Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Clascoterone (Winlevi)

Indication: For the topical treatment of acne vulgaris in patients 12 years of age and older

Sponsor: Sun Pharma Canada Inc.

Recommendation: Do Not Reimburse

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that clascoterone not be reimbursed for the topical treatment of acne vulgaris in patients 12 years of age and older.

Rationale for the Recommendation

Acne vulgaris is a common condition with many treatment options available; however, CDEC highlighted that unmet needs still exist. Patients and clinicians identified the need for additional treatment options that improve skin clearance, prevent acne sequelae (scarring and pigmentation), reduce irritative side effects, have a quicker onset of action, and improve health-related quality of life (HRQoL). CDEC noted that compared to vehicle cream, clascoterone may provide an additional treatment option that may reduce acne lesions as well as reduce irritative side effects. However, CDEC could not substantiate that clascoterone meets many of the unmet needs relative to other acne treatments, including improved skin clearance, reduction in scarring, and improving HRQoL and mental health.

Two double-blind, phase III, randomized controlled trials (RCTs) (CB-03-01/25 and CB-03-01/26) in patients aged 9 years and older with moderate to severe acne vulgaris demonstrated that, compared with the vehicle cream, treatment with clascoterone resulted in more patients achieving treatment success, defined as an investigator's global assessment (IGA) score of clear (0) or almost clear (1) and a 2-point or greater reduction in the IGA scale from baseline (18.8% and 20.8% in the clascoterone groups versus 8.9% and 6.5% in the vehicle groups, odds ratio [OR], 2.36 [95% CI, 1.4 to 3.9; P = 0.0008]; and 3.8 [95% CI, 2.2 to 6.4; P < 0.0001], respectively). However, although the results for clinically relevant skin clearance outcomes — change from baseline in non-inflammatory lesion counts (NILCs), inflammatory lesion counts (ILCs), and total lesion counts (TLCs) — were statistically significant in the pivotal trials compared to vehicle cream, the evidence was uncertain due to a high level of missing data, and the results did not reach the threshold for a minimally clinical important difference compared to vehicle cream. Furthermore, CDEC emphasized the lack of direct comparative data with other acne treatments. These limitations precluded CDEC from determining whether clascoterone addressed the unmet needs identified.

Despite the number of alternative treatments available, there is a lack of direct comparative evidence for clascoterone and other treatments in acne vulgaris. There were important limitations in the sponsor-submitted network meta-analyses (NMAs), namely heterogeneous populations and missing comparators. Thus, CDEC could not draw firm conclusions on the comparative efficacy of clascoterone versus other active treatments.

Discussion Points

- **Unmet Needs:** CDEC discussed multiple unmet needs identified by patients and clinicians. Patients emphasized the need for additional treatments that improve skin clearance and prevent acne sequelae (e.g., scarring and pigmentation) while reducing irritative side effects (e.g., erythema, skin atrophy, dryness), and subsequently improving HRQoL and mental health, often linked to appearance due to acne. CDEC noted that compared to vehicle cream, clascoterone may meet some of these needs (i.e., it results in treatment success and reduces acne lesions and irritative side effects); however, CDEC was uncertain whether clascoterone meets the unmet needs identified versus active acne treatments due to a lack of direct comparative evidence, and the uncertainty in the indirect evidence. Further, CDEC was also unable to determine the impact of clascoterone on HRQoL or mental health given the lack of evidence for these endpoints in the CB-03-01/25 and CB-03-01/26 trials. CDEC, as well as the patient and clinician input provided for this review, noted that clascoterone is the first topical androgen receptor inhibitor and the first androgen receptor inhibitor that can be prescribed to male patients, however, there was no evidence submitted that investigated the efficacy or harms of clascoterone specifically in the male population. Overall, CDEC was unable to conclude that clascoterone addressed the unmet needs identified within this review.
- **Certainty of Evidence:** While the results for IGA were statistically significant in favour of clascoterone over vehicle cream at 12-weeks in studies CB-03-01/26 and CB-03-01/26, and were given a GRADE of 'Moderate' certainty (18.8% vs. 8.9%; OR, 2.36 [95% CI, 1.4 to 3.9], and 20.8% vs. 6.5%; OR, 3.8 [95% CI, 2.2 to 6.4], respectively), CDEC did not consider the results to be clinically meaningful based on the thresholds identified. As one of the most important outcomes of treatment to patients, CDEC discussed the certainty of the evidence for changes in lesion counts (NILC, ILC, and TLC) which was considered 'very low' or 'low' as determined by GRADE in the CB-03-01/25 and CB-03-01/26 trials due to high levels of missing data (ranging from 18% to 22%), the duration of the trial and timing of assessments, and the inability of clascoterone to reach the threshold of minimally clinically important difference.
- **Indirect Evidence:** CDEC noted that there are many effective treatment options available for patients with acne vulgaris. CDEC discussed the uncertainty of the comparative efficacy of clascoterone due to the absence of direct comparative evidence. CDEC discussed the sponsor-submitted NMAs comparing clascoterone to benzoyl peroxide, tretinoin, tazarotene, adapalene, and trifarotene. However, due to the numerous limitations including the heterogenous populations enrolled in the included studies, relevant comparators that were missing from the analyses, and wide 95% CIs that included the potential for no difference or that either treatment could be favoured, CDEC was unable to draw meaningful conclusions on how clascoterone compares to other acne treatments with regards to efficacy and safety.
- **Adverse Effects:** Patient groups concluded that patients weigh the adverse effects associated with treatment against effectiveness when deciding to start, stop, or continue their therapy for acne. Results of the sponsor-submitted NMA suggested that clascoterone was associated with a reduced frequency of discontinuations compared to tazarotene, however, there was insufficient evidence to detect a difference in the comparative safety versus other acne treatments.
- **Generalizability:** CDEC and the clinical expert consulted for this review discussed the treatment duration of 12 weeks, where the clinical expert noted that it would be unlikely to observe a meaningful change in outcomes until at least 6 months of treatment, particularly for NILC. However, in terms of harms (i.e., localized skin reactions), it was noted that given the mechanism of action, and cream base of clascoterone, the 12-week duration was considered sufficient. Further CDEC discussed the impracticality of absolute lesion counts in real-world clinical practice.
- **Supportive Studies:** CDEC also discussed one long-term extension study (CB-03-01/27) that provided additional long-term safety and efficacy evidence for 9 months of treatment with clascoterone. While the results were supportive of the findings from the pivotal trials, numerous limitations including the open-label design, selection bias, and high rate of attrition limited the interpretability of the results.

