▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
SOHONOS®
(palovarotene) hard capsules

WARNING: CAUSES BIRTH DEFECTS AND PREMATURE PHYSEAL CLOSURE IN GROWING PATIENTS

- SOHONOS must not be used by female patients who are, or intend to become, pregnant. Due to the risk of teratogenicity and to minimise fetal exposure, SOHONOS is to be administered only if conditions for pregnancy prevention are met (see sections 4.4 and 4.6).
- SOHONOS may cause premature physeal closure in growing patients. Close monitoring is recommended (see sections 4.4 and 4.8).

1 NAME OF THE MEDICINE

palovarotene

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SOHONOS hard capsule contains 1 mg, 1.5 mg, 2.5 mg, 5 mg or 10 mg of palovarotene as the active ingredient.

The capsules contain sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

The capsules are white, opaque, size “0” elongated, hard-gelatin capsules containing white to off-white powder containing palovarotene.

SOHONOS 1 mg hard capsules are printed with black ink “PVO 1” on the body.

SOHONOS 1.5 mg hard capsules are printed with black ink “PVO 1.5” on the body.

SOHONOS 2.5 mg hard capsules are printed with black ink “PVO 2.5” on the body.

SOHONOS 5 mg hard capsules are printed with black ink “PVO 5” on the body.

SOHONOS 10 mg hard capsules are printed with black ink “PVO 10” on the body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SOHONOS is indicated to reduce the formation of heterotopic ossification in adults and children aged 8 years and above for females and 10 years and above for males with fibrodysplasia ossificans progressiva (FOP).

4.2 DOSE AND METHOD OF ADMINISTRATION

SOHONOS should only be prescribed under the supervision of specialist medical practitioners with expertise in managing fibrodysplasia ossificans progressiva (FOP).

Dosing and administration considerations

Testing Prior to the Initiation of Therapy

Pregnancy testing and contraceptive measures must be followed prior to dosing SOHONOS in females of childbearing potential (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.6 FERTILITY, PREGNANCY AND LACTATION).

Precautions to be taken before handling or administering the medicinal product

Women who are pregnant or who intend to become pregnant should avoid contact with SOHONOS. Additionally, to avoid unintended exposure caregivers administering SOHONOS by emptying the capsule contents onto soft food should wear disposable gloves when handling and use disposable paper towels and a container to collect waste (e.g. a resealable bag).

Recommended chronic/flare-up treatment regimen

The recommended dosing includes a chronic treatment dose which can then be adjusted in the event of flare-up symptoms (flare-up treatment dose).

Flare-ups can occur in the absence of any apparent causative factor, but there is a high risk that substantial traumatic events (e.g. surgery, intramuscular immunisation, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses), can lead to a flare-up and result in heterotopic bone formation.

Flare-up treatment should begin 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. Symptoms of a FOP flareup typically include but are not limited to localised pain, soft tissue swelling/inflammation, redness, warmth, decreased joint range of motion, and stiffness.

Flare-up treatment should be initiated at the time of such events.

Chronic treatment should stop at the time of initiation of flare-up treatment and re-initiated after completion of the flare-up treatment.

Flare-up only regimen

If the patient experiences intolerable adverse reactions while taking chronic daily treatment and dose reduction does not alleviate the adverse reaction, then the patient may take SOHONOS only at the time of flare-up (or substantial high-risk traumatic event).

Dosage in adults and children aged 14 years and over

Chronic treatment dose

Recommended dose: 5 mg once daily. Weight-adjusted dosing is required in children who are under 14 years of age (see Table 1).

Flare-up treatment dose

Recommended dose: 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment) even if symptoms resolve earlier. Weight-adjusted dosage is required in children who are under 14 years of age (see Table 1).

In the presence of persistent flare-up symptoms, treatment may be extended in 4-week intervals with 10 mg SOHONOS and continued until the flare-up symptoms resolve.

Should the patient experience another flare-up (new flare-up location or marked worsening of the original flare-up) at any time during flare-up treatment, the flare-up 12-week treatment should be restarted.

Dose adjustment in children under 14 years of age

SOHONOS dosing is weight-adjusted in patients under 14 years of age (see Table 1). The physician should prescribe the most appropriate dosage based on weight for children aged from 8 years (females) and 10 years (males) to less than 14 years (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.1 PHARMACODYNAMIC PROPERTIES).

Table 1: Weight-adjusted dosage for children < 14 years

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

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

Dose modification for adverse reactions:

If the patient experiences adverse reactions that require dose reduction during either the chronic or flare-up (weeks 1-12) treatment, the daily dose should be reduced to the next lower dose as shown in Table 2 at the discretion of the physician; additional dose reduction should occur if adverse reactions do not improve. If the patient is already receiving the lowest possible tolerated dose, then consideration should be given to discontinue therapy temporarily or permanently or switching to flare-up treatment only (see Flare-up only regimen below). Subsequent flare-up treatment should be initiated at the same reduced treatment that was tolerated previously.

Table 2: Dose reduction of SOHONOS for Flare-up and Chronic treatment

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

Missed Dose

If a dose of medication is missed, patients should take the missed dose as soon as possible. If the dose has been missed by more than 6 hours, instruct the patient to skip the missed dose and continue with the next scheduled dose. Instruct the patient not to take two doses at the same time or on the same day.

Method of administration

For oral administration.

SOHONOS should be taken with food preferably at the same time each day. SOHONOS may be swallowed whole, or capsules may be opened, and the contents emptied onto a teaspoon of soft food (e.g. apple sauce, low fat yogurt, low fat chocolate pudding, warm oatmeal, warm rice cereal, chocolate milk, warm baby formula) and taken within 1 hour of opening provided it was maintained at room temperature and not exposed to direct sunlight (see section 6.4 SPECIAL PRECAUTIONS FOR STORAGE AND OTHER HANDLING).

4.3 CONTRAINDICATIONS

SOHONOS is contraindicated in patients with a history of allergy or hypersensitivity to the active substance, or to other retinoids or to any of the excipients (see Section 6.1 LIST OF EXCIPIENTS).

SOHONOS is contraindicated in women who are pregnant or breastfeeding.

SOHONOS is contraindicated in females of childbearing potential unless all of the conditions of the pregnancy prevention are met, or they are not at risk for pregnancy (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Pregnancy

Teratogenic effects

The teratogenic potential of systemic retinoids is well established regarding the risk to the developing embryo and fetus. Studies in pregnant rats have shown that administration of palovarotene resulted in fetal malformations typical of retinoids (e.g. cleft palate, misshapen skull bones, shortening of the long bones). There have been no reports of pregnancy or in utero exposure reported in clinical studies with SOHONOS.

Pregnancy Testing

According to local practice, medically documented blood or urine pregnancy tests are recommended to be performed, as follows:

Prior to starting therapy

At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with SOHONOS and should be documented within the patient medical records.

