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CADTH Reimbursement Recommendation

Palovarotene (Sohonos)

Indication: To reduce the formation of heterotopic ossification in adults and children aged 8 years and above for females and 10 years and above for males with fibrodysplasia (myositis) ossificans progressiva

Sponsor: Ipsen Biopharmaceuticals Canada, Inc.

Final recommendation: Reimburse with conditions

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Summary

What Is the CADTH Reimbursement Recommendation for Sohonos?

CADTH recommends that Sohonos be reimbursed by public drug plans 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), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Sohonos should only be covered to treat patients who have a clinical diagnosis of FOP and the R206H *ACVR1* mutation as confirmed by genetic testing, and who do not have completely fused joints over the whole body.

What Are the Conditions for Reimbursement?

Sohonos should only be reimbursed if prescribed by an expert in the diagnosis and management of FOP and if the cost of Sohonos is reduced. While receiving Sohonos, patients (and their caregivers, for pediatric patients) and their physicians should have ongoing and regular discussions to assess the benefits and risks of treatment with Sohonos.

Why Did CADTH Make This Recommendation?

- FOP is a debilitating and very rare disease that is associated with a shortened lifespan; there are no other effective treatments.
- Evidence from 1 clinical trial demonstrated that treatment with Sohonos may reduce the formation of HO (new bone), which was 1 of the needs identified by patients.
- Based on CADTH's assessment of the health economic evidence, Sohonos does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Sohonos is estimated to cost the public drug plans approximately $14,336,341 over the next 3 years.

Additional Information

What Is FOP?

FOP is a very rare disease in which muscles and tendons are gradually replaced by bone, creating a second skeleton of extra bone. Patients with FOP have painful episodes of muscle swelling, lose function as joints fuse, and have a shortened lifespan. Patients gradually lose the ability to move and perform daily self-care activities, with the main cause of death being complications from a restricted chest wall. There are approximately 20 known patients with FOP in Canada.

Summary

Unmet Needs in FOP

There is a need for treatments to help patients maintain or improve mobility, improve episodes of muscle swelling, stop or slow new bone formation, and reduce pain.

How Much Does Sohonos Cost?

Treatment with Sohonos is expected to cost approximately $1,022,894 per year for patients aged 14 years and older and $622,373 per year for patients younger than 14 years.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that palovarotene be reimbursed 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 (myositis) Ossificans Progressiva (FOP), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

CDEC recognized the significant unmet need in a small patient population with a condition with high morbidity for which no other effective treatments are currently available. FOP is a disease of progressive immobilization and shortened lifespan, for which there are no other disease-modifying treatments. It is an ultra-rare disease, and there were approximately 20 known patients with FOP in Canada at the time of the review.

There was evidence from 1 single-arm, open-label, phase III study (MOVE) that treatment with palovarotene may result in added clinical benefit for patients with FOP aged 8 years and older for females and 10 years and older for males (referred to as the target population). Patients in the MOVE study, who were treated with palovarotene, were compared to untreated patients in an external cohort from the sponsor's natural history study, and the analysis in the target population included 77 patients from the MOVE study and 79 patients from the natural history study. Palovarotene treatment was associated with a reduction in annualized new HO volume, with an estimated percent reduction of 48.6% (mean reduction of 10,443 mm^3; 95% confidence interval [CI], −23,538 mm^3 to 26,534 mm^3) using a weighted linear mixed-effects (wLME) model and 25% (ratio of mean change = 0.75; 95% credible interval [CrI], 0.51 to 1.11) using a Bayesian analysis. There are no minimal important difference (MID) estimates available for HO volume, but the treatment effect was considered to be clinically meaningful according to clinical expert opinion. Patients identified a need for treatments that reduce or stop new HO, help them maintain or improve mobility, reduce frequency and severity of flare-ups, and reduce pain. No improvements were observed with palovarotene in the number of reported flare-ups, range of motion, physical function, or health-related quality of life (HRQoL). CDEC recognized the significant unmet need of patients with FOP and concluded that palovarotene may meet 1 of the needs identified by patients, the reduction of new HO.

Using the sponsor-submitted price for palovarotene and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for palovarotene plus standard of care (SoC) was $13,055,900 per quality-adjusted life-year (QALY) gained, compared with SoC alone. At this ICER, palovarotene plus SoC is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for adults and children aged 8 years and older for females and 10 years and older for males with FOP. A price reduction is required for palovarotene to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must have a clinical diagnosis of FOP and the R206H *ACVR1* mutation as confirmed by genetic testing.	Evidence from the MOVE trial, when compared with the natural history study cohort, supported the efficacy of palovarotene. The main analyses in the MOVE trial, including those in the target population, only included patients with the R206H *ACVR1* mutation.	CDEC does not anticipate issues with access to genetic testing for FOP, based on clinical expert input.
2. Patients must not have complete ankylosis of the whole body.	According to clinical expert input, patients without ankylosis of the whole body may benefit from treatment with palovarotene. In addition, evidence from the MOVE trial, when compared with the natural history study cohort, supported the efficacy of palovarotene in the studied population. In the MOVE trial, none of the patients had complete ankylosis of the whole body, as baseline CAJIS score ranged from 0 to 26.	CDEC noted the difficulty and complexity in assessing the potential benefits and risks of palovarotene in growing children with FOP who are at risk of premature physeal closure with palovarotene treatment. CDEC emphasized the need for a thorough discussion of the potential benefits and risks of palovarotene between patients, caregivers, and physicians, and the need for ongoing safety monitoring, including monitoring of skeletal maturity.
Discontinuation		
3. The patient (and their caregivers, for pediatric patients) and their physician should have ongoing and regular discussions to assess the benefits and risks of palovarotene treatment. Palovarotene should be discontinued if it is agreed that the perceived balance of benefits and risks is no longer acceptable. These discussions should include an assessment of the following: ability to eat and feed and perform other activities of daily living, pain, mobility, joint range of motion, and pulmonary function.	CDEC noted the challenges associated with assessing treatment response, including the lack of patient-centred instruments that are both validated and sufficiently responsive, and the heterogeneity in the rate of disease progression and flare-ups among patients and over time within patients. CDEC was not able to define specific requirements for determining whether patients are benefiting from treatment and indicated that the assessment of benefit must be individualized and focus on factors that are important to patients.	These discussions should occur at least annually.
4. Palovarotene should be discontinued if the disease has progressed such that the patient has complete ankylosis of the whole body.	Patients with complete ankylosis of the whole body were not studied in the MOVE trial. According to clinical expert input, it is patients without complete ankylosis of the whole body who may benefit from treatment with palovarotene.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
5. Palovarotene must be prescribed by an expert in the diagnosis and management of FOP.	The clinical experts noted that this is important due to the rarity of the disease.	Based on clinical expert input, patients (or their caregivers, in the case of pediatric patients) have adequate expertise to identify a flare-up and initiate the flare-up regimen.
Pricing		
6. A reduction in price.	The ICER for palovarotene plus SoC is $13,055,900 when compared with SoC alone. A price reduction of at least 99% would be required for palovarotene plus SoC to achieve an ICER of $50,000 per QALY gained, compared to SoC alone.	—

CAJIS = Cumulative Analogue Joint Involvement Scale; FOP = fibrodysplasia ossificans progressiva; HO = heterotopic ossification; ICER = incremental cost-effectiveness ratio; SoC = standard of care.