Background

Acne vulgaris is a chronic inflammatory skin condition of the pilosebaceous glands that typically begins during puberty and can continue through adulthood with flares often coinciding with increasing serum androgens. When assessing the severity of acne, considerations include the distribution (back, chest, upper arms), type and number of lesions (comedones, papules, pustules, nodules), and the presence or absence of scarring. Acne is diagnosed by physicians in the community by visual assessment and no specific procedures are required. Acne is one of the most common dermatological disorders worldwide affecting 5.6 million people living in Canada. Although it predominantly affects the adolescent population (approximately 80%), it can also affect pre-adolescents (aged 7 to 12 years) and post-adolescents. Adolescent acne usually begins during the onset of puberty, with the increase in androgen hormone production, which affects acne development and severity. Acne is more common in males than in females in adolescence, while it is more common in females than in males in adulthood.

Treatment depends on the severity and type of acne, the age and treatment preferences of the patient, and adherence and response to previous therapies. Mild acne is typically treated with topical medications (e.g., antibiotics and topical retinoids). The main side effects of topical medications are local irritation and erythema. Most topical preparations require at least 6 to 8 weeks before an improvement is seen, though response can be observed earlier with antibiotics (as early as 5 days) or later with retinoids (after 12 weeks). Moderate acne is treated with the same topical treatments and the addition of an oral antibiotic or an oral anti-androgen for females (e.g., combined oral contraceptive or spironolactone). According to the updated 2024 American Academy of Dermatology guidelines for managing acne, clascoterone is conditionally recommended for acne treatment (with a conditional recommendation based on the current high cost of the drug) and is not restricted to first-line use or to moderate and severe acne. Oral antibiotics, hormonal therapies, and isotretinoin are the mainstay systemic therapies for acne when topical therapy is insufficient or not tolerated. However, a major concern for antibiotics is the development of treatment resistance in bacteria, while hormonal agents (e.g., spironolactone) may have side effects, such as hyperkalemia, menstrual irregularities, and feminization of a male fetus. For severe acne (e.g., nodular and/or inflammatory acne, acne conglobata, and recalcitrant acne that is treatment-resistant), oral isotretinoin is the treatment of choice according to the clinical expert consulted for this review and Canadian practice guidelines. For patients unwilling or unable to use oral isotretinoin and those with intolerance, systemic antibiotics in combination with topical benzoyl peroxide, with or without a topical retinoid, may be considered. For females, hormonal therapy with a combined oral contraceptive may also be considered. For males, current hormone therapies are not suitable. According to the clinical expert, nondrug treatments include diet (e.g., reducing low glycemic index foods and dairy) and laser therapy. Treatment goals include clearing acne and preventing acne sequelae such as post-inflammatory hyperpigmentation and scarring. The main therapies currently used for acne are aimed at reducing severity and recurrence of skin lesions as well as improving appearance. According to the clinical expert, with the exception of oral isotretinoin, most acne treatments control symptoms but are not curative, therefore, patients must continue treatment to maintain benefit.

Clascoterone has been approved by Health Canada for the topical treatment of acne vulgaris in patients 12 years of age and older. Clascoterone is an androgen receptor inhibitor. It is available as a 10 mg/g cream and the dosage recommended per application in the product monograph is approximately 1 gram or 2 fingertip units applied in a thin uniform layer twice per day, in the morning and the evening, over the area prone to acne.

