Changes have been made to this item. Details of the corrigendum are at the end of this document.

5.16 PALOVAROTENE
Capsule 1 mg,
Capsule 1.5 mg,
Capsule 2.5 mg,
Capsule 5 mg,
Capsule 10 mg,
Sohonos®,
IPSEN PTY LTD.

1 Purpose of submission

1.1 The Category 1 submission requested a General Schedule Authority Required (Written) listing for chronic treatment of Fibrodysplasia ossificans progressiva (FOP) and an Authority Required (STREAMLINED) listing for flare-up treatment of FOP.

1.2 Listing was requested on the basis of a cost-utility analysis versus standard of care (SoC).

1.3 The submission made a claim of palovarotene for the rule of rescue.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with FOP aged ≥8 years for females and ≥10 years for males
Intervention	PVO: presented as a hard capsule for oral administration and comprises a chronic treatment regimen which can be adjusted in the event of flare-up symptoms (i.e., flare-up treatment) • Chronic treatment: 5 mg once daily for patients ≥14 years. Weight-adjusted for children <14 years • Flare-up treatment: 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks, even if symptoms resolve, for patients ≥14 years. Weight-adjusted for children <14 years. - Treatment may be extended in 4-week intervals until the flare-up symptoms resolve. - Treatment restarted (i.e., 12-week regimen) if the patient experiences another flare-up during flare-up treatment.
Comparator	SoC comprising symptomatic treatment of flare-ups
Outcomes	Annualised change in new HO volume
Clinical claim	PVO demonstrates superior efficacy and inferior safety to SoC

Source: Table 1.1-1, p13 of the submission.
FOP = Fibrodysplasia ossificans progressiva; HO = Heterotopic ossification; PVO = Palovarotene; SoC = Standard of care;

2 Background

Registration status

2.1 Palovarotene was registered on the ARTG on 28 November 2023 for the following indication: "to reduce the formation of heterotopic ossification [HO] in adults and

children aged 8 years and above for females and 10 years and above for males with fibrodysplasia ossificans progressiva (FOP)".

2.2 The ESC noted that the U.S. Food and Drug Administration (FDA) approved palovarotene for FOP in August 2023, however the European Medicines Agency (EMA) rejected marketing authorisation for palovarotene, stating that "no firm conclusions could be drawn on the benefits of the medicine, as the applicant's conclusion was based on a post-hoc analysis which was neither scientifically nor clinically justified and pre-specified study objectives were not met. In addition, results from other studies and the limited long-term clinical data available did not support efficacy. Regarding safety, the risk of premature physeal closure (a disruption to the areas of new bone growth in the end of long bones, which keeps them from growing normally), which is a known risk with retinoid treatment in growing patients, could not adequately be mitigated with the risk minimisation measures proposed by the company".

2.3 The ESC considered that the risk-benefit profile for palovarotene appears marginal, but noted that the TGA Advisory Committee on Medicines (ACM) considered the risk-benefit profile supported use in the context of a very rare, life-limiting condition with no effective treatments available.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Palovarotene (Chronic treatment)					
Palovarotene 1 mg capsule	$10,153.00 (published price) $[redacted] (effective price)	1*	28*	5	SOHONOS
Palovarotene 1.5 mg capsule	$15,148.20 (published price) $[redacted] (effective price)	1*	28*	5	
Palovarotene 2.5 mg capsule	$25,138.60 (published price) $[redacted] (effective price)	1*	28*	5	
Palovarotene 5 mg capsule	$50,114.60 (published price) $[redacted] (effective price)	1*	28*	5	
Palovarotene (Flare-up treatment)					
Palovarotene 1 mg capsule	$10,153.00 (published price) $[redacted] (effective price)	1^	28^	2	SOHONOS
Palovarotene 1.5 mg capsule	$15,148.20 (published price) $[redacted] (effective price)	1^	28^	2	
Palovarotene 2.5 mg capsule	$25,138.60 (published price) $[redacted] (effective price)	1^	28^	2	
Palovarotene 5 mg capsule	$50,114.60 (published price) $[redacted] (effective price)	1^	28^	2	
Palovarotene 10 mg capsule	$100,066.60 (published price) $[redacted] (effective price)	1^	28^	2	

Source: Table 1.4-1, pp51-52 of the submission.

*at the time of written authority application, prescribers should request the appropriate number of packs based on the patients age and weight to provide sufficient drug for up to one month of treatment

^at the time of telephone authority application, prescribers should request the appropriate number of packs based on the patients age and weight to provide sufficient drug for the stages of flare-up treatment. Flare-up treatment consists of four weeks at a high dose followed by eight weeks at a lower dose. Treatment may continue beyond 12 weeks in four weekly intervals if symptoms persist. Treatment may be restarted if the patient experiences another flare-up during treatment.

Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Condition: Fibrodysplasia ossificans progressive (FOP)
Indication: Fibrodysplasia ossificans progressive (FOP)
Treatment Phase: Chronic phase
Clinical criteria: The condition must be FOP, confirmed by genetic testing
Treatment criteria: Must be treated by a specialist medical practitioner experienced in the diagnosis and management of FOP; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of FOP.
Population criteria: Patient must be a female aged 8 years and above or a male aged 10 years and above
Prescribing Instructions: The prescriber should select the appropriate combination of packs for provide for four weeks of treatment at the recommended dose for chronic treatment of the patient based on their age and weight, according to the specified dosage in the approved Product Information (PI). Genetic testing constitutes testing for a pathogenic mutation of the Activin A receptor type I (ACVR1) gene.
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (Streamlined)
Condition: Fibrodysplasia ossificans progressive (FOP)
Indication: Fibrodysplasia ossificans progressive (FOP)
Treatment phase: Flare-up treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Patient must be experiencing symptoms indicative of a FOP flareup or a substantially high-risk traumatic event likely to lead to a flare-up event.
Treatment criteria: Must be treated by a specialist medical practitioner experienced in the diagnosis and management of FOP; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of FOP.
Population criteria: Patient must be a female aged 8 years and above or a male aged 10 years and above.
Prescribing Instructions: 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. Examples of a high risk substantial traumatic event include surgery, intramuscular immunisation, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses.
Administrative advice: The prescriber should select the appropriate combination of packs such that the maximum quantity together with two repeats provides 12 weeks of treatment at the recommended dose for flare-up treatment of the patient based on their age and weight or in the presence of persistent flare-up symptoms to extend treatment in 4-week intervals. If the patient experiences another flare-up (i.e., 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.

Source: Tables 1.4.2 and 1.4.3, pp53 and 55 of the submission.

3.1 A special pricing arrangement was requested for palovarotene. The pricing of the different doses reflected an effective AEMP of $ per mg.

3.2 The submission noted that the proposed restriction allows patients to be treated for flare-ups initially for 12 weeks, with the possibility of extending treatment in 4-week intervals if symptoms persist. This aligns with the TGA-recommended flare-up dosing regimen for palovarotene. In MOVE, the median and mean treatment duration for a flare-up cycle was 84 days (i.e., 12 weeks) and 110 days (approx. 16 weeks), respectively. This suggested that 50% of the time, patients required more than 12 weeks of medication to resolve symptoms of a flare-up. If this is reflective of clinical practice the elements of listing may have insufficient repeats to provide treatment for the entire flare-up duration for many patients. The PBAC noted that input from a clinician experienced in treating FOP patients with palovarotene (at the sponsor hearing) indicated that patients would initially be treated at an increased (high or medium) flare dose for 4 weeks, followed by tapering of the dose. The clinician also noted that the dose used is individualised to patients.

3.3 The DUSC considered it may be necessary to more accurately define what constitutes a flare-up given the substantial difference in costs between acute and chronic treatment. The pre-PBAC response highlighted the definition of a flare up was provided in a prescribing instruction.

3.4 The requested restriction is consistent with the TGA product information and consistent with the MOVE study. Specifically, the restriction is most reflective of the subgroup analysis of MOVE patients with matching minimum ages. The PBAC agreed with the ESC that this was appropriate.

3.5 The submission noted that genetic testing is already conducted as part of the diagnosis of FOP in Australia. As genetic testing occurs for the purpose of diagnosis rather than for the purposes of accessing a treatment, the submission argued that a codependent submission is not expected to be required. The ESC and PBAC agreed with the submission that it was reasonable to assume that testing already occurs for the purpose of diagnosis and noted that testing may currently be claimed under MBS items for genetic testing for neuromuscular disorders (items 73422-73428).

3.6 There were no monitoring or discontinuation criteria in the proposed restriction, and no guidance as to what constitutes a clinical response, making it difficult to judge the value of continuing treatment. The ESC considered that it would be preferable for the restrictions to include some monitoring requirements to confirm benefit from ongoing treatment, but acknowledged the Pre-Sub-Committee Response (PSCR) comments that FOP does not lend itself to a typical 'response' definition with which to assess the treatment benefit. This is due to periods of flare ups, because changes in HO volume and functioning (e.g. CAJIS) are only observed over the longer term, and because the primary outcome in the clinical trial (HO) is not practical to measure in clinical practice. The ESC noted that the ACM was of the view that radiological evaluation for HO and premature physeal closure (PPC) would be used when considered appropriate rather than routinely as cumulative WBCT and X-ray exposure risks are a consideration.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 FOP is an ultra-rare genetic disease characterised by congenital skeletal malformations, resulting in severe disability and premature death (Kaplan 2010; Pignolo 2011). The pathogenesis of FOP is driven by HO, a process defined as the formation of extraskeletal bone in the non-skeletal tissues such as muscles and joint capsules (Diolintzi 2024; Meyers 2019).

4.2 FOP is caused by a gain-of-function mutation in the *ACVR1* gene which encodes the ALK2 receptor, a bone morphogenetic protein (BMP) type I receptor. The most common mutation in patients with FOP is the *ACVR1*^{R206H} pathogenic variant (also referred to as the R206H mutation). The R206H mutation occurs in approximately 97% of patients (Zhang 2013). There are 15 other pathogenic mutations of the *ACVR1* gene which occur in approximately 3% of FOP patients (Qi 2017; Rauner 2019).

4.3 All identified *ACVR1* mutations in FOP patients result in the dysregulation of the normal BMP-dependent signalling pathway, which is the key regulator of bone development and homeostasis in chondrocytes and osteoblasts (Ventura 2021). The gain-of-function mutation in the *ACVR1/*ALK2 receptor results in abnormal signalling with activin A. Binding of activin A to the mutated *ACVR1/*ALK2 receptor mimics the binding and signalling of BMP ligands and ultimately causes bone growth. Binding of BMP ligands to the mutated receptor can also lead to hyperactive responses. Altogether, these changes promote overactive BMP signalling and HO formation, resulting in soft and connective tissue being transformed into bone (Felix-Ilemhenbhio 2022; Kaplan 2009; Towler and Shore 2022; Ventura 2021).

4.4 Common clinical features of FOP are as follows:

- FOP is clinically defined in 97% of cases by malformations of the great toes and progression of HO in a characteristic anatomical pattern.
- Other typical clinical features observed in FOP patients are shortened malformed thumbs, clinodactyly, short broad femoral necks and proximal medial tibial osteochondromas.
- Approximately 65% of patients develop spinal deformities, including scoliosis, kyphosis and thoracic lordosis. Spinal deformities may lead to rapid immobility and thoracic insufficiency syndrome (TIS) which is the most common cause of death in FOP.
- Other features that contribute to TIS include costovertebral malformations with orthotopic ankylosis of the costovertebral joints and HO of intercostal muscles, paravertebral muscles and aponeuroses.
- Patients may also experience ankylosis of the jaw which may lead to severe weight loss.

- Approximately 3% of patients develop atypical FOP which is characterised by additional or missing common clinical features such as mild or no toe deformities.
- In all patients with FOP, the diaphragm, tongue, and extra-ocular muscles are spared from HO. Cardiac muscle and smooth muscle are also spared in FOP.

4.5 HO progressively restricts movement leading to cumulative disability and severe physical impairments. Patients are typically confined to a wheelchair by their third decade of life and require lifelong assistance in performing activities of daily living (Cohen 1993; Connor and Evans, 1982; Nakahara 2019; Pignolo 2022; Pignolo 2018). Other severe physical impairments include ankylosis of the jaw which typically occurs in the late stages of FOP and leads to difficulties in eating and speaking (Pignolo and Kaplan, 2018). In addition to the severe physical impairments, patients can present with other symptoms attributed to HO, with the most common being auditory complaints (e.g., hearing loss), poor sleep quality, difficulty breathing, rash, abdominal pain, headaches, flank pain, menstrual abnormalities and heart palpitations (Pignolo 2020). Patients with FOP have a shortened lifespan owing to complications related to HO accumulation including TIS, pneumonia and traumatic falls (Connor 2014; Kaplan 2010).

