjects 8/10 years and older in Clinical Trials[3]

Adverse Reaction	Chronic Dosing 5 mg N=131 n (%)	Flare-up dosing 20/10 mg N=105 n (%)
Dry skin	80 (61)	60 (57)
Lip dry	62 (47)	40 (38)
Arthralgia	47 (36)	32 (31)
Pruritis	45 (34)	50 (48)
Pain in extremity	38 (29)	29 (28)
Rash	36 (28)	31 (30)
Alopecia	32 (24)	31 (30)
Erythema	25 (19)	34 (32)
Headache	25 (19)	20 (19)
Back pain	22 (17)	12 (11)
Skin exfoliation	20 (15)	30 (29)
Nausea	20 (15)	14 (13)

Musculoskeletal pain	18 (14)	14 (13)
Myalgia	15 (12)	9 (9)
Dry eye	13 (10)	23 (22)
Hypersensitivity	13 (10)	21 (20)
Peripheral edema	12 (9)	20 (19)
Fatigue	7 (5)	12 (11)

Low-dose WBCT revealed decreased bone mineral density and a trend toward increased vertebral fracture.[2,3] Palovarotene has a boxed warning for premature epiphyseal closure and also embryo-fetal toxicity/teratogenicity.[3] It is contraindicated in pregnancy and requires the use of strict contraception in patients of childbearing potential.[3] Night blindness has also been associated with palovarotene use.[3] Other safety risks associated with palovarotene and listed in the retinoid class product labels include psychiatric disorders, pseudotumor cerebri, pancreatitis, hepatotoxicity, hypertriglyceridemia, hearing impairment, inflammatory bowel disease, and hyperostosis.[2,3]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved survival
2) Functional Improvement
3) Use of mobility aids and personal care tools
4) Health related quality of life
5) Serious adverse events (e.g. hearing loss)
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Total volume heterotopic ossification

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Pignolo R, et al. MOVE[1,2] NCT03312634 OL, MC, single-arm, study N=107	1. Chronic Dosing Palovarotene 5 mg once daily (or weight-based equivalent) x 24 months -and- Flare-up Dosing (if needed) Palovarotene 20 mg once daily (or wt-based equivalent) for 4 weeks, followed by palovarotene	Demographics: Male: 1. 53.5% 2. 54.1% Mean age: 1. 15.1 years 2. 17.8 years Race: White 1. 70.7% 2. 73% Black or African American 1. 1% 2. 0% Asian	ITT: 107 PP: 97 Attrition: 19/107 (18%) -per patient request (10.3%) -per sponsor request (1.9%)	Primary Endpoint: Annualized change in new HO volume 1. 9.4 cm^3/year 2. 20.3 cm^3/year MD 10.9 cm^3/year (95% CI, -21.1 to -0.6) Secondary Endpoints: Proportion of patients with new HO at month 12 1. 64% 2. 62%	NA	Important AEs SAEs 29.3% DC due to AE 9.1% Retinoid-associated TEAEs 97% Deaths none	NA	**Risk of Bias (low/high/unclear)**: *Risk of bias unable to be fully assessed as study was open-label and non-randomized. Confounding cannot be ruled out.* Selection Bias: HIGH. No information on patients screened but not included. No randomization or blinding. Baseline characteristics not fully reported; older age and more frequent flare-ups may indicate more severe disease in NHS patients compared to treated subjects; baseline imbalances were not adjusted or controlled. Intervention Bias: HIGH. Open label study design. Radiologists blinded to WBCT scan groups (MOVE study and NHS) but unblinded