Sources of Information Used by the Committee

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

- a review of 2 double-blind RCTs in patients with facial acne, 1 long-term extension (LTE) study, and 1 NMA
- patients' perspectives gathered by 2 patient groups, Acne and Rosacea Society of Canada (ARSC) and Canadian Skin Patient Alliance (CSPA)
- input from public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with acne
- input from 2 clinician groups, the Dermatology Association of Ontario (DAO) and the Primary Care Dermatology Society of Canada (PCDSC)

- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

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

Patient Input

Two national, not-for-profit organizations, ARSC and CSPA, jointly conducted a survey in June 2022 with 154 patients living in Canada diagnosed with acne. ARSC is comprised of dermatologists, patients, educators, and communicators providing information and raising awareness about the disease. CSPA strives to improve the lives of people affected by skin, hair, and nail conditions through collaboration, advocacy, and education.

Patient groups emphasized that acne not only affects appearance, but also impacts patients' lives and mental health. Many patients reported having diminished self-image, self-esteem, self-confidence, and assertiveness. This emotional distress caused by unhappiness with appearance can lead to bad mood, anxiety, anger, loneliness, self-consciousness, shame, depression, pain, and anxiety in social situations, generally making them feel poor health overall. Furthermore, patient groups said these factors impede their ability to be social and conduct daily activities, e.g., forming friendship and dating, avoiding social interaction, being seen on camera, swimming, and changerooms that make patients expose acne on their body. Financial burden was cited as another challenge and some respondents reported paying out-of-pocket costs for prescription, over the counter, and self-care products, such as cleansers and make-up, which increase with acne severity (4% of patients with mild acne, 5% of patients with moderate acne, 14% of overall respondents spending $100 or more per month). More than half of patients had facials and peels (53%; 12% of them paying more than $500) and light or laser therapy (65%; 15% of them paying more than $500) that exacerbate financial burden on patients. As such, patients prioritize treatments that help them enjoy personal relationships and cause less scarring or changes in skin pigmentation. Other goals include clearer skin, better mental health, increased confidence, ability to be social, and improved overall quality of daily life.

To improve their lives, respondents want increased access to new treatment that is safe and effective, health care providers to be aware of all the new and existing treatment options for acne, and evaluation for depression and anxiety that could lead them to getting support.

Three individuals who had experience with clascoterone felt that their acne was well controlled with the drug (also resulting in greater confidence) and did not experience the typical side effects associated with topical treatments for acne. However, it was noted that the medication was very expensive compared to other treatment options, with patients paying out-of-pocket or accessing treatment through insurance.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

According to the clinical expert, a major limitation of current acne therapy is that the most efficacious topical treatments, such as retinoids and benzoyl peroxide, tend to be irritative and exhibit a slow onset of effect, which may contribute to the issue of poor adherence to treatment. The clinical expert noted that as the majority of treatments are not curative, their continuation becomes imperative to sustain benefits. Moreover, acne severity varies over time, thus requiring treatment modifications as time progresses.

According to the clinical expert, clascoterone will likely be used as a first-line topical treatment for mild and moderate acne if it is effective and accessible. Clascoterone has a novel mechanism in that it is the first topical androgen receptor blocker and the first androgen blocker that can be used in males with acne. The clinical expert anticipates that clascoterone may be used alone or in combination with other topical treatments for mild acne and in combination with oral antibiotics for moderate acne. The clinical expert did not feel that clascoterone can be used as first-line treatment for severe acne, however, it could be considered in combination with systemic treatment if a patient requests alternatives to first-line treatment of severe acne (i.e., isotretinoin).

According to the clinical expert, topical clascoterone is appropriate for use by any patient with mild to moderate acne. It is least suited for use in patients with severe or treatment-resistant moderate acne since oral retinoids are better suited for this patient population. However, the clinical expert noted that clascoterone 1% cream could be used in combination with other treatments if a patient requests alternatives to first-line treatment to severe acne. The clinical expert noted that clascoterone could potentially be used in combination with oral contraceptives or spironolactone in female patients to see if there would be added benefit. It should not be used in patients who are pregnant, nursing, or contemplating pregnancy.

The clinical expert noted that treatment success for most drugs should be determined at 3 months, apart from oral contraceptive and spironolactone, which would require 4 to 6 months to improve acne. Of note, some physicians elect to reevaluate their patients on treatment with isotretinoin monthly. The clinical expert noted that a physician will examine acne lesions and record acne as clear, minimal or almost clear, moderate, or severe; comment on acne sequalae, including pigmentation and scarring; and note how patients think they are doing with their treatment upon evaluation. The goal of treatment is minimal (1 to 2 lesions on examination) or no acne. Given that patients' expectations can be variable, patient satisfaction is also an important factor in assessing treatment success. The clinical expert noted that both family physicians and dermatologists may prescribe clascoterone. According to the clinical expert patients would discontinue treatment if there was a lack of response or worsening of disease, adverse effects, or patient dissatisfaction with treatment. The clinical expert also noted that they would discontinue treatment in patients who are attempting to conceive or pregnant or nursing.

