PRESS RELEASE

US FDA approves Ipsen's Sohonos™ (palovarotene) capsules, the first and only treatment for people with fibrodysplasia ossificans progressiva

- Breakthrough treatment reduces new, abnormal bone formation in soft and connective tissues, in people living with ultra-rare bone disease, fibrodysplasia ossificans progressiva (FOP)
- FOP impacts about 400 people in the U.S., it leads to progressive mobility loss, severely limits quality of life and shortens median life expectancy to 56 years
- Sohonos™ may be prescribed immediately in the U.S. for eligible patients, aged 8 years and older for females and 10 years and older for males

PARIS, FRANCE, 16 August 2023 – Ipsen (Euronext: IPN; ADR: IPSEY) announced today approval by the U.S. Food and Drug Administration (FDA) of Sohonos™ (palovarotene) capsules as a retinoid 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).

"The FDA approval of Sohonos is a breakthrough for the U.S. FOP community. For the first time doctors have an approved medicine available to them, shown to reduce the formation of new, abnormal bone growth, known as heterotopic ossification (HO), which causes debilitating mobility challenges and has a devastating impact on the lives of people with FOP," said Howard Mayer, Head of Research and Development, Ipsen. "Development of medicines for rare diseases takes commitment and belief from everyone involved. We at Ipsen are sincerely grateful to the FOP community of patients and medical experts, as the first-ever treatment in the U.S. for managing FOP would not be possible without their participation in the clinical trials and ongoing support."

FOP impacts the lives of an estimated 400 people in the U.S. and 900 people globally.[1,2] As the disease continuously progresses with flare-up episodes causing rapid bone growth, HO severely restricts mobility and function.[3,4] Most people living with FOP inevitably lose the ability to eat and drink on their own, cannot provide selfcare or use the restroom themselves, and are unable to maintain employment.[5] By the age of 30 years old, the majority of people with FOP require a wheelchair and full-time caregiver assistance.[3,6] The management of FOP has previously been limited to palliative care and ultimately, FOP shortens the median life expectancy to 56 years, untimely death is often caused by bone formation around the ribcage leading to breathing problems and cardiorespiratory failure, or falls resulting in fractures or head injuries because joint ankylosis prevents bracing from a fall.[7]

"FOP is life-altering to the individuals diagnosed and their families. There's not a day that goes by where those impacted don't worry about the debilitating physical pain of muscle that is replaced by bone, another joint locking or the relentless emotional toll of losing the ability to do an activity they love, or hold a loved one close," explained Michelle Davis, Executive Director of International FOP Association. "The first treatment for FOP has been proven to reduce the volume of new abnormal bone growth, which may result in better health outcomes for people living with FOP."

The FDA approval is based on the pivotal efficacy and safety data from the Phase III MOVE trial, the first and largest multicenter, open-label trial in adult and pediatric patients. The 18-month data published in the *Journal of Bone and Mineral Research*,[8] included 107 patients (12 percent of the estimated number

of individuals worldwide living with FOP) who received oral palovarotene compared with untreated individuals from Ipsen's global FOP Natural History Study.[9] The study results demonstrated palovarotene effectively reduced annualized heterotopic ossification volume compared with no treatment beyond standard of care, (54% reduction with weighted linear mixed effect model).[8] The study also demonstrated that palovarotene has a well-characterized safety profile, with adverse events consistent with the systemic retinoid class. The most common treatment emergent adverse reactions reported in the study were mucocutaneous events such as dry skin, lip dryness, alopecia, drug eruption, rash, and pruritus and musculoskeletal events such as arthralgia and premature growth plate closure in growing children. [8]

"As a clinician caring for patients with FOP, I personally see the daily challenges and stresses that our patients and their families must contend with," said Dr Edward Hsiao, Professor of Medicine, Division of Endocrinology and Metabolism, University of California, San Francisco. "The published Phase III MOVE study showed that Sohonos can decrease new heterotopic ossification, and that palovarotene can be tolerated by many patients with FOP. Sohonos is not for everyone. As with all medicines there are risks in this case especially for young children who may develop early growth plate closure. In addition, Sohonos has the same side effects as other retinoids, including dryness of the skin and mucus membranes. However, since the accumulation of HO in FOP is progressive, irreversible, and life altering, this medication is an important treatment option for our FOP community."

Sohonos, the first and only treatment for FOP

Sohonos is an oral medicine with particular selectivity for the gamma subtype of retinoic-acid receptors, which are an important regulator of skeletal development and ectopic bone in the retinoid signaling pathway. The medicine is designed to mediate the interactions between the receptors, growth factors and proteins within the retinoid signaling pathway to reduce new abnormal bone formation in FOP. The recommended dosing for Sohonos includes a chronic daily dosage of 5 mg (or weight-based equivalent for pediatric patients under 14 years of age), which can be modified/increased for flare-up symptoms. Sohonos may be prescribed immediately in the U.S. for eligible patients.

To ensure access to Sohonos for eligible individuals in the U.S., Ipsen Cares patient support program is available as a resource to people living with FOP and their caregivers to provide educational support and address coverage, access and reimbursement questions (1-866-435-5677).

Sohonos received Orphan Drug and Breakthrough Therapy Designations from the U.S. Food and Drug Administration (FDA) for the treatment of FOP and was granted Priority Review of the New Drug Application (NDA). Sohonos, under the generic name palovarotene, is also under review with a number of other regulatory authorities. In July 2023, the European Commission did not grant marketing authorization for palovarotene. Sohonos™ (palovarotene capsules) is currently authorized for use in eligible patients in U.S., Canada,[10] and with a conditional approval in the United Arab Emirates.