Follow-up pregnancy testing during treatment

Follow-up pregnancy tests should be done monthly. The need for repeated medically documented pregnancy tests every month is required and should be determined according to local practice including consideration of the patient's sexual activity and extent of FOP disease burden.

End of treatment

1 month after stopping treatment, women should undergo a final pregnancy test.

Contraception

SOHONOS is contraindicated in females of childbearing potential unless all the following conditions for pregnancy prevention are met, or they are not at risk of pregnancy.

Females

- The potential for pregnancy must be assessed for all female patients.
- She understands the teratogenic risk and the need to rapidly consult her physician if there is a risk of pregnancy or if she might be pregnant.
- Females of child-bearing potential must use at least one highly effective method of contraception (e.g. intrauterine device (IUD)) or two effective methods (e.g.

combined hormonal contraception in combination with another method of contraception such as a barrier method) during treatment with SOHONOS.
- She understands the need and accepts to undergo regular pregnancy testing before, during treatment, and 1 month after stopping treatment when taking SOHONOS.
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 1 month after the end of treatment.
- For those patients taking the flare-up regimen only, patients **must** continue to use effective contraception even during periods when SOHONOS is not being taken as the timing of flare-ups may not be predictable.
- Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of SOHONOS.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult her physician if there is a risk of pregnancy or if she might be pregnant.

These conditions also concern women who are not currently sexually active unless the prescriber attests that there are compelling reasons to indicate that there is no risk of pregnancy.

Premature physeal closure (PPC) in growing children

Premature physeal closure (PPC) has been demonstrated to be an important risk associated with palovarotene treatment in growing children with FOP. In clinical studies, PPC was identified as an irreversible serious risk associated with SOHONOS treatment. Twenty-four (24%) palovarotene treated paediatric subjects <18 years of age reported PPCs, comprising 10 of 77 subjects from ≥8/10 to <18 years (13%), 10 of 39 subjects from ≥8/10 to <14 years (26%) and 14 of 25 subjects <8/10 years (56%) (SOHONOS is not indicated in children aged 7 years and below for females and 9 years and below for males; <8/10 years) (see sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES).

Bone Safety

In clinical studies with SOHONOS, assessments of growth and bone safety in growing children included linear and knee height, femur and tibia length measured by Whole-body Computed Tomography (WBCT), and hand/wrist and knee radiographs.

Generally, linear height increased over time in most subjects with FOP in the SOHONOS clinical studies and in the FOP Natural History Study (NHS). In SOHONOS treated subjects, as well as in untreated subjects in the NHS, there was a notable trend of declining height z-scores in adolescent subjects, potentially due to increasing spinal deformity, and an apparent loss of linear height related to spinal deformities, including kyphosis and scoliosis,

or measurement error. However, linear height z-scores also showed greater variability and apparent decreasing trends in younger subjects treated with SOHONOS in that same study compared with the untreated subjects from the NHS. Some subjects with premature physeal closure (PPC) showed a decline in linear height z-scores that were greater in magnitude compared with treated subjects without PPC. Greater proportions of SOHONOS treated subjects in all age categories had slow growth velocities at month 12 of <4 cm/year than similarly aged untreated subjects from the NHS.

Knee height increased similarly in both the treated study subjects as well as untreated NHS subjects with a few subjects with PPC demonstrating minimal changes in knee height over time. Femur and tibia length measured by WBCT also increased over time in most SOHONOS treated subjects and in the NHS. A greater proportion of children <8/10 years with PPC in one study had femur length growth velocities that were slower relative to those without PPC and those who were untreated. Tibial length and growth velocity were not demonstrably different between treated and untreated subjects or between treated subjects with or without PPC and untreated subjects. Femur and tibial length growth also demonstrated symmetric growth in treated subjects (both with and without PPC).

Premature physeal closure has been identified as an irreversible serious risk associated with SOHONOS treatment. PPC findings were observed as early as 6 months after initiating therapy with the majority occurring at or after 12 months (See 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Potential longer-term consequences of PPC include growth arrest, leg length discrepancy, disproportionate growth (epiphyseal growth plate closure preferentially affecting the lower extremities), angular deformity in affected joints, and gait disturbance. Consistent with the retinoid literature, all but one of the PPC events was observed first in the knee, illustrating that PPC preferentially affects the lower extremities. When contralateral growth plate evaluations were available, growth plate closure was symmetric. Additionally, femur and tibia length growth also demonstrated symmetric growth although differences leading to leg length discrepancy would likely take a longer amount of time to manifest. Lateral distal femoral angle, a measure of angular deformity at the knee, was highly variable and generally within the physiologic range. Similar to leg length discrepancy, angular deformity should asymmetric physeal fusion occur would likely take a longer amount of time to manifest. Given the relatively short follow-up times to date, longer-term consequences have not been identified in subjects treated with palovarotene. It is assumed that upon initiation of treatment with SOHONOS, all growing children should be considered to be at risk of developing PPC and the potential long-term consequences.

Monitoring Recommendations:

There are no clear characteristics that define or predict who will develop PPC, over what period, or after what duration of SOHONOS exposure. Therefore, prior to starting treatment with SOHONOS, it is recommended that all growing children undergo baseline clinical and radiological assessments including but not limited to an assessment of skeletal maturity via hand/wrist and knee x-rays, standard growth curves and pubertal staging. Continued

monitoring is recommended every 6-12 months until patients reach skeletal maturity or final adult height. Once the patients have reached skeletal maturity or the patient has reached final adult height, no further monitoring for PPC is necessary.

Monitoring of linear growth is recommended in growing children. Should evidence of adverse effects on growth and/or PPC be observed, further evaluation and increased monitoring may be required. The decision to temporarily interrupt SOHONOS during the evaluation period or permanently discontinue should be made based on individual benefit-risk determination (see sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Mucocutaneous effects

Mucocutaneous effects are the most commonly reported adverse reactions across all doses during clinical studies with SOHONOS (98%) and were generally mild to moderate in severity. Mucocutaneous adverse reactions observed in over 10% of subjects were dry skin (78%), pruritis (55%), alopecia (41%), rash (39%), erythema (32%), skin exfoliation [skin peeling] (31%), drug eruption (17%) and skin irritation (12%). In addition, lip dry occurred in 55% of subjects and dry eye occurred in 26% of subjects. 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 mucocutaneous effects such as dry and peeling skin. Some of these mucocutaneous adverse reactions led to dose reductions which occurred more frequently during flare-up dosing suggesting a dose response relationship (see sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Prophylactic measures to minimize risk and/or treat the mucocutaneous effects are recommended (e.g. skin emollients, sunscreen, lip moisturizers, artificial tears, or other helpful treatments).