4.6 Palovarotene is a retinoid acid receptor gamma (RARγ)-selective agonist which activates the retinoid signalling pathway. Activation of the retinoid signalling pathway reduces the phosphorylation of SMAD 1/5/8 transduction proteins, resulting in the dampening of overactive BMP signalling caused by the mutated *ACVR1*/ALK2 receptor. This in turn reduces HO formation and allows stem cells to develop into soft tissue rather than bone (Brasil 2022, Felix-Ilemhenbhio 2022; Rauner 2019).

4.7 The anatomical therapeutic chemical (ATC) classification code for palovarotene is M09AX11. Palovarotene is categorised as a drug for disorders of the musculoskeletal system.

4.8 There were no active treatments for FOP available on the PBS at the time of this submission. Palovarotene treatment would be initiated as soon as the patient meets minimum age criteria and would be expected to continue indefinitely.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated standard of care (SoC) as the main comparator. The main argument provided in support of this nomination was that there are no other disease-modifying treatments for FOP. SoC includes symptomatic treatments that alleviate inflammation and pain during flare-ups. Overall, the ESC and the PBAC agreed with the commentary that this was reasonable.

5.2 Current SoC is focused on anti-inflammatory medications to alleviate pain and inflammation associated with flare-ups. The International Clinical Council (ICC 2022) treatment guidelines recommend symptomatic treatment with corticosteroids

(prednisone or prednisolone), NSAIDs (ibuprofen or indomethacin/indometacin) and COX-2 inhibitors (celecoxib). The submission noted that these are considered class I medications that are widely used to control symptoms of acute flare-ups in FOP (swelling and pain), or chronic arthropathy, with generally minimal side effects. Prednisone is recommended for acute flare-ups within 24 hours of onset, with a maximum treatment duration of 4 days due to safety concerns including accelerated HO, osteoporosis, and Cushing's disease. If the flare-up responds to prednisone and recurs after treatment is discontinued, a repeat 4-day course with a subsequent 10-day taper can be considered. When prednisone is discontinued or a flare-up persists for more than 48 hours, symptomatic treatment with an NSAID or COX-2 inhibitor is recommended.

5.3 The submission noted that corticosteroids prednisone and prednisolone and the NSAID ibuprofen have unrestricted PBS listings. Ibuprofen and indomethacin also have restricted PBS listings for chronic arthropathies with an inflammatory component. Celecoxib has a restricted PBS listing for osteoarthritis and rheumatoid arthritis and is not subsidised for acute pain or soft tissue injury.

5.4 The submission also considered that other medicines may be used for symptomatic relief of flare-ups such as leukotriene inhibitors (montelukast), mast cell stabilisers (cromolyn), bisphosphonates (pamidronate, zoledronate) and specific tyrosine kinase inhibitors (imatinib); however, these medications are considered class II and are defined as those with a theoretical application in FOP, are approved for the treatment of other disorders and recommended to be used with caution at the physician's discretion (ICC 2022).

5.5 Most patients received systemic corticosteroids in the MOVE study and the comparator natural history study (NHS), as this is considered the SoC for the treatment of flare-ups. Anti-inflammatory and anti-rheumatic products were also taken by approximately half of patients in both treatment arms. As anticipated with the mucocutaneous effects of palovarotene, patients in MOVE used topical dermatologic preparations including steroids and systemic/topical antibiotics.

5.6 During the evaluation, a paper was identified (Shaikh 2023[1]) that reviewed new disease modifying therapies for FOP. These include: INCB000928, caretosmab, IPN60130, KER-047, BX9250. However, none of these were on the market at the time of this submission and were not assessed as near-term comparators.

For more detail on PBAC's view, see section 7 PBAC outcome.

[1] Shaikh U, Khan A, Kumari P, Ishfaq A, Ekhator C, Yousuf P, Halappa Nagaraj R, Raza H, Ur Rehman U, Zaman MU, Lakshmipriya Vetrivendan G, Nguyen N, Kadel B, Sherpa TN, Ullah A, Bellegarde SB. Novel Therapeutic Targets for Fibrodysplasia Ossificans Progressiva: Emerging Strategies and Future Directions. Cureus. 2023 Jul 28;15(7):e42614. doi: 10.7759/cureus.42614. PMID: 37521595; PMCID: PMC10378717.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease and experience in treating patients with FOP, noting that patients experience significant functional impairment that is directly related to the locations of growth of new bone. New bone in legs and arms results in loss of mobility and reduced capacity for self-care. New bone growth in the jaw can result in severe issues with airway management and new bone in the chest wall can result in cardiorespiratory failure. As such, the clinician noted that HO is very likely causally related to mortality, although this was not demonstrated in the clinical trial. The clinician stated that, as FOP is a progressive disease, it is difficult to know whether a patient is benefiting from treatment, but most patients tolerate treatment well and are likely to continue on chronic treatment and receive additional dosing for flares, where dosing is individualised for the patient. The clinician noted that results from the MOVE trial indicated that the ability to respond rapidly to flares was significant in prevention of new bone growth. The clinician indicated that patients would initially be treated at an increased (high or medium) flare dose for 4 weeks, followed by tapering of the dose. The clinician also noted that the dose used is individualised to patients. The clinician noted that low dose CT scanning was achievable for most patients and that assessment of physical function was also useful in monitoring progression in the longer term. The clinician noted that patients require a high level of care which is associated with high costs, as many patients are restricted to a wheelchair and unable to transfer without assistance. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating and monitoring this uncommon disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from 2 organisations (FOP Australia and International FOP Association) via the Consumer Comments facility on the PBS website. The PBAC noted that the comments from FOP Australia reflected input from 12 individuals including people living with FOP, their friends and family members. The comments described the experience of living with FOP, and the challenges and priorities for people with FOP and their families. FOP Australia summarised the key messages from the input:

1. Living with FOP means living with the constant threat of unpredictable bone growth, causing progressive and painful loss of independence and mobility. Every individual patient's progression and cumulative functional restrictions is different. The bone growth of FOP leads to a wide range of complications, including death.
2. Anything that can reduce or delay any amount of bone growth is of huge value to patients, including those at advanced stages, as even tiny amounts of bone can be extremely functionally significant.

3. Many people with FOP are in situations where they would choose to accept significant risk of side effects. This includes patients who have been on palovarotene, including those who have experienced side effects, and chosen to continue.
4. Having the potential to choose a therapy, or not, would be a life-changing shift in how people with FOP can engage with medical care. Living with FOP includes constantly adapting to physical limitations and psychological challenges, with a struggle to retain any sense of control and bodily autonomy. A PBS-listing of palovarotene would provide people with FOP with the dignity of having some choice.
5. The practical barriers that people seeking care for FOP in Australia face compound the challenges inherent to the disease itself. This complicates all aspects of diagnosis and monitoring. Although having a potential treatment doesn't directly alleviate these challenges, it would positively influence how patients and clinicians can engage in treatment decisions. Having access to an oral treatment that can be administered at home is of practical significance to people with FOP.
6. The progressive disability caused by FOP takes a huge toll physically, socially, psychologically and financially on people with FOP and their families (including those who become carers). Any treatment that reduces any amount of bone growth would reduce each of these impacts.

6.3 The PBAC noted that FOP Australia also provided examples of the impact of FOP using case studies with photos and patient details of disease progression over time. The examples described the sudden loss of mobility due to joint fusion, deaths resulting from thoracic involvement and falls, and flares resulting in deformities.

6.4 The PBAC noted that input from International FOP Association was also in support of providing patients with funded access to palovarotene treatment. The input described the path and timing of FOP's progression as variable and unpredictable for each individual and noted that there is a critical need for interventions to slow the progression of FOP to reduce daily anxieties and improve health outcomes.

Clinical studies

6.5 The pivotal evidence for palovarotene was based on a comparison of:

- The phase 3, single-arm, open-label clinical study MOVE (N=107), a 24-month study of FOP patients treated with palovarotene which also included a 24 month extension period; with
- The NHS (PVO-1A-001, Pignolo 2019, 2022: N=114), a prospective, non-interventional, longitudinal study which assessed the natural history of patients with FOP over 36 months.

6.6 Although treatment durations for MOVE were intended to be 24 months, with a 24-month extension period, the efficacy data presented in the submission was based on

18 months of study duration, or the study duration prior to the pausing of the study due to meeting the futility threshold.

6.7 A clinical claim of superior efficacy was presented for palovarotene (MOVE) versus SoC (NHS) based on a *post−hoc* analysis conducted for the primary outcome of the annualised change in new HO volume. Since the NHS only enrolled patients with the *ACVR1*^{R206H} mutation, efficacy was assessed in a matched population of those with the *ACVR1*^{R206H} mutation which included 99/107 patients (92.5%) in MOVE and all patients in the NHS (114/114, 100%).

6.8 On 4 December 2019, the FDA instituted a partial clinical hold on the dosing of palovarotene in patients <14 years of age due to the risk of PPC. Due to these risks the submission proposed minimum age criteria for initiating palovarotene (see paragraph 2.1).

6.9 The clinical claim is also based on a subgroup analysis of females ≥8 years and males ≥10 years, to reflect the requested PBS restriction.

6.10 Details of the studies presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
MOVE (PVO-1A-301) NCT03312634	A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP) Interim clinical study report	Interim CSR Report: 4 April 2022 Final CSR report 4 August 2023
	Pignolo RJ, Hsiao EC, Al Mukaddam M, Baujat G, Berglund SK, Brown MA, Cheung AM, De Cunto C, Delai P, Haga N, Kannu P, Keen R, Le Quan Sang KH, Mancilla EE, Marino R, Strahs A, Kaplan FS. Reduction of New Heterotopic Ossification (HO) in the Open-Label, Phase 3 MOVE Trial of Palovarotene for Fibrodysplasia Ossificans Progressiva (FOP).	Journal of Bone and Mineral Research 2023; 38, 381-394.
Natural history study		
NHS (PVO-1A-001) NCT02322255	A Natural History, Non-Interventional, Two-Part Study in Subjects with Fibrodysplasia Ossificans Progressiva (FOP)	CSR report: 21 March 2022
	Robert J. Pignolo1, Geneviève Baujat, Matthew A. Brown3, Carmen De Cunto, Maja DiRocco, Edward C. Hsiao, Richard Keen, Mona Al Mukaddam, Kim-Hanh Le Quan Sang, Amy Wilson, Barbara White, Donna R. Grogan and Frederick S. Kaplan. Natural history of fibrodysplasia ossificans progressiva: cross-sectional analysis of annotated baseline phenotypes.	Orphanet Journal of Rare Diseases 2019; 14, 98
	Robert J. Pignolo, Genevieve Baujat, Matthew A. Brown, Carmen De Cunto, Edward C. Hsiao, Richard Keen, Mona Al Mukaddam, Kim-Hanh Le Quan Sang, Amy Wilson, Rose Marino, Andrew Strahs, Frederick S. Kaplan The natural history of fibrodysplasia ossificans progressiva: A prospective, global 36-month study.	Genet Med 2022; 24, 2422-2433.

Source: Table 2.2-5, p73 of the submission.

6.11 Table 3 presents the key features of the included evidence.

Table 3: The key features of the included studies

Trial	N	Design, duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Pre-specified comparison of single arm study (MOVE) and NHS						
MOVE	107[a]	SAS, 18[c] months	High	FOP patients	Annualised new HO, CAJIS, FOP-PFQ, PROMIS	Yes
NHS	114[b]	PL, 36 months				
***Post-hoc* subgroup analysis: adults and children aged ≥ 8 years for females and ≥ 10 years for males**						
MOVE	77	SAS, 18 months	High	FOP patients -adults and children aged ≥ 8 years for females and ≥ 10 years for males	Annualised new HO	Yes
NHS	79	PL, 36 months				

Source: pp68-130 of the submission

CAJIS = Cumulative Analogue Joint Involvement Scale for FOP; FOP = fibrodysplasia ossificans progressive; FOP-PFQ = Fibrodysplasia Ossificans Progressiva Physical Function Questionnaire; HO = heterotopic ossification; NHS = natural history study; PL = prospective longitudinal study; PROMIS = patient-reported outcomes measurement information system; SAS = single arm study;

[a] 107 patients were enrolled but only 97 were included in the full analysis set.

[b] 114 were enrolled but only 101 were included in the full analysis set.

[c] The submission claimed that the duration of the trial was 24 months. However, the efficacy results were based on interim analysis 3 which had a maximum duration of 18 months.

