



## CADTH Reimbursement Recommendation

# Roflumilast (Zoryve)

**Indication:** For topical treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older.

**Sponsor:** Arcutis Biotherapeutics, Inc.

**Final recommendation:** Reimburse with conditions



# Summary

## What Is the CADTH Reimbursement Recommendation for Zoryve?

CADTH recommends that Zoryve be reimbursed by public drug plans for the treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Zoryve should only be covered to treat patients who have a clinical diagnosis of plaque psoriasis with an Investigator Global Assessment (IGA) score of at least 2 (mild) and an area of plaque psoriasis appropriate for topical treatment covering a body surface area of 2% to 20% (inclusive).

### What Are the Conditions for Reimbursement?

Zoryve should be discontinued if a response has not been demonstrated by 8 weeks. A response to treatment is defined as at least a 2-grade improvement from baseline in IGA score or an IGA score of “clear” or “almost clear” (0 or 1). The cost of Zoryve should not exceed the drug program cost of treatment with the least costly topical therapy reimbursed for the treatment of plaque psoriasis.

## Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Zoryve improved severity of psoriasis, including in intertriginous areas (skin folds), and reduced the severity of itch compared to treatment with vehicle.
- Evidence from 1 indirect comparison (ITC) suggests that Zoryve may provide a benefit compared to other topical treatments used alone, including vitamin D analogues (VDAs), tazarotene (TAZ), and corticosteroids (CSs), but the magnitude of benefit is uncertain due to limitations of the analysis. Also, the results of the ITC did not clearly demonstrate that treatment with Zoryve offered a benefit over combination therapies, including CSs plus VDAs, and CSs plus TAZ, or calcineurin inhibitors for patients with intertriginous involvement.
- Overall, Zoryve may meet some of the needs that are important to patients, such as providing an alternative topical treatment option that is effective.
- Based on CADTH’s assessment of the health economic evidence, Zoryve does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence



# Summary

to justify a greater cost for Zoryve compared with the least expensive topical therapy reimbursed for the treatment of plaque psoriasis.

- Based on public list prices, Zoryve is estimated to cost the public drug plans approximately \$83 million over the next 3 years. However, the actual budget impact is uncertain given large differences between the sponsor's and CADTH's reported budget impact estimates.

## Additional Information

### What Is Plaque Psoriasis?

Plaque psoriasis is a skin disease that causes red, flaky, crusty patches of the skin that may be itchy and painful. It is estimated that 3% of the general adult population in Canada is living with psoriasis.

### Unmet Needs in Plaque Psoriasis

Although there are many topical options available for the treatment of plaque psoriasis, the treatment of intertriginous areas (skin folds) may represent an area of unmet need.

### How Much Does Zoryve Cost?

Treatment with Zoryve is expected to cost approximately \$270 per patient per 4-week cycle.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that roflumilast be reimbursed for the treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older, only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

Two phase III, double-blind, parallel-group, randomized, vehicle-controlled trials (DERMIS-1 and DERMIS-2), in patients aged 2 years or older with chronic plaque psoriasis, demonstrated that 8 weeks of treatment with roflumilast improved overall severity of psoriasis as measured by the proportion of patients experiencing treatment success based on the Investigator Global Assessment (IGA), defined as a score of 0 (clear) or 1 (almost clear) plus an improvement of 2 grades or more from baseline, compared to vehicle (which contained only the excipients of roflumilast cream). Roflumilast also demonstrated improvement in the severity of psoriasis of the intertriginous areas, as well as the extent and severity of psoriasis, and the severity of itch compared to vehicle as measured by the proportion of patients experiencing treatment success based on the Intertriginous-Investigator Global Assessment (I-IGA), defined as a score of 0 or 1 plus an improvement of 2 grades or more from baseline; a prespecified reduction in the Psoriasis Area and Severity Index (PASI) from baseline; and treatment success based on the Worst Itch-Numeric Rating Scale (WI-NRS), defined as a reduction of 4 or more points from baseline, respectively. There were no safety or tolerability concerns associated with the use of topical roflumilast identified by the CADTH review. As such, roflumilast may provide an alternative, nonsteroidal topical treatment option for patients living with plaque psoriasis, including psoriasis in the intertriginous area. Patients identified a need for alternative topical treatments that are effective, have few side effects, are better tolerated for patients with intertriginous involvement, and can be used long-term for this chronic condition. The evidence included in the CADTH review suggests that roflumilast may meet some of these needs (an alternative topical treatment that is effective).

At the sponsor-submitted price for roflumilast and publicly listed prices of all relevant comparators, roflumilast was more costly than most topical treatments used in the treatment of patients aged 12 years and older with plaque psoriasis, including individuals with intertriginous psoriasis involvement. Direct comparative clinical evidence for roflumilast compared to currently used topical treatments was not identified. Further, findings from the sponsor-submitted network meta-analysis (NMA) may suggest a benefit of unknown magnitude for roflumilast compared to monotherapies (including vitamin D analogues [VDAs], tazarotene [TAZ], or corticosteroids [CSs]) but did not clearly favour treatment with roflumilast compared to combination therapies (CSs plus VDAs, or CSs plus TAZ) or calcineurin inhibitors for patients with intertriginous involvement. As such, there is insufficient evidence to suggest that roflumilast should be priced higher than topical treatments for plaque psoriasis.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. Patients must have a clinical diagnosis of plaque psoriasis with all of the following characteristics: <ol style="list-style-type: none"> <li>1.1. an IGA score of at least 2 (mild)</li> <li>1.2. an area of plaque psoriasis appropriate for topical treatment covering a BSA of 2% to 20% (inclusive).</li> </ol>	The results of the DERMIS-1 and DERMIS-2 vehicle-controlled RCTs demonstrated that roflumilast is an effective and safe treatment for patients living with plaque psoriasis, including psoriasis with intertriginous involvement, who met the criteria listed in the condition.	There are many topical options available for the treatment of plaque psoriasis, but the treatment of intertriginous areas may represent an area of unmet need. Drug plans may consider that patients who may benefit most from treatment with roflumilast are those who have a clinical diagnosis of plaque psoriasis with intertriginous involvement.
<b>Discontinuation</b>		
2. Treatment should be discontinued if a response has not been demonstrated by 8 weeks. A response to treatment is defined as at least a 2-grade improvement from baseline in IGA score or an IGA score of “clear” or “almost clear” (0 or 1).	Treatment success based on the IGA, defined as a score of “clear” or “almost clear” (0 or 1) plus at least a 2-grade improvement from baseline, after 8 weeks of treatment with roflumilast was the primary end point in the DERMIS-1 and DERMIS-2 trials.  In addition, the clinical expert indicated that 8 weeks was considered an appropriate amount of time to assess the efficacy and safety of roflumilast. According to the clinical expert, in the context of topical therapy for plaque psoriasis, 4 weeks is often sufficient to determine whether an adequate response will be achieved, while extensive psoriasis may require more time to achieve adequate response.	—
<b>Pricing</b>		
3. Roflumilast should be negotiated so that it does not exceed the drug program cost of treatment with the least costly topical therapy reimbursed for the treatment of plaque psoriasis.	Given the uncertainty in the magnitude of clinical benefit of roflumilast vs. monotherapy treatments, and the absence of clinical evidence to suggest a benefit for roflumilast vs. combination therapies or roflumilast for intertriginous use, there is limited evidence to support a price premium for roflumilast over the least expensive topical therapy reimbursed for plaque psoriasis.	—
<b>Feasibility of adoption</b>		
4. The feasibility of adoption of roflumilast must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of	—

Reimbursement condition	Reason	Implementation guidance
	adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	

BSA = body surface area; ICER = incremental cost-effectiveness ratio; IGA = Investigator Global Assessment; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life-year; RCT = randomized controlled trial; vs = versus.