Radiological Vertebral Fractures

In clinical trials palovarotene has resulted in decreased vertebral bone mineral content, bone density and bone strength as well as an increased risk of radiologically observed vertebral (T4 to L4) fractures in treated adult and paediatric patients compared to untreated patients. Periodic radiological assessment of the spine is recommended. See section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Photosensitivity

Photosensitivity reactions, such as exaggerated sunburn reactions (e.g.: burning, erythema, blistering) involving areas exposed to the sun have been associated with the use of retinoids. Although palovarotene and its major metabolites were negative for phototoxicity when tested *in vitro*, precautionary measures for phototoxicity are still recommended. Excessive exposure to sun or artificial ultraviolet 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).

Psychiatric disorders

Depression, depression aggravated, anxiety, mood alterations, and suicidal thoughts and behaviours have been reported in patients treated with systemic retinoids and individuals with a personal history of psychiatric illness appear to be more susceptible. There is a relatively high background prevalence (24%) of depression in untreated patients with FOP with 9.4% of patients having a medical history of depression when enrolled in SOHONOS clinical trials.

In FOP clinical trials, there was no treatment related increase in suicide ideation or suicidal behaviour or psychiatric disorders overall relative to untreated FOP subjects. Particular care should be taken in patients with history of psychiatric illness. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary.

Night blindness

Night blindness (nyctalopia) has been reported in patients exposed to systemic retinoids and palovarotene (see section 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES). A single instance of night blindness has been observed in the SOHONOS development program. Therefore, the product should be used with caution. Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion.

Use in hepatic impairment

There was no evidence that mild hepatic impairment status affected palovarotene pharmacokinetics. No dose adjustment is required in patients with mild hepatic impairment. The use of palovarotene has not been studied in patients with moderate and severe hepatic impairment. Use with caution in patients with moderate hepatic impairment. Use in patients with severe hepatic impairment is not recommended. See section 5.2 PHARMACOKINETIC PROPERTIES.

Use in renal impairment

The influence of renal impairment on the pharmacokinetics of SOHONOS has not been evaluated. Given palovarotene is hepatically eliminated, no need for dose adjustment is expected in patients with mild or moderate renal impairment. Use in patients with severe renal impairment is not recommended. See section5.2 PHARMACOKINETIC PROPERTIES.

Use in the elderly

No dose adjustment is necessary in elderly patients. See section 5.2 PHARMACOKINETIC PROPERTIES.

Paediatric use

The safety and effectiveness of SOHONOS for the treatment of FOP has been established in subjects aged 8 years and older (females) and 10 years and older (males). Use of SOHONOS for this indication is supported by evidence from clinical studies in adults and paediatric subjects. The use of SOHONOS in paediatric patients aged less than 8 years (females) and less than 10 years (males) is not recommended. Clinical studies in subjects aged 4 years and

above have shown that growing patients with open epiphyses are at risk of developing premature physeal closure (PPC) of growth plates when treated with SOHONOS (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Strong CYP3A4 Inhibitors

Palovarotene exposures at steady-state increased approximately 3-fold when co-administered with ketoconazole (a strong CYP3A4 inhibitor). Avoid concomitant use of a strong CYP3A4 inhibitor such as azole antifungals (e.g. ketoconazole, itraconazole), protease inhibitors (e.g. ritonavir, nirmatrelvir), and macrolide antibiotics (e.g. clarithromycin) with SOHONOS. Advise patients to avoid grapefruit or grapefruit juice that are known to inhibit CYP3A4 during SOHONOS treatment.

Moderate CYP3A4 inhibitors

Co-administration of moderate CYP3A4 inhibitors with palovarotene may increase palovarotene exposure. Avoid concomitant use of a moderate CYP3A4 inhibitor such as fluconazole, erythromycin, aprepitant, and diltiazem with SOHONOS.

Strong CYP3A4 inducers

Coadministration of palovarotene with rifampicin, a strong CYP3A4 inducer, decreased the exposure of palovarotene approximately 10-fold. Avoid concomitant use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin, rifabutin, St John’s Wort extract) with SOHONOS.

Moderate CYP3A4 inducers

Co-administration of moderate CYP3A4 inducers with palovarotene may decrease palovarotene exposure. Avoid concomitant use of moderate CYP3A4 inducers (e.g. bosentan) with SOHONOS.

Vitamin A

Palovarotene belongs to the same pharmacological class as vitamin A. Therefore, 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.

Tetracyclines

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 coadministration of SOHONOS with tetracyclines derivates.

Systemic corticosteroids

Corticosteroids were administered per standard of care in the FOP clinical trials (e.g. prednisone at 2 mg/kg to a maximum dose of 100 mg daily for 4 days). In the population PK analysis, there was no evidence that administration of prednisone affected palovarotene pharmacokinetics. Palovarotene had no effect on the pharmacokinetics of prednisone or its metabolite prednisolone.

Other potential interactions

Palovarotene was shown not to inhibit CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4; UGTs 1A2, 1A3, 1A4, 1A6, 1A9 and 2B7; or P-glycoprotein, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K at clinically relevant concentrations in vitro. Accordingly, interactions with other medicinal products caused through enzyme and transporter inhibition by palovarotene are not expected.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data on the effect of palovarotene or its metabolites on fertility are available. Palovarotene did not affect fertility in male or female rats at oral doses up to 1 mg/kg/day (yielding exposure to palovarotene [plasma AUC] below that of patients at the maximum recommended human dose [MRHD] of 20 mg/day). Testicular toxicity (including seminiferous tubule degeneration) was observed in male rats treated at 5 mg/kg/day, and disruption of oestrus cycling and reduced ovulation were observed in female rats at 3 mg/kg/day. These adverse effects were only encountered at doses that were not tolerated (males) or poorly tolerated (females), and may reflect secondary effects related to stress/poor animal condition rather than direct effects of palovarotene.

Use in pregnancy (Category X)

Pregnancy is an absolute contraindication to treatment with palovarotene (see section 4.3 CONTRAINDICATIONS) due to the potential of severe and life-threatening birth defects.
Females of childbearing potential must follow the conditions for pregnancy prevention (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

SOHONOS is contraindicated during pregnancy and in females of childbearing potential who are sexually active and not using contraception because palovarotene can cause serious fetal harm when administered to a pregnant woman. In animal reproduction studies, palovarotene induced fetal malformations typical of retinoids (e.g. cleft palate, malformed skull bone, shortening of the long bones) when orally administered to pregnant rats during the period of organogenesis at a dose of ≥0.25 mg/kg/day. Teratogenicity in rats occurred at doses yielding

exposure to palovarotene well below that in patients. There are no available data on palovarotene use in pregnant women to inform drug-associated risks. If pregnancy occurs in a woman treated with palovarotene, treatment must be stopped, and the patient should be referred to a physician for evaluation and advice. If pregnancy occurs within 1 month of treatment discontinuation, there remains a risk of severe and serious malformation of the fetus. The patient should be referred to her physician.

Males

Administration of SOHONOS to a male patient is considered unlikely to affect development of an embryo or fetus carried by a pregnant female sexual partner exposed to palovarotene via the patient's semen. See section 5.2 PHARMACOKINETIC PROPERTIES.

