Original Effective Date: 03/07/2024
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Policy Number: C27173-A

Sohonos (palovarotene)

PRODUCTS AFFECTED

Sohonos (palovarotene)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Fibrodysplasia ossificans progressiva (FOP)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. FIBRODYSPLASIA OSSIFICANS PROGRESSIVA:
   1. Documented diagnosis of fibrodysplasia ossificans progressiva (FOP) or myositis ossificans progressiva
      AND

2. Documentation diagnosis has been confirmed by genetic testing that shows mutation of ACVR1 R206H [DOCUMENTATION REQUIRED]
   AND
3. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal.
   AND
4. Prescriber attests a recent review of member's current medication has been completed and member is avoiding concomitant use of strong/moderate 3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, etc.), Vitamin A, and tetracyclines per the FDA label.
   AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Sohonos (palovarotene) include: pregnancy, and hypersensitivity to retinoids or any component of Sohonos]

CONTINUATION OF THERAPY:

A. FIBRODYSPLASIA OSSIFICANS PROGRESSIVA:
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation.
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity.
   AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms as per the treating physician.
   AND
4. Prescriber attests a recent review of member's current medication has been completed and member is avoiding concomitant use of strong/moderate 3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, etc.), Vitamin A, and tetracyclines per the FDA label.

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified orthopedic specialist, rheumatologist, geneticist, or physician who specializes in rare connective tissue disorders [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

8 years and older for females
10 years and older for males

QUANTITY:

Adults and pediatrics 14 years and older:
Daily dose: 5mg daily
Flare-up dose: 20mg daily for 4 weeks, followed by 10mg daily for 8 weeks, then return to 5mg daily dosing.

Pediatric patients less than 14 years of age:
Daily dose: Weight based on 2.5 to 5mg daily.

Flare-up dose: Weight based on 10 to 20mg for 4 weeks, followed by 5 to 10mg for 8 weeks, then return to 2.5 to 5mg daily dosing.

Maximum Quantity Limits – See Appendix

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Retinoic Acid Receptor Gamma Selective Agonists

FDA-APPROVED USES:
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)

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

Recommended Dosage for Adults and Pediatric Patients 14 Years and Older

- Daily Dose: The recommended SOHONOS daily dosage for adults and pediatric patients 14 years and older is 5 mg daily. Stop daily dosing when flare-up dosing begins.
- Flare-up Dose:
  - o the recommended SOHONOS flare-up dosage for adults and pediatric patients 14 years and older is 20 mg daily for 4 weeks, followed by 10 mg daily for 8 weeks (for a total of 12 weeks of flare-up treatment), even if symptoms resolve earlier, then return to daily dosing of 5 mg.
  - o If during the course of flare-up treatment, the patient experiences marked worsening of the original flare-up site or another flare-up at a new location, restart the 12-week flare-up dosing at 20 mg daily.
  - o for flare-up symptoms that have not resolved at the end of the 12-week period, the 10 mg daily dosage may be extended in 4-week intervals and continued until the flare-up symptoms resolve. If new flare-up symptoms occur after the 5 mg daily dosing is resumed, flare-up dosing may be restarted.

Recommended Dosage for Pediatric Patients Aged 8 to 13 Years for Females and Aged 10 to 13 Years for Males

- Daily Dose: The recommended SOHONOS daily dosage for patients under 14 years of age is weight-based ranging from 2.5 mg to 5 mg daily (see Table). Stop daily dosing when flare-up dosing begins.
- Flare-up Dose:
  - o the recommended flare-up SOHONOS dosage for patients under 14 years of age is weight-based (see Table). Administer the initial flare-up dosage once daily for 4 weeks, then administer the lower flare-up dosage once daily for 8 weeks (for a total of 12 weeks of flare-up treatment), even if symptoms resolve earlier, then return to daily dosing (see Table 1).

- o If during the course of flare-up treatment, the patient experiences marked worsening of the original flare-up site or another flare-up at a new location, restart the 12-week flare-up dosing with the Week 1 to 4 dose.
- o for flare-up symptoms that have not resolved at the end of the 12-week period, the Week 5 to 12 flare-up dose may be extended in 4-week intervals and continued until the flare-up symptoms resolve. If new flare-up symptoms occur after daily dosing is resumed, flare-up dosing may be restarted.

Recommended Sohonos Weight-Based Dosage for Pediatric Patients Aged 8 to 13 Years for Females and 10 to 13 Years for Males (once daily)

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

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Fibrodysplasia Ossificans Progressiva (FOP), or myositis ossificans progressiva, is an ultra-rare, genetic connective tissue disorder characterized by severe, progressive development of bone in areas outside of the skeleton, such as the ligaments, tendons, and muscles (heterotopic ossification; HO). The hallmark symptom of FOP is malformation of the big toes at birth. Episodes of painful soft tissue swelling (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 fusion of affected joints. 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.