With this approval the FDA also issued a Rare Pediatric Disease Priority Review Voucher (PRV). The voucher can be used for subsequent drug applications that would not qualify for a priority review.

Important Sohonos Safety Information

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

Embryo-Fetal Toxicity

SOHONOS is contraindicated in pregnancy. SOHONOS can 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.

Contraindications
SOHONOS is contraindicated in patients during pregnancy, or with a history of allergy or hypersensitivity to retinoids, or to any component of SOHONOS.

Warnings and Precautions
- **Embryo-Fetal Toxicity**: SOHONOS can cause fetal harm and is contraindicated during pregnancy. Advise females of reproductive potential to use an effective method of contraception during treatment with SOHONOS and for 1 month after the last dose. If a pregnancy occurs during Sohonos treatment, discontinue treatment immediately and refer the patient to an obstetrician/gynecologist experienced in reproductive toxicity.
- **Premature Epiphyseal Closure in Growing Pediatric Patients:** SOHONOS can cause irreversible premature epiphyseal closure and potential adverse effects on growth. 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 appropriate, temporary or permanent discontinuation may be warranted.
- **Mucocutaneous Adverse Reactions:** Dry skin, lip dry, pruritis, rash, alopecia, erythema, skin exfoliation [skin peeling] and, dry eye occurred with SOHONOS. 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 have been associated with the use of retinoids and may occur with SOHONOS. Precautionary measures for phototoxicity are recommended (e.g., use of sunscreens, protective clothing, and use of sunglasses).
- **Metabolic Bone Disorders**: Increased risk of radiologically observed vertebral fractures and decreased vertebral bone mineral content and bone density. 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. Monitor for development of new or worsening psychiatric symptoms during treatment with SOHONOS. 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%) in clinical trials include 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 CYP3A3 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.

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 full Prescribing Information, including BOXED WARNING on Ipsen.com/us

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About Ipsen

Ipsen is a global, mid-sized biopharmaceutical company focused on transformative medicines in Oncology, Rare Disease and Neuroscience. With total sales of €3.0bn in FY 2022, Ipsen sells medicines in over 100 countries. Alongside its external-innovation strategy, the Company's research and development efforts are focused on its innovative and differentiated technological platforms located in the heart of leading biotechnological and life-science hubs: Paris-Saclay, France; Oxford, U.K.; Cambridge, U.S.; Shanghai, China. Ipsen has around 5,300 colleagues worldwide and is listed in Paris (Euronext: IPN) and in the U.S. through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information, visit ipsen.com

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Ipsen's forward-looking statements

The forward-looking statements, objectives and targets contained herein are based on Ipsen's management strategy, current views and assumptions. Such statements involve known and unknown risks and uncertainties that may cause actual results, performance or events to differ materially from those anticipated herein. All of the above risks could affect Ipsen's future ability to achieve its financial targets, which were set assuming reasonable macroeconomic conditions based on the information available today. Use of the words 'believes', 'anticipates' and 'expects' and similar expressions are intended to identify forward-looking statements, including Ipsen's expectations regarding future events, including regulatory filings and determinations. Moreover, the targets described in this document were prepared without taking into account external-growth assumptions and potential future acquisitions, which may alter these parameters. These objectives are based on data and assumptions regarded as reasonable by Ipsen. These targets depend on conditions or facts likely to happen in the future, and not exclusively on historical data. Actual results may depart significantly from these targets given the occurrence of certain risks and uncertainties, notably the fact that a promising medicine in early development phase or clinical trial may end up never being launched on the market or reaching its commercial targets, notably for regulatory or competition reasons. Ipsen must face or might face competition from generic medicine that might translate into a loss of market share. Furthermore, the research and development process involves several stages each of which involves the substantial risk that Ipsen may fail to achieve its objectives and be forced to abandon its efforts with regards to a medicine in which it has invested significant sums. Therefore, Ipsen cannot be certain that favorable results obtained during preclinical trials will be confirmed subsequently during clinical trials, or that the results of clinical trials will be sufficient to demonstrate the safe and effective nature of the medicine concerned. There can be no guarantees a medicine will receive the necessary regulatory approvals or that the medicine will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements. Other risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and healthcare legislation; global trends toward healthcare cost containment; technological advances, new medicine and patents attained by competitors; challenges inherent in new-medicine development, including obtaining regulatory approval; Ipsen's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Ipsen's patents and other protections for innovative medicines; and the exposure to litigation, including patent litigation, and/or regulatory actions. Ipsen also depends on third parties to develop and market some of its medicines which could potentially generate substantial royalties; these partners could behave in such ways which could cause damage to Ipsen's activities and financial results. Ipsen cannot be certain that its partners will fulfil their obligations. It might be unable to obtain any benefit from those agreements. A default by any of Ipsen's partners could generate lower revenues than expected. Such situations could have a negative impact on Ipsen's business, financial position or performance. Ipsen expressly disclaims any obligation or undertaking to update or revise any forward-looking statements, targets or estimates contained in this press release to reflect any change in events, conditions, assumptions or circumstances on which any such statements are based, unless so required by applicable law. Ipsen's business is subject to the risk factors outlined in its registration documents filed with the French Autorité des Marchés Financiers. The risks and uncertainties set out are not exhaustive and the reader is advised to refer to Ipsen's latest Universal Registration Document, available on ipsen.com.

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