Oscar Clinical Guideline: Sohonos (palovarotene) (PG183, Ver. 3)

Sohonos (palovarotene)

Summary

Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, severely disabling genetic disorder characterized by progressive extraskeletal bone formation in muscles, tendons and other soft tissues, caused by a mutation in the ACVR1/ALK2 gene encoding for a bone morphogenetic protein receptor. FOP can result in painful episodes ("flare-ups") of swelling and heterotopic ossification. Long-term, FOP can cause immobility, weight loss, and thoracic insufficiency syndrome. Therapeutic approaches are primarily based on supportive care, prevention of flare-ups, and lifestyle modifications (e.g., avoiding activities with a high-risk of falls, handhold installations, avoiding IM injections of vaccines).

Sohonos (palovarotene), approved in 2023, is an oral retinoid approved by the FDA for the reduction in volume of new heterotopic ossification (HO) in those aged 8 years and older for females and 10 years and older for males with FOP.

Sohonos is the first FDA-approved therapy for FOP. However, the current clinical evidence is insufficient to conclude that Sohonos provides clinically meaningful benefits that outweigh its risks. The efficacy data have significant limitations due to reliance on post-hoc analyses, lack of a concurrent control group, and unanswered questions about the clinical meaningfulness of the primary endpoint. Additional randomized controlled trials are needed to establish substantial evidence of efficacy and support Sohonos as medically necessary for FOP. Until more conclusive data are available, the Plan considers Sohonos to be unproven for FOP.

Sohonos (palovarotene) has a boxed warning for the risk of embryo-fetal toxicity and premature epiphyseal closure in growing pediatric individuals. Sohonos (palovarotene) is contraindicated in pregnancy due to the risk of teratogenicity and should only be administered in those who have the conditions in place to prevent pregnancy to minimize fetal exposure. Sohonos (palovarotene) may cause premature epiphyseal closure in pediatrics with open growth plates and FOP, close monitoring is recommended.

Definitions

"Fibrodysplasia ossificans progressiva (FOP)" is an ultra-rare autosomal dominant genetic disorder characterized by progressive heterotopic ossification of the skeletal muscle and connective tissue.

"Heterotopic ossification (HO)" refers to ectopic bone formations in extraskeletal tissue, typically within skeletal muscle and connective tissue. HO leads to progressive loss of mobility in patients with FOP.

"Retinoid" refers to a compound structurally related to vitamin A. Retinoids bind to and activate nuclear retinoic acid receptors involved in cellular differentiation and proliferation.

"Activin A receptor, type 1 (ACVR1)" is a gene which when mutated is the underlying genetic cause of FOP.

"Concurrent control" refers to a control group recruited and evaluated concurrently alongside the treatment group within the same study. Use of a concurrent control helps minimize confounding and improves comparability between groups.

"Post-hoc analysis" refers to statistical analysis conducted after the conclusion of a study that was not pre-specified in the original study protocol or statistical analysis plan. Post-hoc analyses are generally considered exploratory in nature.

"[s]" indicates state mandates may apply.

Policy Statement on Sohonos (palovarotene) Efficacy Information[s]

Based on review of the available clinical data, there is insufficient evidence to indicate that Sohonos (palovarotene) provides clinically meaningful benefits that outweigh the potential risks for patients with fibrodysplasia ossificans progressiva (FOP). The plan considers Sohonos (palovarotene) to be unproven and therefore not medically necessary for FOP at this time, as evidence of efficacy has not been established.

The current efficacy data for Sohonos in FOP have significant limitations:

- The phase 3 MOVE trial (NCT03312634), a single-arm, open-label natural history study, failed to meet its prespecified primary endpoint of annualized volume of new HO. The efficacy analysis relied entirely on post-hoc analyses, which are generally considered hypothesis-generating and not appropriate for definitive conclusions. The mean number of body regions with new HO at 12 months, and changes in functional endpoints at 18 months were not significantly different compared to the usual care group. No significant benefits were seen in range of motion, or quality of life.
- The MOVE trial lacked a concurrent control group. Efficacy comparisons were made to an external natural history study (NCT02322255), introducing potential bias. There are concerns about comparability of the populations and unmeasured confounding factors.
- The clinical meaningfulness of the primary endpoint (change in HO volume) is unclear. Data are lacking to show that small changes in HO volume translate to tangible clinical improvements for patients.
- Consistency between the phase 2 (NCT02190747, PVO-1A-201) and phase 3 trials is lacking regarding the primary endpoint. The phase 2 data do not provide robust confirmatory evidence. At weeks 6 (primary outcome measure) and 12 (secondary outcome measure), the proportion of responders (defined as no or minimal new HO flare-up body regions as determined by radiographic evidence) did not differ between Sohonos (palovarotene) and placebo.
- In a post-hoc analysis of phase 3 MOVE trial, at 18 months it was found a 99.4% probability of reduced new HO formation in those on Sohonos (palovarotene) compared to the NHS participants - conferring a 60% lower annualized new HO volume rate. This study also found reduced bone mineral density and a high risk of premature epiphyseal closure (36.8% in those < 14 years of age).