Discussion Points

- There was uncertainty in the magnitude of the treatment effect for annualized new HO volume due to the potential for bias from imbalances in baseline characteristics between the MOVE and natural history study groups, unmeasured confounding, and attrition, as well as the inclusion of the null in the 95% CI and 95% CrI for the between-groups difference. In addition, futility was declared at an interim analysis based on the prespecified analysis in the full population, and all the analyses in the target population were post hoc. As there was uncertainty with the clinical evidence, CDEC considered the criteria for significant unmet need described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews when deliberating on palovarotene. FOP is a disease of progressive immobilization and shortened lifespan, for which there are no other disease-modifying treatments. It is an ultra-rare disease and there are approximately 20 known patients with FOP in Canada. Considering the rarity and severity of the condition, and the absence of clinically effective alternatives, the committee concluded that the available evidence suggests that palovarotene has the potential to reduce the formation of HO.
- CDEC discussed ethical and equity considerations related to palovarotene, including the substantial impact of FOP on patients' quality of life, mental health, functional status, and life expectancy, as well as the high rates of misdiagnosis and diagnostic delays, and absence of disease-modifying therapies for this ultra-rare disease. They also discussed how the uncertainty in the magnitude of the treatment effect and absence of long-term safety and efficacy data for palovarotene presented challenges for assessing its cost-effectiveness and for informed consent. The committee also discussed how palovarotene presented the potential for several harms, including premature growth inhibition in children; however, they noted the clinical potential of palovarotene on an individual basis given the severity of FOP and lack of treatment alternatives. Barriers to access to specialist care for

the use of palovarotene, such as those due to geography or limited English or French proficiency, may be mitigated in part through technological and systems-level supports. The committee discussed how palovarotene, as a treatment for an ultra-rare disease, highlights the potential tension between meeting population health needs and the needs of a smaller population of patients severely impacted by FOP.

- Growing children with FOP are at risk of premature physeal closure with palovarotene treatment, and the Health Canada–approved product monograph contains a serious warning about this risk. According to the clinical experts, this risk can translate to smaller stature and uneven limb length in patients. CDEC noted that the perception of this risk may vary across patients and that pediatric patients are uniquely vulnerable due to their reliance on parents or guardians for treatment decisions. This underscores the need for ongoing conversations between patients, caregivers, and physicians about an acceptable balance of risks and benefits.
- The Health Canada–approved product monograph contains a serious warning about the teratogenic effects of palovarotene and outlines a palovarotene-specific pregnancy prevention plan. As outlined in the pregnancy prevention plan, patients of childbearing potential must undergo regular pregnancy testing before, during, and 1 month after stopping treatment. In keeping with the product monograph guidance, CDEC emphasized that patients of childbearing potential must have a documented negative pregnancy test at the time of initiating palovarotene treatment and must discontinue treatment if pregnancy occurs or if they are planning to become pregnant.
- Given the variability and subjectivity inherent with assessment of treatment response in this patient population (i.e., lack of patient-centred instruments that are both validated and sufficiently responsive, as well as heterogeneity in the rate of disease progression and flare-ups among patients and over time within patients), CDEC acknowledged clinical expert input suggesting that adjudication of eligibility for continued palovarotene treatment be confirmed by more than 1 expert in the diagnosis and management of FOP. CDEC recognized that some jurisdictions might not have access to a sufficient number of specialists to implement this approach. If it were to be implemented, public drug plans should consider whether a pan-Canadian approach would be feasible, such as leveraging clinical expertise in larger jurisdictions through the establishment of a centralized panel or committee of specialists with expertise in FOP that could assess the suitability for continued treatment with palovarotene.
- HO volume is not a patient-centred outcome nor is it used in clinical practice. Barriers to the use of HO volume for monitoring treatment response include radiation safety concerns from whole-body CT and challenges with implementing a CT-based measure that is not part of clinical practice. Considering these limitations and clinical expert input, CDEC decided that HO volume assessment should not be required for initiation, renewal, or discontinuation of treatment with palovarotene.
- CDEC discussed the uncertainty in the economic analysis, specifically that in the absence of robust comparative evidence, the incremental gain in QALYs with palovarotene plus SoC predicted in CADTH's reanalysis may still overestimate the incremental benefits relative to SoC, and further price reductions may therefore be required. CDEC additionally discussed that the acquisition cost of

palovarotene in CADTH's reanalysis assumed that patients would receive the flare-up regimen for 12 weeks, with the annual number of flare-ups based on observations from the MOVE trial. If patients in clinical practice experience more flare-ups per year or flare-ups that last longer than 12 weeks, the predicted drug acquisition costs may be underestimated.

- CDEC discussed the uncertainty in the number of patients eligible for palovarotene. Estimates in the literature for the prevalence of FOP range from 0.56 patients to 1.36 patients per million population. CADTH's estimated budget impact of reimbursing palovarotene is based on an estimated prevalence of 0.56 per million, based on Canadian registry data from 2016, resulting in approximately 19 patients with FOP in Canada; however, the Canadian FOP Network estimates that there are 34 patients with FOP in Canada. Should the prevalence of FOP be higher than estimated, the budget impact of reimbursing palovarotene will be greater.

