sohonos™
(palovarotene) capsules
1 mg | 1.5 mg | 2.5 mg | 5 mg | 10 mg

DOSING GUIDE

INDICATION

SOHONOS™ is 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).

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY and PREMATURE EPIPHYSEAL CLOSURE IN GROWING PEDIATRIC PATIENTS

- **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 occurs in growing pediatric patients treated with SOHONOS, close monitoring is recommended.**

Contraindications

SOHONOS is contraindicated in patients during pregnancy, or with a history of allergy or hypersensitivity to retinoids, or to any component of SOHONOS. Anaphylaxis and other allergic reactions have occurred with other retinoids.

Please see additional Important Safety Information on pages 6-8 and full Prescribing Information, including BOXED WARNING for Embryo-fetal Toxicity and Premature Epiphyseal Closure in Growing Pediatric Patients.

SOHONOS IS A CAPSULE AVAILABLE IN 5 DIFFERENT STRENGTHS[1]

The powder-filled gelatin capsules should be taken with food, preferably at the same time each day. Do not administer with grapefruit, pomelo, or juices containing these fruits.

1 mg | 1.5 mg | 2.5 mg | 5 mg | 10 mg

For patients who have difficulties swallowing intact capsules:

The contents of the capsule may be sprinkled onto a teaspoon of soft food (such as applesauce, low-fat yogurt, or warm oatmeal) and taken within 1 hour after sprinkling if maintained at room temperature without being exposed to direct sunlight.

If a dose is missed, take it as soon as possible:

If missed by more than 6 hours, skip the dose and continue with the next scheduled dose. Do not take two doses at the same time or in the same day.

SOHONOS in women of childbearing potential:

Pregnancy testing and contraceptive measures must be followed prior to dosing SOHONOS in women of childbearing potential.

Please review Section 8.3 of full Prescribing Information for complete pregnancy and birth control considerations.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions

- **Embryo-Fetal Toxicity:** SOHONOS can cause fetal harm and is contraindicated during pregnancy. SOHONOS is a retinoid which is associated with birth defects in humans. Advise females of reproductive potential to use an effective method of contraception at least 1 month prior to treatment, during SOHONOS treatment and for 1 month after the last dose. If a pregnancy occurs during treatment, discontinue treatment immediately and refer the patient to an obstetrician/gynecologist experienced in reproductive toxicity. Inform patients not to donate blood during SOHONOS treatment and for 1 week following discontinuation.

Please see additional Important Safety Information on pages 6-8 and full Prescribing Information, including BOXED WARNING.

SOHONOS IS A ONCE-DAILY ORAL TREATMENT WITH DOSE ESCALATIONS DURING A FLARE-UP[1]

The recommended dosing for SOHONOS includes a chronic (daily) dose, which is increased when symptoms of an FOP flare-up occur.

- Stop chronic (daily) dosing when flare-up dosing begins
- Return to chronic (daily) dosing after flare-up treatment

Dosing for patients 14 years and older

DAILY (CHRONIC) DOSING	FLARE-UP DOSING
5 mg once daily	**20 mg once daily, for 4 weeks** **FOLLOWED BY** **10 mg once daily, for 8 weeks** (even if symptoms resolve earlier)

Please see the full Prescribing Information for information on drug interactions that can impact the recommended dose

Dosing for females 8-13 and males 10-13 years of age

Weight-based dosing is required for children aged from 8 years (females) and 10 years (males) to less than 14 years of age.

WEIGHT-BASED DOSAGE FOR FEMALES 8-13 AND MALES 10-13 YEARS OF AGE[1]

	Chronic Dosage	Flare-up (Weeks 1 to 4)	Flare-up (Weeks 5 to 12)
10-<20 kg	**2.5 mg**	**10 mg**	**5 mg**
20-<40 kg	**3 mg**	**12.5 mg**	**6 mg**
40-<60 kg	**4 mg**	**15 mg**	**7.5 mg**
≥60 kg*	**5 mg**	**20 mg**	**10 mg**

In the Phase 3 trial, dosing was adjusted according to body weight in skeletally immature children (children who had not reached at least 90% skeletal maturity, defined as a bone age of ≥12 years for girls and ≥14 years for boys).[1]

*All children ≥14 years of age and adults should receive the dose in the ≥60 kg weight category.

Please see additional Important Safety Information on pages 6-8 and full Prescribing Information, including BOXED WARNING.