6.12 The submission described the comparison as 'pre-specified.' Although the comparison of new HO volume against data from the NHS, was pre-specified, it should be noted that the specific statistical analysis that was pre-specified did not meet the statistical threshold for superiority, and consequently, the claim is based on a different *post-hoc* analysis of this outcome. Details of the pre-specified and post-hoc HO analyses are discussed in paragraphs 6.22, 6.24 and 6.25 below.

6.13 The nominated primary outcome in MOVE was annualised change in new HO volume as assessed by low-dose whole body computed tomography (WBCT) (excluding head).

6.14 Annualised change in new HO volume was defined as the sum of the increases in HO volume (mm^3) per 12-month period across all body regions in which new HO occurred between WBCT scans. In MOVE, WBCT scans were performed at baseline and Months 6, 12, 18 and 24. In the NHS, WBCT scans were performed at baseline and Months 12, 24 and 36. Both studies also assessed WBCT at the time of early study discontinuation.

Surrogate to final outcome (STFO) Framework for HO

6.15 The submission argued that the effects of HO result in a shortened life-expectancy in patients with FOP; immobility and HO in the chest wall can interfere with cardiopulmonary function causing thoracic insufficiency syndrome, the most common cause of premature mortality in patients with FOP.

6.16 Whilst current SoC only manages symptoms of pain and inflammation, the goal of disease-modifying treatments such as palovarotene is to prevent HO formation allowing patients to maintain their mobility and independence for as long as possible.

6.17 HO is consequently a surrogate endpoint. The submission presented an assessment for translating the comparative treatment effects of palovarotene, measured by the surrogate outcome of annualised new HO volume, to the target clinical outcome (TCO) of overall survival (OS) using the surrogate to final outcome (STFO) framework

(Appendix 5 of the PBAC Guidelines, v.5). The submission did not consider other potential TCOs, such as improvement in quality of life or prevention or slowing of FOP.

6.18 The submission presented evidence to support the following statements:

- Higher HO volume is associated with older age and a decline in physical functioning. Supported by data from NHS, Verburg-Baltussen 2023 and Pignolo 2023b, but the ESC agreed with the commentary that the assumed link between HO volume and an excess mortality was not adequately supported as age was a key confounder.
- Patients with FOP have a significantly shortened lifespan with [estimates of] a median life expectancy ranging from 44 years (Liljesthröm and Betsy, 2016) to 56 years (Kaplan 2010). Although a shortened lifespan was demonstrated, there is uncertainty about the actual life expectancy in the FOP population.
- Severe physical impairments associated with higher HO volume are common causes of death in FOP. Statistically significant correlation between measures of physical functioning and HO volume was established in the NHS, Verburg-Baltussen 2023 and Pignolo 2023b. However, the evidence linking HO of particular joints to a particular cause of death (either thoracic insufficiency syndrome [TIS]-related complications or a fatal fall, two of the three most frequently observed causes of death in FOP patients according to Kaplan 2010) is limited to four autopsy reports (Connor 2014, Wentworth 2018, Bolcato 2021) and the recorded causes of death of five participants in LUMINA-1 trial (Di Rocco 2023). There are also theories that the increased risk of death in FOP was related to immune regulation and not just HO (Bolcato 2021).

6.19 Overall, the ESC agreed with the commentary that while it is biologically plausible that reduction in new HO could lead to better survival outcomes and better quality of life (QoL) outcomes, the submission has not adequately demonstrated the magnitude of benefit in clinical outcomes gained by improvements in HO outcomes.

6.20 During the evaluation, it was noted that the Canadian Agency for Drugs and Technology in Health (CADTH) had considered palovarotene for FOP. With regard to HO, the CADTH clinical experts:

- "[A]greed that while HO volume is a good outcome for proof of concept, clinically, overall HO volume alone is not relevant. The clinical experts noted that relevant clinical outcomes for this patient population are related to HRQoL, physical function, [range of motion], and frequency of flare-ups." (p90).
- Noted that location of HO (the functional area affected) may be more important than total HO for some patients. While cross-sectional studies suggest a modest correlation between overall HO and the clinical end points of CAJIS and FOP-PFQ, it is uncertain if overall HO volume is a definitive surrogate for disease progression because the location of the HO is an important consideration when evaluating the impact of changes in HO volume on functional outcomes (p98).

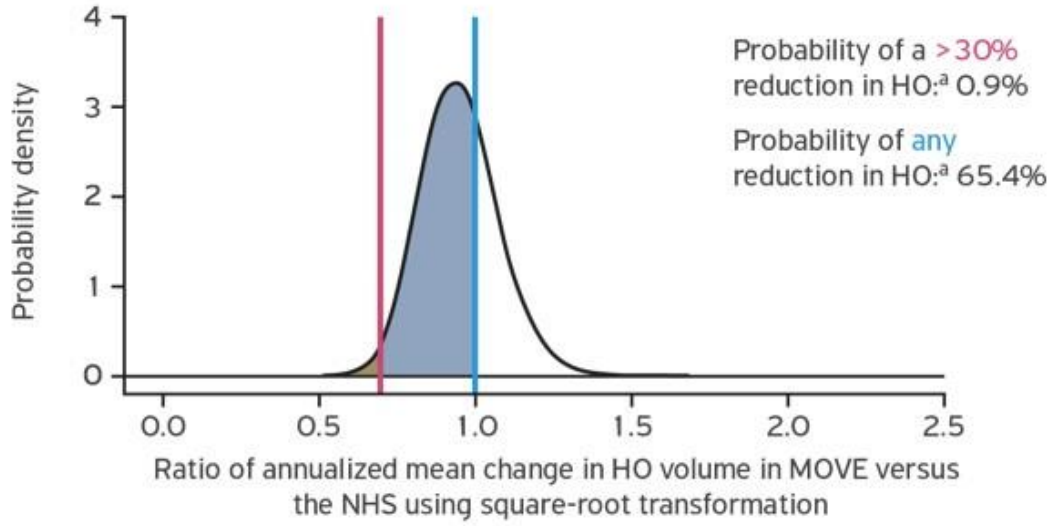
- Concluded that, "The clinical relevance of the results is unclear because HO volume is neither a patient-centred outcome nor used in clinical practice, and there are no available MID [minimally important difference] estimates. No reductions in the number of reported flare-ups, [range of motion], physical function, or HRQoL [health-related quality of life] were observed, and clinically important outcomes, such as respiratory function (including the need for ventilation and survival) were not assessed in the MOVE trial." (p100).

6.21 The pre-PBAC response noted that the standard framework for health technology assessment relies on minimum clinically important differences (MCIDs). This approach fails to capture the impact a small amount of new HO can have in a critical location (e.g., thorax, jaw or hip). In these critical locations a small amount of HO can lead to immediately debilitating, lifelong and life limiting impacts on a patient. The PBAC noted this was consistent with input from the sponsor hearing and consumers regarding FOP progression.

Comparative effectiveness

6.22 Figure 1 presents the results of the pre-specified analysis (i.e. weighted linear mixed effects (wLME) model using square-root transformed values and negative values set to zero) of annualised HO in MOVE compared to the NHS in the matched population. There was no significant difference in the square-root transformed mean volume of annualised new HO in palovarotene-treated versus untreated patients (140.2 mm^3 versus 149.8 mm^3; probability of any reduction in new HO: 65.4%) when setting body region negative HO volumes to zero.

Figure 1: Prespecified primary analysis for palovarotene-treated (MOVE) versus untreated (NHS) patients at IA3: Bayesian model using square-root transformed values and negative values set to zero by body region (Principal FAS)



Source: Table 2.5-2, p108 of the submission.

6.23 One of the submission's identified sources of a minimum clinically important difference for HO, Smilde 2022, considered a reduction of 50% to be meaningful; it was unclear what clinical importance a reduction of 30% would have.

6.24 During an advisory committee meeting, the FDA (palovarotene advisory committee meeting 28 June 2023)[2] had noted that in the pre-specified analysis, the rate of growth in HO volume was estimated based on the square root transformation of each incremental change in HO by region between scans. As these were not equivalent between the studies, there was a high risk of bias against palovarotene. Consequently, the FDA allowed a protocol amendment specifying a post-hoc analysis (on which the submission's clinical claim is based) where no square root transformation was applied. The commentary considered this would not be expected to be a key risk of bias in the post-hoc analysis. The TGA considered the use of the post-hoc wLME analysis acceptable.

6.25 The ESC considered that the pre-specified analysis in MOVE (wLME using square root transformation, Bayesian corrected Poisson Model) appeared to have been a flawed approach and the correction to the approach in the protocol amendment was therefore reasonable. However, the ESC also considered that the change in approach was substantial, the revised approach remained unusual, and the change in modelling strategy did contribute to an increase in the potential for type I error.

6.26 Table 4 presents the results of new HO using the *post-hoc* wLME model. The submission did not present baseline HO in MOVE or the NHS. It would be expected based on the higher age in NHS that baseline HO would be higher in the NHS. However, the analysis included the covariate of baseline total HO volume/baseline age. It was unclear whether this adequately adjusted for potential differences in baseline HO. The submission claimed that patients treated with palovarotene had a statistically significant reduction in annualised new HO volume compared to untreated patients (wLME treatment effect: p=0.0392). However, there are no thresholds on which to base statistical success, and no adjustment made for the multiple changes in primary outcome and as such any claims of statistical significance may not be substantiated. The Wilcoxon rank-sum test, which depends only on the numeric rank order of the observed volumes of new HO rather than their magnitudes and is thus less influenced by extreme values, also suggests a difference in annualised new HO volume between palovarotene-treated versus untreated patients (nominal p=0.0003).

6.27 The submission also presented wLME results for the subgroup of patients in MOVE and the NHS that aligned with the proposed PBS population of adults and children aged ≥8 years for females and ≥10 years for males. The submission only presented results for the PBS population subgroup analysis for new annualised HO. All other outcomes were based on the full analysis set (FAS). The proportion of patients in the

[2] Food and Drug Administration. Endocrinologic and Metabolic Drugs Advisory Committee Meeting on palovarotene. 28 June 2023. Available at: https://www.fda.gov/media/169787/download

Principal FAS who aligned with the proposed PBS population was 79.4% (77/97) in MOVE and 78.2% (79/101) in the NHS. The results of this subgroup and its complement are also presented in the table below.

6.28 In the proposed PBS population subgroup, the least square mean (LSM) annualised new HO volume was 48.6% lower in palovarotene-treated versus untreated patients which the submission claimed was consistent with the results in the whole trial population (53.8% lower in palovarotene-treated patients). The difference between palovarotene-treated and untreated patients in the proposed PBS population was not considered statistically significant (wLME treatment effect p = 0.1124). The submission considered this was likely a result of small patient numbers and the trial not being powered to detect a statistically significant difference in the proposed PBS population. The PSCR clarified the MCID of at least a 50% reduction was exceeded in the whole trial population where patients treated with PVO had a statistically significant 53.8% reduction in adjusted mean annualised new HO volume versus untreated patients using the wLME method. However the MCID was not reached in the PBS population where there was a 49% reduction in adjusted mean annualised new HO volume for PVO versus untreated patients.

Table 4: *Post-hoc* wLME model of annualised HO volume using non-transformed values (Principal FAS, PBS population subgroup and complement

	Principal FAS		PBS population (females ≥ 8 and males ≥ 10 years old)		Complement (females < 8 and males < 10 years old)	
	MOVE (PVO-treated) N = 97	NHS (Untreated) N = 101	MOVE (PVO-treated) N = 77	NHS (Untreated) N = 79	MOVE (PVO-treated) N = 20	NHS (Untreated) N = 22
New HO (mm^3)						
Mean (SEM)	9,427.1 (3,084.0)	23,720.2 (4,850.0)	11,418.8 (3,781.5)	25,796.0 (6,065.5)	1,759.1 (2,992.2)	16,266.1 (4,489.4)
% mean reduction	60.3%		55.7%		89.2%	
LSM (SEM)	9,366.8 (4,101.7)	20,273.0 (3,266.6)	11,033.2 (4,973.2)	21,476.0 (4,068.9)	845.4 (4,815.1)	15,876.1 (3,460.5)
% LSM reduction	53.8%		48.6%		94.7%	
wLME estimate (95% CI); p value						
Intercept	16,174.1 (7,470.37, 2,4877.88); p = 0.0003		16,746.9 (5622.12, 27871.77); p = 0.0035		16,573.2 (7658.37, 25488.04); p = 0.0006	
Baseline total HO/Baseline age	0.3 (-0.10, 0.66); p = 0.1440		0.3 (-0.17, 0.76); p = 0.1974		-0.1 (-0.82, 0.68); p = 0.8024	
Absolute difference in LSM (96% CI)	-10,906.2 (-21,240.69, -571.63); p = 0.0392		-10,442.8 (-23538.93, 2653.36); p = 0.1124		-15,030.7 (-31046.08, 984.68); p = 0.0597	
Wilcoxon test p value	p = 0.0003		p = 0.0107		p = 0.0034	

Source: Table 2.6-1, p130 of the submission.