Background

FOP is an ultra-rare congenital disease of uncontrolled, progressive, and abnormal growth of bone in nonskeletal tissues (e.g., muscles, tendons, and ligament) through the process of HO. FOP is caused by a recurrent heterozygous activating mutation of *ACVR1*, which is a member of the protein family bone morphogenetic protein type I receptors. The mutation occurs as a random event during the formation of reproductive cells (eggs or sperm) in the patient's biological parent or in early embryonic development. Although FOP is a congenital condition, ossification does not occur before birth. HO occurs in infancy and progresses throughout life. It may occur without warning or following a flare-up induced by trauma (e.g., intramuscular childhood immunizations, falls, surgery, biopsy) or various viral illnesses. In the affected areas, ossification eventually leads to stiffness and limited movement of joints. As the disease progresses, patients with FOP experience increasingly limited mobility — affecting balance, walking, and sitting — and/or joint range of motion. The development of bone at multiple soft tissue sites eventually leads to ankylosis (fusion) of the affected joints, including the spine and thoracic cage. Patients whose jaws are affected have difficulty eating and/or speaking. Eventually, FOP may result in complete immobilization. The permanent and cumulative effects of HO result in severe functional limitations in joint mobility and progressive disability, such that most patients with FOP require a wheelchair by their third decade of life. As mobility begins to deteriorate due to HO, patients with FOP are at increased risk for a multitude of health morbidities, including fractures, severe restrictive lung disease, right-sided congestive heart failure, scoliosis, pressure ulcers, severe weight loss due to jaw ankylosis, gastrointestinal issues, and acute and chronic pain. Hearing impairment occurs in approximately half of all patients with FOP. As disability progresses, HRQoL decreases. In addition to being extremely debilitating, FOP is associated with shortened lifespan, with an estimated median lifespan of 56 years. Death among patients with FOP is mainly due to complications of restrictive chest wall disease. The worldwide prevalence of FOP is estimated to be 1 in 2 million, although due to global high rates of misdiagnosis, the number of those with FOP may be closer to 1 in 1 million. The prevalence of FOP does not differ across sex, race, ethnicity, or geography. There are approximately 900 confirmed cases of FOP worldwide. Based on registry data, the estimated prevalence of FOP in Canada is 0.559 per million persons. Based on clinical expert input, there are approximately 20 known patients with FOP in Canada.

Palovarotene has been approved by Health Canada to reduce the formation of HO in adults and children aged 8 years and older for females and 10 years and older for males with FOP. Palovarotene is a selective agonist of retinoic acid receptor gamma. It is available as an oral tablet and the dosage recommended in the product monograph is 5 mg once daily for chronic treatment. At the onset of the first symptom indicative of an FOP flare-up — or substantial high-risk traumatic event likely to lead to a flare-up — Health Canada recommends, under the guidance of a health care professional, a flare-up regimen of 20 mg once daily for 4 weeks followed by 10 mg once daily for 8 weeks, for a total of 12 weeks (20 mg to 10 mg flare-up regimen) even if symptoms resolve earlier. Chronic treatment with palovarotene should reinitiated after completion of the flare-up treatment. A weight-based dosage is required in children who are younger than 14 years of age.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 single-arm, open-label, phase III study in patients aged 4 years and older with FOP with patients from a natural history study forming a control group
- patients' perspectives gathered by patient groups: the Canadian FOP Network (CFOPN) and the Canadian Organization for Rare Disorders (CORD)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 4 clinical specialists with expertise diagnosing and treating patients with FOP
- input from 1 clinician group: clinicians who attended the Canadian Endocrine Update
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to palovarotene.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Patient input was provided from the CFOPN and the CORD in 1 joint submission. Together, these patient groups provided input from 3 patients with FOP currently receiving palovarotene, and 1 caregiver of a patient living in Canada with FOP. Patient input was collected via telephone interviews between October 31, 2022, and November 9, 2022. In addition, a summary of patient and caregiver public testimonies given before the FDA Endocrinologic and Metabolic Drugs Advisory Committee (October 31, 2022) was included.

Patients and caregivers reported experiencing stress from "unrelenting vigilance" to avoid activities that may result in injury and trigger flare-ups (with onset that is often unpredictable or without a precipitating event) resulting in permanent bone growth, which contributes to progressive loss of physical movement and independence The disease deprives patients of normal activities and life experiences, contributing

to stigmatization, isolation, and despair. The extreme mental and physical toll of FOP is underscored by the following quote from a caregiver: "…my child is well aware of [her] body slowly failing […] outward deformations, the inability to take full breaths […] limited abilities to participate in social events and no […] physical events […] Each day brings with it additional agonizing truths […] not knowing what tomorrow will bring or the real potential for a much-shortened life span." Due to absence of approved effective therapies for FOP, patents are left to restricting their lifestyle to protect against potentially injurious flare-ups and control disease progression. However, giving up all potentially injurious activities deprives patients of experiences of pleasure and meaning, with no assurance of preventing flare-ups or disease progression. Patients with FOP expressed a desire for access to treatments that reduce symptoms and prevent disease progression. Patients listed the following treatment outcomes as important: maintenance of or increased mobility, reduced frequency and severity of flare-ups, reduced pain, and reduced or halted new bone growth. For some patients, simply halting disease progression such that they could adapt to their existing disease state and continue to enjoy activities that provide meaningful experiences would bring them satisfaction. Of those patients who have had experience with palovarotene, all expressed a desire to continue its use for as long as possible. Treatment with palovarotene has allowed these patients to maintain or even increase their mobility and has provided them with hope for improved quality of life and independence with continued use.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical experts consulted by CADTH for the purpose of this review, an ideal treatment for patients with FOP would be one that could be administered as early as possible — even in utero — and that could prevent and/or reduce HO, while prolonging life lived with good quality of life. The clinical experts agreed that palovarotene should be used as first-line therapy, with supportive pharmacological and non-pharmacological measures in place. However, the clinical experts cautioned that the optimal time to start treatment with palovarotene for pediatric patients is uncertain. The clinical experts agreed that palovarotene would be the main treatment for both adults and children. The clinical experts agreed that for patients aged 16 years and older, palovarotene may be combined with corticosteroids during flare-ups. Bisphosphonates may also be used concurrently with palovarotene, regardless of age. The clinical experts highlighted the practice of minimizing polypharmacy in the pediatric population younger than 16 years of age. Accordingly, consideration should be given to initiating palovarotene as the sole treatment in patients younger than 16 years; corticosteroids or other drugs may be added when it is deemed clinically that adjuvant therapy is needed.

