**National Institute for Health and Care Excellence**

**Highly specialised technology evaluation**

# Palovarotene for preventing heterotopic ossification associated with fibrodysplasia ossificans progressiva

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**Comment 1: the draft remit**

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| Appropriateness | Ipsen | Yes, it is appropriate to refer palovarotene via the NICE Highly Specialised Technology (HST) appraisal pathway.<br>Fibrodysplasia ossificans progressiva (FOP) is a very rare, life-shortening, genetic disorder[1] and treatment of patients with FOP is currently concentrated in a small number of specialist centres.<br>FOP is characterised by heterotopic ossification (HO), whereby soft tissue is gradually replaced by bone. Accumulation of HO drives the progressive disability and premature death in patients with FOP.[2]<br>There are currently no approved treatments for FOP and current management involves symptom management. There is therefore a clear unmet need for disease-modifying treatments.<br>Palovarotene is a novel treatment that reduces new HO in patients with FOP. Given that HO drives progressive disability in FOP, palovarotene is likely to slow disease progression. Palovarotene therefore meets the unmet need for | Thank you for your comment. No action required. |

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| | | a disease-modifying treatment in FOP and timely UK reimbursement is essential.<br>Further information is provided below regarding how palovarotene meets all four criteria in the new NICE topic selection manual for the HST Programme (implemented from 01 February 2022). | |
| Wording | Ipsen | Yes, the wording is accurate. | Thank you for your comment. No action required. |
| Timing Issues | Ipsen | There is an urgency for palovarotene to be available in the UK as FOP is a seriously debilitating and progressive condition.<br>FOP is progressively disabling due to progressive HO. Most patients need to use a wheelchair by early adulthood and require lifelong assistance in performing everyday activities. The median life expectancy for people with FOP in the UK is around 56 years.[3] Thoracic insufficiency syndrome is the primary cause of death (54% of patients) and is linked to HO in the cardiothoracic region.[4] Thus, preventing HO is likely to reduce mortality.<br>There are currently no disease-modifying treatment options for patients with FOP, so there is a clear unmet need. Palovarotene meets this unmet need and there is, therefore, a clear urgency for palovarotene to be reviewed by NICE in a timely manner. | Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information, please see https://www.nice.org.uk/guidance/awaiting-development/gid-hst10032 |

**Comment 2: the draft scope**

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| Background information | FOP Friends | The background does not include mention of the impact FOP has on education, employment, schooling, and the family.<br><br>FOP patients also suffer from issues outside of flare-ups and bone-growth. Issues such as joint issue, kidney stones, neurological complaints, mental health in dealing not only with restriction but the progressive nature of FOP and not knowing if they will awake with another restriction.<br><br>Inclusion of FOP being triggered by viruses such as Flu and Covid and because trauma causes FOP to progress intramuscular immunizations are high-risk of trigging FOP and therefore losing mobility in that limb.<br><br>There are also more dental and health issues related with limited or no jaw movement and mouth opening, choking, concerns over vomiting, food intake and malnutrition.<br><br>FOP patients are subject to high mortality due to head injuries from falling without patients being able to move to “break their fall”. We have had recent deaths within the FOP community due to falls of this nature.<br><br>Because FOP is also trauma induced that there is no-way to remove unwanted bone-growth without triggering more. Without a treatment FOP progression is irreversible.<br><br>It should be noted that FOP converts muscle, tendons and ligaments to bone so even at the point a treatment allows for unwanted bone to be removed what was there before is gone. | Thank you for your comment. The background section aims to provide a brief overview of the disease. The scope background mentions that people with FOP experience flare-ups and that bone growth may be triggered by trauma and viral infection. |

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| | | The extra-skeletal bone restricting the chest and lungs of a FOP patient also means that they often succumb to pneumonia.<br><br>A proportion of FOP patients suffer from sever scoliosis of the spine resulting in the constriction of internal organs and further shortened life expectancy.<br><br>FOP patients also must live in a world where any injury, trip, fall, knock, bump could trigger their FOP and irreversible progression. This is a difficult, stressful and anxiety causing, situation for the patient to live with but also anyone who is tasked with caring for a person with FOP, from family and carers through to teachers, employers.<br><br>Inclusion of the impact of living with FOP on mental health of patients and carers should be considered. The impact of living with FOP goes beyond the patient to the family and carers whose lives are also irreversibly changed.<br><br>A severely restricted FOP patient requires multiple full-time carers and once mobility is further impacted, specialist wheelchairs and transport. “normal” wheelchairs do not work.<br><br>FOP restrictions result in many physical limitation and contortions that traditional household adaptations for daily living do not meet a patient need. Patients often must fashion their own solutions to daily living including hygiene, toileting, and dressing. | |
| | Ipsen | Within the Background Information it is stated: “*The abnormal bone formation results in progressive movement restriction in the affected areas*".<br><br>Ipsen would like to amend this sentence to: “*HO in the soft tissue surrounding the joints drives the disability in FOP, as it causes loss of joint* | Thank you for your comment. The scope background has been updated with the |