Use in lactation

No data are available on the presence of palovarotene or its main metabolites in breast milk, or the effects of palovarotene on the breastfed child, or on milk production. Because of the potential for serious adverse reactions from palovarotene in a breastfed child, women who are breastfeeding should not take SOHONOS and should not breast feed for at least 1 month following cessation of SOHONOS.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

SOHONOS may have a minor influence on the ability to drive and use machines. No studies on the effects of SOHONOS on the ability to drive or use machines have been performed. However, night blindness (nyctalopia) has been identified as a potentially dangerous effect associated with systemic retinoids, including palovarotene. This may be dose-dependent, making driving a vehicle at night potentially hazardous during treatment. Night blindness is generally reversible after cessation of treatment but can also persist in some cases.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of safety profile

In clinical studies the most common adverse reactions reported in FOP subjects aged ≥ 8 years (females)/10 years (males) were: cutaneous, including dry skin (78%), pruritus (55%), alopecia (41%), rash (39%), erythema (32%), skin exfoliation (31%), drug eruption (17%), and skin irritation (12%); gastrointestinal, including lip dry (55%), chapped lips (17%), dry mouth (13%), cheilitis (11%) and nausea (11%); infections, including paronychia (14%); musculoskeletal, including arthralgia (14%); ocular, including dry eye (26%); injury, poisoning and procedural complications, including skin abrasion (21%); respiratory, including epistaxis (12%) and neurological, including headache (17%).

Serious adverse reactions reported in FOP subjects aged ≥ 8/10 years old include premature physeal closure (PPC; [Preferred Term (PT): Epiphysis premature fusion]) (see

Description of selected adverse reactions below) and cellulitis (1.4%). All others were reported in single subjects and included the following: ankle fracture, epiphyseal disorder, anaemia and seizure, each in 0.7% of subjects.

Adverse events leading to permanent discontinuation occurred in 10 (7%) SOHONOS treated subjects with dry skin being the most common in 2 subjects (1.4%). No study drug discontinuations were reported in placebo/untreated subjects due to adverse events. Mucocutaneous adverse events leading to dose reductions were more common during SOHONOS 20/10◦mg flare-up treatment (35%) than during chronic treatment (3%).

Tabulated list of adverse reactions

Table **3** contains very common (≥ 1/10) and common (≥ 1/100 to < 1/10) adverse reactions which occurred in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse reactions reported in FOP subjects ≥ 8/10 years in clinical trials

System organ class	**Very common**	**Common**
Infections and infestations	paronychia	cellulitis conjunctivitis, skin infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)		pyogenic granuloma
Blood and lymphatic system disorders		anaemia
Metabolism and nutrition disorders		decreased appetite
Psychiatric disorders		irritability, depressed mood, suicidal ideation
Nervous system disorders	headache	seizure
Eye disorders	dry eye	ocular hyperaemia
Vascular disorders		flushing
Respiratory, thoracic and mediastinal disorders	epistaxis	

System organ class	Very common	Common
Gastrointestinal disorders	lip dry, chapped lips, dry mouth, cheilitis, nausea	vomiting, diarrhoea, abdominal pain, gastroesophageal reflux disease
Skin and subcutaneous tissue disorders	dry skin, alopecia, pruritus, erythema, skin exfoliation, rash, drug eruption, eczema, skin irritation	onychoclasis, skin fissures, blister, decubitus ulcer, dermatitis, skin reaction, ingrowing nail, madarosis, urticaria, skin fragility, swelling face
Musculoskeletal and connective tissue disorders	arthralgia	back pain, epiphyses premature fusion[1]*, joint swelling
Renal and urinary disorders		proteinuria
General disorders and administration site conditions		fatigue
Investigations		lipase increased
Injury, poisoning and procedural complications	skin abrasion, radiological spinal fracture**	sunburn, ankle fracture

*Refer to "Description of selected adverse reactions" section

** Based on vertebral fracture analysis applied to whole body computed tomography (WBCT) scans obtained in the Phase 3 PVO-1A-301 FOP study

[1]Epiphysis premature fusion is PT used to capture premature physeal closure or PPC.

Table 4 presents the frequency of the most common adverse events in ≥ 10 % of FOP subjects ≥ 8/10 years in clinical trials.

Table 4: Most common adverse events reported in ≥ 10 % of FOP subjects ≥ 8/10 years in clinical trials

System Organ Class Preferred Term	Placebo/ Untreated (N=20)	Palovarotene Treatment Period				PVO Total (N=139)
		Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	
Any TEAE	19 (95.0)	126 (96.9)	7 (100)	25 (100)	95 (95.0)	139 (100)

System Organ Class Preferred Term	Placebo/ Untreated (N=20)	Palovarotene Treatment Period				PVO Total (N=139)
		Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	
Skin and subcutaneous tissue disorders	9 (45.0)	114 (87.7)	6 (85.7)	24 (96.0)	91 (91.0)	136 (97.8)
Dry skin	3 (15.0)	75 (57.7)	5 (71.4)	22 (88.0)	58 (58.0)	109 (78.4)
Alopecia	0	31 (23.8)	0	1 (4.0)	30 (30.0)	58 (41.7)
Pruritus	1 (5.0)	28 (21.5)	0	8 (32.0)	31 (31.0)	56 (40.3)
Erythema	0	22 (16.9)	2 (28.6)	5 (20.0)	29 (29.0)	47 (33.8)
Rash	0	26 (20.0)	1 (14.3)	2 (8.0)	25 (25.0)	44 (31.7)
Pruritus generalised	0	21 (16.2)	1 (14.3)	9 (36.0)	25 (25.0)	43 (30.9)
Skin exfoliation	0	20 (15.4)	0	2 (8.0)	29 (29.0)	43 (30.9)
Drug eruption	0	12 (9.2)	0	0	15 (15.0)	23 (16.5)
Eczema	0	13 (10.0)	1 (14.3)	5 (20.0)	8 (8.0)	21 (15.1)
Skin irritation	0	8 (6.2)	0	1 (4.0)	8 (8.0)	16 (11.5)
Gastrointestinal disorders	9 (45.0)	93 (71.5)	5 (71.4)	20 (80.0)	56 (56.0)	115 (82.7)
Lip dry	1 (5.0)	48 (36.9)	4 (57.1)	14 (56.0)	29 (29.0)	78 (56.1)
Nausea	3 (15.0)	19 (14.6)	0	6 (24.0)	14 (14.0)	33 (23.7)
Vomiting	4 (20.0)	19 (14.6)	0	3 (12.0)	13 (13.0)	32 (23.0)
Chapped lips	2 (10.0)	10 (7.7)	0	6 (24.0)	12 (12.0)	24 (17.3)
Abdominal pain	2 (10.0)	12 (9.2)	0	4 (16.0)	7 (7.0)	22 (15.8)
Diarrhoea	1 (5.0)	17 (13.1)	0	3 (12.0)	7 (7.0)	20 (14.4)
Dry mouth	0	9 (6.9)	1 (14.3)	4 (16.0)	6 (6.0)	18 (12.9)
Cheilitis	0	5 (3.8)	0	0	11 (11.0)	15 (10.8)
Infections and infestations	8 (40.0)	82 (63.1)	3 (42.9)	11 (44.0)	56 (56.0)	109 (78.4)
Upper respiratory tract infection	1 (5.0)	25 (19.2)	2 (28.6)	5 (20.0)	8 (8.0)	33 (23.7)
Nasopharyngitis	0	23 (17.7)	1 (14.3)	0	12 (12.0)	31 (22.3)
Paronychia	0	13 (10.0)	0	0	11 (11.0)	22 (15.8)
Ear infection	0	10 (7.7)	0	0	6 (6.0)	14 (10.1)
Musculoskeletal and connective tissue disorders	12 (60.0)	79 (60.8)	4 (57.1)	16 (64.0)	58 (58.0)	102 (73.4)
Arthralgia	10 (50.0)	40 (30.8)	1 (14.3)	11 (44.0)	30 (30.0)	61 (43.9)
Pain in extremity	5 (25.0)	34 (26.2)	2 (28.6)	6 (24.0)	24 (24.0)	52 (37.4)
Back pain	0	15 (11.5)	0	1 (4.0)	11 (11.0)	25 (18.0)
Musculoskeletal pain	2 (10.0)	13 (10.0)	0	2 (8.0)	14 (14.0)	24 (17.3)
Joint swelling	0	9 (6.9)	1 (14.3)	2 (8.0)	14 (14.0)	23 (16.5)
Neck pain	0	11 (8.5)	1 (14.3)	1 (4.0)	7 (7.0)	17 (12.2)
Musculoskeletal chest pain	0	9 (6.9)	0	2 (8.0)	7 (7.0)	14 (10.1)