Regarding gene mutations associated with FOP, the clinical experts noted that since palovarotene works downstream of the *ACVR1* receptor, patients harbouring any gene mutations of the receptor resulting in HO formation through the Smad 1/5/8 pathway may benefit from palovarotene treatment. Accordingly, any mutation that works on the Smad pathway and upregulates it should be amenable to treatment with palovarotene. The clinical experts noted that assessment of patients or caregiver compliance to the treatment regimen is important to determine suitability before prescribing palovarotene. The clinical experts agreed that patients who do not have ankylosis of the whole body would benefit from treatment

with palovarotene to prevent progressive disability. The clinical experts highlighted that patients with more advanced disease may benefit less from palovarotene, since the extent to which HO can be reversed is unclear; however, they may still derive benefits from palovarotene through the prevention of new bone formation or HO reversal to preserve jaw function and lung capacity. Of note, the clinical experts stressed that the use of palovarotene in young patients whose growth plates have not fused should only be undertaken after careful consideration and consultation with patients and their families. The clinical experts opined that when considering treatment with palovarotene in patients with open epiphyses, there is still uncertainty with regard to whether the potential benefits of treatment with palovarotene outweigh the potential harms.

The clinical experts noted that the preservation of function is the most important marker of treatment response. The clinical experts advocated the use of clinical parameters (e.g., Cumulative Analogue Joint Involvement Scale [CAJIS]) to assess response to treatment. In addition, the clinical experts noted that response to treatment with palovarotene should also include assessing prevention of comorbidities such as the inability to walk, need for a wheelchair, inability to work, inability to continue performing activities of daily living, decreased respiratory function, hearing loss, and — for patients with advanced disease — loss of jaw function and lung function. The clinical experts anticipate that treatment with palovarotene would continue indefinitely. Accordingly, the clinical experts advocated for continual assessment of the risks and benefits of its use. The clinical experts suggested that the efficacy and safety of palovarotene be assessed annually in adults, and in children, every 6 months for efficacy and every 3 months for safety. Given the progressive nature of FOP, the clinical experts suggested that treatment response should be monitored for at least 2 years before a decision to discontinue treatment is made, unless the decision to stop treatment is by patient choice, there is nonadherence to treatment, or the patient is experiencing intolerable adverse events (AEs). The clinical experts noted increasing HO load as detected by whole-body CT scan (excluding the head) and deteriorating CAJIS score may suggest lack of treatment response.

The clinical experts agreed that all patients with FOP should be diagnosed and managed by a specialist physician who is either experienced in the management of FOP or has academic expertise in FOP, due to the rarity of the condition. In addition, palovarotene should be prescribed by such a specialist. The clinical experts suggested that all patients should be seen in person by their specialist for baseline assessment with the CAJIS before prescribing palovarotene, and for periodic reassessments. The clinical experts agreed that a family doctor could collaborate with the expert physician in the continued monitoring and treatment of palovarotene. In children, the palovarotene prescription would typically be in the hands of their bone disease specialist. Using a team approach, led by a specialist, the clinical experts agreed that patients experiencing mucocutaneous AEs may see their family doctor for follow-up care. The clinical experts agreed that oral treatment with palovarotene can be taken at home or in any outpatient setting. In the event of a flare-up, the clinical experts encouraged the practice of instructing patients to take pictures of the flare-up site and inform their physician of the event. The clinical experts added that all patients should be provided with up to a 3-day supply of flare-up dosing in the event that a flare-up occurs during pharmacy closure or unavailability of a physician over a weekend. Given the issues associated with treatment assessment in this patient population (i.e., lack of validated instruments, heterogeneity among patients, heterogeneity over time within each

patient, and flare-ups), the clinical experts suggested the creation of a pan-Canadian expert panel accessible to each jurisdiction to adjudicate both initiation and renewal of palovarotene treatment and thereby facilitate a national, consensus-based approach to access.

Clinician Group Input

Clinical group input was provided by 5 clinicians with experience treating patients with FOP who attended the Canadian Endocrine Update. Some of the clinicians providing input have participated in clinical trials for the drug under review, with 1 clinician reporting on a patient with experience using palovarotene. The main unmet need of patients with FOP identified by the clinician group was the nonavailability of treatment(s) that alter the natural course of the disease. The clinician group anticipates that palovarotene would be used as a single drug (with or without corticosteroids) administered daily, with the potential for short-term dose increases during flare-ups. Further, the clinical group noted that palovarotene has the potential to be used in combination with other investigational drugs with different mechanisms of action in the future. The clinical group suggests that all patients who meet the approved Health Canada indication for palovarotene should be considered for treatment. Accordingly, consideration for treatment initiation as listed by the clinical group suggested lifetime patient monitoring by a multidisciplinary care team that includes specialists in pediatric and adult orthopedics, surgeons, and rheumatologists. The clinician group suggests that treatment with palovarotene should be discontinued in the event of notable adverse effects (e.g., premature epiphyseal fusion in children) or in the event of, or intention for, pregnancy in individuals of childbearing potential. According to input by the clinical group, there are no current tools for measuring outcomes in patients with FOP. The clinician group indicated that the following outcomes should be used to determine response to treatment: annualized change in HO volume, maintenance of mobility, reduction in rate of flare-ups, disease stability, and maintenance of HRQoL. The clinical group stressed that the decision to initiate and discontinue treatment with palovarotene should be made with careful patient counselling and shared decision-making.

Drug Program Input

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
In the pivotal trial submitted by the sponsor, eligible patients were required to have been clinically diagnosed with FOP with the R206H *AVCR1* mutation or other FOP variants reported to be associated with progressive HO. Should the other FOP variants be specified in the criteria?	The clinical experts noted that as palovarotene works downstream of the *ACVR1* receptor, patients harbouring any mutations of the receptor resulting in HO formation through the Smad 1/5/8 pathway would benefit from palovarotene. Accordingly, any mutations that work on the Smad pathway and upregulate it should be amenable to treatment with palovarotene. The clinical experts suggested that eligibility be based on a clinical diagnosis of FOP, and specific variants should not be used in the criteria to initiate palovarotene. CDEC noted that of the total enrolled population in the MOVE trial, 99 patients presented with the R206H *ACVR1* mutation and 8 patients with ACVR1 mutations other than R206H. The main analyses of the MOVE trial, including the analyses in the target population (females aged 8 years and older and males aged 10 years and older), were in