FLARE-UP DOSING

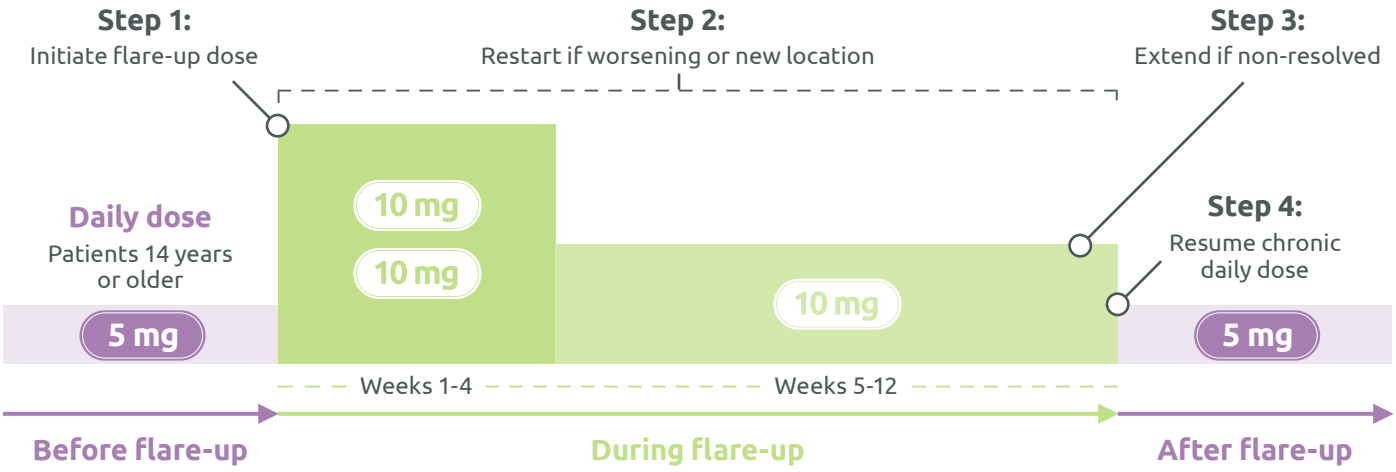
Flare-up symptoms

Symptoms of an 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.

Flare-up treatment initiation and steps

Initiate flare-up treatment at the onset of the first symptom indicative of an FOP flare-up or substantial high-risk traumatic event likely to lead to a flare-up (e.g., surgery, intramuscular immunization, mandibular blocks for dental procedures, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses).

Flare-up dosing for patients 14 years or older



Step 1: Initiate flare-up dose At onset of flare-up or substantial high-risk event, initiate 12-week flare-up treatment and stop chronic daily 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 even if symptoms resolve earlier

Step 2: Restart if worsening or new location 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.

Step 3: Extend if non-resolved 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.

Step 4: Resume chronic daily dose If symptoms have resolved by the end of the 12-week period or the 4-week extension, then return to the chronic daily dose (ie, 5 mg daily for adults and pediatric patients 14 years and older). If new flare-up symptoms occur after the 5 mg daily dosing is resumed, flare-up dosing may be restarted.

Dosage adjustments during a flare-up for female patients 8-13 years old and male patients 10-13 years old should follow the weight-based recommendations on page 3.

Please see additional Important Safety Information on pages 6-8 and full Prescribing Information, including BOXED WARNING.

DOSAGE REDUCTION FOR ADVERSE REACTIONS[1]

If the patient experiences adverse reactions during SOHONOS treatment that require dose reduction, the daily or flare-up dose should be reduced to the next lower dosage

Additional dose reduction should occur if adverse reactions do not improve.

- If the patient is already receiving the lowest possible dose, consider discontinuing therapy temporarily or permanently. Subsequent flare-up treatment should be initiated at the same reduced dose that was tolerated previously

DOSAGE REDUCTION[1]	
Dose Prescribed	**Reduced Dose**
20 mg	15 mg
15 mg	12.5 mg
12.5 mg	10 mg
10 mg	7.5 mg
7.5 mg	5 mg
6 mg	4 mg
5 mg	2.5 mg
4 mg	2 mg
3 mg	1.5 mg
2.5 mg	1 mg

In clinical trials, some patients experienced mucocutaneous adverse reactions that led to dose reductions.

- Dose reductions were more frequent during flare-up dosing suggesting a dose-response relationship

Please see additional Important Safety Information on pages 6-8 and full Prescribing Information, including BOXED WARNING.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY and PREMATURE EPIPHYSEAL CLOSURE IN GROWING PEDIATRIC PATIENTS

- **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 occurs in growing pediatric patients treated with SOHONOS, close monitoring is recommended.**

Contraindications

SOHONOS is contraindicated in patients during pregnancy, or with a history of allergy or hypersensitivity to retinoids, or to any component of SOHONOS. Anaphylaxis and other allergic reactions have occurred with other retinoids.