Clinician Group Input

Two clinician groups, DAO represented by 10 clinicians and PCDSC represented by 5 physicians who make up the group's board of directors submitted input. The clinician groups and clinical expert consulted by CADTH both agreed that clascoterone provides a novel mechanism of action as a first topical androgen blocker that can also be used in males with acne. Both clinician groups and the clinical expert consulted by CADTH agreed that minimal or no acne (clear to almost clear skin) is a goal of acne treatment. PCDSC noted that patients using clascoterone should be advised that treatment effect may not be observed for several months. The clinician groups indicated that severe acne should be treated with isotretinoin, which is consistent with the feedback received from the clinical expert consulted by CADTH. However, the clinician groups stated that clascoterone may be used as adjunctive treatment to isotretinoin or in place of isotretinoin in case of serious intolerance or contraindication, which differs from input received from the clinical expert consulted by CADTH who indicated that clascoterone would not be used for severe or treatment-resistant moderate acne. The clinical expert also mentioned that the benefit of adding clascoterone to oral contraceptives or off-label spironolactone is uncertain. A clinically meaningful response to treatment, according to DAO, would be a 30% reduction in lesion counts and 2-point (or even 1-point) reduction in Investigator's Global Assessment (IGA) scores. Additionally, DAO suggested that transmasculine patients, gender minority, mature patients (29 to 40 years of age) with acne, or those with sensitive, eczema-prone skin may benefit from clascoterone. Overall, the input provided by the clinician groups and clinical expert were consistent with the unmet needs, treatment goals, patient population, assessment of response, and discontinuation of treatment.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for clascoterone:

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues

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

Clinical Evidence

Systematic Review

Description of Studies

Two identically designed, randomized, double-blind, vehicle-controlled, parallel-group trials (CB-03-01/25; N = 708; and CB-03-01/26; N = 732) assessed the safety and efficacy of clascoterone 1% cream versus the vehicle cream (without active drug) applied twice daily for 12 weeks in patients with facial acne.

CB-03-01/25 was conducted primarily in the US and CB-03-01/26 was conducted primarily in Europe. Neither trial had any study sites in Canada. In CB-03-01/25, 708 patients were randomized to treatment with either clascoterone 1% cream (N = 353) or vehicle cream (N = 355). In CB-03-01/26, 732 patients were randomized to treatment with either clascoterone 1% cream (N = 369) or vehicle cream (N = 363). In CB-03-01/25, the median age for both treatment groups was 18 years of age (range, 9 to 58 years) and in CB-03-01/26 the median age for both treatment groups was 18 years of age (range, 10 to 50 years). Block randomization was used for both studies. Patients were enrolled from January 21, 2016, to April 11, 2018, for CB-03-01/25 and from November 16, 2015, to February 21, 2018, in CB-03-01/26.

Both studies are now complete and consisted of the following study periods:

- Screening phase: Visit 1
- Treatment phase: 12 weeks (consisting of 3 study visits at week 4, week 8, and week 12)
- Follow-up phase: Patients in both studies had the option to continue for up to 12 months in the LTE study (CB-03-01/27)

Patients eligible for inclusion were required to have acne vulgaris of the face (which can include the nose) with an IGA score of 3 or 4, at least 30 to a maximum of 75 inflammatory lesions (papules, pustules, and nodules), and at least 30 to a maximum of 100 non-inflammatory lesions (open and closed comedones). Patients were excluded from the trials if they had nodulocystic acne, if they were pregnant, lactating, or planning to become pregnant during the study, were planning to be or needed to be exposed to artificial tanning devices or excessive sunlight during the trial, if they had been using any topical antiacne preparations within 2 to 6 weeks of treatment initiation or had used any of the following systemic antiacne medications: corticosteroids, antibiotics, spironolactone, or retinoids within 1 week to 6 months of treatment initiation.

The demographic characteristics were similar between the treatment groups. With respect to acne severity, the majority of patients in CB-03-01/25 had an IGA rating of moderate (82.7% clascoterone, 82.0% vehicle) with the remainder rated severe. Mean ILC was 42.4 lesions for clascoterone and 42.9 lesions for vehicle (range, 30 to 83), mean NILC was 59.1 lesions for clascoterone and 60.7 lesions for vehicle (range, 30 to 144), and mean TLC was 101.5 lesions for clascoterone and 103.6 lesions for vehicle (range, 60 to 196). In CB-03-01/26, the majority of patients had an IGA rating of moderate (82.7% in the clascoterone group and 86.2% in the vehicle group) with the remainder rated severe. Mean ILC was 42.9 lesions for clascoterone and 41.3 lesions in vehicle group (range, 30 to 75), mean NILC was 62.8 lesions and 63.3 lesions for the clascoterone group and vehicle group respectively (range, 30 to 177 lesions), and mean TLC was 105.7 lesions and 104.6 lesions in the clascoterone group and vehicle group, respectively (range, 60 to 241 lesions).

Efficacy Results

Global Success

Proportion of patients aged 12 years or older achieving success at week 12

Success was defined as an IGA score of clear (0) or almost clear (1) and a 2-point or greater reduction in the IGA scale compared with baseline. The IGA is a static, investigator-reported measure of overall (qualitative and quantitative) acne severity. It uses an ordinal scale with 5 severity grades from 0 (clear skin) to 4 (severe) based on morphologic descriptions.

