Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Sohonos®
Common Name: palovarotene
PDL Category: Endocrine Metabolic Agents

Pharmacology/Usage: Palovarotene, the active ingredient of Sohonos®, is an orally bioavailable retinoid that acts as a retinoic acid receptor (RAR) agonist with particular selectivity at the gamma subtype of RAR.

In patients with fibrodysplasia ossificans progressiva (FOP), abnormal bone formation, including heterotopic ossification (HO), is driven by a gain-of-function mutation in the bone morphogenetic protein (BMP) type I receptor ALK2 (ACVR1). Through binding to the RAR gamma, palovarotene decreases the BMP/ALK2 downstream signaling pathway by inhibiting the phosphorylation of SMAD1/5/8, which reduces ALK2/SMAD-dependent chondrogenesis and osteocyte differentiation resulting in reduced endochondral bone formation.

Indication: For the reduction in volume of new heterotopic ossification in adults and pediatric patients aged 8 years and older for females and 10 years and older for males with fibrodysplasia ossificans progressiva (FOP).

There is no pregnancy category for this medication; however, the risk summary indicates that Sohonos® is contraindicated during pregnancy. Based on the findings in animal studies and class effects of retinoids, Sohonos® can cause fetal harm when administered during pregnancy. There are no available human data with use in pregnant women. If pregnancy occurs during treatment with Sohonos®, discontinue treatment immediately and refer the patient to an obstetrician/gynecologist or other specialist experienced in reproductive toxicity for further evaluation and counseling. Sohonos® can cause fetal harm when administered during pregnancy. Obtain a negative serum pregnancy test within one week prior to Sohonos® therapy. Verify that the patient is not pregnant periodically, as needed, over the course of treatment and one month after treatment discontinuation unless they are not at risk of pregnancy. Advise females of reproductive potential to use effective contraception at least one month prior to treatment, during treatment with Sohonos®, and for one month after the last dose, unless continuous abstinence is chosen. The safety and efficacy of use have not been established in the pediatric population less than 8 years of age in females and less than 10 years of age for males.

Dosage Form: Hard-gelatin Capsules: 1mg, 1.5mg, 2.5mg, 5mg, and 10mg.

Recommended Dosage: For females of productive potential, obtain a negative pregnancy test within one week prior to starting and periodically during Sohonos® therapy. If pregnancy occurs, stop Sohonos® treatment immediately and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity.

Take Sohonos® with food, preferably at the same time each day. The recommended dosing includes a chronic daily dosage (daily dose) which can then be modified/increased in the event of FOP flare-up symptoms (flare-up dose).

Start flare-up treatment at the onset of the first symptom indicative of a FOP flare-up or substantial high-risk traumatic event likely to lead to a flare-up (e.g., surgery, IM immunization, mandibular blocks for dental procedures, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses). Symptoms of a FOP flare-up typically include but are not limited to localized pain, soft tissue swelling/inflammation, redness, warmth, decreased joint range of motion, and stiffness.

The recommended dosage for adults and pediatric patients 14 years and older includes the following:

- *Daily Dose*: 5mg daily. Stop daily dosing when flare-up dosing begins.
- *Flare-up Dose:*
    - 20mg daily for 4 weeks, followed by 10mg daily for 8 weeks (for a total of 12 weeks of flare-up treatment), even if symptoms resolve earlier, then return to the daily dosing of 5mg.
    - 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 20mg daily.
    - For flare-up symptoms that have not resolved at the end of the 12-week period, the 10mg 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 5mg daily dosing is resumed, flare-up dosing may be restarted.

The recommended dosage for pediatric patients aged 8 to 13 years for females and aged 10 to 13 years for males includes the following:

- *Daily Dose*: This is weight-based ranging from 2.5mg to 5mg daily. Stop daily dosing when flare-up dosing begins. Refer to the table below, which was adapted from the prescribing information, for further information regarding weight-based dosages for pediatric patients.
- *Flare-up Dose:*
    - The recommended dose is weight-based. Refer to the table below, which was adapted from the prescribing information. 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.
    - 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 weeks 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.

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

If a dose of Sohonos® is missed, take the missed dose as soon as possible. If the dose has been missed by more than 6 hours, skip the missed dose, and continue with the next scheduled dose. Do not take 2 doses at the same time or in the same day.

