palovarotene (Sohonos™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO297

Description

Palovarotene (Sohonos) is a selective retinoic-acid receptor gamma (RARγ) agonist.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form*	Quantity Limit
palovarotene (Sohonos)	Fibrodysplasia ossificans progressiva (FOP)	1 mg capsule	30 capsules/30 days
		1.5 mg capsule	
		2.5 mg capsule	
		5 mg capsule	
		10 mg capsule	

**See appendix for weight-based dosing for pediatric patients*

Initial Evaluation

I. **Palovarotene (Sohonos)** may be considered medically necessary when the following criteria are met:
   A. Member is 8 years of age or older and female; **OR**
      1. Member is 10 years of age or older and male; **AND**
   B. Documentation of weight within the last three months if under the age of 18 years; **AND**
   C. Medication is prescribed by, or in consultation with, a specialist from the FOP centers of excellence [found here: Research Centers - IFOPA - International Fibrodysplasia Ossificans Progressiva Association]; **AND**
   D. A diagnosis of **fibrodysplasia ossificans progressiva (FOP)** when the following are met:
      1. Documentation of the *ACVR1* mutation; **AND**
      2. Provider attestation that the member has the following clinical features:
         i. Member has bilateral malformation of the big toes [characteristically short and laterally deviated (hallux valgus) and absent or fused joint]; **AND**
         ii. Member has presence of soft tissue ossification

II. Palovarotene (Sohonos) is considered investigational when used for all other conditions, including but not limited to:
   A. Juvenile fibromatosis/desmoid tumors
   B. Progressive osseous heteroplasia (POH)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation that palovarotene (Sohonos) continues to slow or stabilize the progression of disease and treatment provides clinical benefit to the member.

Supporting Evidence

I. Palovarotene (Sohonos) was approved for the reduction in the volume of new heterotrophic ossification (HO) in adults and children aged eight and older for females and ten and older for males with a diagnosis of fibrodysplasia ossificans progressiva (FOP).
II. Due to the rarity and complexity of FOP, diagnosis and treatment should be done by, or in consultation with, a physician who specializes in rare connective tissue diseases. Currently there are four centers that specialize in FOP in the continental United States, and it is recommended that the patients primary care physician consult with one in the path to treatment.
III. FOP is an ultra-rare, genetic connective tissue disorder characterized by severe, progressive development of bone in areas outside of the skeleton (heterotopic ossification; HO), such as the ligaments, tendons, and muscles. The hallmark symptom of FOP is malformation of the big toes at birth; the big toe presents as short, bent, and usually curved inward with a missing joint. Episodes of painful soft tissue swelling, known as flare-ups, begin during the first decade of life, and these are often precipitated by soft tissue injury, intramuscular injections, viral infections, or falls. These flare-ups may lead to extra skeletal HO, which progresses throughout life. Over time, HO eventually leads to stiffness in affected areas, limited movement, and eventual ankylosis (fusion) of affected joints. Many individuals with FOP are confined to a wheelchair by their 30s, requiring lifelong assistance with activities of daily living. The estimated median lifespan of individuals with FOP is 56 years; death is often due to cardiorespiratory failure as a result of severe restriction of the chest wall.
IV. FOP is caused by mutations in the activin A receptor type 1 gene (*ACVR1*), which encodes a bone morphogenetic protein (BMP) type I receptor that is important during the formation of the skeleton in the embryo and the repair of the skeleton following birth. The mutation in the *ACVR1* gene increases BMP signaling, resulting in the formation of heterotopic bone. Approximately 97% of patients with FOP have the same *ACVR1* point mutation (arginine to histidine [R206H]), which is considered classic FOP. A diagnosis of FOP may be confirmed by clinical evaluation, characteristic physical findings, and sequencing of the *ACVR1* gene; historically patients were confirmed by physical findings and diagnosis by elimination, the

ACVR1 gene is more routinely tested for in patients in present day. Palovarotene (Sohonos) helps decrease this BMP signaling, allowing normal tissue repair.

V. Whole body computed tomography (WBCT) can be done to assess and track new HO; however, this is not routinely done in practice outside of the four FOP centers or in a clinical trial. The majority of providers assess patient disease progression based on physical exam and provider or patient assessment tools such as the Fibrodysplasia Ossificans Progressiva Physical Function Questionnaire (FOP-PFQ) or the Cumulative Analogue Joint Involvement Scale (CAJIS). There are several FOP-PFQ depending on age, but those 15 and over are self-reported with 28 items rated 1 to 5 with 5 being able to do the task without help and without use of any assistive device or aid, including a wheelchair. A higher score is more normal functioning, whereas a lower score is worsened disease. CAJIS is a provider scoring of mobility limitations of 15 sites of the body (three axial: neck, jaw, thoraco-lumbar spine), six upper body and six lower body (including each shoulder, wrist, hip, socket, ankle, knee). Each site is assessed for regular movement (score zero), partially impaired (score one), and fully immobile (score two), with a higher score meaning more HO over the body and more immobilization. It is important to note that these tools are newer in development and physicians may use other non-traditional scales or monitoring to track patients, such as ability to fully expand and reach arms out from the body (assessing shoulder and elbow HO).