System Organ Class Preferred Term	Placebo/ Untreated (N=20)	Palovarotene Treatment Period				PVO Total (N=139)
		Chronic 5 mg (N=130)	Flare-up 5/2.5 mg (N=7)	Flare-up 10/5 mg (N=25)	Flare-up 20/10 mg (N=100)	
Injury, poisoning and procedural complications	5 (25.0)	66 (50.8)	0	7 (28.0)	41 (41.0)	89 (64.0)
Skin abrasion	0	13 (10.0)	0	2 (8.0)	22 (22.0)	32 (23.0)
Contusion	1 (5.0)	15 (11.5)	0	1 (4.0)	5 (5.0)	19 (13.7)
Fall	2 (10.0)	10 (7.7)	0	2 (8.0)	8 (8.0)	17 (12.2)
General disorders and administration site conditions	10 (50.0)	39 (30.0)	3 (42.9)	14 (56.0)	41 (41.0)	65 (46.8)
Condition aggravated	8 (40.0)	15 (11.5)	1 (14.3)	10 (40.0)	18 (18.0)	31 (22.3)
Pyrexia	3 (15.0)	11 (8.5)	2 (28.6)	2 (8.0)	12 (12.0)	21 (15.1)
Peripheral swelling	1 (5.0)	6 (4.6)	0	2 (8.0)	12 (12.0)	19 (13.7)
Fatigue	0	5 (3.8)	1 (14.3)	0	10 (10.0)	15 (10.8)
Respiratory, thoracic and mediastinal disorders	6 (30.0)	45 (34.6)	1 (14.3)	6 (24.0)	27 (27.0)	62 (44.6)
Cough	2 (10.0)	13 (10.0)	0	2 (8.0)	11 (11.0)	23 (16.5)
Epistaxis	0	13 (10.0)	1 (14.3)	1 (4.0)	10 (10.0)	20 (14.4)
Oropharyngeal pain	0	9 (6.9)	0	0	9 (9.0)	16 (11.5)
Nervous system disorders	8 (40.0)	38 (29.2)	2 (28.6)	10 (40.0)	32 (32.0)	60 (43.2)
Headache	4 (20.0)	18 (13.8)	0	7 (28.0)	17 (17.0)	36 (25.9)
Dizziness	0	5 (3.8)	1 (14.3)	1 (4.0)	10 (10.0)	14 (10.1)
Eye disorders	2 (10.0)	24 (18.5)	1 (14.3)	6 (24.0)	32 (32.0)	49 (35.3)
Dry eye	0	13 (10.0)	1 (14.3)	5 (20.0)	21 (21.0)	36 (25.9)
Metabolism and nutrition disorders	2 (10.0)	19 (14.6)	1 (14.3)	9 (36.0)	17 (17.0)	37 (26.6)
Decreased appetite	0	6 (4.6)	0	2 (8.0)	9 (9.0)	16 (11.5)

TEAE=treatment-emergent adverse event; PVO=palovarotene.

Description of selected adverse reactions

Paediatric population

Subjects <18 years with open epiphyses were assessed for growth during the clinical study. PPC was identified in 24 of 102 subjects (24%) <18 years of age and was more common in younger (<8/10 years: 14 of 25 subjects, 56%) compared with older (≥8/10 to <18 years: 10 of 77 subjects, 13%; ≥8/10 to <14 years: 10 of 39 subjects, 26%) subjects. In subjects who received only chronic dosing, PPC, when observed, typically occurred between 12 and 18 months. The higher proportion of younger subjects with PPC is not unexpected given that pre-adolescent individuals are not expected to have physiologic growth plate closure. Thus, any narrowing, partial closure, or closure are likely to be assessed as premature by the clinician. However, the possibility that younger subjects are predisposed to developing PPC

or are more sensitive to the effects of SOHONOS cannot be excluded (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.1 PHARMACODYNAMIC PROPERTIES).

SOHONOS is indicated in children aged 8 years and above for females and 10 years and above for males. However, children between the ages of 4 years and 8/10 years were included in the clinical studies and exposed to palovarotene. The safety profile for palovarotene in subjects with FOP was consistent across adult (≥18 years) and paediatric (≥8/10 to <18 years) age subgroups except for epiphyses premature fusion, which was more common in younger (<8/10 years, 56.0%) than older (≥8/10 to <18 years, 11.7%) paediatric subjects.

Some mucocutaneous effects such as decubitus ulcers had a higher incidence in adult subjects, which was consistent with disease burden, increasing disability, and prolonged exposure to corticosteroids.

A total of 8 subjects experienced severe cases of epiphyses premature fusion, of these 5 were in the <8 age group. SOHONOS must not be used in children under 8 years of age for females and 10 years of age for males.