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| | | *function, stiffness and, over time, movement restriction in the affected areas*.[5]"<br><br>A recent study by Baujat et al (2017)[6] identified a total number of 89 FOP patients based on a population of 65 million in mainland France. The authors estimated a prevalence of FOP of 1.36 per million. Using the same estimated prevalence rate, this would give 91 patients in the UK (based on a UK population of 67.1 million). According to the FOP Friends website (UK patient group), there are around 80 known people with FOP in the UK. [redacted]<br><br>Ipsen also notes that the median life expectancy is 56 years according to a registry study involving ~90% of known FOP patients,[4] rather than the 40 years stated in the draft scope. Most deaths among patients with FOP (54%) are related to thoracic insufficiency syndrome. Thoracic insufficiency syndrome is fatal and is the inability of the thorax to support normal breathing or lung growth and is primarily caused by HO in the thoracic region. By preventing HO, palovarotene may prevent or slow the onset of thoracic insufficiency syndrome, in turn prolonging survival.[4]<br><br>The background information states: "*There are currently no curative treatment options for the condition*;". IPSEN recommends amending the sentence to include "*disease modifying*" instead of (or in addition to) curative. A key aim of FOP treatments is to reduce HO, which drives the progressive disability in FOP. Disease modifying may therefore be a more appropriate term to use. | proposed change. The life expectancy of people with FOP has been updated to around 56 years. The phrase 'curative treatment' has been replaced with 'disease modifying treatment' as discussed and agreed at the scoping workshop. |
| The technology/ intervention | Ipsen | No. Please replace with the following:<br>*Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist. FOP is a genetic condition caused by a gain-of-function mutation in the ACVR1/ALK2 gene, which encodes activin receptor type* | Thank you for your comment. NICE no longer routinely includes a description of |

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| | | *1A/activin receptor-like kinase 2, a bone morphogenetic protein (BMP) type I receptor. This ALK2 gain-of-function mutation aberrantly activates the BMP-mediated Smad1/5/8 signalling pathway, diverting normal soft tissue (muscles, tendons and ligaments) injury repair mechanisms away from tissue regeneration by promoting chondrogenesis and HO formation.*<br><br>*RARγ is expressed in chondrogenic cells and chondrocytes operating as an unliganded transcriptional repressor. Through binding to RARγ, palovarotene decreases BMP signalling and inhibits SMAD1/5/8 signalling, which are deeply involved in the pathogenesis of myositis ossificans, hence in FOP. By interfering with these pathways, palovarotene prevents chondrogenesis and ultimately HO by enabling normal muscle tissue repair or regeneration to take place, which reduces damage to muscle tissue.* | the technology in the scope, so the proposed changes have not been incorporated. |
| Population | Genetic Alliance | Clarity on whether this scope includes adults and children with fibrodysplasia ossificans progressiva (FOP) would be appreciated and we wish to stress the importance that the scope of the evaluation is in line with the market authorisation in terms of eligible patients for this treatment. | Thank you for your comment. As discussed at the workshop, the scope population has been defined as 'people with clinically diagnosed fibrodysplasia ossificans progressiva confirmed by genetic testing'. This broad population includes adults and children in line with the MOVE trial. |
| | Ipsen | Ipsen notes that the population is not defined accurately.<br>It would be more appropriate to define the population as "people with clinically diagnosed fibrodysplasia ossificans progressiva confirmed by genetic testing". | Thank you for your comment. It was agreed at the scoping workshop that the |

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| | | Because of its rarity, FOP is challenging to diagnose and in 80% of the cases, it is initially misdiagnosed. Most individuals are diagnosed in mid-childhood, the first flare-ups occurring usually before the age of 10.<br>Genetic testing can confirm a diagnosis of FOP through the detection of the ALK2/ACVR1 gene.[7] | population should be 'people with clinically diagnosed fibrodysplasia ossificans progressiva confirmed by genetic testing'. |
| Comparators | Ipsen | Ipsen agrees that the best supportive care is an appropriate comparator, defined as established clinical management without palovarotene.<br><br>Currently there are no effective medical treatment options to prevent HO in FOP, nor have there been well-controlled trials for other disease-modifying therapeutics to date.<br><br>Established clinical management entails symptomatic therapies alongside avoidance of trauma.[8,9] Symptomatic therapy are not indicated specifically in FOP and do not treat the underlying cause. They include:<br>• Glucocorticoids to manage symptoms of flare-ups affecting major joints of the appendicular skeleton and jaw, especially when used immediately after the onset of a flare-up.<br>• Non-steroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, mast cell stabilisers, and leukotriene inhibitors, used to manage chronic pain and ongoing symptoms.<br><br>Established clinical management also includes avoidance of trauma, as trauma can trigger flare-ups leading to HO. Trauma includes surgery (including surgery to remove HO), intramuscular immunisations, blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, or falls, and influenza-like viral illnesses.[10] In one survey, flare-ups were induced in two-thirds of falls and resulted in permanent loss of movement in 93% of patients, resulting in both increased treatment costs to treat flare-ups and | Thank you for your comment. No action required. |