	10 mg once daily (or wt-based equivalent) for 8 weeks -Total flare-up treatment duration: 12 weeks Total treatment duration: 48 mo. -Part A = 24 mo. -Part B = 24 mo. 2. Natural History (no treatment) N=101	1. 9.1% 2. 8.1% Unknown 1. 11.1% 2. 14.4% History of flare-ups 1. 100% 2. 97.3% Time since previous flare-up (mos) 1. 24.5 2. 18.9 Mean number of flare-ups past year 1. 1.4 2. 2.5 Mean WBHO volume, cm^{3*} 1. 208.0 2. 389.4 CAJIS score, mean* 1. 9.4 2. 13.1 Number of body regions with HO, mean* 1. 6 2. 6.8 <u>Key Inclusion Criteria</u>: -FOP Dx -R206H mutation • ≥4 years of age • ≥2 acute symptomatic flare-ups in the past 2 years • no flare-up Sx within 4 wks • no prior palovarotene use • abstinence; use two forms of birth control <u>Key Exclusion Criteria</u>: • Weight < 10 kg • Refusal to d/c use of vit A or preps containing vit A • Synthetic oral retinoids last 4 wks • Concurrent Tx with TCN • Hx of allergy or hypersensitivity to retinoids, gelatin, or lactose • Use of strong inhibitors or inducers of cypP450 3A4 activity; or kinase inhibitors, such as imatinib	-due to AE (5.6%)	Mean number of body regions at month 12 with new HO since baseline 1. 1.3 2. 1.5 *Not statistically significant*		Common AEs <u>Skin and SC tissue disorders</u> 97% <u>GI disorders</u> 77.8% <u>Infection</u> 75.8% <u>Musculoskeletal and connective tissue disorders</u> 65.7%		to timing of image collection. Imaging protocols were inconsistent between groups. High variability in radiologist ability to detect HO. <u>Data Collection Bias</u>: UNCLEAR. Eligibility criteria and flare-up management modifications made mid-trial based on interim futility analysis. Changes detected from baseline used post-hoc analysis data. <u>Attrition Bias</u>: UNCLEAR. 17.8% of the 107 enrolled patients discontinued the study before data cutoff for the third interim analysis. <u>Reporting Bias</u>: HIGH Funded by Clementia Pharmaceuticals Inc., which was acquired by Ipsen in April 2019. **Applicability**: <u>Patient</u>: Eligible patients were subject to many exclusions including comorbidities and conditions such as liver dysfunction and hypertriglyceridemia which may not be representative of the OR Medicaid population. <u>Intervention</u>: Doses fixed or based on body weight and flare-up status. <u>Comparator</u>: Natural history study. Untreated patients may have had different disease severity. <u>Outcomes</u>: (Surrogate) - HO volume changes not directly linked to functional improvement. Long term impact on disease progression unknown. <u>Setting</u>: 16 sites in Argentina, Australia, Brazil, Canada, France, Italy, Japan, Spain, Sweden, the United Kingdom, and the United States of America.

		• Amylase or lipase > 2× ULN or a hx of chronic pancreatitis • Elevated AST or ALT > 2.5 × ULN • Fasting TGs > 400 mg/dL • Uncontrolled CVD, hepatic, pulmonary, GI, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease • SI/suicidal behavior previous month						

Abbreviations: AE = adverse event; ALT =alanine transaminase; ARR = absolute risk reduction; AST = aspartate transaminase; CAJIS = cumulative analog joint involvement scale; CI = confidence interval; cm = centimeters; CVD = cardiovascular disease; dL = deciliter; Dx = diagnosis; FDA = food and Drug Administration; GI = gastrointestinal; HO = heterotopic ossification; Hx = history; ITT = intention to treat; MC = multicenter; MD = mean difference; mg = milligrams; mITT = modified intention to treat; mo/mos = month/months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NHS = natural history study; NNT = number needed to treat; OL = open label; OR = Oregon; PP = per protocol; SAE = serious adverse effects; SI = suicidal ideation; Sx = symptoms; TCN = tetracycline; TEAE = treatment emergent adverse effects; TG = triglyceride; Tx = treatment; ULN = upper limit of normal; WBCT = whole body commuted tomography; wks = weeks; wt = weight
*=information from FDA Review

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SOHONOS® safely and effectively. See full prescribing information for SOHONOS.

SOHONOS (palovarotene) capsules, for oral use
Initial U.S. Approval: 2023

WARNING: EMBRYO-FETAL TOXICITY and PREMATURE EPIPHYSEAL CLOSURE IN GROWING PEDIATRIC PATIENTS
See full prescribing information for complete boxed warning.