Radiological vertebral fractures

Radiological vertebral fractures (PT: Spinal fracture) were identified as a risk associated with palovarotene based on analyses performed on WBCT data in FOP subjects in the Phase 3 (MOVE) study. See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

4.9 OVERDOSE

No clinical experience with an overdose of SOHONOS has been reported. A single supratherapeutic dose of 50 mg SOHONOS had no apparent effects on vital signs, ECGs, or clinical laboratory parameters. Palovarotene is a derivative of vitamin A. In case of accidental overdose, signs of hypervitaminosis A could appear, including severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Any overdose should be treated with supportive care according to the signs and symptoms exhibited by the patient.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other drugs for disorders of the musculo-skeletal system

ATC code: M09AX11

Mechanism of action

Palovarotene is a retinoic acid receptor gamma (RARγ) selective agonist. FOP (formerly referred as myositis ossificans progressiva) is a genetic condition caused by a gain-of-function mutation in the gene encoding activin A receptor type 1 (ACVR1; also known as

activin receptor-like kinase 2 [ALK2]), a bone morphogenetic protein (BMP) expressed by chondrocytes and osteoblasts. The mutant protein aberrantly activates the Smad1/5/8 signalling pathway, diverting mesenchymal progenitor cells from a soft tissue fate (allowing for normal tissue repair) to an osseous fate (promoting chondrogenesis and heterotopic bone formation). RARγ is expressed in chondrogenic cells and chondrocytes, where it operates as an unliganded transcriptional repressor. Activation of RARγ downregulates BMP signalling by reducing phosphorylation of downstream effectors Smad1/5/8. In this way, palovarotene prevents chondrogenesis and heterotopic ossification in FOP, and enables normal muscle tissue repair or regeneration to take place, reducing damage to muscle tissue.

Cardiac Electrophysiology

In a dedicated QT study, doses of SOHONOS up to 2.5 times the maximum approved recommended dose do not prolong the QT interval to any clinically relevant extent.

Clinical trials

Chronic/Flare-up Regimen

The MOVE study PVO-1A-301 (NCT03312634) was a Phase 3, single arm study in subjects with FOP aged 4 years and older. The study evaluated the efficacy and safety of the chronic/flare-up SOHONOS regimen in preventing new HO as assessed by low-dose, whole body CT (WBCT) imaging (excluding head) as compared to data from the Natural History Study (NHS, PVO-1A-001). The NHS was an international, 3-year, longitudinal, non-interventional study in 114 subjects with FOP with R206H mutation, with 98 subjects providing at least one post-baseline assessment. All WBCT images from treated subjects in the MOVE study and untreated subjects in the NHS were read in a manner blinded to study origination. Of the 107 subjects enrolled in the MOVE study, 99 had the R206H mutation and 8 had other FOP mutations. Of the 99 with the R206H mutation, 97 had at least one post-baseline HO volume measurement and were included in the Full Analysis Set.

MOVE study subjects received SOHONOS 5 mg daily with increased dosing at the time of a flare-up defined as at least one symptom (e.g. pain, swelling, redness) consistent with a previous flare-up or a substantial high-risk traumatic event likely to lead to a flare-up to 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks (denoted as the chronic/flare-up regimen), 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 a substantial high-risk traumatic event. The 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 0 months for girls and ≥14 years 0 months for boys). The treatment groups assessed in the chronic/flare-up regimen were well matched for baseline demographics.

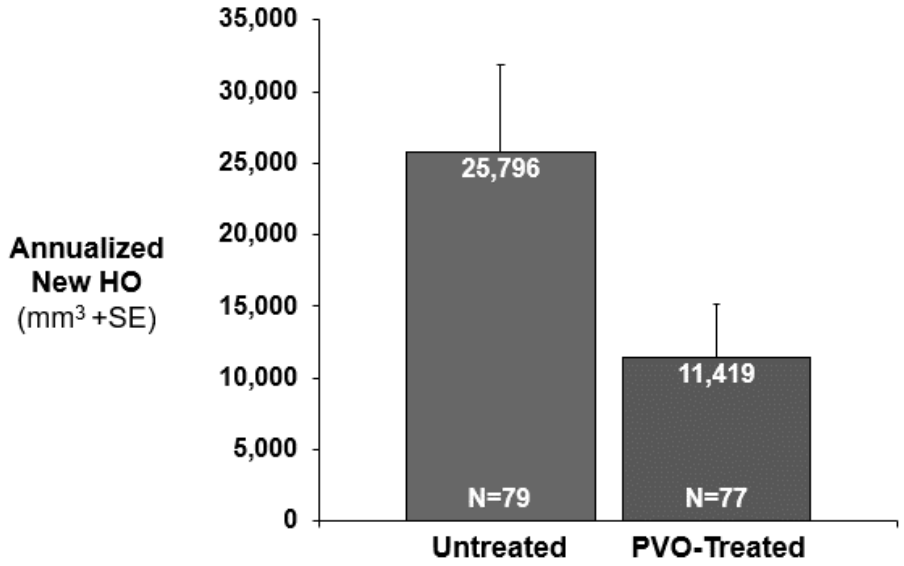
The median age (range) of subjects in the overall population in the SOHONOS group (N=99) was 13 (4, 61) years; and 15 (4, 56) years in the untreated group (N=111). There were more male than female subjects in both the SOHONOS (53.5% and 46.5%, respectively) and untreated (54.1% and 45.9%, respectively) groups.

The median age (range) of subjects in the target population aged 8 years and older for females or 10 years and older for males (≥8/10) in the SOHONOS group (N=79) was 14 (8,61) years; and 18 (9,56) years in the untreated group (N=88). There were more male than female subjects in both the SOHONOS (54.4% and 45.6%, respectively) and untreated (51.1% and 48.9%, respectively) groups.

In this study, post-hoc analyses showed that mean annualized new HO volume in the overall population was 60% lower in subjects receiving the chronic/flare-up SOHONOS-treatment (9,427 mm^3) versus untreated subjects from the NHS (23,720 mm^3). The weighted linear mixed effect (wLME) analysis showed 54% lower fitted mean annualized new HO volume in SOHONOS treated subjects (9,367 mm^3) versus untreated subjects in the NHS (20,273 mm^3) yielding 2-sided nominal p-value p=0.0392.

The mean annualized new HO volume in the target population of subjects ≥8/10 years in treated and untreated subjects is shown in Figure 1. Results were similar to the overall population, with the mean annualized new HO volume in SOHONOS treated subjects (11,419 mm^3) 56% lower than that observed in untreated subjects (25,796 mm^3). The wLME analysis showed 49 % lower fitted mean annualized new HO volume in SOHONOS treated subjects (11,033 mm^3) versus untreated subjects in the NHS (21,476 mm^3), yielding 2-sided nominal p-value p=0.1124.

Figure 1: Mean Annualized New HO Volume in subjects ≥8/10 years of Age in the MOVE Study



HO=heterotopic ossification; MOVE= study PVO-1A-301; SE=standard error; Figure summarizes mean observed annualized new HO.