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. Most cases of FOP occur sporadically; however, in a small number of cases, the condition is inherited in an autosomal dominant pattern. The diagnosis of FOP may be confirmed by clinical evaluation, characteristic physical findings, and sequencing of the ACVR1 gene.

FOP is estimated to affect 900 people globally and there is no cure. Standard of care includes palliative care, symptom management, and flare management and prevention with NSAIDs, corticosteroids, and avoiding trauma to the muscles and tissues.

Sohonos is an oral, selective retinoic acid receptor gamma (RARγ) agonist that inhibits the BMP/activin receptor-like kinase-2 (ALK2) downstream signaling pathway, resulting in reduced extrachondral bone formation. The approval of Sohonos was based on the single-arm, open-label, Phase 3 MOVE trial (NCT03312634), which included patients with FOP 4 years of age and older. Efficacy data from patients enrolled in the MOVE trial were compared with data from FOP Natural History Study (NHS) participants who were untreated. The NHS study was a prospective, longitudinal, 36-month study (NCT02322255).

The MOVE trial failed to meet the prespecified primary efficacy analysis, however, the NDA submission included 18-month post hoc analyses from the MOVE trial that showed evidence of benefit for Sohonos in FOP. The 12-month interim analysis met futility criteria. There was no significant difference in the primary endpoint of annualized new HO, however an independent data monitoring committee recommended trial continuation. The 18-month post hoc analysis showed the mean annualized new HO volume was 9.4 cm3/year in patients receiving Sohonos and 20.3 cm3/year in untreated patients in the NHS study based on a linear mixed effect model. The treatment effect was about 10.9 cm3/year (95% CI: −21.2 cm3/year, −0.6 cm3/year). The mean annualized new HO volume was 54% lower in the MOVE trial versus the NHS study. There was no difference in the secondary endpoint of proportion of patient with any new HO (64% in treated patients; 62% in untreated patients) at month 12. Also, there was no difference in the mean number of body regions with new HO since baseline at month 12.

The label comes with a black box warning for embryo-fetal toxicity and premature epiphyseal closure in growing pediatric patients. Females of reproductive potential should be advised to use an effective method of contraception at least 1 month prior to treatment, during treatment, and for 1 month after the last dose. Baseline skeletal maturity should be assessed before Sohonos therapy and linear growth should be monitored in growing pediatric patients. Premature epiphyseal closure was identified in 27% of patients who were less than 18 years of age at enrollment. The safety of Sohonos was evaluated in clinical studies that included 164 patients with FOP. The most common adverse reactions (incidence ≥10%) were 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.
Serious adverse reactions occurred in 21 (15%) patients treated with Sohonos with the most common serious adverse reaction being premature epiphyseal closure. Adverse reactions leading to permanent discontinuation occurred in 11 (8%) patients treated with Sohonos, with dry skin being the most common, occurring in 2 (1%) patients.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Sohonos (palovarotene) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Sohonos (palovarotene) include: pregnancy, hypersensitivity to retinoids or any component of Sohonos.

OTHER SPECIAL CONSIDERATIONS:
Sohonos (palovarotene) has a BLACK BOX WARNING for embryo-fetal toxicity and premature epiphyseal closure in growing pediatric patients. Sohonos is contraindicated in pregnancy. Because of the risk of teratogenicity and to minimize fetal exposure, Sohonos is to be administered only if conditions for pregnancy prevention are met. Sohonos causes premature epiphyseal closure in growing pediatric patients with FOP, close monitoring is recommended.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Sohonos CAPS 1MG
Sohonos CAPS 1.5MG
Sohonos CAPS 2.5MG
Sohonos CAPS 5MG
Sohonos CAPS 10MG

REFERENCES

1. Sohonos (palovarotene) capsules, for oral use [prescribing information]. Cambridge, MA: Ipsen Biopharmaceuticals, Inc.; August 2023.
2. Kaplan FS, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Proc Intl Clin Council FOP 2: 1-127, 2022.
3. National Organization for Rara Disorders. (2023, August 21). Fibrodysplasia Ossificans Progressiva - NORD (National Organization for Rare Disorders). Retrieved November 7, 2023, from NORD (National Organization for Rare Disorders) website: https://rarediseases.org/rare-diseases/fibrodysplasia-ossificans-progressiva/
4. Pignolo, R. J., Baujat, G., Brown, M. A., De Cunto, C., Hsiao, E. C., Keen, R., … Kaplan, F. S. (2022). The natural history of fibrodysplasia ossificans progressiva: A prospective, global 36-month study. Genetics in Medicine: Official Journal of the American College of Medical Genetics, 24(12), 2422–2433. https://doi.org/10.1016/j.gim.2022.08.013

SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q1 2024