## Discussion Points

- CDEC discussed the place in therapy and considered feedback from the clinical expert consulted by CADTH. The committee concluded that roflumilast may offer an additional option for treating patients with plaque psoriasis, and the decision to use roflumilast is likely to follow a patient-centred approach. For example, it may be a preferred option for certain patients with intertriginous involvement, but it may not be appropriate to treat severe plaques.
- CDEC discussed how roflumilast may meet an unmet need for patients living with plaque psoriasis in the intertriginous areas. In consultation with the clinical expert who participated in the CADTH review of roflumilast, the committee noted the availability of other therapies for the topical treatment of plaque psoriasis, such as CSs, TAZ, and VDAs), which are commonly used to treat intertriginous areas. Although a direct comparison of roflumilast to other topical therapies was not available, the committee concluded that the evidence suggests that roflumilast may offer an alternative topical treatment for plaque psoriasis, that is also appropriate for use in patients with intertriginous involvement.
- Feedback from the clinical expert indicated that combination use of roflumilast with other treatment options is anticipated in clinical practice. Further, the expert noted that topical therapies are often offered to patients along with phototherapy, systemic therapy, or biologic therapy. The committee noted that this submission did not include evidence to support combination therapy, but did not anticipate the use of roflumilast alongside other topical treatments that may be used by an individual to treat separate areas affected by psoriasis as being an area of concern.
- CDEC discussed the evidence for long-term safety and efficacy of treatment with roflumilast, which was limited to a phase III, open-label, long-term safety and efficacy study (DERMIS-OLE). In the DERMIS-OLE study, patients with chronic plaque psoriasis involving up to 25% body surface area (BSA) applied roflumilast once daily for up to 24 weeks. No new safety signals were reported in the DERMIS-OLE study. Of note, the DERMIS-OLE study was subject to the following limitations: potential for selection bias, lack of a control group, and an open-label (unblinded) study design.
- CDEC discussed the results from the sponsor-submitted NMA for treatment success based on the IGA scores. No difference in efficacy in terms of treatment success based on the IGA scores could be concluded for roflumilast relative to combination therapies such as CS plus VDA and CS plus TAZ. Additionally, comparisons of roflumilast to calcineurin inhibitors for I-IGA treatment response did not clearly favour either treatment. Comparisons between roflumilast and monotherapies (high-potency

CS, TAZ, and VDA) may suggest a clinical benefit in favour of roflumilast; however, there is uncertainty in the validity of the results of the NMA, as several potential sources of heterogeneity were not assessed and no stratified analyses were conducted to adjust for effect modifiers such as baseline disease severity. Also, an assumption was made that all vehicles in the included studies were equally effective which may violate the similarity assumption of the NMA; however, the extent of the potential bias is unknown. Given that there was no direct or indirect clinical evidence comparing roflumilast to CS for intertriginous use, and the uncertainty in the results of the NMA, there is limited evidence to support a price premium for roflumilast over other topical treatments used for plaque psoriasis.

- CDEC noted the large potential budget impact of reimbursing roflumilast, estimated to be \$82,850,237 over 3 years. Price negotiations and implementation of initiation and discontinuation criteria could assist in reducing the budget impact.

## Background

Psoriasis is a chronic, immune-mediated, inflammatory skin disease that is associated with multiple comorbidities such as psoriatic arthritis, obesity, and metabolic syndrome. Psoriasis can present similarly in children and adults; the peak ages of onset are between 30 years and 39 years and between 50 years and 69 years. A panel of 11 dermatologists with expertise in psoriasis estimated that the median prevalence of psoriasis is 3% of the general adult population in Canada. The panel estimated that approximately 78% of patients with psoriasis have less than 10% BSA involved (i.e., mild or moderate disease) and 22% of patients have 10% or more BSA involved. The panel further estimated that 50% of patients have less than 3% BSA involved (i.e., mild disease) and 2% of patients have more than 50% BSA involved. Based on estimates in the US, 50% of patients have facial involvement and 21% to 30% of patients have intertriginous area involvement.

Chronic plaque psoriasis (also known as psoriasis vulgaris) is the most common clinical subtype of psoriasis, representing approximately 90% of patient cases in Canada. Plaque psoriasis is characterized by well-demarcated, erythematous cutaneous plaques with overlying, coarse, silvery scales. Plaques can be asymptomatic; however, pruritus and pain are often reported by patients. Common areas of involvement include the scalp, elbows, knees, and gluteal cleft. Additionally, intertriginous areas (inverse psoriasis), the ear canal, umbilicus, palms, soles, and nails are possible areas of involvement. Intertriginous psoriasis is characterized by well-demarcated, smooth, shiny plaques with no to minimal scales.

Plaque psoriasis requires lifelong follow-up and treatment. Measures of treatment success in clinical practice may include clearance (absence of signs of disease), control (satisfactory response to therapy as defined by the patient and/or clinician), and remission (disease control maintained, or suppression of signs and symptoms over time).

Management of mild plaque psoriasis, involving the trunk, limbs, and neck, includes topical therapies that can be broadly categorized as CSs, VDAs, retinoids, anthralin (commercial formulations are not currently available in Canada), and tars, as well as combination therapy. The therapeutic options for pediatric patients are generally similar to the options for adult patients. Management of intertriginous psoriasis – affecting the

groin, axillae, inframammary region, abdominal body folds, gluteal cleft, perianal region, and retroarticular fold areas – can be a challenge, as these areas are at an increased risk of adverse reactions to topical therapy because the skin tends to be thinner in these regions. Moreover, there are currently no available treatments indicated for intertriginous psoriasis. Topical calcineurin inhibitors may be an appropriate treatment option for the management of intertriginous psoriasis; however, they are not currently approved for an indication in psoriasis (hence its off-label use). Treatment selection should be individualized to the patient to improve adherence and patient satisfaction, and achieve treatment success. Management of moderate to severe plaque psoriasis, affecting the trunk and extremities that cannot be adequately controlled by the approaches described above (adequate control is defined by the patient’s perception of the disease and its burdens), includes systemic therapy, phototherapy, combination therapy, and topical therapy as adjunct therapy.

Roflumilast cream 0.3% has been approved by Health Canada for topical treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older. Roflumilast is a selective phosphodiesterase-4 (PDE-4) inhibitor and a nonsteroidal, anti-inflammatory drug. It is available as a cream and the dosage recommended in the product monograph is to apply to affected areas once daily.