HO = Heterotopic ossification; NHS = Natural history study; PVO = Palovarotene; IA3 = Interim analysis 3; FAS = Full Analysis Set; DCO = Data cut-off; wLME = weighted linear mixed effect; WBCT = Whole-body computed tomography; CI =Confidence interval; SEM = Standard error mean; LSM = Least square mean; PBS = Pharmaceutical Benefits Scheme

Statistical analyses conducted using a mixed model with annualised new HO as the dependent variable and fixed effects of treatment as the independent variable and baseline total HO/baseline age as a random subject effect.

6.29 The TGA ACM concluded that the wLME efficacy analysis demonstrated a clinically meaningful benefit. The ACM also noted that "studies relying on volumetric measures are hard, because there is an appreciable error with estimating volume of lesions (in any technology), and likely to be increased by the low-density scanning used. However, the ACM acknowledged the use of low-density scanning is understandable in this paediatric population."

6.30 CADTH experts noted that the 49% reduction in the adjusted mean annualised new HO volume may be considered meaningful, despite the finding of no difference between patients treated with palovarotene and untreated patients in the overall proportion with no new HO. The PSCR also noted that the clinical meaningfulness of a reduction in HO volume can be difficult to assess at the population level since any HO for a given patient may have a profound impact if this occurs in a location that impairs functioning.

6.31 The treatment effect was larger for palovarotene-treated patients in the complement (94.7% reduction), although there were only 20 palovarotene-treated patients and 22 untreated patients. It was likely that these differences were due to the younger age in the complement group, as younger patients undergo more ossification. In addition to the complement group not being included in the proposed population, the risk of PPC generally precludes use in the population.

6.32 Table 5 presents the key secondary outcome, proportion of patients with new HO volume at Month 12. There was no statistically significant difference for the proportion of palovarotene-treated (64.1%) and untreated (62.2%) patients who developed any new HO at Month 12 (p = 0.8780).

Table 5: Proportion of patients with new HO at Month 12 (Principal FAS)

	MOVE (PVO-treated) N = 97	NHS (Untreated) N = 101
Number of patients at risk at Month 12	N = 92	N = 90
Patients with new HO volume at Month 12, n (%)	59 (64.1)	56 (62.2)
	p = 0.8780	

Source: Table 2.5.3, p112 of the submission.
Statistical analyses conducted using Fisher's exact test
The DCO for efficacy analyses in MOVE was December 2019 for patients aged <14 years and January 2020 for patients ≥ 14 years. The DCO for the NHS was February 2020.
Abbreviations: HO = Heterotopic ossification; NHS = Natural history study; PVO = Palovarotene; FAS = Full Analysis Set; DCO = Data cut-off

6.33 Table 6 presents the proportion of patients who reported at least one flare-up event (defined as having ≥2 symptoms) at Month 12. A higher proportion of patients treated with palovarotene in MOVE experienced a flare-up event at Month 12 compared to patients in the NHS (64.6% vs 54.1%). The submission considered this may be due to the more frequent visits in MOVE compared with the untreated patients in the NHS. It is also possible that untreated patients in the NHS may have been less motivated to report flare-ups because flare-ups would not be treated. It may also be due to the younger population in MOVE, who are known to have a greater frequency of flare-ups, or potentially treatment with palovarotene may be associated with a greater

frequency of flare-ups. The ESC considered that the potential for increase in the frequency of flare-up events with palovarotene was a concern.

6.34 The submission stated that flare-up rate per patient-month exposure was higher in palovarotene-treated (0.13, 95% CI: 0.09, 0.17) versus untreated patients (0.07, 95% CI: 0.05, 0.08), with the difference being statistically significant (p = 0.001). Given flare-ups were a secondary outcome and not part of the statistical analysis plan, it was unclear if a claim of statistical significance was substantiated.

6.35 In the economic analysis, the submission reported a mean number of flare-ups per annum of 1.59 in MOVE. The ratio of the annual flare-up rate for palovarotene versus untreated was reported to be 1.65. These estimates appeared to be based on individual patient data (IPD) and could not be confirmed during the evaluation.

Table 6: Flare-up rates (Principal Safety Set)

	MOVE (PVO-treated) N = 99	NHS (Untreated) N = 111
Proportion of patients reporting flare-ups at Month 12, n (%)	64 (64.6%)	60 (54.1%)
Flare-up rate per patient-month exposure (95% CI)	0.13 (0.09, 0.17)	0.07 (0.05, 0.08)
	p = 0.0010	

Source: Table 2.5.5, p113 of the submission.
HO = Heterotopic ossification; NHS = Natural history study; PVO = Palovarotene; DCO = Data cut-off; CI = Confidence interval
Estimates are obtained from a generalised Poisson model.
Statistical analysis for flare-up rate was based on a negative binomial model.
Flare-up events were defined as having 2 or more symptoms.
The DCO for efficacy analyses in MOVE was December 2019 for patients aged <14 years and January 2020 for patients ≥ 14 years. The DCO for the NHS was February 2020.

6.36 The CADTH clinical experts considered that flare-ups are expected to occur more frequently at younger ages (i.e., in teenagers and those in their twenties). Consequently, this frequency on its own may not be a reliable marker of response to treatment because it would be difficult to ascertain whether any decrease was a result of treatment or of patients getting older. This would be compounded by the imbalances between the studies in patients aged younger than 18.

6.37 Range of motion was assessed using the Cumulative Analogue Joint Involvement Scale (CAJIS) performed by trained investigators. The submission considered that CAJIS is a simple, rapidly administered, functionally-validated assessment of body and regional mobility which can be performed in any clinical setting. CAJIS was assessed at baseline and every 6 months in MOVE and at baseline and every 12 months in the NHS.

6.38 Table 7 presents the change from baseline in CAJIS scores for palovarotene-treated and untreated patients. The CAJIS scores slightly increased over 18 months in both treatment arms, indicating a worsening in range of motion. The submission stressed that the heterogenous nature of FOP and the short timeframe (24 months) of MOVE means that any possible improvements in range of motion associated with palovarotene treatment may not have been captured in a clinical trial setting. There were no statistically significant differences between the two treatment arms.

Table 7: Change in CAJIS total scores over time (Principal Safety Set)

	MOVE (PVO-treated) N = 99	NHS (Untreated) N = 111
Baseline mean (SD)	10.0 (6.1)	11.8 (7.0)
Mean change from baseline at Month 6 (SD)	N = 88 0.2 (1.5)	NA
Mean change from baseline at Month 12 (SD)	N = 86 0.5 (2.0)	N = 99 0.6 (2.4)
Mean change from baseline at Month 18 (SD)	N = 63 0.7 (2.1)	NA
Mean change from baseline at Month 24 (SD)	N = 0	N = 70 0.8 (2.5)

Source: Table 2.5-7, p116 of the submission.
NHS = Natural history study; PVO = Palovarotene; DCO = Data cut-off; SD = Standard deviation; CAJIS = Cumulative Analogue Joint Involvement Scale for FOP
Scores range from 0-30, with higher scores representing decreased range of motion
At baseline all patients having a valid value are included. For the post-baseline timepoints, only patients with a non-missing baseline and post-baseline value are included.
The DCO for efficacy analyses in MOVE was December 2019 for patients aged <14 years and January 2020 for patients ≥ 14 years. The DCO for the NHS was February 2020.

6.39 Table 8 presents the mean change in physical function using age-appropriate forms of the FOP Physical performance questionnaire (FOP-PFQ) percentage of worst score over time. The FOP-PFQ is a disease-specific, validated PRO which measures physical impairment in FOP. Physical function was assessed using age-appropriate forms of the FOP-PFQ. Both trials assessed FOP-PFQ at baseline and every 6 months. The FOP-PFQ includes questions about the activities of daily living and physical functioning. Patients aged ≥15 years self-completed the adult form which consists of 28 questions. Two Paediatric forms were to be utilised in patients under the age of 15 years: a self-completed form developed for patients aged between 8 and 14 years and a proxy-completed form developed for patients aged between 5 to 14 years. Both paediatric questionnaires consisted of 26 questions. The proxy-completed forms were used for analyses unless only the self-completed forms were available. The mean baseline FOP-PFQ values were similar across the treatment arms. There was a similar increase in FOP-PFQ worst scores over time in palovarotene-treated and untreated patients. Patients treated with palovarotene had a mean increase in the FOP-PFQ worst score of 2.53% at Month 6, 2.76% at Month 12, and 4.12% at Month 18. Untreated patients had a mean increase of 3.18% at Month 6, 4.5% at Month 12, and 4.11% at Month 18.

Table 8: Change in FOP-PFQ percentage of worst score over time (Principal Safety Set)

	MOVE (PVO-treated) N = 99	NHS (Untreated) N = 111
Baseline mean (SD)	44.28 (26.86)	46.97 (28.06)
Mean change from baseline at Month 6 (SD)	N = 82 2.53 (9.62)	N = 76 3.18 (9.34)
Mean change from baseline at Month 12 (SD)	N = 71 2.76 (7.77)	N = 82 4.50 (8.88)
Mean change from baseline at Month 18 (SD)	N = 51 4.12 (12.98)	N = 56 4.11 (10.08)
Mean change from baseline at Month 24 (SD)	N = 0	N = 61 4.46 (9.10)

Source: Table 2.5-8, p117 of the submission.
Abbreviations: NHS = Natural history study; PVO = Palovarotene; DCO = Data cut-off; SD = Standard deviation; FOP-PFQ = FOP-Physical Function Questionnaire
Percentage of worst score is calculated as (Best Possible score – Actual score) / (Max – Min of possible scores) and it is specific to each age-appropriate questionnaire.
Results are expressed as a percentage of the worst possible score (0–100%), with higher scores represent worse physical functioning.
Only patients with a non-missing baseline and post-baseline percentage of worst value are included.

6.40 HRQoL was assessed using age-appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health scale short form. The submission considered that the PROMIS Global Health scale was a reliable, validated generic patient reported outcome (PRO) instrument that evaluates and monitors physical, mental, and social health in adults and children in the general population or who are living with chronic conditions. These scales measure what individuals are able to do and how they feel.

6.41 Table 9 presents the mean change from baseline in PROMIS scores over time for adult physical and mental health, and paediatric global health. The change in PROMIS T-scores were generally similar across both treatment arms for adults and children. Reductions in score represent worsening of quality of life. The ESC noted that there was a trend to worsening scores in paediatric global health for patients treated with palovarotene compared with untreated patients. The PBAC noted the AE profile of palovarotene, which commonly affects skin and appearance, may have impacted the score in this young age cohort.

Table 9: Change in PROMIS T-scores over time (Principal Safety Set)

	Adult physical health (≥ 15 years old)		Adult mental health (≥ 15 years old)		Paediatric global health (< 15 years old)	
	PVO N = 37	Untreated N = 58	PVO N = 37	Untreated N = 58	PVO N = 62	Untreated N = 53
Baseline mean (SD)	N = 36 43.15 (7.93)	N = 57 43.35 (8.66)	N = 36 52.17 (7.94)	N = 57 52.70 (9.40)	N = 43 50.72 (8.49)	N = 26 45.36 (8.41)
Mean change at:						
Month 6 (SD)	N = 33 -0.15 (3.92)	N = 43 -0.37 (6.79)	N = 33 -2.10 (4.10)	N = 45 -1.57 (5.61)	N = 37 -0.80 (5.99)	N = 16 1.23 (5.50)
Month 12 (SD)	N = 33 0.20 (5.16)	N = 49 -1.19 (6.62)	N = 33 -0.79 (5.57)	N = 49 -1.95 (6.99)	N = 31 -0.91 (8.83)	N = 17 3.61 (8.60)
Month 18 (SD)	N = 27 -1.91 (6.28)	N = 35 -0.66 (5.57)	N = 27 -2.89 (7.19)	N = 35 -2.72 (7.20)	N = 23 -3.90 (8.31)	N = 9 3.19 (7.73)
Month 24 (SD)	N = 0	N = 38 -1.13 (6.09)	N = 0	N = 38 -1.22 (6.91)	N = 0	N = 11 2.68 (7.26)

Source: Table 2.5.9, p120 of the submission.
NHS = Natural history study; PVO = Palovarotene; DCO = Data cut-off; SD = Standard deviation; PROMIS = Patient Reported Outcomes Measurement Information System
Scores were converted to T-scores for adult and paediatric scales; a value of 50 (SD 10) represents the average for the general population in the USA.
At baseline all patients having a valid value are included. For the post-baseline timepoints, only patients with a non-missing baseline and post-baseline value are included.
Higher scores represent increased quality of life

6.42 The economic model relied on analyses of individual patient data for HO volume, CAJIS score, flare-ups and PROMIS scores in a sensitivity analysis. Additionally, treatment effect was directly modelled from reduction in annualised HO in the PBS population subgroup.