On-going studies (pending results):

- A roll-over study of the original parent studies noted above (NCT05027802) has been completed but results have not yet been published.
- In a phase 2, multicenter, open-label extension study of PVO-1A-201 (NCT02279095), evaluated the safety and efficacy of Sohonos (palovarotene). While completed, the study data has yet to be published.

- An international observational registry study has begun recruiting to evaluate the long-term safety and efficacy of Sohonos (palovarotene) in those with FOP (NCT06089616).

Safety Considerations

- In the MOVE trial, all participants (n=99) experienced at least one treatment emergent adverse event (TEAE), 97% reported at least one retinoid-related TEAE. Most TEAEs were moderate (45.5%), and 22.2% were severe. The most common TEAE were dry skin (68.7%), lip dryness (46.5%), alopecia (34.3%), drug eruption (28.3%), pruritus (26.3%), musculoskeletal and connective tissue disorders (65.7%), infections and infestations (75.8%).
- A major concern, and a boxed warning for Sohonos (palovarotene) includes the risk of premature epiphyseal fusion, which occurred in 18.2% of those in the MOVE study. It is recommended that skeletal maturity be assessed before initiation of Sohonos (palovarotene). Linear growth in pediatrics should be monitored as well. Pediatrics administered Sohonos (palovarotene) should be assessed using skeletal maturity, linear growth models and radiographic monitoring every 6-12 months until the individual reaches their skeletal maturity or final adult height.
- There is a risk for loss of bone mineral density with the use of Sohonos (palovarotene), fall risk should be evaluated and vertebral fractures should be assessed as needed by the provider.
- Other risk factors to assess include: night blindness and psychiatric disorders such as depression, anxiety, and suicidal thoughts or behavior.
- There is a boxed warning for the risk of teratogenicity, Sohonos (palovarotene) may cause fetal harm. Sohonos (palovarotene) should only be administered in those who have the conditions in place to prevent pregnancy to minimize fetal exposure

Guidelines/Position Statements:

- The International Clinical Council on FOP (ICCFOP) recommends the following regarding Sohonos (palovarotene):
    - "If a patient with FOP considers palovarotene, the potential benefits and risks, as detailed in the package insert, by the MOVE trial publication, and in subsequent publications, must be discussed in detail with the patient and the patient's medical team.
    - Additional risks should be explicitly discussed, including potential effects on bone health (loss of bone mass), skin/mucosal dryness and complications, potential for eye complications, and the risk of fetal malformations in pregnancy. The ICC supports continued close long-term follow-up of these potential complications.
    - A long term, detailed study of the safety and efficacy of palovarotene should be pursued, such as through a registry or formalized long-term study.
    - Standard-of-care therapies, as recommended by the FOP Treatment Guidelines (available at ICCFOP.org), should still be used in combination with palovarotene as appropriate, and with guidance from the patient's medical team.
    - Worldwide affordable access to palovarotene should be facilitated, including ensuring reasonable cost for therapy.
    - Careful monitoring of patients to prevent pregnancy while on palovarotene should be required, due to the known teratogenicity of the retinoid class of medications.

    - Careful education of potential drug interactions, including with antibiotics like tetracycline or doxycycline, should be required.
    - Patients should not use non-pharmaceutical grade palovarotene."
- The ICCFOP does not make an explicit recommendation for or against the use of Sohonos (palovarotene). They note that while members of the ICC believe there are benefits to Sohonos (palovarotene), many still have concerns about the approval process and use - including the risk of premature epiphyseal closure in pediatrics, drug-interactions, lack of long-term safety data and patient participation in future clinical trials.

Due to the limited and inconsistent efficacy data, unanswered questions remain regarding whether Sohonos (palovarotene) provides any clinically meaningful therapeutic effect for FOP. Additional randomized controlled trials with longer follow-up are needed to establish substantial evidence of efficacy.

Medical Necessity Criteria for Sohonos (palovarotene)[s]

Due to insufficient efficacy data, potential safety risks, and the absence of robust clinical efficacy data, the Plan has determined that it does not have established medical necessity criteria for coverage of Sohonos at this time.

Given the current evidence and concerns, Sohonos (palovarotene) does not meet the Plan's criteria for proven efficacy and medical necessity for FOP. The Plan remains committed to providing coverage for treatments that demonstrate solid evidence of both safety and effectiveness. We will continue to monitor the evolving clinical data for Sohonos and will reassess our position as more conclusive information becomes available. Until then, we encourage our members to explore other proven treatment options with their healthcare providers.

Experimental or Investigational or Unproven / Not Medically Necessary[s]

Sohonos (palovarotene) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, unproven, or not medically necessary.

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