August 16, 2023

Statement regarding palovarotene from the International Clinical Council (ICC) on FOP

The International Clinical Council (ICC) on FOP is aware of the recent decisions by the United States Food and Drug Administration (FDA), the European Medicines Agency, and Health Canada on the use of palovarotene for the treatment of fibrodysplasia ossificans progressiva (FOP). The ICC has no direct influence on these regulatory decisions, as we believe it is important that the review and regulatory processes play out in accordance with established scientific and legal principles.

On August 16th, 2023, the US FDA announced the approval of palovarotene for the treatment of FOP. Palovarotene has been evaluated by other regulatory agencies, including approval by Health Canada in January 2022, and rejection by the European Medicines Agency (EMA) in June 2023. The FDA advisory committee in June 2023 made a non-unanimous positive recommendation, with notable concerns regarding the benefit/risk balance, significant risks of side effects, and reliance on post-hoc analyses of the data.

FOP is a devastating genetic disease where progressive abnormal bone formation (heterotopic ossification, HO) leads to loss of mobility, independence, and quality of life. To date, only symptomatic treatments are available. Palovarotene is a small molecule in the retinoid class and represents the first drug approved specifically for decreasing new HO formation in patients with FOP.

The ICC has reviewed the data publicly presented to the FDA advisory committee in June 2023, as well as reviewed the publications of the Natural History Study (Pignolo, et al. Genet. Med 2022) and the Phase III MOVE Trial (Pignolo et al., J Bone Mineral Res 2023). The primary analysis of the data raised significant concerns about the efficacy of palovarotene in blocking new HO formation, and in fact met the futility criteria for stopping the trial due to these concerns. Examination of the data after unblinding revealed deficiencies in the planned analysis method. Multiple subsequent post-hoc analyses, performed both by Ipsen and the FDA, suggested that palovarotene likely reduced new HO formation by 50-60%. The Phase III MOVE trial also showed that palovarotene had significant side effects, including the risk of early growth plate closure in younger patients with FOP and complications related to the retinoid class of medications (skin rash, dry skin and eyes, possible bone loss, etc.).

The members of the ICC strongly support the continued development of therapies for treating the devastating consequences of FOP.

Palovarotene represents a first step in that direction, with approval in the USA, Canada, and UAE. However, the ICC also feels that there are significant limitations to the existing data – specifically the necessarily short-term results of a clinical trial for a drug that is expected to be used lifelong; the still unanswered questions regarding the exact efficacy of reduction of HO bone formation; the unclear impact on long-term functional outcomes; and the potential for significant side effects and bone toxicity especially in children.

Therefore, the ICC recommends:

- If a patient with FOP considers palovarotene, the potential benefits and risks, as detailed in the package insert, by the MOVE trial publication, and in subsequent publications, must be discussed in detail with the patient and the patient's medical team.
- Additional risks should be explicitly discussed, including potential effects on bone health (loss of bone mass), skin/mucosal dryness and complications, potential for eye complications, and the risk of fetal malformations in pregnancy. The ICC supports continued close long-term followup of these potential complications.
- A long term, detailed study of the safety and efficacy of palovarotene should be pursued, such as through a registry or formalized long-term study.
- Standard-of-care therapies, as recommended by the FOP Treatment Guidelines (available at ICCFOP.org), should still be used in combination with palovarotene as appropriate, and with guidance from the patient's medical team.
- Worldwide affordable access to palovarotene should be facilitated, including ensuring reasonable cost for therapy.
- Careful monitoring of patients to prevent pregnancy while on palovarotene should be required, due to the known teratogenicity of the retinoid class of medications.
- Careful education of potential drug interactions, including with antibiotics like tetracycline or doxycycline, should be required.
- Patients should not use non-pharmaceutical grade palovarotene.

The ICC continues to support open discussions and data sharing in all clinical trials and studies as potential therapies for FOP are examined.

While the majority of ICC members believe that palovarotene may have benefits for the care of patients with FOP, a number of ICC members had serious concerns about its approval and use. These concerns include the high risk of growth plate effects in young children with FOP, leading to a potential consideration that palovarotene should never be used in growing children. In addition, the long-term risks of treatment with palovarotene remain unknown, and could result in significant secondary complications that have yet to be identified. Furthermore, the use of palovarotene may impact a patient's ability to take certain medications or participate in clinical trials.

The FOP treatment guidelines at ICCFOP.org will be updated with additional information once palovarotene is available commercially in the jurisdictions where it has been approved. In addition, the ICC is planning a future review manuscript regarding palovarotene.

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The ICC is an international collaboration of 21 clinicians worldwide with expertise in the care of patients with FOP. The ICC seeks to consolidate and coordinate clinical knowledge and advice on clinical care, symptomatic treatment, and clinical trial development into a framework that best serves the needs of FOP patient community

worldwide. Details and current membership of the ICC can be found on the ICCFOP.org website. Individuals on the ICC may have roles as volunteer or paid advisors, consultants, or research investigators affiliated with pharmaceutical companies. These disclosures are available on request. Statements credited to an individual reflect the opinion of that person, and do not reflect the opinion of the ICC.