Comparative harms

6.43 The submission noted that in the NHS, adverse events (AEs) were only captured if they resulted from procedures performed during the study. Therefore, direct comparisons with treatment-emergent adverse events (TEAEs) reported in MOVE were not possible.

6.44 Table 10 presents a summary of the most common adverse events reported in MOVE. The most commonly reported TEAEs were mucocutaneous events such as dry skin (68.7%), lip dry (46.5%), alopecia (34.3%), drug eruption (28.3%), pruritus (26.3%) and musculoskeletal events such as arthralgia (33.3%).

Table 10: Common TEAEs experienced by > 10% of patients (Principal Safety Set)

TEAE, n (%)	Chronic treatment N = 99	Flare-up treatment N = 70	Overall N = 99
Skin and subcutaneous tissue disorders	83 (83.8)	59 (84.3)	96 (97.0)
Dry skin	52 (52.5)	32 (45.7)	68 (68.7)
Alopecia	17 (17.2)	18 (25.7)	34 (34.3)
Drug eruption	13 (13.1)	19 (27.1)	28 (28.3)
Pruritus	16 (16.2)	11 (15.7)	26 (26.3)
Rash	19 (19.2)	8 (11.4)	23 (23.2)
Erythema	10 (10.1)	13 (18.6)	22 (22.2)
Pruritus generalized	14 (14.1)	10 (14.3)	21 (21.2)
Skin exfoliation	10 (10.1)	10 (14.3)	19 (19.2)
Gastrointestinal disorders	63 (63.6)	33 (47.1)	77 (77.8)
Lip dryness	34 (34.3)	14 (20.0)	46 (46.5)
Chapped lips	6 (6.1)	8 (11.4)	14 (14.1)
Vomiting	9 (9.1)	3 (4.3)	12 (12.1)
Nausea	7 (7.1)	3 (4.3)	10 (10.1)
Infections and infestations	58 (58.6)	37 (52.9)	75 (75.8)
Upper respiratory tract infection	20 (20.2)	5 (7.1)	22 (22.2)
Nasopharyngitis	12 (12.1)	6 (8.6)	16 (16.2)
Paronychia	9 (9.1)	8 (11.4)	16 (16.2)
Musculoskeletal and connective tissue disorders	48 (48.5)	34 (48.6)	65 (65.7)
Arthralgia	24 (24.2)	12 (17.1)	33 (33.3)
Pain in extremity	18 (18.2)	8 (11.4)	22 (22.2)
Epiphyses premature fusion	11 (11.1)	7 (10.0)	18 (18.2)*
Injury, poisoning, and procedural complications	40 (40.4)	24 (34.3)	56 (56.6)
Contusion	8 (8.1)	7 (10.0)	14 (14.1)
Skin abrasion	5 (5.1)	8 (11.4)	12 (12.1)
Fall	6 (6.1)	6 (8.6)	11 (11.1)

Source: Table 2.5.11, p122 of the submission.
TEAE = Treatment-emergent adverse event
* Two further events of epiphyses premature fusion occurred post-treatment (115 and 305 days after last dose of palovarotene) and so are not listed here. One event of epiphyseal disorder also occurred, captured under a separate MedDRA term. In addition, one additional patient with a treatment-emergent TEAE was identified in the resubmission for MOVE.

6.45 The submission noted that retinoids are known regulators of growth plate chondrogenesis, and PPC has previously been reported with retinoids; as such, additional bone safety monitoring was implemented in MOVE. PPC is also a special warning and precaution for use in growing patients in the TGA PI. PPC can lead to a higher risk of bone deformities and compromised growth and is therefore a risk in younger individuals, rather than in older patients who are skeletally mature (Noyes 2016).

6.46 Table 11 presents the occurrence of PPC in the overall population up to the final DCO.

6.47 There were 24 patients who developed PPC and all events were considered serious adverse events (SAEs) that were at least possibly related to treatment. As discussed above, this caused the FDA to pause the study. The ESC noted that around a third of patients aged 8/10 to 14 years (who would be included in the proposed PBS population) developed PPC events.

Table 11: Premature physeal closure (Principal and Supplementary Safety Set)

	< 8/10 years N = 21	≥8/10 - <14 years N = 36	< 14 years N = 57	All patients N = 107
PPC, n (%)	12 (57.1)	12 (33.3)	24 (42.1)	24 (22.4)

Source: Table 2.5-12, p123v of the submission.
PPC = Premature physeal closure; TEAE = Treatment-emergent adverse event
Note: Includes TEAEs and post-treatment AEs

6.48 Although the submission did not present a comparison of adverse events between palovarotene and SoC, the submission presented a comparison of growth velocities for palovarotene compared to the SoC. A greater proportion of palovarotene-treated patients in MOVE had worst and last growth velocities of <4 cm/year than similarly aged SoC patients in the NHS.

6.49 Overall, despite the lack of comparative adverse event data, the high risk of PPC associated with palovarotene supports a claim of inferior safety. There are also other cutaneous adverse events associated with palovarotene which require additional treatment. Additionally, comparative data around growth velocity shows substantially worse growth outcomes in patients under the age of 18 in the palovarotene arm. This may have an impact on the QoL in paediatric patients treated with palovarotene.

6.50 The submission did not include adverse events in the economic model base case.

Benefits/harms

6.51 The unanchored indirect comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of palovarotene and SoC. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.52 The submission described palovarotene (in combination with SoC) as having superior efficacy and inferior safety compared to SoC.

6.53 The therapeutic conclusion of efficacy is supported by lower annualised HO in the PBS relevant subgroup. This was consistent with the view of the TGA ACM, which concluded that the results of the *post-hoc* comparison of annualised new HO demonstrated meaningful benefit. The ESC agreed with the commentary that the magnitude of this benefit was highly uncertain as:

- It was based on an unanchored indirect comparison of two single arm cohort studies (MOVE and the NHS). MOVE also had a high risk of Type 1 error due to a protocol change as the futility threshold was crossed and alternative post-hoc analytic methods were relied upon.
- The clinical claim was reliant on a surrogacy of HO outcomes to overall survival. While this surrogacy is biologically plausible, no quantifiable relationship has been adequately demonstrated in the submission, and there may be other pathways beyond HO such as immunogenicity pathways which may lead to reduced life expectancy in FOP patients. The pre-PBAC response stated that although there are

insufficient data for the relationship between HO outcomes and overall survival to be quantifiable, ample evidence was presented to support HO volume as the major driver of the progressive nature of FOP and the corresponding shortened lifespan.

- Although possibly due to insufficient follow-up, MOVE did not demonstrate any statistically significant differences in clinically meaningful outcomes such as CAJIS, FOP-PFQ or PROMIS.

6.54 With regard to the claim of inferior safety, the ESC agreed with the commentary that this was supported by the risk of serious adverse events such as PPC and other cutaneous adverse events.

6.55 The PBAC considered that the claim of superior comparative effectiveness was reasonable, though the magnitude of benefit on patient function was highly uncertain due to the limitations of the clinical data.

6.56 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.57 The submission presented a stepped economic evaluation based on the MOVE study. The type of economic evaluation presented was a cost-utility analysis.

6.58 The evaluation considered the base case incremental cost effectiveness ratio (ICER) was extremely high (> $1,055,000/QALY excluding caregiver utilities), and it was likely that there was no plausible scenario in which palovarotene would be considered conventionally cost-effective. The ESC considered that overall, the economic model is unlikely to be informative for decision making in this context, primarily because it relied on a number of poorly supported key assumptions, including the correlation between annualised HO and survival, and because many of the variables and approaches in the model could not be verified.

6.59 Table 12 presents an overview of the economic evaluation.

Table 12: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Palovarotene plus SoC versus SoC
Time horizon	80 years in the model base case versus 18 months in the interim analysis of MOVE.
Outcomes	Life years and quality-adjusted life years gained
Methods used to generate results	Markov model
Health states	Six health states defined by HO volume categories and one absorbing health state (death) • HO 1: 0 - 150,000 mm^3, • HO 2: 150,001 – 400,000 mm^3, • HO 3: 400,001 - 550,000 mm^3, • HO 4: 550,001 -750,000 mm^3, • HO 5: 750,001 – 1,200,000 mm^3 • HO 6: >1,200,000 mm^3 Within each health state, patients are distributed across four CAJIS score categories: • CAJIS 1 (0-8) • CAJIS 2 (9-15) • CAJIS 3 (16-24) • CAJIS 4 (25+)
Cycle length	12 months
Transition probabilities or Allocation to health states (if partitioned survival model)	Health state transitions between HO volume categories are based on the annualized change in new HO volume for patients aged <25 years and ≥25 years as observed in NHS. The treatment effect of PVO on annualised new HO volume as observed in MOVE is applied for all patients in the model who receive treatment with PVO. Mortality is informed by age and HO volume specific SMRs. The SMRs are then used to adjust the corresponding age specific Australian general population to derive FOP specific mortality for PVO treated and untreated patients.
Health related quality of life	Derived from the International BOI survey and informed by patient CAJIS score. The submission included caregiver utilities in the base case. This was not appropriate.

Source: Table 3.1-1, pp149-150 of the submission.
BOI; burden of illness; CAJIS: Cumulative Analogue Joint Involvement Scale, HO: heterotropic ossification; PVO; palovarotene, SoC = standard of care; SMR = standardised mortality rate

HO and survival

6.60 A Markov cohort model with six HO volume categories and one absorbing health state 'death' was used to evaluate the cost-effectiveness of palovarotene versus SoC. Patients enter the model and are distributed between the different HO heath states based on their baseline HO volume measurement. In each subsequent model cycle, patients may remain in their current health state, progress to the next highest HO volume health state or die. Patients do not transition back to lower HO volume health states.

6.61 The submission argued that to model the impact of palovarotene on FOP it is necessary to employ a lifetime horizon. The submission noted that while patients have a significantly reduced life expectancy when compared to the general population, published data shows that patients with FOP have a median life expectancy of 56 years (Pignolo 2019). The submission considered that with the average starting age of 19.9 years for patients in the model corresponding to that reported in MOVE (noting, this was actually 17.4 years in the PBS population subgroup) the lifetime time horizon

corresponds to 80 years at which time nearly all patients (~98% in both treatment arms) have died. It was unlikely that any FOP patients would live to 100 years of age.

6.62 To inform the transition probabilities in the base case, the rate of HO progression was assumed to be the same regardless of the existing HO volume of the patient, as such the submission considered that HO is assumed to form at a constant rate throughout the duration of the economic model (dependent on patient age <25 years or ≥25 years). No justification was provided to support this assumption.

6.63 To estimate the age and treatment dependent rates of HO progression, the ratio of the raw annual mean new HO volume was estimated from a combined analysis of MOVE and NHS individual patient data for patients aged <25 years and ≥25 years. The PBAC noted that calculation of these values could not be verified during the evaluation and appeared to include errors which were not addressed in the PSCR or pre-PBAC response. The PBAC noted that the model assumed that palovarotene causes a long-term constant reduction in new HO formation for up to 80 years, although the efficacy data set was only 18 months.