VI. To date, the 2022 International Clinical Council on FOP lists management as predominantly supportive and focuses on prevention of flare-ups and improving quality of life. These preventive measures include things like preventing falls by installing handrails or wearing headgear, avoiding unnecessary surgeries, and preventing viral illnesses via hand washing and hand sanitizer, as routine immunizations may cause flares. The first line pharmaceutical treatment option is a short course of glucocorticoids taken within 24 hours of trauma and continued over three to four days to decrease HO from flare-up or the use of a nonsteroidal anti-inflammatory drug (NSAID) like ibuprofen; there is no preventive therapy in the guidelines.

VII. Palovarotene (Sohonos) was studied in a single-arm, multicenter, 48-month, Phase 3 clinical trial (MOVE) evaluating the safety and efficacy in those with FOP using an outside control, the National Health Service's (NHS) FOP registry in untreated individuals (n=101); matched as closely as possible to those in the NHS registry by age and gender. Patients (n=99) were four years of age and older, weighing at least 10 kilograms, with a diagnosis of FOP. Patients were allowed in the study without a known *ACVR1* gene mutation, but the primary analysis only included those with the *ACVR1-R206H* gene mutation. All patients received chronic treatment, 5mg once daily, with increased dosing at the time of a flare-up or a substantial high-risk traumatic event likely to lead to a flare-up, 20 mg once daily for four weeks followed by 10 mg once daily for 8 weeks, before returning to maintenance. The primary endpoint was the annualized change in new HO volume versus untreated NHS patients measured by low-dose whole-body computed tomography [WBCT]. At the end of the 48 months, the mean annualized HO in cm^3/year was 9.4 in those treated with palovarotene (Sohonos) and 20.3 in the NHS registry. This was a treatment

difference of 10.9 cm^3/yr (95% CI; -21.9, -0.6 p=0.039) or a reduction of 54% in the new volume with palovarotene (Sohonos) versus untreated NHS registry.

VIII. The overall quality of evidence is considered low. Although, palovarotene (Sohonos) showed a statistically significant change in the annualized new HO volume, this is not a validated endpoint in FOP and the clinical significance of this remains unknown. Additionally, the trial did not show differences between the number of flares the patients in the trial experienced, the number of new HO sites, or quality of life measures in the patients of the study. The true significance of palovarotene (Sohonos) will be learnt in real-world application. Additionally, the International Clinical Council put out a statement in August 2023 acknowledging palovarotene (Sohonos) as the first next steps in disease treatment, but noted caution with use due to the serious adverse effects of the drug and the unknown clinical meaning of the decrease in new HO.

IX. All patients in the trial experienced at least one adverse event (AE). The most commonly reported were mucocutaneous events such as dry skin (68.7%), lip dryness (46.5%), alopecia (34.3%), pruritus (26.3%), and musculoskeletal events such as arthralgia (33.3%). There was also a large number of dose reductions, mainly related to mucocutaneous ADE. The incidence of dose reduction was higher during flare-up treatment (34.3%) than during chronic treatment (5.1%), as was the overall incidence of dose reduction due to other TEAEs (flare-up treatment: 40.0%; chronic treatment: 11.1%). Adverse reactions leading to permanent discontinuation occurred in 11 (8%) palovarotene treated subjects with dry skin being the most common cause in 2 (1%) subjects. The label also includes a warning for embryo-fetal toxicity and premature epiphyseal closure in growing pediatric patients. The latter occurred in 21 (15%) of the 8 to 10 year or older palovarotene (Sohonos) population.

Investigational or Not Medically Necessary Uses

I. Palovarotene (Sohonos) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Juvenile fibromatosis/desmoid tumors
   B. Progressive osseous heteroplasia (POH)

Appendix

I. Once daily dosing recommendation for pediatric patients aged 8 to 13 years for females and 10 to 13 for males:

Weight	Daily Dosage	Week 1 to 4 Flare-up Dosage	Week 5 to 12 Flare-up Dosage
10 kg to 19.9 kg	2.5 mg	10 mg	5 mg
20 kg to 39.9 kg	3 mg	12.5 mg	6 mg
40 kg to 59.9 kg	4 mg	15 mg	7.5 mg
≥ 60 kg	5 mg	20 mg	10 mg

References

1. Sohonos. Package Insert. Ipsen Biopharmaceuticals, Inc. Cambridge, MA. August 2023.
2. International Clinical Council on FOP (ICC) and Consultants. The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations. 2022. Accessed October 10, 2022. ICC_guidelines-updated-May-2022.pdf
3. Pignolo RJ, Hsiao EC, Al Mukaddam M, et al. Reduction of New Heterotopic Ossification (HO) in the Open-Label, Phase 3 MOVE Trial of Palovarotene for Fibrodysplasia Ossificans Progressiva (FOP). *J Bone Miner Res*. 2023;38(3):381-394. doi:10.1002/jbmr.4762

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2024