Sohonos® may be swallowed whole, or capsules may be opened and the contents emptied onto one teaspoon (5ml) of soft food (such as applesauce, low-fat yogurt, or warm oatmeal) and taken within 1 hour of opening, provided it was maintained at room temperature and not exposed to direct sunlight. Do not administer with grapefruit, pomelo, or juices containing these fruits.

Refer to the prescribing information for dosage reduction if patients experience adverse reactions that require dosage reduction during either the daily dosing or flare-up dosing. If the patients is already receiving the lowest possible tolerated dose, then consider discontinuing Sohonos® temporarily or permanently. Start subsequent flare-up dosing at the same reduced dose that tolerated previously.

The effect of renal impairment on the pharmacokinetics of palovarotene has not been evaluated. Given that palovarotene is hepatically eliminated, no dose adjustment of Sohonos® is recommended in patients with mild or moderate renal impairment. Use of Sohonos® in patients with severe renal impairment is not recommended. The

effect of moderate or severe hepatic impairment on the pharmacokinetics of palovarotene has not been evaluated. Sohonos® undergoes extensive hepatic metabolism. No dose adjustment is recommended in patients with mild hepatic impairment. Use of Sohonos® in patients with moderate or severe hepatic impairment is not recommended.

Drug Interactions: Avoid concomitant use of a strong CYP3A4 inhibitor during Sohonos® treatment.

Avoid concomitant use of a moderate CYP3A4 inhibitor with Sohonos®, if possible. If co-administration will occur, reduce the Sohonos® dose by half when co-administered with moderate CYP3A inhibitors. Refer to the prescribing information for additional information on reduced dosing.

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Palovarotene belongs to the same pharmacological class as vitamin A. Thus, the use of both vitamin A and Sohonos® at the same time may lead to additive effects. Concomitant administration of vitamin A in doses higher than the recommended daily allowance (RDA) and/or other oral retinoids with Sohonos® must be avoided because of the risk of hypervitaminosis A.

Systemic retinoid use has been associated with cases of benign intracranial hypertension (also called pseudotumor cerebri), some of which involved the concomitant use of tetracyclines. Avoid co-administration of Sohonos® with tetracycline derivatives.

Box Warning: Sohonos® has a box warning regarding embryo-fetal toxicity and premature epiphyseal closure in growing pediatric patients.

- *Embryo-fetal toxicity*: Sohonos® is contraindicated in pregnancy. Sohonos® may cause fetal harm. Because of the risk of teratogenicity and to minimize fetal exposure, Sohonos® is to be administered only if conditions for pregnancy prevention are met.
- *Premature epiphyseal closure*: Premature epiphyseal closure occurs in growing pediatric patients treated with Sohonos®; close monitoring is recommended.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Sohonos®) in chronic 5mg dosing (N=131). There was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included dry skin (61%), lip dry (47%), arthralgia (36%), pruritus (34%), pain in extremity (29%), rash (28%), alopecia (24%), erythema (19%), headache (19%), back pain (17%), skin exfoliation [skin peeling] (15%), nausea (15%), musculoskeletal pain (14%), myalgia (12%), dry eye (10%), hypersensitivity (10%), peripheral edema (9%), and fatigue (5%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Sohonos®) in flare-up dosing 20mg/10mg (N=105). There was no placebo data in the prescribing information to compare with. The most frequently reported adverse events included dry skin (57%), lip dry (38%), arthralgia (31%), pruritus (48%), pain in extremity (28%), rash (30%), alopecia (30%), erythema (32%), headache (19%), back pain (11%), skin exfoliation [skin peeling] (29%), nausea (13%), musculoskeletal pain (13%), myalgia (9%), dry eye (22%), hypersensitivity (20%), peripheral edema (19%), and fatigue (11%).

Mucocutaneous adverse reactions occurred in most patients (98%) treated with Sohonos®. Sohonos® may contribute to an increased risk of skin and soft tissue infections. Prophylactic measures to minimize risk and/or treat the mucocutaneous adverse reactions are recommended (e.g., skin emollients, sunscreen, lip moisturizers, or artificial tears). Some may require dose reduction or drug discontinuation.

Photosensitivity reactions, such as exaggerated sunburn reactions involving areas exposed to the sun, have been associated with the use of retinoids and may occur with Sohonos®. Precautionary measures for phototoxicity are

recommended. Excessive exposure to sun or artificial UV light should be avoided, and protection from sunlight should be used when exposure cannot be avoided (use of sunscreens, protective clothing, and use of sunglasses).