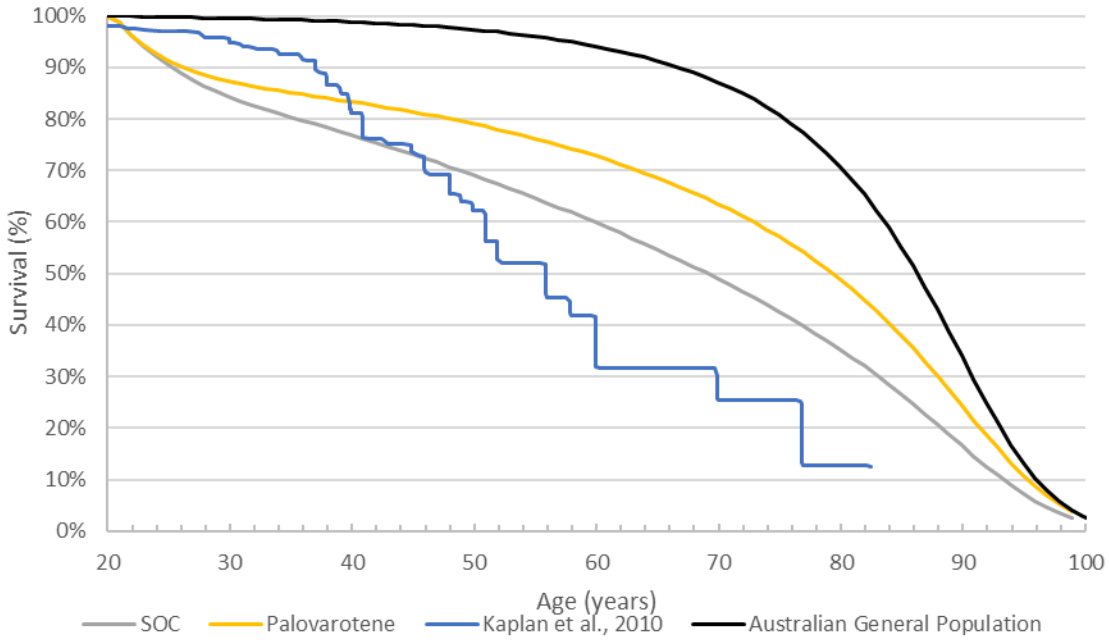
6.64 The submission argued that there is a biologically plausible relationship between HO volume and OS for patients with FOP and that it is clinically plausible that medicines such as palovarotene which slow the progressive accumulation of HO volume are likely to have an impact on OS. The approach used in the economic evaluation was to apply age and HO volume specific standardised mortality ratios (SMRs) to Australian general population mortality to estimate the OS for palovarotene treated patients and those managed with SoC. The evaluation considered it was uncertain whether the correlation between HO and age from the NHS to segments of a survival analysis from a different study (Kaplan 2010) will accurately inform the relationship between annualised HO and survival. It was unclear if Kaplan 2010 would supply accurate survival estimates given the 86% censoring rate.

6.65 The model applied two assumed survival benefits associated with palovarotene, which may indicate double counting. The two assumptions were:

1) That patients with higher HO volume categories will have Australian population mortality equal to older patients; and
2) An increased SMR applied to the calculated HO health state (which was informed by the corresponding age category mortality).

6.66 The PBAC noted that the modelled survival for both treatment arms appeared implausible compared with the data from Kaplan et al (2010), as shown in Figure 2.

Figure 2: Kaplan-Meier for modelled overall survival of palovarotene treated and untreated patients compared to the Australian general population and Kaplan 2010



Source: Figure 3.7-1, p186 of the submission.

6.67 Overall, the submission's approach to modelling HO health states and survival is based on the complex and poorly understood connection between new HO and overall survival.

Quality of life

6.68 Patients in each of the six HO volume health states were distributed across four CAJIS score categories based on a visual fit exercise, with CAJIS scores mapped to utility values based on a published burden of illness (BOI) study (Al Mukaddam 2022) for both patients and carers. There were substantial differences between the utilities estimated using the PROMIS scores in MOVE compared to the values used in the base case; for example, the utility in CAJIS 4 (25+) based on the BOI survey was 0.05 compared to 0.61 when based on MOVE. The ESC considered that mapping of utility values based on the proposed relationship between HO volume and CAJIS/PRMA score was another key unsupported assumption in the economic model.

6.69 While quality of life impacts on care givers is likely, the PBAC Guidelines (v5.0, p65) state that these should be considered as a supplementary analysis only. Consequently, inclusion of carer utility in the base case was inappropriate. Base case results presented herein refer to the results with caregiver utilities removed.

Treatment costs

6.70 In estimating treatment costs, the submission assumed that the modelled cohort comprised three age groups at baseline (8 years to <15 years = 37% of patients; 15 years to <25 years = 37% of patients; ≥25 years = 26% of patients), with each group

having different average doses of chronic and flare-up dosing, based on differences in annual number of flare-up days in between the three groups, and the application of weight-based dosing in the <15 age group. The submission claimed these proportions were based on IPD data from MOVE, but this could not be verified and did not appear to reflect data from MOVE. The proportion of patients in each group changed throughout the model but the proportions could not be verified or reconciled with the information from the MOVE and NHS studies.

6.71 A higher proportion of palovarotene-treated patients in MOVE experienced a flare-up event at Month 12 compared to untreated patients in the NHS (64.6% vs 54.1%). The submission claimed that the mean number of flare-ups per annum was 1.59 in patients treated with palovarotene in MOVE. The ratio of the annual flare-up rate for palovarotene versus untreated was reported to be 1.65, suggesting a trend for an increase in the number of flare-ups experienced per year for those on palovarotene. The submission considered that this may be due to the more frequent monitoring visits in MOVE compared with the monitoring of untreated patients in NHS. It is also possible that untreated patients in the NHS may have been less motivated to report flare-ups because flare-ups would not be treated. The mean number of flare-ups per patient was not presented in the clinical section of the submission and could not be confirmed during the evaluation.

6.72 Despite the difference in flare-up events between MOVE and the NHS, in the base case analysis, the rate of flare-ups for both treatment arms was assumed to be the same as for palovarotene treated patients in MOVE, with the rate differing by age group.

6.73 The submission calculated palovarotene costs for a chronic treatment regimen and flare-up treatment regimen for each of the three age groups used in the model based on the age-specific flare-up rate. The duration of flare-up was based on the median (12 weeks, or 84 days) rather than mean (110 days) duration of flare-ups, which may underestimate the duration of flare-up treatment.

6.74 In the first year of MOVE, 4.70% of patients receiving chronic treatment discontinued due to adverse events. This probability was applied to all patients on palovarotene treatment in the first cycle of the model to estimate discontinuation. In all subsequent cycles it was assumed the 2.35% of patients still on treatment at the start of the cycle will discontinue treatment. This estimate of discontinuation was based on clinician feedback. Based on the discontinuation rate applied, in combination with the estimated mortality in the submission, the mean duration of treatment was estimated to be 26.9 years. It was unclear if this was a reasonable estimate.

6.75 The submission did not consider the cost of managing adverse events due to palovarotene treatment in the base case analysis. This was inappropriate and also inconsistent with the submission's clinical claim of inferior safety. Furthermore, although the submission did not present a clinical comparison of safety outcomes between palovarotene and SoC, the safety profile of palovarotene is associated with risks of severe events such as PPC, which would be expected to be associated with

high management costs and substantial clinical harm. The ESC noted that the economic model did not include any costs or disutility for PPC events or impacts on growth velocity associated with palovarotene and agreed with the commentary that that this was not reasonable.

Economic evaluation base case

6.76 Table 13 presents the results of the stepped economic analysis.

Table 13: Results of the stepped economic evaluation

Step and component	PVO	SoC	Increment
Step 1: 24 month time horizon and medicine costs only			
Costs	$	$230	$
LYG	5.64	5.61	0.03
Incremental cost/extra LY gained			$[1]
Step 2: time horizon extended to 80 years			
Costs	$	$506	$
LYG	16.20	15.14	1.06
Incremental cost/extra LY gained			$[1]
Step 3: include resource use costs			
Costs	$	$21,113	$
LYG	16.20	15.14	1.06
Incremental cost/extra LY gained			$[1]
Step 4: LYs to QALYs, FOP and caregiver QALYs			
Costs	$	$21,113	$
QALYs	22.21	20.29	1.92
Incremental cost/extra QALY gained			$[1]
Evaluation base case: remove caregiver utilities			
Costs	$	$21,113	$
QALYs	6.49	5.60	0.89
Incremental cost/extra QALY gained			$[1]

Source: Table 3.8-1, p190 of the submission.
FOP = fibrodysplasia ossificans progressiva; LY = life years; PVO = palovarotene; QALY = quality adjusted life-year; SoC = standard of care
The redacted values correspond to the following ranges:
[1] > $1,055,000

6.77 The model was most sensitive to time horizon, discount rate, manipulation of annualised HO assumptions and relationship to mortality.

6.78 Overall, given the concerns regarding the validity and reliability of the approach to modelling HO to survival and quality of life outcomes, the results of the model across all sensitivity analyses were widely variable and uncertain.

6.79 With regard to costs, the greatest source of uncertainty was the assumptions regarding the age of patients expected to initiate palovarotene treatment. Due to the complexity of the modelling assumptions regarding age-based dosing and outcomes, assumptions regarding the age of patients initiating treatment could not be changed during the evaluation. Small changes in discontinuation rates also had a moderate impact on the ICER.

Drug cost/patient/course

Table 14: Drug cost per patient for palovarotene

	Palovarotene Trial dose and duration	Palovarotene Model	Palovarotene Financial estimates
Duration of Chronic treatment all patients, mean	365.4 days	26.9 years[j]	Varies based on year of initiation
Age 8 years to < 15 years			
Chronic (5mg dose equivalent) Cost/ year[a]($)	[redacted]		
Flare-up (20mg dose equivalent) cost/year[b]($)			
Flare-up (10mg dose equivalent) cost/year[c]($)			
Total cost/year 8 years to < 15 years ($)			
Age ≥ 15 to < 25 years			
Chronic (5mg) Cost/ year[d] ($)	[redacted]		
Flare-up (20mg) cost/year[e]($)			
Flare-up (10mg) cost/year[f]($)			
Total cost/ year ≥ 15 to < 25 years($)			
Age ≥ 25 years			
Chronic (5mg) Cost/ year[g] ($)	[redacted]		
Flare-up (20mg) cost/year[h] ($)			
Flare-up (10mg) cost/year[i] ($)			
Total cost/year ≥ 25 years ($)			
Total cost/course[k] ($)	[redacted][l]	[redacted]	**NR**

Source: Attached economic and financial models

[a] Assuming 4 x 1mg capsules (5mg dose equivalent for paediatric patients weighing between 40 and 60kg), equating to 34.04 packs per year based on 238 treatment days.

[b] Assuming 3 x 5 mg capsules (20mg dose equivalent for paediatric patients weighing between 40 and 60kg), equating to 4.53 packs per year based on 42 treatment days

[c] Assuming 1 x 5mg and 3 x 1mg capsules (10mg dose equivalent for paediatric patients weighing between 40 and 60kg), equating to 3.02 packs and 9.07 packs per year, respectively, based on 85 treatment days

[d] Assuming 1 x 5mg capsules, equating to 6.52 packs based on 182 treatment days

[e] Assuming 2 x 10 capsules, equating to 4.35 packs, based on 61 treatment days

[f] Assuming 1 x 10 capsules, equating to 4.35 packs based on 122 treatment days

[g] Assuming 1 x 5 mg capsules, equating to 10.22 packs per year based on 286 treatment days

[h] Assuming 2 x 10 mg capsules, equating to 1.88 packs per year, based on 26 treatment days

[i] Assuming 1 x 10mg capsules, equating to 1.88 packs, based on 53 treatment days

[j] based on discontinuation rate and estimated mortality of patients over an 80 year time horizon

[k] Undiscounted - based on annual cost of palovarotene by age group and changing proportions of age groups, and proportion of patients alive and on treatment each model year for the duration of the model

[l] Estimated from Year 1 palovarotene costs of the economic model, based on the distribution of age groups calculated from MOVE IPD data

Note: The economic model, though not the financials, included low cost treatments based on prednisone, several NSAID's, antihistamines, and other drugs in both the SoC and palovarotene arms. These included complex calculations for medicines that are low cost and low impact, and thus for clarity, are not presented.

Note: The submission claims that flare-up days on treatment were based on clinical data from MOVE, but this was not presented in the clinical evaluation of the submission.

6.80 The submission calculated annual costs per year based on estimated doses for three age groups: 8 years to <15 years, ≥15 to <25 years, and ≥25 years. The annual costs estimated for each of these age groups were $[redacted], $[redacted], and $[redacted], respectively. The annual costs were calculated for each age group based on weight adjusted dosing as per the TGA PI for both chronic and treatment and flare-up treatment. Flare-up treatment was estimated based on IPD estimating duration of flare-ups, at each adjusted dose.

Estimated PBS usage & financial implications

6.81 This submission was considered by DUSC. The submission used an epidemiological approach to estimate use and financial implications.