In CB-03-01/25, the adjusted proportion of patients aged 12 and older achieving success at week 12 was 18.8% in the clascoterone group versus 8.9% in the vehicle group (OR = 2.36; 95% CI, 1.4 to 3.9; P = 0.0008). Similarly, in CB-03-01/26, the adjusted

proportion of patients aged 12 and older achieving success at week 12 was 20.8% in the clascoterone group versus 6.5% in the vehicle group (OR = 3.8; 95% CI, 2.2 to 6.4; P < 0.0001). At week 12, the results of the pooled analysis were consistent across both studies.

Sensitivity analyses in the intention-to-treat (ITT) population were consistent with the primary efficacy results in both trials with the exception of the worst-case analysis. Results of the last observation carried forward (LOCF) and baseline outcome carried forward (BOCF) analyses confirmed the robustness of the results obtained on the ITT set for the primary efficacy end points.

Lesion Counts

Absolute change from baseline in NILC at week 12

In CB-03-01/25, a greater absolute decrease from baseline in NILC was seen in patients treated with clascoterone (–19.4 lesions) compared to patients treated with vehicle (–13.1 lesions) at week 12 (–6.3 lesions difference between treatment groups; 95% CI, –10.2 to –2.4 lesions; P = 0.0016). Similarly, in CB-03-01/26, the absolute change in NILC from baseline to week 12 was –19.4 lesions in the clascoterone group versus –10.9 lesions in the vehicle group (−8.4 lesions difference between treatment groups; 95% CI, −12.4 to −4.5 lesions; P < 0.0001).

The sensitivity analyses in the ITT population were consistent with the primary efficacy results in both pivotal trials. However, results of the worst-value and worst-case analysis were inconsistent with the results obtained on the ITT set for this outcome. Results of the LOCF and BOCF analyses confirm the robustness of the results obtained on the ITT set for the primary efficacy end points.

Percent change in NILC from baseline at week 12

In CB-03-01/25, the percent change from baseline to week 12 was greater in the clascoterone group than the vehicle group for NILC (−30.7% versus −21.6%, −8.8% for the treatment group difference; 95% CI, −15.9% to −1.8%; P = 0.0141). In CB-03-01/26, the percent change from baseline to week 12 was greater in the clascoterone group than the vehicle group for NILC (−29.3% versus −15.8%; −13.5% for the treatment group difference; 95% CI, −19.8% to −7.1%; P < 0.0001).

Absolute change from baseline in ILC at week 12

In CB-03-01/25, the absolute change in ILC from baseline at week 12 was −19.4 lesions in the clascoterone group versus −15.5 lesions in the vehicle group (−3.9 lesions for the treatment group difference; 95% CI, −6.5 to −1.3 lesions; P = 0.0029). Similarly, in CB-03-01/26, at week 12, the absolute change from baseline in ILC was also −20.0 lesions in the clascoterone group versus −12.6 lesions in the vehicle group (−7.4 lesions for the treatment group difference; 95% CI, −9.8 to −5.0 lesions; P < 0.0001).

The sensitivity analyses in the ITT population were consistent with the primary efficacy results in both pivotal trials. However, results of the worst-value and worst-case analysis were inconsistent with the results obtained on the ITT set for this outcome in CB-03-01/25 and the results of the worst-case analysis were inconsistent with results obtained from the ITT set for this outcome in CB-03-01/26.

Percent change in ILC from baseline at week 12

In CB-03-01/25, the percent change from baseline to week 12 was greater in the clascoterone group than the vehicle group for ILC (−44.8% versus −36.6%; −8.3% for the treatment group difference; 95% CI, −14.3% to −2.3%; P = 0.0070). In CB-03-01/26, the percent change from baseline to week 12 was greater in the clascoterone group than the vehicle group for ILC (−47.0% versus −29.8%; −17.2% for the treatment group difference; 95% CI, −22.9% to −11.5%; P < 0.0001).

Absolute change from baseline in TLC at week 12

In CB-03-01/25, the absolute change from baseline to week 12 was greater in the clascoterone group than the vehicle group for TLC (−39.2 lesions versus −28.9 lesions; −10.3 lesions for the treatment group difference; 95% CI, −15.7 to −5.0 lesions; P = 0.0002). In CB-03-01/26 the absolute change from baseline to week 12 was greater in the clascoterone group than the vehicle group for TLC (−40.3 lesions versus −23.7 lesions, −16.6 lesions for the treatment group difference; 95% CI, −22.0 to −11.1 lesions; P < 0.0001).

Percent change in TLC from baseline at week 12

In CB-03-01/25, the percent change from baseline to week 12 was greater in the clascoterone group than the vehicle group for TLC (−37.1% versus 28.5%, −8.7% for the treatment group difference; 95% CI, −14.0% to −3.3%; P = 0.0016). In CB-03-01/26, the percent change from baseline to week 12 was greater in the clascoterone group than the vehicle group for TLC (−37.7% versus −22.2%, −15.6% for the treatment group difference; 95% CI −20.9% to −10.3%; P < 0.0001).