## Sources of Information Used by the Committee

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

- a review of 2 phase III, randomized, double-blind, parallel-group, vehicle-controlled clinical studies in patients with chronic plaque psoriasis involving 2% to 20% BSA (excluding the scalp, palms, and soles)
- patients’ perspectives gathered by patient groups (the Canadian Skin Patient Alliance [CSPA], Canadian Psoriasis Network [CPN], and the Canadian Association of Psoriasis Patients [CAPP])
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with plaque psoriasis
- input from 3 clinician groups, including Fraser Health Dermatology, the Canadian Dermatology Association, and the Atlantic Provinces Dermatology Association and Dermatology Association of Ontario
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

Three patient groups submitted a joint patient input submission. CSPA, CPN, and CAPP are national, not-for-profit organizations that are dedicated to improving the lives of people with psoriasis across Canada.





According to the input, the impact of psoriasis symptoms is considerable in various areas of patients' lives, such as mental well-being, daily tasks, intimate relationships, and social lives. Most patients considered effectiveness to be the most important factor to be addressed in any new treatment for psoriasis. In addition, patients valued lack of side effects, affordability, treatments that are easy to apply, and treatments that are conducive to their schedules.

More than half of survey respondents reported having moderate psoriasis, and the body area with the most impact was the scalp, followed by the legs, arms, genitals, hands, torso, skin folds, and palms. Based on the survey, respondents were using topical CSs, topical combination treatment, and/or biologic drugs. Most psoriasis patients have discontinued their treatment at some point during their disease, with the most frequent reasons being that the treatment stopped working, caused side effects, was unaffordable, or ineffective. Among respondents, 10 patients reported experience with roflumilast, accessed through a clinical trial. Nine of the patients reported benefits of treatment including clearing of skin, reduced itch and redness, clearing of skin lesions (plaques), and treatment's ease of application. All 10 respondents tolerated roflumilast well, except for 1 who experienced some itching. The patient group input emphasized that psoriasis is a chronic and potentially debilitating disease that poses many challenges and is linked to anxiety, depression, and social isolation. This disease can interfere with social and intimate relationships, productivity, family life, and work life. Furthermore, due to the chronicity of this disease, patients are concerned about recurrence and resistance to treatments in the future.

## Clinician Input

### **Input From the Clinical Expert Consulted by CADTH**

The clinical expert indicated that there are currently no available treatment options that can permanently reverse the course of plaque psoriasis, but systemic therapies can suppress psoriasis while they are being used. The clinical expert also indicated that many patients do not respond to currently available topical treatments; in particular, patients with widespread psoriasis and psoriasis of the scalp, palms, and soles are often refractory to topical treatment. The clinical expert noted that topical therapies are generally well tolerated and that topical steroids are used long-term for many patients in clinical practice; however, clinical guidelines advise caution with long-term use of topical steroids for plaque psoriasis. As such, the clinical expert agreed that more effective, safer, and better tolerated treatment options are an unmet need, particularly for long-term use and in patients with facial, genital, and intertriginous involvement. The clinical expert further suggested that topical formulations that are less messy and more effective may improve adherence, in particular in patients with intertriginous involvement who are offered topical tacrolimus, which is only available as an ointment and not widely available, as it is not indicated (is used off-label) for the treatment of psoriasis.

For most patients with plaque psoriasis, the clinical expert noted that they would consider roflumilast as an alternative to other first-line topical treatments for psoriasis within the current stepped approach that could prevent patients from stepping up to systemic therapy. For patients with facial, genital, and intertriginous involvement, the clinical expert anticipated roflumilast would be a first-line treatment. The clinical expert further suggested that roflumilast may be preferred for long-term use in some patients and clinicians,

given that it is not a steroid. For mild disease, the clinical expert suggested that roflumilast would be used as monotherapy. Additionally, depending on patient preference, roflumilast could be used simultaneously with other topical treatments. Roflumilast could also be used in combination with systemic therapy or phototherapy, as topical treatments are typically continued as needed.

The clinical expert identified patients with active psoriasis, regardless of being actively treated or not, as being the most in need of intervention. The clinical expert noted that there is a need for an intervention for the hair-bearing scalp area; however, the clinical expert indicated that this need would not be addressed by roflumilast. Clinician examination and judgment, with shared decision-making with the patient, would determine whether the drug is best suited for the patient. The clinical expert suggested that patients with psoriasis of limited BSA are most likely to respond to therapy with roflumilast as monotherapy.

The clinical expert indicated that clearance or near clearance of psoriasis lesions is commonly used to assess psoriasis severity; this is analogous to IGA scales used in clinical trials. The clinical expert also indicated that patient satisfaction is important and is assessed in a gestalt manner that likely differs between physicians. According to the clinical expert, extensive scales – such as PASI, Dermatology Life Quality Index (DLQI), WI-NRS, and Psoriasis Symptom Diary (PSD) – are not typically used in clinical practice; however, PASI and DLQI may be used if mandated by the insurer to fund a drug.

According to the clinical expert, intolerance (e.g., stinging at application site) and ineffectiveness (i.e., minimal improvement after 2 to 8 weeks of application) are factors to consider when deciding to discontinue treatment with roflumilast. The clinical expert further indicated that roflumilast would be discontinued when lesions have cleared and can be restarted if and when lesions have recurred. The clinical expert indicated that phototherapy or systemic therapy may be considered for extensive psoriasis regardless of improvement with roflumilast, and if there is substantial improvement with phototherapy or systemic therapy that obviates the need for topical therapy, then roflumilast would be considered for discontinuation.

### **Clinician Group Input**

Three different clinician groups provided input, including Fraser Health Dermatology (4 clinicians), the Canadian Dermatology Association (3 clinicians), and the Atlantic Provinces Dermatology Association and Dermatology Association of Ontario (12 clinicians).

Clinician groups noted that there is a need for a new treatment to substitute existing therapies for plaque psoriasis. Clinician groups noted that limitations of current treatments include unfavourable effects, poor compliance, difficult application, high costs, limited efficacy, intolerability due to irritation, and inability to be administered to all areas of the body. Treatment goals noted include reducing the severity of symptoms, minimizing adverse events (AEs), improving tolerability and efficacy, increasing patient quality of life (QoL), and reducing the burden to patients and health care systems.

One clinician group recommended the use of roflumilast as a first-line treatment for the management of mild to severe plaque psoriasis, while another group suggested roflumilast should be used after nonresponse to topical steroids, as topical steroids are an inexpensive and usually well-tolerated therapy. The input noted that patients best suited for treatment with the drug under review included patients with mild to moderate

psoriasis, patients with different disease phenotypes, patients with psoriasis that has not responded to topical steroids, and patients with intertriginous psoriasis, noting the importance of steroid sparing in these anatomic sites.

One clinician group suggested that the best outcomes to determine treatment response would be physician global assessment (PGA) and BSA involvement. The group noted that PASI score is not commonly used in clinical practice, except when applying for coverage for systemic therapies in moderate to severe patients. Clinician groups noted that assessment of treatment goals is recommended after 8 weeks, and that psoriasis patients are typically initially seen every 3 to 6 months to assess response to treatment, and treatment should be discontinued in cases of lack of efficacy or disease progression. The input received stated that patients with psoriasis are diagnosed and treated as outpatients, typically by both specialists and general practitioners or family doctors.

### Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Responses to Questions From the Drug Programs**

Implementation issues	Response
<b>Relevant comparators</b>	
<p>Roflumilast cream 0.3% was compared to vehicle over 8 weeks in 2 phase III studies.</p> <p>Given the wide range of topical treatment options available for plaque psoriasis, is the vehicle an appropriate comparator?</p>	<p>The clinical expert consulted indicated that an active comparator would have been more appropriate. In particular, the expert suggested that topical steroids and vitamin D analogues would have been appropriate comparators.</p> <p>CDEC agrees that an active comparator would have been more appropriate. In a chronic and common disease like plaque psoriasis, with a wide range of alternative treatment options available, a comparative clinical trial is feasible and should have been included. Furthermore, the limitations of the included NMA resulted in uncertainty.</p>
<p>Roflumilast is a topical selective inhibitor of PDE-4, first-in-class.</p> <p>If roflumilast receives Health Canada approval, it will be the only topical cream indicated for treatment of plaque psoriasis in the intertriginous areas.</p>	<p>Comment from the drug programs to inform CDEC deliberations.</p>
<p>Is there any evidence to suggest what contributes to nonadherence with topical therapies, which may contribute to reduced efficacy of plaque psoriasis treatments?</p>	<p>The clinical expert consulted indicated that anecdotally, patients find topical treatment to be inconvenient due to the messiness, appearance, and time-consuming nature of applying topicals.</p> <p>The clinical expert did not have experience with roflumilast, but based on a survey of patients with eczema they advised that time spent managing the disease was significantly associated with overall disease burden; however, this trial was a cross-sectional study and cannot establish causality.</p> <p>CDEC defers to the expertise of the clinical expert.</p>

Implementation issues	Response
<p>Calcineurin inhibitors are not officially indicated for treatment of plaque psoriasis.</p> <p>Should calcineurin inhibitors be included as a comparator?</p>	<p>The clinical expert consulted suggested that calcineurin inhibitors are a relevant comparator, particularly for intertriginous psoriasis.</p> <p>The clinical expert acknowledged that there may be regulatory or other feasibility issues with conducting a study with an off-label comparator.</p> <p>CDEC agrees that calcineurin inhibitors should be considered a relevant comparator if they are being used in practice for off-label use in plaque psoriasis, particularly in the intertriginous areas, which have been identified as challenging to treat.</p>
<b>Considerations for initiation of therapy</b>	
<p>Patients with plaque psoriasis lesions on the scalp were excluded from clinical trials.</p> <p>These patients would likely require an alternative topical drug for scalp lesions.</p>	<p>Comment from the drug programs to inform CDEC deliberations.</p>
<p>Halobetasol propionate and tazarotene (Duobrii) was the product most recently reviewed by CADTH in this treatment space.</p> <p>The patient population may not align with the clinical criteria recommended for Duobrii.</p> <p>Most jurisdictions list a variety of topical corticosteroids as Full Benefit.</p> <p>Retinoids, vitamin D analogues, and fixed combinations vary in listing status across jurisdictions. Calcineurin inhibitors may or may not be an appropriate comparator and are not listed for plaque psoriasis in a number of jurisdictions.</p>	<p>Comment from the drug programs to inform CDEC deliberations.</p>
<b>Considerations for continuation or renewal of therapy</b>	
<p>Is IGA used commonly in clinical practice?</p> <p>Are family physicians familiar with using IGA?</p>	<p>The clinical expert consulted indicated that formal IGAs are not common in clinical practice, particularly in family practice. However, the clinical expert noted that IGAs are a fairly simple way to capture the clinician's gestalt assessment of disease severity.</p> <p>The clinical expert consulted indicated that physicians (generalists and specialists) commonly use the terms mild, moderate, and severe informally, which can be considered similar to formal IGAs.</p> <p>Additionally, the clinical expert indicated that assessment of response in clinical practice includes a gestalt assessment of disease history, physical examination, and global patient satisfaction.</p> <p>CDEC defers to the expertise of the clinical expert.</p>
<p>Most other restricted drugs in this treatment space do not have assessment criteria for renewal (i.e., no renewal parameters are required to be submitted for evaluation as part of the criteria), with the exception of Duobrii in a number of jurisdictions, which used IGA.</p>	<p>Comment from the drug programs to inform CDEC deliberations.</p>

Implementation issues	Response
<b>Considerations for prescribing of therapy</b>	
<p>Regarding concerns related to combination usage, is there any evidence to support combination use with other topical treatments for plaque psoriasis? Is there any evidence to support combination use with biologic therapies for treatment of plaque psoriasis?</p>	<p>The clinical expert consulted indicated that it is common in clinical practice for individual patients to be using multiple topical medications simultaneously (e.g., apply 1 topical medication to scalp, 1 to intertriginous areas, and 1 to plaques on the body). The clinical expert also indicated that a topical medication is typically offered to patients along with phototherapy, systemic therapy, or biologic therapy in clinical practice to treat any residual disease not responding to phototherapy, systemic therapy, or biologic therapy.</p> <p>The CADTH review team notes that no evidence for the use of roflumilast in combination with other topical or systemic treatments for psoriasis was identified for this review. CDEC defers to the expertise of the clinical expert.</p>
<b>Generalizability</b>	
<p>There may be interest in using this product in children aged younger than 12 years.</p>	<p>Comment from the drug programs to inform CDEC deliberations.</p>
<b>Care provision issues</b>	
<p>Roflumilast would be available in a 60 g tube (\$275.00 per tube) applied once daily (considered convenient).</p>	<p>Comment from the drug programs to inform CDEC deliberations.</p>
<b>System and economic issues</b>	
<p>Consideration should be given to topical therapies that may prevent patients from progressing to more costly, invasive, or systemic therapies, including biologics.</p>	<p>Comment from the drug programs to inform CDEC deliberations.</p>

CDEC = CADTH Canadian Drug Expert Committee; IGA = Investigator Global Assessment; NMA = network meta-analysis; pCPA = pan-Canadian Pharmaceutical Alliance; PDE-4 = phosphodiesterase-4.

## Clinical Evidence

### Pivotal Studies and Randomized Controlled Trial Evidence

#### Description of Studies

Two phase III, randomized, double-blind, parallel-group, vehicle-controlled trials (DERMIS-1, N = 439 and DERMIS-2, N = 442) that assessed IGA success – defined as an IGA score of “clear” or “almost clear” plus an improvement of 2 grades or more from baseline at week 8 – with roflumilast cream 0.3% compared to matching vehicle, in patients with chronic plaque psoriasis involving 2% to 20% BSA (excluding the scalp, palms, and soles), were included in the sponsor’s submission. Patients were excluded if they were unable to discontinue prohibited medications and treatments – defined as systemic, biologic, topical, phototherapy, and investigational treatments that could affect plaque psoriasis – within the prespecified washout period. Patients were randomized in a 2:1 ratio to receive roflumilast or vehicle applied topically once daily for 8 weeks. Secondary outcomes included measures of symptoms and involvement (PASI, I-IGA, WI-NRS, and

IGA) and measure of QoL (PSD). Similarly, exploratory outcomes included measures of involvement (e.g., BSA), measures of health-related quality of life (HRQoL) (e.g., DLQI and CDLQI), local tolerability, and safety.