6.82 Table 15 presents the key inputs relied on in the financial estimates.

Table 15: Key inputs for financial estimates

Data	Value	Source	Comment/DUSC advice
Eligible population			
Incidence of disease	Germany: 0.002 per 100,000 Australia: 0.00167 per 100,000	Calculated using the number of FOP patients in Australia and the modelled duration of disease from economic model	The modelled of duration of disease (expected survival) was highly uncertain and likely inaccurately estimated.
Prevalent patients (number of registered FOP patients)	[redacted] [1] Anticipated number of additional unregistered FOP patient: [redacted] [1] Prevalence rate of 0.762	FOP Australia and Sponsor market data Prevalence rate calculated by registered FOP patients over estimated 2024 Australian population	DUSC considered this estimate to be reasonable and noted the similarity to prevalence used in the Canadian Agency for Drugs and Technology in Health (CADITH) approval which was 1 per million people. DUSC agreed the addition of two extra patients to account for patients who may not be registered with FOP Australia was reasonable.
Distribution of patient age groups	8 years to < 15 years: 41% 15 years to < 25 years: 34% 25 years +: 25%	Economic model, based on MOVE	There was no evidence to support that the distribution of age categories in Australia would reflect those in MOVE. DUSC considered that the current prevalent population will be older than the emerging incident population. DUSC considered building the model according to the FOP Australia age distribution would be more appropriate to form accurate estimates.
Body weight category distribution of patients < 15 years	Proportion skeletally immature: 63% <20 kg: 10% 20 - <40 kg: 74% 40 - <60 kg: 13% >= 60 kg: 3%	Economic model, based on MOVE	This likely reflected the best available evidence. However, this would likely be dependent on the age of initiating patients, which remains highly uncertain.
Annual incidence rate of flare-ups	8 years to < 15 years: 1.51 15 years to < 25 years: 2.18 25 years +: 0.94	IPD analysis of MOVE data	This likely reflected the best available evidence.
Mortality for PVO treated patients	Year Age Survival 2024 19.9 1.00 2025 20.9 0.99 2026 21.9 0.96 2027 22.9 0.94 2028 23.9 0.93 2029 24.9 0.91 2030 25.9 0.90	Economic model	As discussed in the economics section, the mortality in PVO patients was uncertain. DUSC noted that mortality rates would be higher for older prevalent patients with significant pre-existing morbidity.

Data	Value	Source	Comment/DUSC advice
Treatment utilisation			
Treatment duration based on flare-up incidence (annual)	Chronic treatment duration: 8 years to < 15 years: 238 days 15 years to < 25 years: 182 days 25 years +: 286 days Flare-up treatment duration: 8 years to < 15 years: 127 days 15 years to < 25 years: 183 days 25 years +: 79 days	Economic model	Using the median (84 days) rather than mean (110 days) duration of flare-ups likely underestimated the cost of palovarotene. The frequency of flare ups applied in the economic model could not be verified during the evaluation and was uncertain.

Source: Table 4.1-1, pp196-197 of the submission.
DPMQ = dispensed price per maximum quantity; FOP = fibrodysplasia ossificans progressiva; IPD = individual patient data; PI = product information; PVO = palovarotene; qd=daily
The redacted values correspond to the following ranges:
[1] < 500

6.83 A prevalence rate of 0.762 per million was calculated based on the number of registered FOP patients divided by the estimated total Australian population in 2024: < 500/27,562,195. The duration of disease (43.61 years) was assumed to be equal to the total estimated, undiscounted, life-years in the SoC arm of the economic evaluation. The modelling of overall survival in the economic model was highly uncertain and unreliable.

6.84 The submission calculated palovarotene costs in a manner consistent with the economic evaluation, by calculating annual costs by age group, and calculating an average cost based on changing proportions of patients. As discussed above, the estimates of patient age were uncertain, both in terms of the applicability of MOVE patient age to the Australian population and in terms of the method of calculation itself.

6.85 The submission did not estimate changes in use and financial impact of other medicines. SoC treatments associated with FOP was unlikely to change as palovarotene is to be used with SoC. It would be expected that palovarotene would impact use of other treatments, such as medication to manage cutaneous adverse events, although these are relatively low cost treatments compared to palovarotene. Overall use of other medicines would not be expected to impact financial estimates significantly but would likely increase with the listing of palovarotene.

6.86 The average patient co-payment is estimated by applying the current patient co-payment for each beneficiary type to the corresponding total number of prescriptions in each year. Overall, the total patient co-payment, as estimated by the submission, was expected to be $15,377-$17,256 per year. This represents substantial out of pocket payments for patients (more than $800 per patient), however it is likely that co-payments were overestimated in the submission as most patients are likely to be concession card holders.

6.87 Table 16 presents the submission's estimates of financial impact.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Prevalent patients[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Incident & persisting incident patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total treated patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of palovarotene						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Table 4.2-1, p208, Table 4.2-2, p208 and Table 4.2-7, p210 of the submission.

a Based on 20% patients not being treated due to age or medical reasons and 2 unregistered patients (21x.0.8+2=19). Number of patients assumed to decline each year due to death

b Based on Age and weight based dosing for chronic and flare-up treatment as calculated in the economic evaluation.

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

[3] $10 million to < $20 million

6.88 The total cost to the PBS/RPBS of listing palovarotene was estimated to be $10 million to < $20 million in Year 1 increasing to $10 million to < $20 million in Year 2 and decreasing to $10 million to < $20 million in Year 6, for a total of $70 million to < $80 million in the first 6 years of listing.

6.89 Overall, given the uncertainty regarding patient age, the total financial impact of palovarotene is uncertain as the annual palovarotene cost is $[redacted] for patients aged 8 – <15 years old, and $[redacted] for patients ages 15 - <25 years old, reflecting a 46% increase in costs and a $[redacted] difference per year for these two age groups. As for the economic evaluation, the cost of flare-up treatment was based on the median duration from the trial, rather than the mean, which is likely to underestimate the cost to the PBS.

6.90 The submission noted there are currently two patients who received treatment with palovarotene in the MOVE clinical trial who will transition to a company sponsored access program by the end of 2024. The submission anticipated that both patients will commence subsidised treatment with palovarotene in the first year of listing, but considered that both patients are currently registered with FOP Australia and are likely to have already been captured in the analysis. This was reasonable.

6.91 The PBAC noted that communication from FOP Australia indicated that, of patients with FOP in Australia, 4 are too young to initiate treatment and 7 are over 40 years of age, with significant impairment that means they are unlikely to benefit from treatment. This suggests that the submission underestimated the number of patients not treated due to age or medical reasons. The PBAC noted that to reflect the FOP Australia data this proportion would be increased from 20% to 52% ((< 500-4-7)/ < 500), which would reduce the total treated patients from < 500 to < 500 in year 1.

Quality Use of Medicines

6.92 The submission did not provide any details of Quality Use of Medicines activities. DUSC noted it was inappropriate for a submission with limited long term safety data,

complex dosing regimens and the potential for severe adverse events such as premature physeal closure to not have any consideration on the quality use of medicines (QUM) with no planned training programs for patients, carers or practitioners and no planned surveillance programs. The pre-PBAC response noted that active surveillance should already be implemented by prescribers since there is a special warning in the TGA PI for PPC and close monitoring is recommended in growing children every 6-12 months.

Financial Management – Risk Sharing Arrangements

6.93 The submission did not include details of a risk sharing arrangement (RSA).

For more detail on PBAC's view, see section 7 PBAC outcome.

Rule of rescue claim

6.94 The submission made a request for PBAC to consider the 'rule of rescue' or alternatively consider a listing under the Life Savings Drugs Program (LSDP), if the PBAC accepts that PVO is clinically effective but fails to meet the cost effectiveness criteria.

6.95 The PBAC noted it does not make recommendations or give advice to the Minister about which drugs should be listed on the LSDP.

6.96 Table 17 presents the submission's claims regarding the rule of rescue.

Table 17: Addressing the PBS 'rule of rescue' in this submission

PBS rule of rescue	PVO for FOP
The medical condition defined by the requested restriction applies to only a very small number of patients.	PVO is a TGA-approved treatment for FOP, an ultra-rare condition that affects 21 Australian patients.
The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death.	FOP is a progressive disease which is diagnosed based on clinical features and genetic confirmation. The average age at diagnosis is approximately 7 years old. Patients with FOP have a significantly shortened life expectancy, with a median survival ranging from 44 years (Liljesthröm 2016) to 56 years (Kaplan 2010)
The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition.	Patients treated with PVO are expected to have improved survival compared to untreated patients.
	HO is the major driver of disease progression in FOP. PVO has clinically superior efficacy compared to SoC (i.e., untreated patients) in reducing new HO volume.
No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no nonpharmacological or pharmacological interventions for these patients.	PVO is the only TGA-approved disease-modifying treatment for FOP.
	Patients are not recommended to undergo invasive procedures to remove extraskeletal bone as this exacerbates the condition.
	The proposed effective AEMP is $[redacted] for one month of chronic treatment for a patient 14 years or older which is an unreasonable financial burden.

Source: Table 1.1.2, p14 of the submission.
TGA = Therapeutic Goods Administration; FOP = Fibrodysplasia ossificans progressiva; PVO = Palovarotene; HO = Heterotopic ossification; SoC = Standard of care; AEMP = Approved ex-manufacturer's price; PBS = Pharmaceutical Benefits Scheme

6.97 Regarding the requirements for a rule of rescue claim, the evaluation and the ESC considered the following claims were reasonable:

- The medical condition defined by the requested restriction applies to only a very small number of patients; and
- The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death.

6.98 These claims are supported by the available epidemiological evidence that shows that FOP is rare, severe, progressive and associated with shorter life spans.

6.99 Regarding the criteria that the proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition, this was unclear. The TGA has considered that the changes in annualised HO from the MOVE trial are meaningful, but how these translate to clinically meaningful differences is unclear. The submission's claim that the economic evaluation provides evidence for improved survival associated with palovarotene compared to SoC, is based on flawed modelling assumptions and no clinical evidence demonstrating survival. Additionally, the MOVE trial showed no statistically significant differences between palovarotene and SoC in CAJIS range of motion outcomes or quality of life outcomes.

6.100 Lastly, regarding the claim that no alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction, and that there are no nonpharmacological or pharmacological interventions for these patients, this is reasonable. At the time of the submission, there were no effective treatment for FOP available in Australia. However, it was noted during the evaluation and ESC consideration that several new treatments for FOP were in development and may soon be marketed in Australia.

7 PBAC Outcome

7.1 The PBAC recommended the listing of palovarotene for the treatment of fibrodysplasia ossificans progressiva (FOP). The PBAC recognised the high and urgent clinical need for treatments for FOP, which is an ultra-rare disease with very substantial impacts on quality of life for patients and their carers. The PBAC was satisfied that palovarotene provides, for some patients, a reduction in annualised heterotropic ossification (when bone tissue develops in soft tissues) that may have a clinically relevant benefit. The PBAC considered that the proposed cost was very high and uncertain as it was dependent on age-based dosing and the frequency and duration of flares (which require higher dosing). The PBAC considered that the economic model presented in the submission was not sufficiently reliable for decision-making in part due to the limited long-term data available on changes in heterotropic ossification volume and patient functioning that were required to inform the model. The PBAC also advised the clinical trial data and uncertain economic modelling meant the rule of rescue claim that palovarotene provided a worthwhile clinical

improvement sufficient to qualify as a rescue from the condition, could not be adequately supported (see paragraph 6.99). In the context of this ultra-rare and life-limiting disease, and the importance of even small clinical gains in limiting heterotropic ossification, the PBAC considered palovarotene would be acceptably cost-effective with a reduction in cost that resulted in a lower cost per patient per year, in line with that for previously recommended treatments for rare diseases funded on the PBS when accounting for the clinical need, available evidence and size of the patient population. The PBAC noted that the estimated utilisation of palovarotene remains difficult to predict given treatment costs increase when patients experience flares, and as such a risk-sharing arrangement would be an appropriate way to limit costs per patient per year to the agreed amount and contain overall financial expenditure.

7.2 The PBAC recognised the high and urgent clinical need for treatments for FOP, for which there are currently no other disease modifying treatments. The PBAC noted that FOP is an ultra-rare disease with very substantial impacts on quality of life for patients and their carers. The PBAC noted the sponsor hearing and the consumer input descriptions of the disease progression in individuals with FOP, with unpredictable bone growth, which causes progressive and painful loss of independence and mobility, and a range of complications, including death due to thoracic insufficiency syndrome, ankylosis of the jaw and falls. As such, delaying bone growth, even by a small amount, is highly valued by patients with FOP and their carers. The PBAC noted the comments indicating that many patients and families are willing to accept the risk of side effects given the impact of the disease. The PBAC acknowledged that there is also a high financial burden and impact on quality of life for families and carers of people with FOP.

7.3 The PBAC noted that the proposed listing was consistent with the TGA indication for palovarotene and trial inclusion criteria. The PBAC considered it was appropriate to include the population criteria specifying the minimum patient age as per the TGA indication. The PBAC advised that the proposed maximum quantity of the 10 mg capsules should be increased to 2 packs to provide sufficient treatment for the first 4 weeks of the flare dosing at 20 mg per day for patients over 14 years and/or weighing ≥60kg.