Mental Health and HRQOL

Mental health and HRQOL were not assessed in CB-03-01/25 or CB-03-01/26.

Harms Results

The safety profile of clascoterone was similar between the treatment groups for both pivotal trials. In CB-03-01/25 and CB-01-03/26, respectively, 40 (11.3%) and 42 (11.4%) patients who received clascoterone experienced treatment-emergent adverse events (TEAEs) compared to 41 (11.5%) and 50 (13.8%) patients who received the vehicle.

Overall, 1 patient each in CB-03-01/25 and CB-03-01/26 reported a serious adverse event (SAE). In CB-03-01/25, 1 patient (0.3%) in the vehicle group had a SAE of pneumonia. In CB-03-01/26, 1 patient (0.3%) in the vehicle group had a SAE of hematoma.

In CB-03-01/25, there were 9 patients who experienced 9 TEAEs that led to study discontinuation: 3 (0.8%) patients in the clascoterone group and 6 (1.7%) patients in the vehicle group. In CB-03-01/26, 10 patients (1.4%) discontinued due to TEAEs, including 2 (0.5%) patients treated with clascoterone, and 8 (2.2%) patients treated with vehicle.

No deaths were reported in CB-03-01/25 or CB-03-01/26.

In CB-03-01/25 and CB-03-01/26, incidence of LSRs (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling or dryness, stinging or burning, and pruritus) was similar across treatment groups. In CB-03-01/25, 52.6% of patients in the clascoterone group and 54.0% of patients in the vehicle group experienced LSRs. In CB-03-01/26, 55.3% of patients in the clascoterone group and 53.3% of patients in the vehicle groups experienced LSRs. The most notable treatment-emergent LSR in terms of frequency was erythema in both pivotal trials.

Critical Appraisal

There was no notable difference between treatment arms or baseline characteristics in either pivotal trial. Discontinuation was largely driven by patients who were lost-to-follow-up and who chose to withdraw. Missing data in the primary end points were imputed using a multiple imputation approach under the missing at random assumption. The missing at worst-value analyses were not consistent with the primary analysis for absolute change in ILC and NILC. The amount of missing data was considered relatively high in both the clascoterone and vehicle group in both trials (18% to 22%) at week 12. The majority of patients who discontinued dropped out at the beginning of the study period (before visit 2) across both trials, and since patient drop-out was likely driven by lack of response, the multiple imputation approach to account for missing data in the primary analysis may not be sufficient to address this missing data mechanism. Therefore, there was potential for bias due to the amount of missing data in the efficacy results at week 12 and based on results from sensitivity analysis, the true effect of clascoterone on NILC and ILC may be overestimated in the primary analysis. Some secondary end points were not adjusted for multiple comparisons, hence no definitive conclusions can be drawn due to failure of statistical comparison in a prior end point in the testing hierarchy.

Clascoterone is indicated for patients 12 years of age and older, though the data reported in the Clinical Review Report are for patients 9 years of age and older. When comparing the 2 data sets (from the product monograph and the clinical study reports), there were no changes to statistical significance that would meaningfully change conclusions on efficacy or harms. Moreover, the clinical expert consulted for this review highlighted that the number of patients aged 9 to 11 years old who were included in the trials was small and likely had a negligible effect on the study results. Clascoterone is indicated for patients with acne and is not limited by severity of the condition. The pivotal trials for clascoterone included patients with moderate to severe acne; however, the clinical expert felt that the results would still be generalizable to patients with mild acne. The clinical expert indicated that a treatment that is effective for moderate to severe acne would also be expected to show efficacy in patients with mild acne as well. Moreover, a notable group of patients with severe acne (i.e., nodulocystic acne) were excluded from both trials. Hence, the sample population in

the trials may not fully represent the general population of patients with severe acne seen in clinical practice in Canada. The clinical expert felt that 12 weeks of follow-up was a reasonable and standard time point across acne trials and would be considered the earliest time point at which a meaningful change in lesion numbers would be observed. However, the clinical expert noted that the optimal time point for follow-up for the end point of change in NILC would be 6 months. In addition, the clinical expert did note that lesion counts are not relevant to clinical practice as lesion counts are subjective, and it is not feasible for clinicians to be counting lesions. Instead, the clinical expert felt that the patient's impression of change and the percentage change in lesion count was considered more clinically relevant.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for efficacy end points and notable harms (i.e., LSRs) were set according to the presence or absence of an important effect based on thresholds informed by the clinical expert.

For the GRADE assessments, findings from CB-03-01/25 and CB-03-01/26 were considered together and summarized narratively by outcome because these studies were identical in population, interventions, design, and outcome measures.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with the clinical expert, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Global success as measured by the proportion of patients 12 years of age or older achieving success, defined as an IGA score of clear (0) or almost clear (1) and a 2-point or greater reduction in the IGA scale compared with baseline.
- Lesion counts (absolute change from baseline in NILC, ILC, and TLC; percent change from baseline in NILC, ILC, and TLC)
- Mental health and HRQoL (change from baseline in mental health according to the dermatology life quality index and Cardiff Acne Disability Index)
- Notable Harms: LSRs, fertility issues, hypothalamic-pituitary-adrenal axis suppression

Results of GRADE Assessments

Table 1 presents the GRADE summary of findings for clascoterone 1% cream versus vehicle cream.