Retinoids are associated with bone toxicity, including reductions in bone mass and spontaneous reports of osteoporosis and fracture. In FOP clinical trials, Sohonos® resulted in decreased vertebral bone mineral content and bone density, and an increased risk of radiologically observed vertebral (T4 to L4) fractures in treated adult and pediatric patients compared to untreated patients. Periodic radiological assessment of the spine is recommended.

Retinoids have been associated with hyperostotic changes (bone spurs) and calcification of tendons or ligaments and may occur with Sohonos®. These effects generally occur with long-term use, especially at high doses.

New or worsening psychiatric events were reported with Sohonos® use. There is a relatively high background prevalence of psychiatric disorders in untreated patients with FOP. Monitor for the development of new or worsening psychiatric symptoms during Sohonos® treatment. Individuals with a history of psychiatric illness may be more susceptible to these adverse effects.

Night blindness has been associated with systemic retinoids, including Sohonos®. This may be dose-dependent, making driving a vehicle at night potentially hazardous during treatment. Night blindness is generally reversible after treatment cessation, but can also persist in some cases. Advise patients to be cautious when driving or operating any vehicle at night and to seek medical attention in the event of vision impairment.

Contraindications: In the following patients:

- During pregnancy.
- A history of allergy or hypersensitivity to retinoids, or to any component of the product. Anaphylaxis and other allergic reactions have occurred with other retinoids.

Manufacturer: Ipsen Biopharmaceuticals, Inc.

Analysis: Study PVO-1A-301 (Study 301) was a single arm study that included subjects with FOP (N=97) with R206H mutation aged 4 years and older utilizing the Natural History Study (NHS, PVO-1A-001) as an external control (N=101). The primary efficacy endpoint was annualized volume of new heterotopic ossification (HO) as assessed by low-dose, whole body CT (WBCT) imaging (excluding head). All WBCT images from treated subjects in the 301 study and untreated subjects in the NHS were read in a manner blinded to study origination.

Study 301 subjects received Sohonos® 5mg daily, with increased dosing at the time of a flare-up, defined as at least one symptom consistent with a previous flare-up, or a substantial high-risk traumatic event likely to lead to a flare-up, to 20mg QD for 4 weeks followed by 10mg QD for 8 weeks, with flare-up treatment extension in 4-week increments for persistent symptoms. Anytime during flare-up treatment, the 12-week treatment restarted if the subject had another flare-up or substantial high-risk traumatic event. The dosing was adjusted per body weight in skeletally immature children (children who had not reached at least 90% skeletal maturity defined as a bone age of ≥12 years 0 months for girls and ≥14 years 0 months for boys).

The mean age of subjects in the Sohonos® group was 15.1 years and was 17.8 years in the untreated group. There were more male than female subjects in both the Sohonos® (53% and 47%, respectively) and untreated (55% and 45%, respectively) groups.

The mean annualized new HO was 9.4 cm^3/year in subjects receiving the chronic/flare-up Sohonos® treatment and was 20.3 cm^3/year in untreated subjects in the NHS based on a linear mixed effect model. The treatment effect was approximately 10.9 cm^3/year with 95% confidence interval (-21.2 cm^3/year, -0.6 cm^3/year).

Place in Therapy: Sohonos® is a retinoic acid receptor agonist indicated for the reduction in volume of new heterotopic ossification in adults and pediatric patients aged 8 years and older for females and 10 years and older for males with fibrodysplasia ossificans progressiva (FOP). It carries a box warning regarding embryo-fetal toxicity and premature epiphyseal closure in growing pediatric patients. Dosing for Sohonos® includes both chronic daily dosing and flare-up dosing.

Its efficacy was assessed in a single arm study that included subjects with FOP (N=97) and utilized the Natural History Study (NHS, N=101) as an external control. The primary efficacy endpoint was annualized volume of new HO. Results suggested that the mean annualized new HO was 9.4 cm^3/year in subjects receiving the chronic/flare-up Sohonos® treatment and 20.3 cm^3/year in untreated subjects in the NHS based on a linear mixed effect model (treatment effect was about 10.9 cm^3/year).

It is recommended that Sohonos® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Sohonos [package insert]. Cambridge, MA: Ipsen Biopharmaceuticals, Inc; 2023.