Implementation issues	Response
	patients with the R206H *ACVR1* mutation. CDEC decided it would be prudent to limit reimbursement to those reflected in the trial who have a demonstrated R206H *ACVR1* mutation.
In the pivotal trial submitted by the sponsor, patients were required to be able to undergo low-dose, whole-body CT, excluding head, without sedation. How would a patient (e.g., a child) who cannot complete a whole-body CT without sedation be assessed?	For patients unable to undergo low-dose, whole-body CT scans — either due to age or inability to fit into the scanner — the clinical experts noted that measurement of jaw function and lung function may be a more appropriate method of assessing disease burden. CDEC agreed with the clinical experts; in addition, they did not recommend requiring whole-body CT for any of the reimbursement conditions.
While the inclusion criteria of the submitted pivotal trial allowed for males and females aged at least 4 years to enter the study, the inclusion criteria extend beyond the age range of the Health Canada indication (females ≥ 8 years and males ≥ 10 years).	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
Given the heterogeneous and episodic nature of FOP, would HO and/or other parameters be used to measure therapeutic response or lack of therapeutic response?	Given the progressive nature of FOP, the clinical experts stated that treatment response should be monitored for at least 1 to 2 years before a decision to discontinue treatment is made, unless the decision to stop treatment is by patient choice, there is nonadherence to treatment, or the patient is experiencing intolerable AEs. The preservation of function should be the most important marker of treatment response. Patients should be assessed using the CAJIS at each visit. Response to treatment should also include assessing prevention of comorbidities such as the inability to walk, requiring a wheelchair, inability to work, and inability to continue performing ADL. Given the issues associated with treatment assessment in this patient population (i.e., lack of good instruments, heterogeneity among patients, heterogeneity over time, and flare-ups), the clinical experts suggested the creation of a pan-Canadian expert panel accessible to each jurisdiction to adjudicate both initiation and renewal of palovarotene similar to that in place for hypophosphatasia. CDEC agreed with the clinical experts that preservation of function is important for assessing treatment response and that leveraging pan-Canadian expertise would be helpful for informing decisions around continuing treatment.
How often should response to palovarotene be assessed?	According to the clinical experts, in adults, efficacy and safety of palovarotene should be assessed annually, and in pediatrics, palovarotene should be assessed every 6 months for efficacy and every 3 months for safety. With time, safety assessments of every 3 months in children could be extended to every 6 months, if the child is doing well and the impact of premature epiphyseal fusion lessens due to the patient approaching adult height. CDEC deferred to the clinical experts.
Considerations for discontinuation of therapy	
Dosing varies based on the weight of the patient (for children < 14 years of age) and whether the patient is on a chronic or flare-up regimen.	This is a comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Care provision issues	
Palovarotene is available in packages of 28 capsules (2 × 14 blister strips). Based on the cost per package and potential for patients to cycle between chronic and flare-up regimens, it may be prudent to limit dispensing to a 28-day supply to minimize wastage.	This is a comment from the drug programs to inform CDEC deliberations. To ensure patients have access to an adequate supply of palovarotene in case a flare-up occurs during pharmacy closure or when their physician is unavailable, CDEC agreed with the clinical experts that patients should always have enough palovarotene for 3 days of the flare-up regimen on hand.
Palovarotene is a retinoic acid derivative and is teratogenic. As outlined in the product monograph, individuals of childbearing potential who meet the conditions of pregnancy prevention must undergo regular pregnancy testing before, during, and 1 month after stopping treatment.	This is a comment from the drug programs to inform CDEC deliberations.
Palovarotene may cause premature closure of the epiphyseal growth plates in growing children. As outlined in the product monograph, all growing children should undergo baseline clinical and radiological assessments, including an assessment of skeletal maturity via hand and/or wrist and knee X-rays, standard growth curves, and pubertal staging. Continued monitoring of linear growth and skeletal maturity via X-ray should occur every 3 months until patients reach skeletal maturity or final adult height.	The clinical experts noted that premature closure of the epiphyseal growth plates is an irreversible health event. To avoid excessive radiation exposure, the clinical experts suggest that X-ray evaluations of epiphyseal fusion should occur annually as a minimum, and more often if there are concerns about premature epiphyseal fusion based on growth velocity, disproportionate growth of upper to lower body segments, or asymmetric limb growth. This underscores the importance of palovarotene prescription by an expert in pediatric bone disorders and bone growth. CDEC noted the clinical experts' input. CDEC did not stipulate specific requirements regarding assessment of skeletal maturity and left this to the clinical judgment of the prescribing physician.
System and economic issues	
According to the sponsor's submission, approximately 3, 4, and 5 patients with FOP are projected to receive palovarotene in years 1, 2, and 3 postfunding, respectively. The incremental budget impact of funding palovarotene is projected by the sponsor to be $3.0 million, $3.5 million, and $4.0 million in years 1, 2, and 3, respectively. This will result in a total 3-year budget impact of $10.5 million.	This is a comment from the drug programs to inform CDEC deliberations.

ADL = activities of daily living; AE = adverse event; CAJIS = Cumulative Analogue Joint Involvement Scale; FOP = fibrodysplasia ossificans progressiva; HO = heterotopic ossification.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One sponsor-conducted study that met the CADTH review protocol criteria was included in this systematic review. The MOVE study is an ongoing, multicentre, nonrandomized, open-label phase III study evaluating the efficacy of palovarotene in decreasing new HO volume in adults and pediatric patients aged 4 years and older with FOP compared to untreated patients who participated in the sponsor-conducted FOP natural

history study (Study PVO-1A-001). The MOVE study was conducted in 2 parts. In Part A, eligible patients received chronic dosing with palovarotene for up to 24 months and underwent flare-up–based treatment if they experienced a flare-up, as defined a priori, or a traumatic event likely to lead to a flare-up, as confirmed by the investigator. In Part B, all patients were provided palovarotene for an additional 24 months until palovarotene was commercially available to obtain longer-term safety data. No new patients were enrolled into Part B of the MOVE study. The primary efficacy end point for the MOVE study was annualized change in new HO volume, with the key secondary outcome being the proportion of patients with new HO. Secondary outcomes included number of body regions with new HO, proportion of patients reporting flare-ups, and flare-up rate per patient-month exposure. Exploratory outcomes included change in range of motion (ROM) as measured by the CAJIS for FOP; change in physical function as measured by the FOP–Physical Function Questionnaire (FOP-PFQ); change in physical and mental function for patients aged 15 years or older, and mental function for patients younger than 15 years of age using the Patient Reported Outcome Measurement Information System (PROMIS); and incidence and volume of catastrophic HO.

After the discovery of a high rate of premature epiphyseal fusion in growing children enrolled in the MOVE study, and interruption of the study due to futility at the time of interim analysis 2, the target population was amended to only include adults and children aged 8 years and older for females and 10 years and older for males. All analyses related to the target population were based on post hoc analyses.