Table 1: Summary of Findings for Clascoterone versus Vehicle for Patients with Acne

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)	Certainty	What happens
Global Success					
Proportion of patients with treatment success as defined by an IGA score of clear (0) or almost clear (1) and a 2-point or greater reduction in the IGA scale compared with baseline Follow-up: 12 weeks	N = 1,440 (2 RCTs)	**CB-03-01/25:** OR 2.36 (1.43 to 3.88) **CB-03-01/26:** OR 3.8 (2.2 to 6.4)	**CB-03-01/25:** • Clascoterone: 188 per 1,000 • Vehicle: 89 per 1,000 • Difference: 99 more per 1,000 (50 more to 152 more per 1,000) **CB-03-01/26:** • Clascoterone: 208 per 1,000 • Vehicle: 65 per 1,000 • Difference: 143 more per 1,000 (94 more to 192 more per 1,000)	Moderate[a]	Clascoterone likely results in an increase in the proportion of patients with treatment success as measured by the IGA when compared with vehicle cream.
Lesion Count					
Absolute change in NILC Follow-up: 12 weeks	N = 1,440 (2 RCTs)	NR	**CB-03-01/25:** • Clascoterone: 19.4 fewer lesions • Vehicle: 13.1 fewer lesions • Difference: 6.3 fewer lesions (10.2 fewer to 2.4 fewer) **CB-03-01/26:** • Clascoterone: 19.4 fewer lesions • Vehicle: 10.9 fewer lesions • Difference: 8.4 fewer lesions (12.4 fewer to 4.5 fewer)	Very low[b]	The evidence is very uncertain about the effect of clascoterone on absolute change in NILC when compared with vehicle cream.
Percent change in NILC Follow-up: 12 weeks	N = 1,440 (2 RCTs)	NR	**CB-03-01/25:** • Clascoterone: −30.7% • Vehicle: −21.6% • Difference: −8.8% (−15.9% to −1.8%)[c] **CB-03-01/26:** • Clascoterone: −29.3% • Vehicle: −15.8% • Difference: −13.5% (−19.8% to −7.1%)[c]	Very low[b]	The evidence is very uncertain about the effect of clascoterone on percent change in NILC when compared with vehicle cream.
Absolute change in ILC Follow-up: 12 weeks	N = 1,440 (2 RCTs)	NR	**CB-03-01/25:** • Clascoterone: 19.4 fewer lesions • Vehicle: 15.5 fewer lesions • Difference: 3.9 fewer lesions (6.5 fewer to 1.3 fewer)	Low[d]	Clascoterone may result in little to no difference in absolute change in ILC when compared with vehicle cream.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)	Certainty	What happens
			CB-03-01/26 • Clascoterone: 20.0 fewer lesions • Vehicle: 12.6 fewer lesions • Difference: 7.4 fewer lesions (9.8 fewer to 5.0 fewer)		
Percent change in ILC Follow-up: 12 weeks	N = 1,440 (2 RCTs)	NR	**CB-03-01/25:** • Clascoterone: −44.8% • Vehicle: −36.6% • Difference: −8.3% (−14.3% to −2.3%)[c] **CB-03-01/26:** • Clascoterone: −47.0% • Vehicle: −29.8% • Difference: −17.2% (−22.9% to −11.5%)[c]	Very low[d]	The evidence is very uncertain about the effect of clascoterone on percent change in ILC when compared with vehicle cream.
Absolute change in TILC Follow-up: 12 weeks	N = 1,440 (2 RCTs)	NR	**CB-03-01/25:** • Clascoterone: 39.2 fewer lesions • Vehicle: 28.9 fewer lesions • Difference: 10.3 fewer lesions (15.7 fewer to 5.0 fewer)[c] **CB-03-01/26:** • Clascoterone: 40.3 fewer lesions • Vehicle: 23.7 fewer lesions • Difference: 16.6 fewer lesions (22.0 fewer to 11.1 fewer)[c]	Very low[d]	The evidence is very uncertain about the effect of clascoterone on absolute change in TILC when compared with vehicle cream.
Percent change in TILC Follow-up: 12 weeks	N = 1,440 (2 RCTs)	NR	**CB-03-01/25:** • Clascoterone: −37.1% • Vehicle: −28.5% • Difference: −8.7% (−14.0% to −3.3%)[c] **CB-03-01/26:** • Clascoterone: −37.7% • Vehicle: −22.2% • Difference: −15.6% (−20.9% to −10.3%)[c]	Very low[d]	The evidence is very uncertain about the effect of clascoterone on percent change in TILC when compared with vehicle cream.
Mental Health (HRQoL)					
Mental health (e.g., DLQI)	NA	No data available.	No data available.	NA	There is no evidence for the effect of clascoterone on mental health.
Harms					
Proportion of patients with ≥ 1 LSR	N = 1,421 (2 RCTs)	NA	**CB-03-01/25:** There were 52.6% of patients in the clascoterone arm and 54.0% of patients in the vehicle arm who experienced a LSR. Difference: 1.4% in favour of clascoterone (95% CI, −8.8% to 6.1%)	Moderate[e]	Clascoterone likely results in little to no difference in LSRs when compared with vehicle cream.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)	Certainty	What happens
			CB-03-01/26: There were 55.3% of patients in the clascoterone arm and 53.3% of patients in the vehicle arm who experienced a LSR. Difference: 2.0% in favour of vehicle cream (95% CI, −5.2% to 9.2%)		