Flare-up Only Regimen

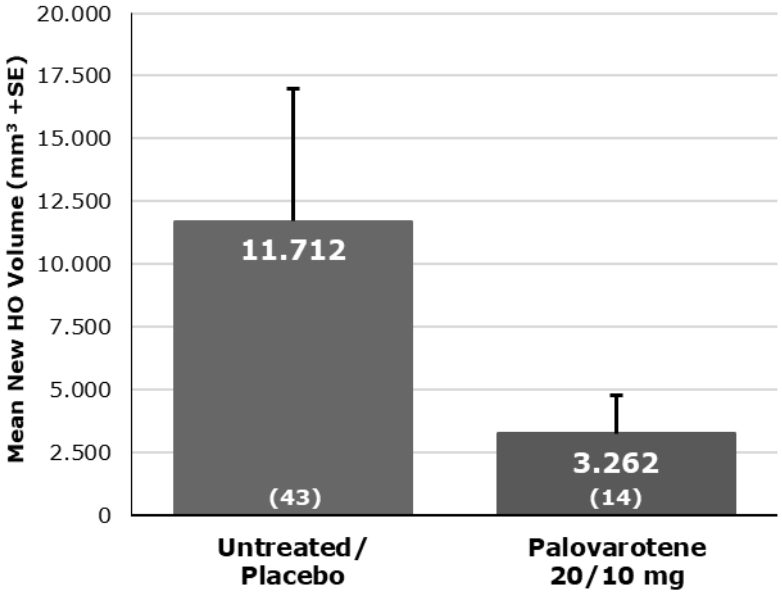
The flare-up only regimen was assessed in the Phase 2 program, including the double-blind, placebo-controlled Study PVO-1A-201 (NCT02190747); and open-label extension Study PVO-1A-202, (NCT02279095). Subjects participating in Study PVO-1A-201 were randomized in a 3:3:2 fashion to SOHONOS 10 mg for 2 weeks, then 5 mg for 4 weeks (10/5 mg treatment), SOHONOS 5 mg for 2 weeks, then 2.5 mg for 4 weeks (5/2.5 mg treatment), or placebo for 6 weeks, followed by a 6-week observation period for all groups. The clinical endpoint of mean volume of new HO following a flare-up at week 12 in evaluable flare-ups was assessed.

In Study PVO-1A-202 Part A subjects experiencing another flare-up received SOHONOS 10/5 mg treatment in an open label manner. In Study PVO-1A-202 Part B, subjects who were at least 90% skeletally mature received chronic 5 mg daily treatment with increased dosing at the time of a flare-up to 20 mg for 4 weeks followed by 10 mg for 8 weeks (chronic/flare-up regimen), with continuation of treatment in 4-week increments for persistent symptoms. Skeletally immature subjects received the 20/10 mg flare-up treatment (weight-adjusted) in Part B. The comparator group includes flare-ups imaged in untreated subjects from the NHS and placebo-treated flare-ups from Study PVO-1A-201. These two sources of subjects were similar with respect to demographics and baseline disease characteristics.

The median (range) age of subjects in the overall population in the SOHONOS 20/10 mg flare-up only treatment group was 11 (7, 34) years (N=12); and 15 (4, 53) years in the untreated group (N=42). The median (range) age of subjects in the target population aged 8 years and older for females or 10 years and older for males (≥8/10) was 11 (7, 34) years (N=12); and 15 (7, 53) years in the untreated group (N=38). The percentage of male subjects was 33.3% and 47.0% in the target population and similarly 33.3% and 50% in the total population in the respective groups.

In the overall population, the Phase 2 studies demonstrated a reduction of 72% (p-value of 0.02) in new HO volume in the 15 flare-ups treated with the 20/10 mg flare-up only dose (3,045 mm^3) compared to 47 placebo/untreated flare-ups (10,780 mm^3). In the target population, the Phase 2 studies demonstrated a reduction of 72% (p-value of 0.04) in new HO volume in the 14 flareups treated with the 20/10 mg flare-up only dose (3,262 mm^3) compared to 43 untreated (from NHS)/placebo flare-ups (11,712 mm^3) (see Figure 2). These results are supported by the 10/5 mg flare-up dose in both the target population (2,807 mm^3; 76% reduction; p-value of 0.10) and total population (3,010 mm^3; 72% reduction; p-value of 0.11).

Figure 2: **Mean Volume of New HO at week 12 in Palovarotene vs Placebo/untreated Flare-ups in subjects ≥8/10 years of Age**



Numbers in parentheses are the number of flare-ups; HO=heterotopic ossification; SE=standard error.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of palovarotene after oral administration have been well characterized from single and multiple dose studies in healthy subjects, in subjects with chronic obstructive pulmonary disease, multiple osteochondromas, and in subjects with FOP. Oral absorption of palovarotene is increased when given with food. For this reason, palovarotene was given with food in all the FOP trials.

Absorption

After administration of palovarotene 20 mg once daily for 14 days administered after a standard breakfast, the mean T_{max} was 4.6 hours, the average C_{max} was 140 ng/mL, and the average $AUC_{(0-\tau)}$ was 942 ng*hr/mL. Little or no accumulation was observed following once-daily dosing. The mean steady-state trough plasma concentration was 3.5 ng/mL after once-daily 20 mg palovarotene.

Effect of Food

Co-administration of 20 mg SOHONOS with a high-fat (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively), high-calorie (800 to 1200 kcal) meal increased mean palovarotene AUC by approximately 40% and mean C_{max} by approximately 16% and delayed T_{max} by approximately 2 hours. Palovarotene should be administered with food.

Plasma palovarotene AUC and C_{max} were comparable when either swallowed whole or the contents sprinkled onto applesauce following a high-fat, high-caloric breakfast.

Distribution

Protein binding of palovarotene is 97.9% to 99.6% *in vitro*. The mean apparent volume of distribution (Vd/F) is 237 L following a single fed 20 mg dose of palovarotene.

The mean blood-to-plasma ratio of palovarotene in humans is 0.62, indicating that palovarotene does not partition into erythrocytes.

Metabolism

Palovarotene is extensively metabolized by CYP3A4 and to a minor extent by CYP2C8 and CYP2C19. Five metabolites, M1 (6,7-dihydroxy), M2 (6-hydroxy), M3 (7-hydroxy), M4a (6-oxo), and M4b (7-oxo), were observed for palovarotene and reached steady-state by day 4 with high variability in plasma levels. M2, M3, M4a and M4b are the major human metabolites, with exposure to these approximately 20%, 60%, 20% and 40% that of the parent drug at steady state. The pharmacological activity of M2, M3, M4a and M4b is approximately 1.2%, 1.7%, 14% and 4.2% of the activity of the parent drug based on an in vitro RARγ transactivation assay.

Excretion

After administration of palovarotene 20 mg once daily for 14 days following a standard breakfast, the mean elimination half-life is 8.7 hours. From a population PK analysis, the apparent total body clearance (CL/F) is estimated at 19.9 L/h across dose levels and across studies, supporting dose linearity.