- **SOHONOS is contraindicated in pregnancy (5.1, 8.1) Because of the risk of teratogenicity and to minimize fetal exposure, SOHONOS is to be administered only if conditions for pregnancy prevention are met (5.1, 8.1)**
- **SOHONOS causes premature epiphyseal closure in growing pediatric patients with FOP, close monitoring is recommended (5.2, 8.4)**

----------INDICATIONS AND USAGE----------
SOHONOS is a retinoid indicated for reduction in the volume of new heterotopic ossification in adults and children aged 8 years and older for females and 10 years and older for males with fibrodysplasia ossificans progressiva (FOP) (1).

----------DOSAGE AND ADMINISTRATION----------
- Obtain a negative pregnancy test in females of reproductive potential before initiation of SOHONOS (2.1)
- Recommended dosage includes a chronic daily dose, which can be increased for flare-up symptoms (2.2)
- For adults and pediatric patients 14 years and older: Recommended dosage is 5 mg once daily, with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment) (2.2)
- For pediatric patients under 14 years: Weight-adjusted for daily and flare-up dosing. Recommended daily dosage range from 2.5 to 5 mg. Refer to Table 1 in Full Prescribing Information for complete pediatric dosing (2.2)
- Take SOHONOS with food preferably at same time each day (2.3).
- Reduce the dose in the event of adverse reactions as appropriate (2.4)
- See Full Prescribing Information for complete dosing instructions (2)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 1, 1.5, 2.5, 5, 10 mg (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4, 5.1, 8.1)
- Hypersensitivity to retinoids or any component of SOHONOS (4, 11)

----------WARNINGS AND PRECAUTIONS----------
- *Premature Epiphyseal Closure:* Premature epiphyseal closure occurred with SOHONOS. Assess baseline skeletal maturity before SOHONOS therapy and monitor linear growth in growing pediatric patients (5.2)
- *Mucocutaneous Adverse Reactions:* Dry skin, lip dry, pruritus, rash, alopecia, erythema, skin exfoliation, and dry eye occurred with SOHONOS. Prevent or treat with skin emollients, sunscreen, artificial tears. Dosage reduction may be required in some patients (2.4, 5.3)
- *Metabolic Bone Disorders:* Decreased vertebral bone mineral content and bone density may occur. Assess for spinal fracture periodically using radiologic method (5.4)
- *Psychiatric Disorders:* Depression, anxiety, mood alterations and suicidal thoughts and behaviors occurred with SOHONOS. Contact healthcare provider if new or worsening symptoms develop in patients treated with SOHONOS (5.5)
- *Night Blindness:* May occur and make driving at night hazardous (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥10%) are dry skin, lip dry, arthralgia, pruritus, pain in extremity, rash, alopecia, erythema, headache, back pain, skin exfoliation, nausea, musculoskeletal pain, myalgia, dry eye, hypersensitivity, peripheral edema, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact IPSEN Biopharmaceuticals, Inc at 1-855-463-5127 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- CYP3A4 Inhibitors: May increase SOHONOS exposure. Avoid concomitant use of strong/moderate CYP3A4 inhibitors. If concomitant use of moderate CYP3A4 inhibitors is unavoidable, reduce the dose of SOHONOS by half (2.5, 7.1)
- CYP3A4 Inducers: May decrease SOHONOS exposure. Avoid concomitant use of strong/moderate CYP3A4 inducers (7.1)
- Vitamin A: May cause additive effects (7.2)
- Tetracyclines: Avoid concomitant use with SOHONOS (7.3)
- Systemic Corticosteroids: No clinically significant drug interaction is expected with concomitant use of SOHONOS (7.4)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm (2.1, 4, 8.1)
- Growing pediatric patients are recommended to undergo baseline assessment of growth and skeletal maturity before starting treatment and continued clinical and radiographic monitoring every 6 to 12 months until patients reach skeletal maturity or final adult height (5.2, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.[2,3]