Overall, patients in the target population were predominately male (MOVE study, 54.4%; natural history study, 51.1%) and white (MOVE study, 74.7%; natural history study, 75.0%). Patients enrolled in the MOVE study were, on average, younger than those enrolled in the natural history study (14.4 years versus 20.4 years). A greater proportion of patients were between the ages of 8 and 14 years for females and 10 to 14 years for males in the MOVE study than in the natural history study (43.0% versus 23.9%). Moreover, patients in the MOVE study were, on average, younger than those in the natural history study at the time of FOP diagnosis (6.5 years versus 7.5 years). Other notable imbalances in baseline characteristics between patients in the MOVE study and the natural history study included: reported hearing loss (MOVE study, 45.6%; natural history study, 35.2%); symptoms of pain (MOVE study, 73.4%; natural history study, 85.2%); lethargy (MOVE study, 7.6%; natural history study, 26.1%) and change in mood and behaviour (MOVE study, 11.4%; natural history study, 39.8%) during last flare-up; unknown (MOVE study, 73.4%; natural history study, 44.3%) or other (MOVE study, 8.9%; natural history study, 23.9%) reported cause of last flare-up; bone formation as a result of last flare-up (MOVE study, 51.9%; natural history study, 0%); and slightly worse loss of movement as a result of last flare-up (MOVE study, 2.5%; natural history study, 20.5%).

Efficacy Results

Annualized New HO

The analysis, using a Bayesian compound Poisson model with no square-root transformation and negatives set to 0 by body region, estimated a 25% reduction (ratio of mean change, 0.75; 95% CrI, 0.51 to 1.11) in the volume of annualized new HO among patients treated with palovarotene in the MOVE study compared to untreated patients in the natural history study.

Post hoc analysis of annualized new HO, with no square-root transformation and negative values included, estimated an annualized new HO volume in patients treated with palovarotene in the MOVE study and untreated patients in the natural history study of 11,419 mm^3 (standard error [SE] = 3,782) and 25,796 mm^3 (SE = 6,066 mm^3), respectively. Compared to patients in the natural history study, a 55.7% reduction in mean annualized new HO volume was observed among patients treated with palovarotene in the MOVE study. Based on the wLME model, patients treated with palovarotene in the MOVE study had an estimated reduction in new HO volume of 10,443 mm^3 per year (95% CI, −23,538 mm^3 to 26,534 mm^3 per year; P = 0.1124) compared to untreated patients in the natural history study when controlling for baseline HO divided by age. Accordingly, the wLME model estimated a 49% reduction in mean annualized new HO volume in patients treated with palovarotene in the MOVE study compared to untreated patients in the natural history study. The Wilcoxon rank sum test reported P value was 0.0107.

Proportion of Patients With Any New HO

The proportions of patients with any new HO among patients treated with palovarotene in the MOVE study and untreated patients in the natural history study at month 12 were 62.2% and 57.4%, respectively.

Body Region With New HO

The proportion of patients with 0 body regions with new HO at month 12 was 37.8% in the MOVE study and 42.6% in the natural history study. The proportion of patients with 1 body region with new HO at month 12 was 31.1% in the MOVE study and 22.1% in the natural history study. No clear, consistent trends were observed differentiating patients in the MOVE study from those in the natural history study.

Catastrophic HO

The proportion of patients with catastrophic new HO volumes exceeding 100,000 mm^3, 50,000 mm^3, or 30,000 mm^3 at month 12 in the MOVE study was 1.3%, 9.1%, and 11.7%, respectively. Among patients in the natural history study, the proportion of patients with catastrophic new HO volumes exceeding 100,000 mm^3, 50,000 mm^3, or 30,000 mm^3 at month 12 was 3.8%, 11.4%, and 13.9%, respectively.

The proportion of patients with catastrophic annualized new HO volumes exceeding 100,000 mm^3, 50,000 mm^3, or 30,000 mm^3 at the last time point in the MOVE study was 1.3%, 6.5%, and 16.9%, respectively. At the last time point in the natural history study, the proportion of patients with catastrophic new HO volumes exceeding 100,000 mm^3, 50,000 mm^3, or 30,000 mm^3 at month 12 was 6.3%, 15.2%, and 24.1%, respectively.

Reported Flare-Up

Among patients in the target population, 67.1% of those in the MOVE study and 63.9% of those in the natural history study reported flare-ups. Based on post hoc analysis of the principal safety set, the rate of flare-up per patient-month was 0.11 (95% CI, 0.08 to 0.16) in the MOVE study and 0.06 (95% CI, 0.05 to 0.08) in the natural history study.

HO at Flare-Up Sites

Overall, the mean volume of new HO at flare-up sites was 19,610 mm^3 (95% CI, 11,135 mm^3 to 28,084 mm^3) among patients in the MOVE study and 40,157 mm^3 (95% CI, 9,189 mm^3 to 71,124 mm^3) among patients

in the natural history study. Mean volume of new HO away from flare-up site (following a flare-up) was 7,626 mm^3 (95% CI, 3,845 mm^3 to 11,407 mm^3) among patients in the MOVE study and 26,399 mm^3 (95% CI, 8,539 mm^3 to 44,259 mm^3) in the natural history study.

Range of Motion

Range of motion (ROM) was assessed on 12 joints (i.e., both shoulders, elbows, wrists, hips, knees, and ankles) and 3 body regions (i.e., jaw, cervical spine [neck], and thoracic and lumbar spine) using the CAJIS. The CAJIS is a clinician-administered analogue scale of gross mobility restriction. Total CAJIS scores range from 0 to 30, with higher scores indicative of greater impairment. At baseline, mean CAJIS scores were similar between patients treated with palovarotene in the MOVE study (10.8; standard deviation [SD] = 6.4) and untreated patients in the natural history study (12.6; SD = 7.0). At month 12, both patients treated with palovarotene in the MOVE study and untreated patients in the natural history study experienced an increase (deterioration) in mean CAJIS score from baseline of 0.6 (SD = 2.1) and 0.6 (SD = 2.4), respectively.

Physical Function

Physical function was assessed using age-appropriate forms of the FOP-PFQ. The FOP-PFQ is a disease-specific, patient-reported outcome measure that assesses physical function. Lower FOP-PFQ scores are indicative of more difficulty and therefore greater functional impairment. At baseline, mean percentages of worse scores on the FOP-PFQ were similar between patients treated with palovarotene in the MOVE study (mean = 46.1; SD = 27.6) and untreated patients in the natural history study (mean = 47.6; SD = 28.0). At month 12, both patients treated with palovarotene in the MOVE study and untreated patients in the natural history study experienced an increase (deterioration) from baseline in mean percentage of worse score on the FOP-PFQ of 2.94 (SD = 8.09) and 4.70 (SD = 9.02), respectively.