At baseline [redacted] and [redacted] of randomized patients in the DERMIS-1 and DERMIS-2 trials, respectively, were in the age category of 12 years to 17 years and [redacted] and [redacted] of randomized patients in the DERMIS-1 and DERMIS-2 trials, respectively, were in the age category of 18 years or older. The mean age of all randomized patients was 48.0 (standard deviation [SD] = 14.69) years in the DERMIS-1 trial and 47.0 (SD = 14.72) years in the DERMIS-2 trial. Most patients were male (64.9% and 62.4% of randomized patients in the DERMIS-1 and DERMIS-2 trials, respectively), while 33.9% to 39.3% of patients were female. The majority of patients were white (81.5% and 82.8% of randomized patients in the DERMIS-1 and DERMIS-2 trials, respectively), while the remainder of the randomized patients (0% to 7.3%) identified as Asian, Black or African American, American Indian or Alaska Native [wording from original source], Native Hawaiian or other Pacific Islander, other, or more than 1 race. Similar proportions of all randomized patients in the DERMIS-1 and DERMIS-2 trials had facial involvement (27.1% and 26.0%, respectively), genital involvement (16.4% and 14.7%, respectively), and a baseline I-GA score (23.0% and 19.9%, respectively). The majority of patients had moderate IGA at baseline (74.7% and 76.5% of randomized patients in the DERMIS-1 and DERMIS-2 trials, respectively). The mean baseline BSA affected by psoriasis in all randomized patients was 6.66% (SD = 4.538) in the DERMIS-1 trial and 7.30% (SD = 4.918) in the DERMIS-2 trial. The mean baseline PASI score for all randomized patients was 6.5 (SD = 3.35) in the DERMIS-1 trial and 6.7 (SD = 3.33) in the DERMIS-2 trial.

## Efficacy Results

### *Investigator Global Assessment*

IGA is an investigator-reported, static evaluation of the overall severity of psoriasis of the whole body. The minimal important difference (MID) in IGA has not been estimated. However, a score of 0 (clear) or 1 (almost clear) on the IGA has generally been accepted as clinically meaningful. Alternatively, or in addition to the score of 0 or 1, the responder analysis may also consider the proportion of patients with at least a 2-grade improvement from baseline on the static IGA; this was consistent with the definition of IGA success used in both trials. The primary end point in both trials was an improvement in the overall severity of psoriasis that was measured by the proportion of patients who experienced treatment success based on the IGA, defined as a score of 0 or 1 plus at least a 2-grade improvement from baseline at week 8.

The primary end point, IGA success at week 8, was met for both trials in the intention-to-treat (ITT) population. In the DERMIS-1 trial, 42.4% of patients in the roflumilast arm versus 6.1% of patients in the vehicle arm experienced treatment success based on the IGA at week 8; the ratio of the odds of IGA success with roflumilast relative to the odds of IGA success with vehicle was [redacted] (95% CI, [redacted]) at week 8 from baseline, in favour of roflumilast. In the DERMIS-2 trial, 37.5% of patients in the roflumilast arm versus 6.9% of patients in the vehicle arm experienced treatment success based on the IGA at week 8; the ratio of the odds of IGA success with roflumilast relative to the odds of IGA success with vehicle was [redacted] at week 8 from baseline, also in favour of roflumilast. In both studies, the results of the primary analyses were generally consistent with the sensitivity analyses of the primary end point. IGA success at

week 4 was also reported, and was also in favour of roflumilast when compared to vehicle in the DERMIS-1 trial (13.44 [95% CI, 3.72 to 48.58; ■■■■]) and the DERMIS-2 trial (3.91 [95% CI, 1.76 to 8.70; P = 0.0011]).

### ***Intertriginous-Investigator Global Assessment***

I-GA was defined as the IGA scale but was used to evaluate only intertriginous areas in the trials. In both trials, an improvement in the severity of intertriginous psoriasis was measured by the proportion of patients who experienced treatment success based on the I-GA, defined as a score of 0 or 1 plus at least a 2-grade improvement from baseline at week 8, which was a secondary end point tested in a hierarchical manner and adjusted for multiple comparisons. Note that this analysis was based on the prespecified I-GA-ITT population, a subset of patients with intertriginous area involvement and I-GA score of 2 or more at baseline in the ITT population; 52 patients (82.5%) in the roflumilast arm and 29 patients (90.6%) in the vehicle arm were available in the DERMIS-1 trial for the analysis at week 8, while 47 patients (88.6%) and 27 patients (87.0%), respectively, were available in the DERMIS-2 trial for the analysis at week 8.

In both trials, the proportion of patients who experienced treatment success based on the I-GA at week 8 was greater in the roflumilast treatment groups compared to vehicle. More specifically, in the DERMIS-1 trial, the ratio of the odds of I-GA success with roflumilast relative to the odds of I-GA success with vehicle was 17.94 (95% CI, 2.33 to 138.20; P < 0.0001) at week 8 from baseline, in favour of roflumilast. In the DERMIS-2 trial, the ratio of the odds of I-GA success with roflumilast relative to the odds of I-GA success with vehicle was 11.18 (95% CI, 2.33 to 53.68; P = 0.0004) at week 8 from baseline, also in favour of roflumilast.

### ***Psoriasis Area and Severity Index***

PASI is an investigator-reported evaluation of the extent and severity of psoriasis. An MID in PASI has not been estimated. In both trials, an improvement in the extent and severity of disease was measured based on the proportion of patients who had a 75% improvement in PASI (PASI-75) from baseline at week 8, which was a secondary end point tested in a hierarchical manner and adjusted for multiple comparisons.

In both trials, the proportion of patients who had a PASI-75 was greater in the roflumilast treatment groups compared to vehicle. More specifically, in the DERMIS-1 trial, the ratio of the odds of a PASI-75 with roflumilast relative to the odds of a PASI-75 with vehicle was 12.00 (95% CI, 5.15 to 27.93; P < 0.0001) at week 8 from baseline, in favour of roflumilast. In the DERMIS-2 trial, the ratio of the odds of a PASI-75 with roflumilast relative to the odds of a PASI-75 with vehicle was 10.42 (95% CI, 4.49 to 24.19; P < 0.0001) at week 8 from baseline, also in favour of roflumilast. Time to a PASI-50 was also reported, and was also in favour of roflumilast when compared to vehicle in the DERMIS-1 trial (median Kaplan-Meier [KM] estimate was 31.0 [95% CI, 29.0 to 41.0] days in the roflumilast arm versus 104.0 [95% CI, 85.0 to not estimable (NE)] days in the vehicle arm [P < 0.0001]) and in the DERMIS-2 trial (median KM estimate was 30.0 [95% CI, 29.0 to 42.0] days in the roflumilast arm and NE [95% CI, 71.0 to NE] in the vehicle arm [P < 0.0001]).

### ***DLQI and CDLQI***

DLQI and CDLQI are patient-reported tools used to evaluate HRQoL. The estimated within-group MID is 2.2 to 6.9 points in patients with psoriasis and other inflammatory skin disorders. In both trials, an improvement



in HRQoL was measured by change from baseline in DLQI and CDLQI at week 8, which were exploratory end points that were not included in the statistical hierarchy and not adjusted for multiple comparisons.

A decrease in DLQI score corresponds to an improvement in HRQoL. In the DERMIS-1 trial, the least squares (LS) mean change from baseline in DLQI at week 8 was [REDACTED] in the roflumilast arm and [REDACTED] in the vehicle arm. In the DERMIS-2 trial, the LS mean change from baseline in DLQI at week 8 was [REDACTED] in the roflumilast arm and [REDACTED] in the vehicle arm.