Parameter	
Mechanism of Action	A RARγ selective agonist. Through binding to RARγ, palovarotene decreases BMP signaling at the ALK2 (ACVR1) receptor and inhibits the phosphorylation of SMAD1/5/8, which reduces ALK2/SMAD-dependent chondrogenesis and osteocyte differentiation resulting in reduced endochondral bone formation.
Oral Bioavailability	Not determined.
Distribution and Protein Binding	Vd=237 L; ~99% protein bound
Elimination	Renal 3.2%; Feces 97.1%; Total Body clearance=19.9 L/hr
Half-Life	8.7 hours
Metabolism	Liver (mostly CYP3A4)

Abbreviations: ACVR1=activin A receptor 1; ALK=activin receptor-like kinase; BMP=bone morphogenetic protein; hr=hour; L=liters; RARγ=retinoic acid receptor gamma; Vd=volume of distribution

Appendix 3: Proposed Prior Authorization Criteria

Palovarotene

Goal(s):

- Promote safe and cost-effective therapy for the treatment of fibrodysplasia ossificans progressiva (FOP).
- Incorporate 2-step review process for drugs on the high-cost drug carve-out list.

Length of Authorization:

- Up to 12 months

Requires PA:

- Palovarotene

Covered Populations: FFS and CCO patients beginning 1/1/26

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Minimum Age

Sex	Age
Female	8 years or older
Male	10 years or older

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by FFS system?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis heterotopic ossification (HO) due to fibrodysplasia ossificans progressiva (FOP)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the diagnosis confirmed by molecular genetic testing indicating the presence of a mutation in the activin receptor IA (ACVR1) gene?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for an FDA-approved age in Table 1?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the drug prescribed by or in consultation with a specialist in FOP? (e.g., endocrinologist, geneticist, pediatric orthopedist, pediatric rheumatologist)	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there a baseline assessment of skeletal maturity including • hand/wrist and knee x-rays • standard growth curves • pubertal staging -AND- Is there documentation that indicates plans to continue monitoring these factors for the duration of therapy until skeletal maturity or adult final height is reached?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Has the provider documented goals of therapy with objective baseline assessment(s) for one or more of the following: • Cumulative analog joint involvement scale (CAJIS) score? • Reduction or improvement in HO symptoms? • Reduction of HO flare-ups from baseline? • Reduction, stabilization, or slowing of the rate of annualized volume of new heterotopic ossification (HO)? Note: these same assessments should be evaluated for continuation of treatment	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the prescriber performed a recent review of the patient's current medication regimen and attests that there is no concomitant use of strong/moderate 3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, etc.), Vitamin A, and tetracyclines per the FDA label?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the patient female and of reproductive age?	**Yes:** Go to #11	**No:** Pass to RPh. Pend; Refer to DMAP for secondary review. Duration: Approvals cover 12 months
11. Is there documentation that prescriber has plans to give pregnancy test within 1 week prior to treatment and monitor periodically during therapy?	**Yes**: Pass to RPh. Pend; Refer to DMAP for secondary review. Duration: Approvals cover 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation that skeletal maturity or adult final height has been reached?	**Yes**: Go to #3	**No:** Go to #2
2. Is there documentation that the patient has been assessed in the last year for skeletal maturity including • hand/wrist and knee x-rays • standard growth curves • pubertal staging?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. If the patient is female and of reproductive age?	**Yes**: Go to #4	**No:** Go to #5
4. Is there documentation that the prescriber has plans to monitor pregnancy status periodically during therapy?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been adherent to therapy as verified by claims history or prescriber attestation?	**Yes:** Go to #6 Note: pharmacy profile may be reviewed to verify >80% adherence	**No:** Pass to RPh. Deny; medical appropriateness
6. Has the prescriber performed a recent review of the patient's current medication regimen and attests that the patient is avoiding concomitant use of strong/moderate 3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, etc.), Vitamin A, and tetracyclines per the FDA label?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
7. Has there been a documented positive response to treatment compared to baseline as evidenced by one or more of the following: • Decreased or stabilized cumulative analog joint involvement scale (CAJIS) score? • Reduction or improvement in HO symptoms? • Reduction of HO flare-ups from baseline? • Reduction, stabilization, or slowing of the rate of annualized volume of new heterotopic ossification (HO)?	**Yes:** Pass to RPh. Pend; Refer to DMAP for secondary review. Duration: Approvals cover 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/25 (DE)
Implementation: 1/1/26