Health-Related Quality of Life

HRQoL was assessed using age-appropriate forms of the PROMIS Global Health Scale short form. The PROMIS Global Health Scale is a set of person-centred measures that evaluate and monitor physical, mental, and social health in adults and children in the general population or living with chronic conditions. PROMIS scores were converted to T-scores for analysis. A T-score of 50 is normal, with an increment of 10 representing 1 SD away from the norm. A T-score less than 50 was indicative of worse health, while a T-score greater than 50 was indicative of better health. In patients aged 15 years and older, mean baseline scores were similar between the MOVE study and the natural history study on the PROMIS Global Physical Health (MOVE study, 43.15 [SD = 7.93]; natural history study, 43.35 [SD = 8.66]) and Global Mental Health T-scores (MOVE study, 52.17 [SD = 7.95]; natural history study, 52.70 [SD = 9.40]). Mean change from baseline on the Global Physical Health scale in patients in the MOVE study at months 6, 12, and 18 were −0.15 (SD = 3.92), −0.20 (SD = 5.16) and −1.91 (SD = 6.28), respectively. Among patients in the natural history study, the mean change from baseline on the Global Physical Health Scale at months 6, 12, and 18 were −0.37 (SD = 6.79), −1.19 (SD = 6.62) and −0.66 (SD = 5.57), respectively.

In patients under the age of 15 years, baseline PROMIS Global Health scores were similar among patients in the MOVE study and the natural history study at 43.2 (SD = 7.9) and 43.4 (SD = 8.7), respectively. Mean T-score change from baseline among patients treated with palovarotene in the MOVE study at months 6,

12, and 18 were −0.15 (SD = 3.92), 0.20 (SD = 5.16), and −1.91 (SD = 6.28), respectively. Among untreated patients in the natural history study, mean T-score change from baseline at months 6, 12, and 18 were −0.37 (SD = 6.79), −1.19 (SD = 6.62), and −0.66 (SD = 5.57), respectively.

Harms Results

Adverse Events

In the MOVE study, at least 1 AE was reported by 96% and 94.3% of patients during the chronic dosing and flare-up dosing regimens, respectively. The most commonly reported AEs were related to mucocutaneous issues (83.3%), including dry skin (52.5%) and rashes (19.2%); gastrointestinal issues (63.6%), including dry lips (34.3%); infections and infestations (58.6%), including upper respiratory infection (20.2%); and musculoskeletal and connective tissue disorders, including arthralgia (24.2%) and pain in extremities (18.2%). Overall, the reporting of AEs was similar during the chronic dosing and flare-up dosing regimens, with the exception of AEs related to gastrointestinal issues, which tended to be reported more often with chronic dosing than with flare-up dosing (63.6% versus 47.1%).

Serious Adverse Events

At least 1 serious adverse event (SAE) was reported by 19.2% and 17.1% of patients during chronic dosing and flare-up dosing regimens, respectively. The most common SAE was epiphyses premature fusion, which was observed in 11.1% of patients during chronic dosing and in 10% of patients during the flare-up dosing regimen.

Dose Modification to AEs

More patients required dose modification of palovarotene due to AEs during flare-up treatment (40%) than during chronic treatment (11.1%). The most common reasons for dose modification were due to drug eruption (chronic dose, 3.0%; flare-up dose, 12.9%), generalized pruritis (flare-up dose, 8.6%), erythema (flare-up dose, 4.3%), and pruritis (flare-up dose, 4.3%).

Treatment Interruption Due to AEs

Treatment interruptions due to AEs occurred among 16.2% and 15.7% of patients during the chronic dosing and flare-up dosing regimens, respectively. The most common AE leading to treatment interruption was epiphyses premature fusion, which occurred in 6.1% of patients while on the chronic dosing regimen.

Withdrawals Due to AEs

Withdrawal from the MOVE study due to AEs occurred in 6.1% and 5.7% of patients during the chronic dosing and flare-up dosing regimens, respectively. Withdrawal due to epiphyses premature fusion occurred in 1 patient during each of the dosing regimen phases.

Mortality

There were no deaths to due AEs during the study period.

Notable Harms

Of the notable harms of interest, during chronic treatment, dry skin occurred in 52.5% of patients and dry lips occurred in 34.3% of patients. During flare-up treatment, dry skin occurred in 45.7% of patients and dry

lips occurred in 20.0% of patients. Epiphyses premature fusion was observed in 11.1% of patients during chronic dosing and in 10% of patients during flare-up dosing. Hearing loss, pneumonia, suicidal ideation, and fractures occurred in less than 5% of patients who received treatment in the MOVE study. There were no reported cases of osteoporosis, low bone density, decreased bone density, or onycholysis.

Harms Related to Growth

Mean change in linear height z score in patients aged 8 years (for females) or 10 years (for males) to younger than 14 years was −0.36 (SD = 0.43) in those treated with palovarotene in the MOVE study and −0.20 (SD = 0.34) in untreated patients in the natural history study. Among patients aged 14 years to younger than 18 years, mean change in linear height among those who received treatment with palovarotene in the MOVE study (−0.02; SD = 1.54) was less than the mean change in linear height among those who were untreated in the natural history study (−0.55; SD = 1.61). Compared to untreated patients in the natural history study, a greater proportion of patients in the MOVE study aged 8 years (for females) or 10 years (for males) to younger than 14 years (61.3% versus 41.2%) and aged 14 years to younger than 18 years (92.3% versus 88.9%) were documented with a pathological growth velocity rate of less than 4 cm per year. A similar trend was observed for other growth measures among patients aged 8 years (for females) or 10 years (for males) to younger than 14 years, in which a greater proportion of patients treated with palovarotene in the MOVE study were documented with a pathological growth velocity rate of less than 2 cm per year for knee height (61.3% versus 52.9%), and a pathological growth velocity rate of less than 1.5 cm per year for tibial length (60.7% versus 50.0%). Among patients aged younger than 18 years, the proportion of patients with any epiphyseal growth plate abnormalities documented at month 12 was similar at 45.8% in both the MOVE study and the natural history study.

Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input gathered in the course of this CADTH review, as well as relevant literature, was reviewed to identify ethical considerations relevant to the use of palovarotene to reduce the formation of HO in adults and children aged 8 years and older for females with FOP and 10 years and older for males with FOP.

Ethical considerations arising in the context of FOP highlighted the significant, disabling, and life-shortening impact of the disease on patients, as well as the burden on caregivers and families; challenges to, and harms associated with, delays in timely diagnosis; and the absence of disease-modifying therapies.

Ethical considerations arising in the evidence used to evaluate palovarotene indicated that there is uncertainty about the safety and efficacy of palovarotene, and especially the magnitude of its treatment effect, which limits clinical assessments of risks and benefits associated with pursuing or forgoing treatment, as well as pharmacoeconomic assessments of cost-effectiveness.