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| | | increased resource use to accommodate the worsening conditioning.[11] In addition to minimising the occurrence of falls and other traumas, treatments that may reduce their impact by preventing HO formation may help to slow disease progression.<br><br>In the absence of approved disease-modifying treatments for FOP, there is a high unmet need for treatments that address the underlying pathophysiology of the disease (i.e. excessive formation of bone/HO), which drives the progressive disability seen in patients with FOP.[7] | |
| Outcomes | FOP Friends | Outcomes should also include mental wellbeing alongside outcomes directly related to the clinical side of FOP and its progression. | Thank you for your comment. The outcome 'health-related quality of life' includes both the physical and mental impacts of the disease. |
| | Ipsen | Ipsen agrees that the proposed outcomes capture the most important health-related measures for patients with FOP:<br>• amount of new HO<br>• rate of soft tissue swelling (flare-ups)<br>• changes in movement and physical function (including active range of motion)<br>• overall survival<br>• adverse effects of treatment<br>• health-related quality of life for patients and carers<br><br>Please note that overall survival was not an outcome measure in the MOVE trial for palovarotene, so should be removed. | Thank you for your comment. It was discussed at the workshop that overall survival will likely be relevant for the economic modelling, so it has been retained as an outcome. It was also discussed that respiratory function is an important consideration for people with HO and FOP so it has been added as an |

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| | | Please note that a long period of time may be required to fully realise the efficacy benefit of treatment on some of the efficacy outcomes (e.g. changes in movement and physical functions). | outcome. Due to the discussion of premature physeal closure, the scope also states 'including growth and final height' in brackets for adverse effects of treatment. |
| Equality and Diversity | Ipsen | No comments. | No action required. |
| Other considerations | Ipsen | There is considerable UK public interest in FOP as indicated by an e-petition (564582) on "dedicated funding for research into Fibrodysplasia Ossificans Progressiva (FOP)", which received over 111,000 signatures. This led to a Parliamentary debate on 30 November 2021 (CDP 2021/0204) that included requests to parliament to fund newborn screening for FOP, greater support for unpaid family carers, greater funding for FOP clinical research, and greater funding for specialist care and treatments. The status and timelines of the palovarotene HST were specifically questioned, highlighting the urgent need for this treatment. | Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information, please see https://www.nice.org.uk/guidance/awaiting-development/gid-hst10032 |

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| Innovation | FOP Friends | Yes, this would be the first treatment for FOP that slows progression, this would be massively impactful for the patient and their lives, opening a wider world of possibility in education, work and life as progressive physical restriction would be slowed.<br><br>It would provide one tool in the arsenal of a patient or family living with FOP to slow the damage it causes.<br><br>This not only benefits the patient but their entire support network, both professional and personal, reducing stressors on the family, teachers, carers, NHS and the wider world and would leave open possibilities for societal inclusion and contribution that would otherwise not be available. | Thank you for your comment. No action required. |
| | Ipsen | Ipsen believes that palovarotene is a highly innovative technology that represents a “step-change” because it is the first therapy to address the underlying pathophysiology in patients with FOP.<br>Early intervention with palovarotene has the potential to be disease-modifying by reducing HO and helping to slow down subsequent disability.<br>Thus, treatment with palovarotene has the potential to reduce the socioeconomic burden associated with FOP which occurs from an early age for patients, caregivers and the healthcare system. | Thank you for your comment. No action required. |
| Questions for consultation | Ipsen | **Q. Have all relevant comparators for palovarotene been included in the scope?**<br>A: Yes. Please refer to the “Comparators” section above.<br><br>**Q. Which treatments are considered to be established clinical management in the NHS for preventing heterotopic ossification associated with fibrodysplasia ossificans progressiva?** | Thank you for your comment. No action required. |