Warnings and Precautions

- **Embryo-Fetal Toxicity:** SOHONOS can cause fetal harm and is contraindicated during pregnancy. SOHONOS is a retinoid which is associated with birth defects in humans. Advise females of reproductive potential to use an effective method of contraception at least 1 month prior to treatment, during SOHONOS treatment and for 1 month after the last dose. If a pregnancy occurs during treatment, discontinue treatment immediately and refer the patient to an obstetrician/gynecologist experienced in reproductive toxicity. Inform patients not to donate blood during SOHONOS treatment and for 1 week following discontinuation.
- **Premature Epiphyseal Closure in Growing Pediatric Patients:** SOHONOS can cause irreversible premature epiphyseal closure and potential adverse effects on growth. In clinical studies, premature epiphyseal closure occurred with SOHONOS treatment in growing pediatric patients with FOP. Monitoring of linear growth is recommended in growing pediatric patients. Prior to starting treatment with SOHONOS, all growing pediatric patients should undergo baseline assessment of skeletal maturity and continued monitoring until patients reach skeletal maturity or final adult height. If a patient exhibits signs of premature epiphyseal closure or adverse effects on growth based on clinical or radiologic evaluations, further evaluation may be required, including an assessment of the benefits and risks of continued treatment, or temporary or permanent discontinuation of SOHONOS until the patient achieves epiphyseal closure and skeletal maturity.
- **Mucocutaneous Adverse Reactions:** Dry skin, lip dry, pruritus, rash, alopecia, erythema, skin exfoliation (skin peeling), and dry eye occurred in 98% of patients treated with SOHONOS. SOHONOS may contribute to an increased risk of skin and soft tissue infections, particularly paronychia and decubitus ulcer, due to a decreased skin barrier from adverse reactions such as dry and peeling skin. Some of these adverse reactions led to dose reductions which occurred more frequently during flare-up dosing suggesting a dose response relationship. 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 discontinuation. Photosensitivity reactions (e.g., burning, erythema, blistering) 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 (use of sunscreens, protective clothing, and use of sunglasses).

Please see additional Important Safety Information on pages 6-8 and full Prescribing Information, including BOXED WARNING.

IMPORTANT SAFETY INFORMATION (continued)

- **Metabolic Bone Disorders:** Retinoids are associated with bone toxicity, including reductions in bone mass and spontaneous reports of osteoporosis and fracture. In FOP clinical studies, SOHONOS resulted in decreased vertebral bone mineral content and bone density, and an increased risk of radiologically observed vertebral fractures in treated 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 may occur with SOHONOS.
- **Psychiatric Disorders:** New or worsening psychiatric events were reported with SOHONOS including depression, anxiety, mood alterations, and suicidal thoughts and behaviors. There is a relatively high background prevalence of psychiatric disorders in untreated patients with FOP. Monitor for development of new or worsening psychiatric symptoms during treatment with SOHONOS. Individuals with a history of psychiatric illness may be more susceptible to these adverse effects. Patients and/or caregivers should contact their healthcare provider if new or worsening psychiatric symptoms develop during treatment with SOHONOS.
- **Night Blindness:** This may be dose-dependent, making driving a vehicle at night potentially hazardous during treatment. Advise patients to be cautious when driving or operating any vehicle at night and seek medical attention in the event of vision impairment.

Adverse Reactions

The most common adverse reactions (≥ 10%) are dry skin, lip dry, arthralgia, pruritus, pain in extremity, rash, alopecia, erythema, headache, back pain, skin exfoliation (skin peeling), nausea, musculoskeletal pain, myalgia, dry eye, hypersensitivity, peripheral edema, and fatigue.

Drug Interactions

- CYP3A4 inhibitors may increase SOHONOS exposure. Avoid concomitant use of strong or moderate CYP3A4 inhibitors, as well as grapefruit, pomelo or juices containing these fruits.
- CYP3A4 inducers may decrease SOHONOS exposure. Avoid concomitant use of strong or moderate CYP3A4 inducers.
- 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 and/or other oral retinoids must be avoided due to risk of hypervitaminosis A.
- Systemic retinoid use has been associated with cases of benign intracranial hypertension (pseudotumor cerebri), some of which involved the concomitant use of tetracyclines. Avoid coadministration of SOHONOS with tetracycline derivatives.

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IMPORTANT SAFETY INFORMATION (continued)

Use in Specific Populations

- **Pregnancy:** SOHONOS is contraindicated during pregnancy. Obtain a negative serum pregnancy test within 1 week prior to SOHONOS therapy and periodically, as needed, over the course of treatment with SOHONOS and 1 month after treatment discontinuation unless patient is not at risk of pregnancy. If pregnancy occurs during treatment with SOHONOS, stop treatment immediately and refer the patient to an obstetrician/gynecologist or other specialist experienced in reproductive toxicity for evaluation and advice.
- **Lactation:** Advise females that breastfeeding is not recommended during treatment with SOHONOS, and for at least 1 month after the last dose.
- **Females and Males of Reproductive Potential:** Advise females of reproductive potential to use effective contraception at least 1 month prior to and during treatment, and for 1 month after the last dose unless continuous abstinence is chosen.
- **Pediatric Use:** All growing pediatric patients should undergo baseline assessment of growth and skeletal maturity before starting treatment and continued clinical and radiographic monitoring every 6-12 months until patients reach skeletal maturity or final adult height.
- **Renal or Hepatic Impairment:** Use of SOHONOS in patients with severe renal impairment, or with moderate or severe hepatic impairment is not recommended.

Please see additional Important Safety Information on pages 6-8 and full Prescribing Information, including BOXED WARNING for Embryo-fetal Toxicity and Premature Epiphyseal Closure in Growing Pediatric Patients.

To learn more, visit SOHONOS.com

Reference: 1. SOHONOS Full Prescribing Information. Cambridge, MA: Ipsen Biopharmaceuticals, Inc.

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