7.4 The PBAC noted that the proposed prescribing instructions outlined symptoms of flare-ups and examples of high-risk substantial traumatic events consistent with the Australian PI and considered it would be appropriate for clinicians experienced in the diagnosis and treatment of FOP to make decisions regarding when to initiate flare-up dosing based on this definition.

7.5 The PBAC considered that given the very high cost of treatment, it was important that discontinuation from treatment be considered where patients are no longer receiving clinical benefit. However, the PBAC noted that clinical benefit is difficult to assess given the progressive, variable and unpredictable nature of FOP and trial outcomes of HO and CAJIS are not likely to be suitable for inclusion in the restrictions as

discontinuation criteria. The PBAC considered that patients would be regularly monitored by expert clinical teams and would be expected to discontinue treatment where significant impairment from FOP means that there is little physical function or mobility to preserve.

7.6 The submission nominated standard of care (SoC) as the main comparator. The PBAC considered that this was appropriate as there are no other disease-modifying treatments for FOP available. The PBAC noted that SoC includes symptomatic treatments that alleviate inflammation and pain during flare-ups and these treatments were also allowed for patients treated with palovarotene in the pivotal study (MOVE).

7.7 The pivotal evidence for palovarotene was based on a naïve indirect comparison of outcomes from MOVE (a phase 3, single-arm, open-label clinical study in 107 FOP patients treated with palovarotene) and the Natural History Study (NHS) (a prospective, non-interventional, longitudinal study which assessed the natural history of 114 patients with FOP over 36 months). The PBAC noted that the MOVE study was paused due to concerns with premature physeal closure (PPC) in patients <14 years and the age criteria were revised to include female patients ≥8 years and male patients ≥10 years. The primary outcome (annualised HO volume) was presented for this sub-population. The PBAC also noted that the MOVE study met the futility threshold at the second interim analysis and the statistical analysis of the primary outcome was revised. Although treatment durations for MOVE were intended to be 24 months, with a 24 month extension period, the efficacy data presented in the submission was based on 18 months of study duration, or the study duration prior to the pausing of the study due to meeting the futility threshold. The PBAC noted the ESC's advice that while the amendment to the statistical analysis protocol was reasonable, the change did contribute to an increase in the potential for type I error. The PBAC considered that the clinical data for palovarotene were limited by the changes in the study, the small patient population and the shortened treatment duration, but acknowledged the challenges of conducting trials in an ultra-rare condition.

7.8 The PBAC noted that for the primary outcome of annualised new HO volume (using non-transformed values) the full analysis set (all age groups) reached statistical significance with 53.8% LSM reduction (p=0.0003). For the PBS population subgroup (excluding younger patients) there was a 48.6% LSM reduction, which was not statistically significant and did not meet the proposed MCID of 50% reduction. However, it was acknowledged that the clinical meaningfulness of a reduction in HO volume can be difficult to assess at the population level since any HO for a given patient may have a profound impact if this occurs in a location that impairs functioning. The PBAC noted that for secondary outcomes (proportion with new HO, difference in movement (CAJIS) and HRQoL) there were no significant differences between the patients treated with palovarotene (in MOVE) and SoC (in NHS). The PBAC noted patients treated with palovarotene appeared to experience more flare-ups than those treated with SoC, however considered that the outcome was difficult

to interpret due to differences in the trials that are likely to have impacted on the proportion of patients reporting flare-ups. Overall, the PBAC considered that the claim of superior comparative effectiveness was reasonable based on a reduction in new HO volume, though the magnitude of benefit is highly uncertain due to the limitations of the clinical data.

7.9 The PBAC noted that HO volume alone is not a patient relevant outcome, the most relevant clinical outcomes for patients with FOP are related to HRQoL, physical function, range of motion, and frequency of flare-ups. The PBAC also noted that input from consumers and clinical experts indicated that the location of HO, and functional area affected, is more important than the volume of HO. The submission argued that the effects of HO result in a shortened life-expectancy in patients with FOP; immobility and HO in the chest wall can interfere with cardiopulmonary function causing thoracic insufficiency syndrome, the most common cause of premature mortality in patients with FOP. The submission presented an assessment for translating the comparative treatment effects of palovarotene, measured by the surrogate outcome of annualised new HO volume, to the target clinical outcome of overall survival (OS) using the surrogate to final outcome (STFO) framework (Appendix 5 of the PBAC Guidelines, v.5). The PBAC considered the data available were not adequate to demonstrate the magnitude of benefit in patient relevant outcomes gained by improvements in HO outcomes. However, the PBAC considered that it is biologically plausible that reduction in new HO could lead to better survival outcomes and better quality of life (QoL) outcomes. The PBAC was satisfied that palovarotene provides, for some patients, a reduction in annualised HO that may have a clinically relevant benefit.

7.10 The PBAC noted that direct comparisons with AEs reported in MOVE were not possible because in the NHS, AEs were only captured if they resulted from procedures performed during the study. For palovarotene the most commonly reported TEAEs were skin and subcutaneous tissue disorders (dry skin, dry lips, alopecia, drug eruption, pruritus) which are known side effects of retinoids. The PBAC also noted that PPC also occurred in around a third of patients aged 8/10 to 14, who are included in the proposed PBS population, which was a significant safety concern. Overall, the PBAC considered that the claim of inferior comparative safety was reasonable and consistent with the clinical evidence.

7.11 The submission presented a stepped cost-utility analysis for the economic evaluation, based on results from the MOVE study and the NHS. The base case ICER for the economic model was extremely high (> $1,055,000/QALY gained, excluding caregiver utilities; > $1,055,000/QALY gained, including caregiver utilities). The PBAC noted that the economic model relied on a number of poorly supported key assumptions, including the correlation between annualised HO and survival. The PBAC considered that the data available for palovarotene were not adequate to inform the modelling of survival benefit in the economic model due to the outcomes captured and the short duration of the trial. The PBAC also noted that mapping of utility values based on the proposed relationship between HO volume and CAJIS/PRMA score was another key

unsupported assumption in the economic model. In addition, many of the variables and approaches in the model could not be verified during the evaluation. The PBAC considered that overall, the economic model was not informative for decision making in this context. The PBAC considered that the value proposition was difficult to assess with a traditional incremental cost-effectiveness ratio due to the limited long-term clinical data and lack of patient-relevant outcomes to inform the model, the small number of patients included in the trial, and the highly individualised and unpredictable nature of FOP progression. The PBAC considered the uncertainty in the ICER is unlikely to be adequately resolved with further revision to the model structure.

7.12 The PBAC acknowledged the high and urgent clinical need for effective treatment of FOP, an ultra-rare and life-limiting disease, and the importance of even small clinical gains in limiting heterotropic ossification, and in this context the PBAC considered an alternative approach to achieve cost-effectiveness was required in this instance. The PBAC reflected on previous determinations made for other rare diseases where no effective alternative therapies were available. The PBAC compared the nature of the benefits, ICERs, numbers of patients expected to be treated, and the cost per patient per year for palovarotene at the proposed price, with other high-cost treatments for rare diseases funded on the PBS. The PBAC considered palovarotene would be acceptably cost-effective with a reduction in treatment costs that resulted in a cost per patient per year in the order of $, with calculations as per Table 14. The PBAC considered this would be consistent with that for previously recommended treatments for rare diseases funded on the PBS when accounting for the clinical need, available evidence and size of the patient population.

7.13 The PBAC noted that the submission used an epidemiological approach to estimate use and financial implications and that patient numbers were based on patients registered with FOP Australia with an assumption of an additional < 500 unregistered patients. The PBAC considered that this approach gave a reasonable level of certainty regarding the number of FOP patients. However the PBAC noted that information from FOP Australia indicates that approximately 4 patients are too young to initiate treatment and 7 are over 40 years of age, with significant impairment that means they are unlikely to benefit from treatment. The PBAC considered that the estimated eligible patients should be reduced to remove these patients. The PBAC noted that the duration and rate of flare-ups was important as costs for the flare-up dosing are substantially higher than for chronic treatment and considered that costs for flares are uncertain and likely to be underestimated in the financial estimates. The PBAC noted that costs for both chronic treatment and flare-up dosing were dependent on patient age and considered it would be appropriate to revise the distribution of ages in the estimates to align with Australian patients according to information from FOP Australia to provide more accurate estimates of the financial implications. The PBAC considered that with these changes and a reduction in the cost such that the cost per patient per year is in the order of $ the financial estimates would be acceptable.

7.14 The submission did not include details of a risk sharing arrangement (RSA). The PBAC considered that an RSA with expenditure caps would be required to mitigate the risk of substantially higher costs per patient due to uncertain estimates of the age distribution, duration and frequency of flare-ups. The PBAC considered that the financial estimates, with revisions as per paragraph 7.13, would be a reasonable basis for calculation of the expenditure caps. The PBAC considered that given the level of uncertainty in the cost-effectiveness, the rebate level should be close to 100%.

7.15 The PBAC advised that palovarotene should not be treated as interchangeable with any other drugs.

7.16 The PBAC advised that palovarotene is not suitable for prescribing by nurse practitioners.

7.17 The PBAC recommended that the Early Supply Rule should not apply.

7.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. **Specifically** the PBAC found that in the circumstances of its recommendation for palovarotene:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, as the magnitude of clinically relevant benefit is uncertain;

b) The treatment is expected to address a high and urgent unmet clinical need as there are no other disease-modifying treatment for FOP;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.19 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
PALOVAROTENE					
Palovarotene 1 mg capsule, 28	NEW MP	1	28	5	SOHONOS
Palovarotene 1.5 mg capsule, 28	NEW MP	1	28	5	SOHONOS
Palovarotene 2.5 mg capsule, 28	NEW MP	1	28	5	SOHONOS
Palovarotene 5 mg capsule, 28	NEW MP	1	28	5	SOHONOS

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Condition: Fibrodysplasia ossificans progressiva (FOP)
	Indication: Fibrodysplasia ossificans progressiva (FOP)
	Treatment Phase: Chronic treatment
	Clinical criteria:
	Patient must have a diagnosis of FOP, confirmed by genetic testing
	Treatment criteria:
	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of FOP; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of FOP
	Population criteria:
	Patient must be a female aged 8 years or older; or
	Patient must be a male aged 10 years or older
	Prescribing Instructions: At the time of the authority application, the medical practitioner must request the appropriate combination of packs to provide treatment at the recommended dose for chronic treatment, based on the age and weight of the patient, adequate for 4 weeks according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.
	Prescriber instructions: Appropriate genetic testing constitutes testing for a pathogenic variant of the Activin A receptor type *I (ACVR1)* gene. Confirm that evidence of the presence of a pathogenic mutation of the ACVR1 gene is documented/retained in the patient's medical records once only with the first PBS prescription.
	Prescriber instructions: The authority application must be made in writing and must include: 1) details of the proposed prescription; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

	Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
PALOVAROTENE					
Palovarotene 1 mg capsule, 28	NEW MP	1	28	2	SOHONOS
Palovarotene 1.5 mg capsule, 28	NEW MP	1	28	2	SOHONOS
Palovarotene 2.5 mg capsule, 28	NEW MP	1	28	2	SOHONOS
Palovarotene 5 mg capsule, 28	NEW MP	1	28	2	SOHONOS
Palovarotene 10 mg capsule, 28	NEW MP	2	28	2	SOHONOS

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Condition: Fibrodysplasia ossificans progressiva (FOP)
	Indication: Fibrodysplasia ossificans progressiva (FOP)
	Treatment Phase: Flare-up (acute) treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must be experiencing a FOP flare-up; or
	Patient must be at high risk of a FOP flare-up
	Treatment criteria:
	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of FOP; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of FOP
	Population criteria:
	Patient must be a female aged 8 years or older; or
	Patient must be a male aged 10 years or older
	Prescribing Instructions: 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. Examples of a high risk substantial traumatic event include surgery, intramuscular immunisation, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses.
	Prescribing Instructions: At the time of the authority application, the medical practitioner must request the appropriate combination of packs to provide treatment at the recommended dose for flare-up treatment based on the age and weight of the patient, adequate for 12 weeks of treatment or in the presence of persistent flare-up symptoms to extend treatment in 4-week intervals according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. If the patient experiences another flare-up (i.e., 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.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.

11 Corrigendum

The following changes were made:

Change made	Date of revision
Paragraph 7.13: Amended 'The PBAC considered that with these changes and a reduction in the cost per patient per year in the order of $[redacted] the financial estimates would be acceptable' to 'The PBAC considered that with these changes and a reduction in the cost such that the cost per patient per year is in the order of $[redacted] the financial estimates would be acceptable'.	7 March 2025