The use of palovarotene presents potential risks for patients, including a risk of premature epiphyseal closure in growing children, retinoid-associated AEs, and osteoporosis. Patients and clinical experts expressed a willingness to undertake some risks for the potential benefit of a therapy that could slow or

halt disease progression, given the severity of untreated FOP and absence of alternative disease-modifying therapies. Robust informed consent processes are required to discuss the evidentiary uncertainty and balance of risks and benefits, including for pediatric patients. As an orally administered pill, palovarotene is relatively accessible for patients, but equitable access requires attending to potential geographic and diagnostic barriers to access.

Ethical considerations for health systems related to the implementation of palovarotene highlight the challenges of funding decisions and fair allocation of scarce resources, and issues related to high-cost drugs for rare diseases, including pan-Canadian approaches to providing equitable reimbursement and access, and challenges associated with assessing opportunity costs.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-effectiveness analysis Markov model
Target population	Patients with FOP, aged 8 years and older for females and aged 10 years and older for males
Treatment	Palovarotene plus SoC (assumed to be the symptomatic treatment of flare-ups; comprised of prednisone, anti-inflammatory agents, antihistamines, vitamin D, and pain medication)
Dose regimen	• 14 years and older: 5 mg once daily (chronic regimen); for flares: 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (flare-up regimen) • Under 14 years: 2.5 to 5 mg once daily (chronic regimen); for flares: 10 mg to 15 mg once daily for 4 weeks followed by 5 mg to 7.5 mg daily for 8 weeks (flare-up regimen)
Submitted price	Palovarotene, 1 mg: $324.22 per capsule Palovarotene, 1.5 mg: $486.33 per capsule Palovarotene, 2.5 mg: $810.55 per capsule Palovarotene, 5 mg: $1,621.10 per capsule Palovarotene, 10 mg: $3,242.20 per capsule
Treatment cost	• For patients aged 14 years and older: $1,022,894 per year[a] • For patients aged < 14 years: $622,373 per year[a,b]
Comparator	SoC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (80 years)
Key data sources	Efficacy of palovarotene was informed by the single-arm, phase III MOVE trial; efficacy of SoC based on a historical control group from the sponsor's natural history study

Component	Description
Key limitations	• The model structure, based on HO volume and defined using baseline data from the MOVE trial and the natural history study, does not adequately reflect the management of FOP in clinical practice and does not represent homogenous health states. This modelling approach prevented CADTH from validating the inputs for each health state. • The comparative efficacy of palovarotene plus SoC compared to SoC alone is highly uncertain owing to a lack of robust comparative data. The relative efficacy of palovarotene plus SoC compared to SoC alone was based on a naive comparison of observations from the MOVE trial and the sponsor's historical control study, and did not control for important covariates or baseline imbalances between populations. • The survival benefit predicted by the sponsor in their submitted model for palovarotene plus SoC compared to SoC is highly uncertain and has not been shown in clinical trials. • The long-term relative effectiveness of palovarotene plus SoC compared to SoC alone is highly uncertain, and approximately 99% of the incremental benefit associated with treatment was accrued after the trial period. • The majority of incremental QALYs gained with palovarotene plus SoC were accrued by caregivers, not patients with FOP. The health-state utility values adopted by the sponsor for both patients and caregivers are highly uncertain and may not reflect the preferences of those living in Canada. • The cost of palovarotene treatment was based on the chronic regimen and the 12-week flare-up regimen. If flare-ups last longer than 12 weeks, if a new flare-up starts during the treatment of an initial flare-up, or if the number of annual flare-ups is higher than observed in the MOVE trial, drug costs associated with palovarotene will be higher than predicted by the sponsor.
CADTH reanalysis results	• Given limitations with the sponsor's model structure and the lack of robust comparative effectiveness data, CADTH was unable to derive a reliable base case estimate of the cost-effectiveness of palovarotene plus SoC. CADTH conducted reanalyses that included removing the survival benefit for palovarotene and excluding the impact of palovarotene on caregivers. CADTH was unable to correct for limitations related to the model structure, the lack of robust comparative data, uncertainty in the long-term relative effectiveness of palovarotene plus SoC compared to SoC alone, and uncertainty in the health-state utility values. • Results of the CADTH reanalysis were aligned with those submitted by the sponsor: palovarotene plus SoC is not cost-effective at a WTP threshold of $50,000 per QALY gained. A price reduction of at least 99% (e.g., to less than $3.24 per mg) would be required for palovarotene plus SoC to be cost-effective compared to SoC alone at this WTP threshold. • In the absence of robust comparative evidence, the QALYs gained with palovarotene plus SoC in CADTH's reanalysis (incremental QALYs: 1.46) may overestimate the incremental benefits associated with palovarotene plus SoC relative to SoC alone. Further price reductions may therefore be required.

FOP = fibrodysplasia (myositis) ossificans progressiva; HO = heterotopic ossification; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SoC = standard of care; WTP = willingness-to-pay.

[a]Based on the chronic regimen and flare-up regimen, assuming 1.9 flare-ups per year; annual cost does not account for an extension of the flare-up protocol for persistent flare-ups or reinitiation of the flare-up protocol in the event that new flare-up occurs during the initial flare.

[b]The dosage of palovarotene (chronic and flare-up regimens) is weight-based for patients aged less than 14 years. A weight of 37 kg was assumed for children aged 8 to 14 years (female) and 10 to 14 years (male).

Budget Impact

CADTH identified key limitations with the sponsor's analysis:

- The number of patients eligible for palovarotene is uncertain, owing to uncertainty in the prevalence of FOP in Canada, the proportion of patients accurately diagnosed with FOP, and the proportion of patients who would have public coverage for palovarotene.

- The uptake of palovarotene may be higher than expected by the sponsor.
- Palovarotene drug acquisition costs are uncertain and may be underestimated.
- The cost of SoC was not captured in the estimated budget impact and may vary between those receiving palovarotene plus SoC versus SoC alone.

CADTH reanalysis included changes to the market shares of palovarotene to reflect the number of patients in Canada anticipated to receive palovarotene. In the CADTH base case, the budget impact of reimbursing palovarotene to reduce the formation of HO in patients with FOP (females aged 8 years and older; males aged 10 years and older) is expected to be $4,288,612 in Year 1, $4,775,024 in Year 2, and $5,272,705 in Year 3, for a 3-year total of $14,336,341.The estimated budget impact is highly sensitive to the number of patients eligible for palovarotene and assumptions about its uptake.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: March 24, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None