Medication Assessment for palovarotene (Sohonos®)

Regulatory Pathway

- Traditional Food and Drug Administration (FDA) approval: 08/16/2023

Product Information

- Palovarotene (Sohonos) is a retinoid, FDA approved for the treatment of reduction in the volume of new heterotropic ossification in adults and children aged eight years and older for females and 10 years and older for males with fibrodysplasia ossificans progressiva (FOP).
- Palovarotene (Sohonos) is an orally administered capsule given once daily.

Background

- Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare connective tissue disorder where muscle tissue and connective tissue such as tendons and ligaments are ossified (gradually replaced by bone), forming bone outside of the skeleton thereby limiting movement. Generally, starts in early childhood starting with the neck and shoulders and proceeding down the body into the limbs.
- Patients usually appear normal at birth except for bilateral malformation of the great toes, which are characteristically short and laterally deviated. The first metatarsals are malformed, and the first toes have an absent or fused interphalangeal joint.
- Prevalnce is approximately 1 in 2 million
- No sex, racial, ethnic or geographic predisposition.

Place in Therapy / Guidelines

- Palovarotene (Sohonos) is the first retinoid FDA approved to inhibit chondrogenesis, which is responsible or heterotrophic ossification formation.
- Management of FOP is predominately supportive and focuses on prevention of flare-ups. Palovarotene is recommended to still be used in combination with standard-of-care therapies as recommended by the FOP Treatment Guidelines.
- International Fibrodysplasia Ossificans Progressiva Association treatment guidelines (updated July 2024) recommend the following:
    - A brief four day course of high dose corticosteroids begun within 24 hours of a flare up may help reduce intense inflammation and tissue edema seen in the early stages of the disease
        - Prednisone 2 mg/kg/day (up to 100 mg)
    - Non-steroid anti-inflammatory medication of COX-2 inhibitor (in conjunction with leukotriene inhibitor) may be used symptomatically for the duration of the flare-up
    - Topical NSAIDs can have potential advantages for lower initial rates of systemic absorption, reduced systemic adverse effects and direct application to the area of pain
        - Compounded ketoprofen gel (5%) with upward titration to 15-20%. Pediatric use typically does not exceed 10% gel.
        - Other agents include lidocaine patch, gel, cream or spray
        - Capsaicin cream

Clinical Review

- The approval of palovarotene (Sohonos) was based on the single-arm, open-label, Phase 3 MOVE trial which included patients with FOP four years of age and older. Only patients with ACVr1 R206H pathogenic variant were included in the efficacy analysis. All patients in the pivotal study received

palovarotene daily dosing with temporary dose increases for flare-ups (dosing based on age/weight). A natural history study was used as an external cohort.

- The primary efficacy endpoint was the annualized change in the new heterotopic ossification volume from baseline to Month 18 assessed by low-dose, whole body CT imaging. The mean annualized new heterotopic ossification was 0.4 cm^3/year in patients receiving the chronic/flare-up palovarotene treatment and 20.3 cm^3/year in untreated patients in the natural history study. The treatment effect was about 10.9 cm^3/year (95% CI: -21.2, -0.6).

Safety

- The most common adverse reactions (≥10%) with palovarotene were dry skin, arthralgia, puritis, pain in extremity, rash, alopecia, erythema, headache, back pain, skin exfoliation, nausea, musculoskeletal pain, myalgia, dry eye, hypersensitivity, peripheral edema, and fatigue.
- Contraindications to palovarotene include pregnancy and hypersensitivity to retinoids or any component of palovarotene. Warnings and precautions include premature epiphyseal closure, mucocutaneous adverse reactions, metabolic bone disorders, psychiatric disorders, and night blindness.

Dosing

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:
    - 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.
    - 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.
    - 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 flareup 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).
    - 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.
    - For flare-up symptoms that have not resolved at the end of the 12-week period, the Week 5 to 12 flareup 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

Utilization of palovarotene (Sohonos): Calendar Year 2023

No utilization in FFS and MCO

Apple Health Preferred Drug List (AHDPL) Recommendation

Line of Business	AHPDL Recommendation	Utilization Management
Apple Heath (WA Medicaid)	Currently Preferred	PA

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 3: 1-159, 2024

Date Created: 11/27/2024