Following administration of a 1 mg dose of [^{14}C]-radiolabelled palovarotene in healthy subjects, 97.1% of the dose was recovered in the faeces and 3.2% in the urine. More than 92% of the dose was recovered in the first 6 days post-dose and mass balance was achieved with 100% of the dose recovered by day 14.

Linearity/non-linearity

In a population PK analysis, the pharmacokinetics of palovarotene were linear and dose-proportional from 0.02 to 50 mg (after single dose administration in healthy volunteers). In the target population, dose proportionality was observed following chronic (5 mg) and flare-up (20 mg and 10 mg) dosing.

Special Populations

The pharmacokinetics of palovarotene in pregnant women is unknown.

Palovarotene has minimal renal clearance. No specific studies have been conducted in subjects with impaired renal function. There are no data in patients with severe renal impairment or patients on dialysis.

Palovarotene is metabolised in the liver. No specific studies have been conducted in subjects with impaired hepatic function. There are no data in patients with severe hepatic impairment.

Based on a population PK analysis, there was no evidence that age, sex, race, smoking status, or health status affected palovarotene pharmacokinetics. No clinically significant differences in the PK of palovarotene were observed in subjects with mild and moderate renal impairment and with mild hepatic impairment. Body weight was found to have a significant impact on palovarotene PK resulting in increasing exposure with decreasing weight at the same dose.

Semen Exposure in Males

Based on the results of a clinical study in 24 healthy male subjects, and the maximal palovarotene amount that has been quantified in a single ejaculate (33 ng or ~0.00017% of the daily dose administered), the maximum potential fetal exposure to palovarotene through semen is estimated to be 0.0066 ng/mL which is less than 1/100th of the exposure at the NOAEL for effects on embryofetal development.

Paediatric Patients

Weight-adjusted doses for skeletally immature children in the FOP studies were selected for four defined weight categories (See section 4.2) to provide similar exposure to adolescents and adults receiving doses from 5 to 20 mg palovarotene. The appropriateness of the selected weight-based dosing was assessed in the population PK analysis. Based on simulations in a paediatric population, the derived steady-state exposure metrics ($AUC_{0-\tau}$, and $C_{max,ss}$) following weight-based dosing for 5, 10 and, 20 mg (or dose equivalent) in skeletally immature paediatric patients is presented by weight category in Table 5 below:

Table 5: Summary of Steady-State Exposure (50% Median) Following 5, 10 and, 20 mg SOHONOS in Paediatric Population by Weight Category

Regimen	Weight Category / Dose	$C_{max, ss}$ (ng/mL)*	$AUC_{24, ss}$ (ng·hr/mL)*
5 mg qd	<20 kg / 2.5 mg	50.6 (47.1-54.0)	263 (243-282)
	20-40 kg / 3 mg	40.0 (38.2-42.2)	237 (225-248)
	40-60 kg / 4 mg	36.7 (34.3-39.0)	242 (228-254)
	≥60 kg / 5 mg	35.9 (32.8-39.6)	252 (232-277)
10 mg qd	<20 kg / 5 mg	101 (94.1-108)	527 (485-563)
	20-40 kg / 6 mg	80.0 (76.3-84.4)	474 (450-495)
	40-60 kg / 7.5 mg	68.8 (64.4-73.2)	454 (428-476)
	≥60 kg / 10 mg	71.9 (65.7-79.1)	504 (464-554)
20 mg qd	<20 kg / 10 mg	202 (188-216)	1054 (971-1126)
	20-40 kg / 12.5 mg	167 (159-176)	988 (938-1032)
	40-60 kg / 15 mg	138 (129-146)	909 (856-952)
	≥60 kg / 20 mg	144 (131-158)	1008 (928-1107)

** 50th Median (90% PI)*

The simulated overall exposure ($AUC_{24, ss}$) was comparable for the equivalent doses across the different weight groups, indicating that the weight-based dose scheme provides similar exposure between the paediatric weight groups.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Palovarotene and its four major metabolites were negative in assays for mutagenicity in bacteria (Ames test) and showed no direct clastogenic activity in vitro (chromosomal aberration assays in human lymphocytes). Negative results for clastogenicity were also obtained for palovarotene in vivo in the mouse bone marrow micronucleus test.

Carcinogenicity

Carcinogenicity studies have not been conducted with palovarotene.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content:

Lactose monohydrate
Povidone
Croscarmellose sodium
Sodium lauryl sulfate
Microcrystalline cellulose
Magnesium stearate

Capsule shell:

Gelatin
Titanium dioxide

Printing ink:

Shellac
Propylene glycol
Potassium hydroxide
Iron oxide black

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for other medicinal products which should be avoided during treatment with SOHONOS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Capsules are packaged into a blister strip composed of PVC/PCTFE (polyvinylchloride/poly-chloro-tri-fluoro-ethylene) backed with push-through aluminium foil. The blister strips are then packaged into a carton.

Each pack contains 28 capsules (2 x 14 blister strips).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

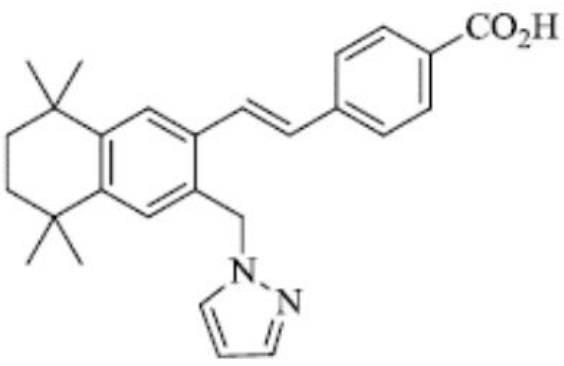
Women who are pregnant or intend to become pregnant should avoid contact with SOHONOS. Additionally, to avoid unintended exposure caregivers administering SOHONOS by emptying the capsule contents onto soft food should wear disposable gloves when handling and use disposable paper towels and a container to collect waste (e.g. a resealable bag).

6.7 PHYSICOCHEMICAL PROPERTIES

Palovarotene is a white to off-white, non-hygroscopic, crystalline solid. It is practically insoluble in aqueous buffer and water, slightly soluble in ethanol, and very slightly soluble in organic solvents.

Chemical structure

The molecular formula of palovarotene is $C_{27}H_{30}N_2O_2$.



IUPAC name: 4-[(E)-2-[5,5,8,8-tetramethyl-3-(pyrazol-1-ylmethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]ethenyl]benzoic acid

4-[(E)-2-[5,5,8,8-tetramethyl-3-(pyrazol-1-ylmethyl)-6,7-dihydronaphthalen-2-yl]ethenyl]benzoic acid

Molecular weight: 414.54 g/mol

CAS number

410528-02-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Ipsen Pty Ltd
Level 5
627 Chapel Street
South Yarra Victoria 3141

Telephone: 1800 317 033

9 DATE OF FIRST APPROVAL

28 November 2023

10 DATE OF REVISION

N/A