Not enough data were collected to carry out an analysis of covariance (ANCOVA) for change in CDLQI at week 8 in both the DERMIS-1 trial and the DERMIS-2 trial.

### ***Worst Itch–Numeric Rating Scale***

WI-NRS is a patient-reported outcome measure that is used to assess the severity of itch. The MID in WI-NRS has been estimated to be an improvement of 4 or more points in patients with plaque psoriasis, which is consistent with the definition of WI-NRS success used in the trials. In the DERMIS-1 and DERMIS-2 trials, a reduction in the severity of itch was measured by the proportion of patients who experienced treatment success based on the WI-NRS, defined as a reduction of at least 4 points from baseline at week 8, which was a secondary end point tested in a hierarchical manner and adjusted for multiple comparisons. Note that this analysis was based on the prespecified PRU4-ITT population, a subset of patients with WI-NRS pruritus score of 4 or more at baseline in the ITT population; 191 patients (87.6%) in the roflumilast arm and 97 patients (84.3%) in the vehicle arm were available in the DERMIS-1 trial for the analysis at week 8, while 206 patients (89.9%) and 101 patients (87.0%), respectively, were available in the DERMIS-2 trial for the analysis at week 8.

In both the DERMIS-1 trial and the DERMIS-2 trial, the proportion of patients who reported a reduction in the severity of itch based on WI-NRS success was greater in the roflumilast treatment groups compared to vehicle. More specifically, in the DERMIS-1 trial, the ratio of the odds of WI-NRS success with roflumilast relative to the odds of WI-NRS success with vehicle was 7.84 (95% CI, 3.85 to 15.94;  $P < 0.0001$ ) at week 8 from baseline, in favour of roflumilast. In the DERMIS-2 trial, the ratio of the odds of WI-NRS success with roflumilast relative to the odds of WI-NRS success with vehicle was 3.59 (95% CI, 2.07 to 6.23;  $P < 0.0001$ ) at week 8 from baseline, also in favour of roflumilast. WI-NRS success at week 4 was also reported and was also in favour of roflumilast when compared to vehicle in the DERMIS-1 trial (4.36 [95% CI, 2.31 to 8.26;  $P < 0.0001$ ]) and in the DERMIS-2 trial (4.93 [95% CI, 2.65 to 9.18;  $P < 0.0001$ ]). However, improvement in the severity of itch as measured by WI-NRS success was not consistently observed at week 2 across trials.

### ***Psoriasis Symptom Diary***

PSD is a patient-reported assessment of the impact of plaque psoriasis on overall QoL. An MID in PSD total score has not been estimated. In both trials, an improvement in QoL was measured based on change from baseline in PSD total score at week 8, which was a secondary end point tested in a hierarchical manner and adjusted for multiple comparisons.

In both trials, a greater improvement in QoL was observed in the roflumilast treatment groups compared to vehicle (lower scores indicate fewer severe or bothersome symptoms). More specifically, in the DERMIS-1 trial, the LS mean difference between roflumilast and vehicle in change from baseline in PSD total score at



week 8 was  $-30.9$  (standard error [SE] = 3.22; 95% CI,  $-37.2$  to  $-24.6$ ;  $P < 0.0001$ ), in favour of roflumilast. In the DERMIS-2 trial, the LS mean difference between roflumilast and vehicle in change from baseline in PSD total score at week 8 was  $-26.5$  (SE = 3.44; 95% CI,  $-33.2$  to  $-19.7$ ;  $P < 0.0001$ ), also in favour of roflumilast. The LS mean difference between roflumilast and vehicle in change from baseline in PSD total score was also reported at week 4, and was also in favour of roflumilast in the DERMIS-1 trial ( $-25.8$  [SE = 3.00; 95% CI,  $-31.7$  to  $-20.0$ ;  $P < 0.0001$ ] and in the DERMIS-2 trial ( $-26.0$  [SE = 3.03; 95% CI,  $-31.9$  to  $-20.0$ ;  $P < 0.0001$ ]).

### ***Body Surface Area***

BSA measures the extent of psoriasis as assessed by the investigator. An MID has not been estimated for BSA. In both trials, an improvement in the extent of disease was measured by percent change from baseline in BSA affected by psoriasis at week 8, which was an exploratory end point that was not included in the statistical hierarchy and not adjusted for multiple comparisons.

A decrease in percent BSA corresponds to an improvement in extent of disease. In the DERMIS-1 trial, the LS mean percent change from baseline in BSA affected by psoriasis at week 8 was  $-57.16$  (SE = 3.371) in the roflumilast arm and  $-13.80$  (SE = 4.058) in the vehicle arm. In the DERMIS-2 trial, the LS mean percent change from baseline in BSA affected by psoriasis at week 8 was  $-50.88$  (SE = 4.259) in the roflumilast arm and  $-8.68$  (SE = 5.137) in the vehicle arm.

## **Harms Results**

### ***Adverse Events***

The proportion of patients in the roflumilast arm with any treatment emergent adverse event (TEAE) was 25.2% in the DERMIS-1 trial and 25.9% in the DERMIS-2 trial, while the proportion of patients in the vehicle arm with any TEAE was 23.5% in the DERMIS-1 trial and 18.4% in the DERMIS-2 trial. The most common TEAEs reported in the roflumilast arm (a frequency of 2% or more of patients in either study) were diarrhea (3.5% in the DERMIS-1 trial and 2.8% in the DERMIS-2 trial) and headache (1.0% in the DERMIS-1 trial and 3.8% in the DERMIS-2 trial). All remaining TEAEs were reported in less than 2% of patients in the roflumilast arm in either study.

### ***Serious Adverse Events***

The proportion of patients in the roflumilast arm with any serious adverse event (SAE) was 0.7% in the DERMIS-1 trial and no patients in the DERMIS-2 trial, while the proportion of patients in the vehicle arm with any SAE was 0.7% in both the DERMIS-1 trial and the DERMIS-2 trial. The SAEs reported in the roflumilast arm were concussion (1 patient in the DERMIS-1 trial) and foot fracture, deformity thorax, and pneumothorax (1 patient in the DERMIS-1 trial).

### ***Withdrawals Due to Adverse Events***

The proportion of patients in the roflumilast arm with any withdrawal due to adverse event (WDAE) was 2.1% in the DERMIS-1 trial and 0.7% in the DERMIS-2 trial, while the proportion of patients in the vehicle arm with any WDAE was 2.0% in the DERMIS-1 trial and 1.3% in the DERMIS-2 trial. All TEAEs leading to discontinuation of treatment and/or study withdrawal were reported in less than 1% of patients in the roflumilast arm in both studies.

### ***Mortality***

Based on information the sponsor provided, no deaths occurred during the DERMIS-1 and DERMIS-2 trials.

### ***Notable Harms***

The proportion of patients with application site pain in the roflumilast arm was 0.7% in the DERMIS-1 trial and 1.4% in the DERMIS-2 trial. All remaining TEAEs of special interest (application site pruritis, urticaria, dryness, dermatitis, and irritation) were reported in less than 1% of patients in the roflumilast arm in both studies.