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| | | A: There are currently no known disease-modifying treatments for FOP. Current medications are not licensed in FOP specifically, only provide symptom relief, and do not reduce HO. Please refer to the "Comparators" section above for more information.<br><br>**Q. Are cytochrome P450 inhibitors or inducers or kinase inhibitors like imatinib used to treat fibrodysplasia ossificans progressiva in the NHS?**<br>A: Ipsen understands such treatments are not used in clinical practice in the UK. This was confirmed to Ipsen at a NICE Office for Market Access meeting and by experts at an advisory board held by Ipsen in 2021.[12,13]<br>Current treatment options with corticosteroids and non-steroidal anti-inflammatory medication provide symptomatic relief.[7] There are no disease-modifying therapies that prevent HO and the related subsequent progressive disability in patients with FOP. There is therefore a clear need for palovarotene.<br><br>**Q. Are the outcomes listed appropriate?**<br>A: Yes. Please refer to the outcomes section.<br><br>**Q. How is new heterotopic ossification measured?**<br>A: HO underpins the pathology of FOP and drives progressive disability. New HO was measured in the MOVE clinical study via low-dose whole body computerized tomography (WBCT) scans. WBCT scans are currently not part of routine clinical assessment and follow-up of patients with FOP.<br><br>**Q. How is fibrodysplasia ossificans progressiva diagnosed in the NHS?**<br>A: FOP is challenging to diagnose, and it is commonly misdiagnosed. Most clinicians do not know about FOP because rare diseases are not covered in | |

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| | | medical training and there is inadequate description of FOP in most medical textbooks. For example, great toe malformations that are characteristic of FOP, are usually not recognised, and clinicians may only start suspecting FOP in the presence of a flare-up.<br>Generally, within the diagnostic pathway for FOP there are two groups of patients:<br>• those who were diagnosed early due to the paediatrician who might have noticed FOP clinical features or come across a patient before; and<br>• those who were diagnosed late as they would have been seen by different specialists (usually due to flare-ups).[2]<br>FOP is in 80% of the cases initially misdiagnosed.[2,7] Misdiagnoses include aggressive juvenile fibromatosis, lymphedema, soft tissue sarcoma which can mean patients have harmful biopsies that exacerbate the progression of disease, or are prescribed treatments with side effects, such as chemotherapy.<br>The diagnosis is usually confirmed using a genetic test once clinically suspected. Genetic testing for FOP is not complicated due to the single point mutation (ALK2/ACVR1 gene) in 97% of patients worldwide.[7]<br>Ipsen has submitted an application for FOP to be included as a new clinical indication in the 2022/23 update to the National Genomic Test Directory. Ipsen has proposed that the genetic testing (ACVR1 gene) should occur at presentation when FOP is suspected following clinical assessment. The genetic testing should be available to all patients regardless of age groups, although it is anticipated there would be a higher number of paediatric patients. The next update concerning the genetic testing application status is expected in Q1 2022. | |

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| | | **Q. Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?**<br>A: Given the high unmet need, low patient numbers, and devastating burden of FOP, Ipsen believes that palovarotene should be made available to all eligible patients.<br><br>**Q. Are there any differences in the treatment of fibrodysplasia ossificans progressiva in children compared with adults?**<br>A: HO and progressive disability starts from childhood and continues into adult life. Most patients are in a wheelchair by the age of 30 years. There is therefore a need to prevent HO in patients from as early an age as possible.[2]<br><br>It should be noted, however, that the palovarotene MOVE trial was halted in 2021 due to premature physeal closure (PPC) in children with immature skeletons.[14] A risk management plan will be put in place as part of the regulatory approval process to mitigate the risk of PPC occurring in real-world practice.<br><br>**Q. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:**<br>• **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which palovarotene will be licensed;** | |

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| | | • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**<br>• **could have any adverse impact on people with a particular disability or disabilities.**<br>**Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.**<br>A: No comments.<br><br>**Q. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?**<br>A: Ipsen believes that palovarotene is a highly innovative technology that represents a 'step-change'. Please refer to the "Innovation" section above.<br><br>**Q. NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process.**<br>A: Ipsen agrees that palovarotene should be reviewed by the NICE Highly Specialised Technologies process as it fulfils the new NICE topic selection manual routing criteria for the HST Programme (implemented from 01 February 2022):[15]<br>• **The disease is very rare:** FOP meets this criterion. It is an ultra-rare genetic disorder with an estimated worldwide prevalence of 1 case in 2 million individuals.[1] | |

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| | | • **Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications:** Palovarotene meets this criterion. FOP is ultra-rare and patient numbers are very low in the UK. According to the FOP Friends website (UK patient group), there are around 80 known people with FOP in the UK.<br>• **The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life:** FOP is a severely disabling and life-shortening disease. Due to HO, patients become progressively immobilised throughout their lifetime. They experience pain and limited mobility and become wheelchair-bound, requiring lifelong assistance for most activities. Therefore, FOP severely impairs quality of life.[16]<br>**There are no other satisfactory treatment options:** There is currently no licensed disease-modifying therapeutic option for patients with FOP. Available treatment options (corticosteroids and non-steroidal anti-inflammatory medication) provide symptomatic relief only.[7] Palovarotene has the potential to be the first disease-modifying therapy for FOP | |

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