Palovarotene (Sohonos\textsuperscript{TM}) was approved on August 17\textsuperscript{th}, 2023, by the U.S. Food and Drug Administration for the treatment of fibrodysplasia ossificans progressiva (FOP) in girls ≥ 8 years old and in boys ≥ 10 years old and adults.

FOP is an incapacitating serious disease that affects connective tissue. It is characterized by early onset progressive heterotopic ossification, either spontaneously or in response to trauma, with painful flares and is due to variants in \textit{ACVR1} \cite{1}. The progressive extra-osseous bone formation is debilitating and can significantly impair mobility and function of the affected areas, leading to shortened life expectancy, caused by cardiorespiratory failure from thoracic insufficiency syndrome. Until this approval, no specific treatments have been available.

Palovarotene is a selective gamma retinoic acid receptor (RAR\textgamma) agonist. RAR\textgamma is a nuclear hormone receptor expressed in chondrogenic cells and chondrocytes and an important regulator of skeletal development and ectopic bone formation in the retinoid signaling pathway. RAR\textgamma agonists potently downregulate the BMP signaling pathway and activate the retinoid signaling pathway, inhibiting chondrogenesis and reducing new abnormal bone formation in FOP \cite{2}.

The pivotal trial that led to Sohonos approval, MOVE phase 3, was a single-arm, open-label trial (NCT03312634) that assessed efficacy and safety of palovarotene in 97 patients with FOP for 18 months \cite{2}. Findings were compared with FOP-untreated participants (n = 101) followed in a natural history study (NHS; NCT02322255). Patients aged ≥4 years [mean 15.1 (SD 9.6) years with range 4 – 61 years] received palovarotene 5 mg once daily with increases in dose during flare-up phases. The flare-up treatment included palovarotene 20 mg daily for 4 weeks, followed by 10 mg daily for 8 weeks, with the option to extend for 4-week intervals at the discretion of the investigator if the flare-up was ongoing, until symptoms resolved \cite{2, 4}. For skeletally immature participants the does were weight-adjusted. The primary endpoint was annualized change in new heterotopic ossification (HO) volume compared to the NHS participants, as assessed by low-dose whole-body computed tomography (WBCT). The study results demonstrated palovarotene effectively reduced new annualized HO volume compared with the untreated NHS cohort [60% reduction in mean annualized new HO volume, and the treatment effect of about 10.9 cm\textsuperscript{3}/year (-21.2, -0.6, p = 0.039) in volume difference] \cite{2, 4}.

Over 97% of palovarotene-treated patients reported retinoid-associated adverse effects with high risk for premature physeal closure/epiphyseal disorder (36.8%) in skeletally immature patients younger than 14 years of age. In addition, WBCT demonstrated decreased vertebral bone mineral density and increased vertebral fracture risk. Other adverse effects include psychiatric disorders, night blindness, mucocutaneous symptoms such as dry skin, lip dryness, alopecia, drug eruption, rash, pruritus, and arthralgia (refer to the FDA label for more information) \cite{2} \cite{4}. Palovarotene has an FDA-issued black-box warning regarding teratogenicity and premature epiphyseal closure \cite{4}. Clinicians must ensure
pregnancy prevention in child-bearing age patients and perform close monitoring of growth and skeletal maturation in growing patients. Skeletal maturity, hand and wrist bone age, and knee x-rays, should be done at baseline and then every 6 – 12 months until skeletal maturity or final adult height [4]. Sohonos is contraindicated in pregnancy due to the risk of teratogenicity and in cases of hypersensitivity.

Sohonos is available in 1, 1.5, 2.5, 5, and 10 mg capsules [4]. The suggested daily oral dose is 5 mg or the weight-based equivalent for pediatric patients under 14 years of age, taken after a full meal at a consistent time each day [4]. The dose can be modified/increased for flare-up symptoms [2,4].

References:

4. FDA label. 2023 label (fda.gov).

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