## **Critical Appraisal**

### ***Internal Validity***

In the DERMIS-1 and DERMIS-2 trials, patients were randomized at baseline according to a computer-generated randomization list; randomization was stratified by study site, baseline IGA (2 versus  $\geq 3$ ), and intertriginous involvement at baseline (I-IGA  $\geq 2$ , yes versus no). Based on input from the clinical expert consulted by CADTH for this review, the extent and severity of disease as measured by baseline BSA and PASI are additional effect modifiers. Note that the median and mean BSA and PASI score were slightly higher in the vehicle arm compared to the roflumilast arm in both trials. IGA assesses severity of lesions, while BSA and PASI account for extent and severity of disease. Therefore, stratification by IGA alone may not result in an optimal comparability in disease severity between treatment arms and this may have introduced bias in the efficacy results against roflumilast due to the aforementioned imbalance (note that the magnitude of this potential bias is not known). No other baseline demographic and clinical characteristics were identified that could have had a potential impact on the results in both studies.

The primary efficacy outcome in both studies was IGA success at week 8. Conclusions about the validity and reliability of the 5-point IGA used in both studies are limited due to the use of the 6-point and 7-point IGA in the psychometric validation studies; no evidence for responsiveness of IGA was identified. However, the clinical expert suggested that this difference in scales was unlikely to have introduced bias in the results. Although an MID has not been estimated, a score of 0 (clear) or 1 (almost clear) on the static IGA has been generally accepted as clinically meaningful (i.e., a responder analysis would consider the proportion of patients with psoriasis who had a score of 0 or 1 in a clinical trial as treatment success). Alternatively, or in addition to a score of 0 or 1, the responder analysis may also consider the proportion of patients with at least a 2-grade improvement from baseline on the static IGA. These were consistent with the definition of IGA success used in the studies.

The primary and secondary outcomes were controlled for multiplicity in both studies using a prespecified hierarchical testing strategy and the Holm procedure to control the familywise type I error. The planned sample size provided sufficient power to analyze up to the first 5 secondary end points; note that the remaining end points demonstrated statistically significant differences between treatment arms that were consistently in favour of roflumilast, with the exception of WI-NRS success at week 2 in DERMIS-1. The relatively small sample size of patients available for subgroup analysis – in particular, patients aged 12 years to 17 years – significantly limited the interpretation of findings and the assessment of treatment benefit in this subgroup of patients. Moreover, as indicated by the clinical expert, potential heterogeneity of

treatment effect by extent and severity of disease as measured by BSA or PASI was not reported. This further compromised the certainty of evidence on treatment effect of roflumilast among patients by different extent and severity of disease.

### ***External Validity***

Based on clinical expert input, the inclusion and exclusion criteria were considered narrow. For example, patients with an IGA score of 1 and a PASI score of 1 would be considered as candidates for treatment with roflumilast in clinical practice in Canada; however, they were excluded from the trials as a score of at least 2 was required for enrolment. Additionally, the clinical expert suggested that patients with plaque psoriasis involving less than 2% or more than 20% BSA, excluding the scalp, palms, and soles, would potentially be treated with roflumilast but were also excluded from the trials. As such, the effect of roflumilast in the broader patient population is unknown. Note that the Health Canada indication does not restrict the patient population according to percent BSA involvement.

Roflumilast was compared to a vehicle, which contained only the excipients of the roflumilast cream, in both studies. However, given the wide range of topical treatment options currently available in clinical practice for plaque psoriasis, the clinical expert agreed that an active comparator would have been more appropriate; in particular, topical steroids and VDAs would have been appropriate comparators. However, the vehicle cream may be considered an appropriate comparator, as there are limited options for intertriginous areas, which have been identified as an area of unmet need by the clinical expert and clinician groups.

The clinician groups and the clinical expert agreed that the primary, secondary, and selected exploratory outcomes in the trials were clinically relevant (i.e., capture the extent and severity of disease and determine treatment response in clinical practice). Moreover, the clinical expert indicated that clearance or near clearance of psoriasis lesions is commonly used in clinical practice to assess psoriasis severity, which is analogous to IGA used in clinical trials. Both the clinician groups and the clinical expert indicated that these tools, such as PASI and DLQI, are not commonly used in clinical practice unless mandated by the payors for reimbursement.

## **Long-Term Extension Study**

### **Description of Study**

The DERMIS-OLE (ARQ-151-306) study is an ongoing, phase III, long-term open-label extension (OLE) study conducted to assess the long-term safety of roflumilast in adult and pediatric patients with chronic plaque psoriasis involving up to 25% BSA. All patients received open-label roflumilast applied once daily to all psoriasis lesions (excluding the scalp) for up to 24 weeks. The study enrolled 267 patients aged 2 years and older, 266 of whom received treatment with roflumilast in the OLE. Patients in cohort 1 (n = 264) had successfully completed a prior roflumilast cream study for psoriasis, in which they had received either roflumilast (n = 171) or vehicle (n = 93). Patients in cohort 2 (n = 2) were naive to treatment with roflumilast and had not yet reached OLE study week 4 at the time of the data cut-off date, and therefore efficacy data were not available for these patients. At the time of data cut-off, a total of 222 patients (83.1%) had

completed the OLE study, 32 patients (12.0%) had prematurely discontinued the study, and 12 patients (4.5%) were ongoing in the study.

### **Efficacy Results**

Among patients in cohort 1, at week 24 of the OLE, 50.0% of patients had IGA scores of “clear” or “almost clear.” A total of 67.8% of cohort 1 patients had a “clear” or “almost clear” IGA status from primary baseline and maintained that status for a median of 93 days. At week 24, a total of 37.1% of cohort 1 patients experienced treatment success based on the IGA score, defined by a score of “clear” or “almost clear” plus at least a 2-grade improvement from baseline, and this was the case for 54.9% of patients for a median duration of 85 days. For cohort 1 patients with intertriginous area involvement (n = 59), at week 24, 77.8% had I-GA scores of clear or almost clear, and 75.6% of patients experienced treatment success based on I-GA, defined as a score of “clear” or “almost clear” plus at least a 2-grade improvement from baseline. The proportions of cohort 1 patients with PASI-50, PASI-75, and PASI-100 scores at week 24 of the OLE were 70.5%, 43.8%, and 16.5%, respectively. The proportion of cohort 1 patients who experienced treatment success based on the WI-NRS, defined as an improvement of 4 or more points, at week 24 was 62.4%. Overall, the results of the DERMIS-OLE study suggest that efficacy was maintained for up to 24 weeks.

### **Harms Results**

No new safety signals were reported based on the OLE study. No AEs were reported among patients in cohort 2. Among patients in cohort 1, 26.1% experienced at least 1 AE, the most common being sinusitis (2.7%), diarrhea (2.3%), COVID-19 (1.9%), and headache (1.9%). Three patients (1.1%) experienced a total of 5 SAEs, including polycythemia vera, COVID-19 pneumonia, palpitations, dehydration, and syncope, none of which were considered related to the drug. One patient (0.4%) discontinued the study due to an AE of application site irritation. No deaths occurred during the OLE study.

### **Critical Appraisal**

Limitations of the extension study include selection bias, lack of a control group, and a lack of blinding. Reporting of harms and subjective efficacy outcomes such as IGA and I-GA success may be biased by knowledge of treatment received. As only descriptive statistics were published in this interim report, and without comparator groups, the interpretation of the results is limited. Moreover, there is potential for selection bias, as patients who discontinued the parent studies due to AEs, lack of efficacy, or other reasons were excluded. Furthermore, most patients were white (> 84%), which may limit the generalizability of results to other racial groups. However, the clinical expert consulted by CADTH indicated that efficacy and safety of roflumilast is not expected to differ by race.

## **Indirect Comparisons**

### **Description of Studies**

One sponsor-submitted indirect treatment comparison (ITC) was included, consisting of a systematic literature review and a Bayesian NMA comparing roflumilast to the other topical therapies available in Canada for patients with plaque psoriasis. The primary outcome of interest was IGA treatment response at week 8, which was informed by data in 8 studies including the DERMIS-1 and DERMIS-2 trials. A subgroup

analysis of I-GA treatment response at week 8 among patients with intertriginous psoriasis was informed by data from 4 studies, including the DERMIS trials.

### Efficacy Results

The NMA results for IGA treatment response at week 8 favoured roflumilast over vehicle, VDAs, TAZ, or CSs. IGA treatment response data for roflumilast versus CSs plus VDAs, or CSs plus TAZ, did not clearly favour either treatment [REDACTED]. For the fixed-effect NMA of I-GA treatment response at week 8, roflumilast was associated with [REDACTED] treatment response versus vehicle [REDACTED]. Results found that roflumilast versus calcineurin inhibitors did not clearly favour either treatment [REDACTED].

### Critical Appraisal

Potential sources of heterogeneity could not be fully assessed in the NMA due to the limited reporting of study design characteristics (i.e., inclusion criteria, frequency of treatment withdrawal, and handling of missing data) and patient baseline characteristics (i.e., disease history duration, prior treatment experience, PASI score, and BSA involvement), and as such, there is uncertainty in the validity of the results of the NMA. The clinical expert consulted for this review noted that there were imbalances across treatment groups in the effect modifier of baseline disease severity. As a result, it is possible that the heterogeneity in this baseline characteristic could result in changing relative treatment effects. The outcomes were limited to the analysis of IGA and I-GA treatment response, and therefore other relevant efficacy outcomes such as PASI and HRQoL (i.e., DLQI) were not assessed. Long-term efficacy and safety outcomes were not assessed, limiting the external validity of results. These limitations result in uncertainty in the relative treatment effect estimates between roflumilast and other comparable topical therapies.

### Studies Addressing Gaps in the Pivotal and Randomized Controlled Trial Evidence

No additional studies were included in the report for the review of roflumilast.

## Economic Evidence

**Table 3: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients aged 12 years and older with plaque psoriasis, including individuals with intertriginous psoriasis involvement
Treatment	Roflumilast topical
Dose regimen	Application once daily to affected areas of skin.

Component	Description
Submitted price	Roflumilast, 0.3% cream: \$275.00 per 60 g tube
Treatment cost	\$269.50 per 4-week cycle
Comparators	Topical treatments for plaque psoriasis were considered by class: high-potency CS, VDA, TAZ, CS + VDA, and CS + TAZ
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	5 years
Key data source	Pooled results from the sponsor's DERMIS-1 and DERMIS-2 clinical trials and the sponsor's NMA
Key limitations	<ul style="list-style-type: none"> <li>The full Health Canada indication was not modelled. Effectiveness of roflumilast in the model was based on the DERMIS trials, which only investigated roflumilast as monotherapy and excluded patients with BSA &lt; 2% and &gt; 20%. The cost-effectiveness of roflumilast in these patients, as well as its use as combination therapy, is unknown.</li> <li>The model structure, based on response defined by IGA success, did not adequately reflect the management of plaque psoriasis in clinical practice and did not represent homogenous health states. It is uncertain whether health benefits and costs have been adequately captured.</li> <li>The comparative efficacy of roflumilast vs. other topical treatments is highly uncertain, owing to a lack of robust comparative data. The sponsor's NMA is suggestive of a benefit of unknown magnitude for roflumilast vs. monotherapies. For roflumilast vs. combination therapies, no difference in clinical efficacy could be concluded. Furthermore, the long-term relative efficacy of roflumilast is unknown.</li> <li>The incorporation of maintenance treatment was deemed to be uncertain by the clinical expert consulted by CADTH and the parameterization of relapse on maintenance treatment was based on naive comparisons of trial data using different definitions of relapse. Relapse was not formally assessed in the pivotal trials.</li> <li>Health state utility values lacked face validity, as they included values higher than the maximum observed value of the general population in Canada and were based on a different response measure than used in the sponsor's model.</li> <li>The baseline percentage of affected BSA in the model may not be generalizable to Canadian clinical practice. Higher affected BSA will lead to higher drug acquisition costs for all treatments.</li> </ul>
CADTH reanalysis results	<ul style="list-style-type: none"> <li>The CADTH reanalysis adjusted the modelled treatment pathway, such that patients were not re-treated with their initial topical treatment upon relapse on maintenance treatment; assumed that the probability of relapse among all maintenance treatments was equal; and limited the maximum utility value to reflect observed Canadian values. CADTH was unable to address limitations related to the model structure and the lack of robust comparative data.</li> <li>In the CADTH base case, similar to the sponsor's results, CS, CS+TAZ, and roflumilast remained on the cost-effectiveness efficiency frontier. Compared with CS, roflumilast was associated with incremental QALYs of 0.0005 (equivalent to 4 quality-adjusted life hours over a 5-year time horizon) and incremental costs of \$506 (ICER of \$1,085,171 per QALY gained). A price reduction of at least 74% is required for roflumilast to be considered cost-effective compared to CS at a WTP threshold of \$50,000 per QALY.</li> <li>Given the findings of no difference in clinical efficacy for roflumilast vs. combination treatments for plaque psoriasis, or Caln for those specifically with intertriginous involvement, there is no evidence to support a price premium for roflumilast over these comparators.</li> </ul>

BSA = body surface area; Caln = calcineurin inhibitor; CS = corticosteroid; ICER = incremental cost-effectiveness ratio; IGA = Investigator Global Assessment; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; TAZ = tazarotene; VDA = vitamin D analogue; WTP = willingness to pay.



## Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients eligible for roflumilast is uncertain owing to uncertainty in proportion of patients with severe plaque psoriasis using topical treatments and the proportion of patients who would have public coverage; the uptake of roflumilast may be higher than expected by the sponsor; and the number of tubes of topical treatment required per year is uncertain and may be underestimated. CADTH reanalysis included changes to the proportion of patients with severe psoriasis using topical treatments, adjusted market shares of roflumilast to reflect anticipated use in clinical practice, and adjusted public coverage rates based on the proportion of enrolled patients in the public drug plan by jurisdiction. In the CADTH base case, the budget impact of reimbursing roflumilast for the topical treatment of plaque psoriasis (including treatment of psoriasis in the intertriginous areas) in patients 12 years of age and older is expected to be \$15,487,922 in Year 1, \$28,067,209 in Year 2, and \$39,295,106 in Year 3, for a total budget impact of \$82,850,237.

## CDEC Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, 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:** June 28, 2023

**Regrets:** None

**Conflicts of interest:** None





**ISSN:** 2563-6596

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