CI = confidence interval; DLQI = Dermatology Life Quality Index; IGA = investigator's global assessment; ILC = inflammatory lesion count; LSR = local skin reactions; NA = not applicable; NILC = non-inflammatory lesion count; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; TLC = total lesion count.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] –1 level for serious indirectness as the treatment assessment scheduled was not reflective of clinical practice based on clinical expert input noting that meaningful change is unlikely to be observed until at least 6 months, thus limiting generalizability to clinical practice in Canada.

[b] –1 level for serious study limitations. This is due to high rates of missing data with insufficient accounting for the likely missing data mechanism. –1 level for serious indirectness as the treatment assessment scheduled was not reflective of clinical practice based on clinical expert input noting that meaningful change is unlikely to be observed until at least 6 months thus limiting generalizability to clinical practice in Canada. –1 level for serious imprecision. The clinical expert identified MID (10 lesions) threshold was not met; CI for difference between groups includes possibility of no difference.

[c] Statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[d] –1 level for serious study limitations. This is due to high rates of missing data with insufficient accounting for the likely missing data mechanism. –1 level for serious indirectness as the treatment assessment scheduled was not reflective of clinical practice based on the clinical expert input noting that meaningful change is unlikely to be observed until at least 6 months thus limiting generalizability to clinical practice in Canada. The outcome of percent change in ILC and NILC was –1 level for serious inconsistency. The 95% CI for the difference included the threshold for clinical meaningfulness (reduction of lesion by 10%), which was compatible with both a benefit and little to no difference.

[e] –1 level for serious study limitations. This is due to high rates of missing data with insufficient accounting for the likely missing data mechanism. –1 level for serious indirectness. This is due to limitations in generalizability to clinical practice in Canada.

Source: Clinical Study Reports for CB-03-01/25 and CB-03-01/26 and Additional Information Request August 28, 2023. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

CB-03-01/27 was a multicentre, open-label, LTE study following CB-03-01/25 and CB-03-01/26. The primary objective was to determine the long-term safety of clascoterone cream, applied twice daily (morning and evening) for an additional 9 months in patients with acne who participated in the phase 3 studies for a total treatment time of up to 12 months. For patients assigned to the vehicle cream in the pivotal trials, the total duration of treatment was 9 months. The end points for the primary objective were systemic and local TEAEs including LSRs (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling or dryness, stinging or burning, and pruritus). The number of patients with each IGA severity score was the efficacy end point. The study consisted of a baseline visit, long-term follow-up visits at months 1, 3, 6, and 9, and follow-up phone calls at months 4.5 and 7.5.

Efficacy Results

The majority (83.1%) of patients showed facial IGA scores that were mild or moderate in severity at baseline, with the overall proportion of patients who were clear or almost clear increasing over time being greatest (ITT: 181/609, 29.7%) at the end of the study (day 274). The proportion of patients who were clear or almost clear increased over time with clascoterone, from 9.9% at baseline to 29.7% at day 274. A similar proportion of patients originally assigned to vehicle (ITT: 30.2%) and clascoterone (ITT: 29.3%) in the pivotal studies had clear or almost clear skin on the face at the end of the study at day 274. A similar trend has been observed in patients whose trunks had been treated with clascoterone during the LTE period.

Harms Results

Of 607 patients in the Safety set, 110 (18.1%) patients experienced at least 1 TEAE. The only TEAEs reported for at least 1.0% of patients were nasopharyngitis (2.6%) and upper respiratory tract infection (1.3%). Six patients experienced serious TEAEs: coronary artery dissection, depression and suicide attempt, dizziness, eosinophilic gastroenteritis, fatigue, and induced abortion. Ten (1.7%) patients discontinued study drug due to TEAEs, 9 of whom discontinued the study due to the TEAEs. Overall, the most frequently reported LSRs were erythema (6.9% on the face, 1.2% on the trunk), scaling or dryness (4.0% on the face, 0.7% on the trunk), and pruritus (1.6% on the face, 0% on the trunk). According to the clinical expert consulted by CADTH, atrophy (5% in the clascoterone group versus 1% in the vehicle group) was another noteworthy LSR.

Critical Appraisal

Based on the LTE results and discussion with the clinical expert consulted by CADTH, clascoterone 1% cream appears to be safe when used for up to 1 year of treatment. According to the clinical expert, among TEAEs that occurred more frequently in the clascoterone cohort compared to the vehicle cohort, skin atrophy (5% in the clascoterone group versus 1% in the vehicle group) seems to be the most noteworthy event. Even though the effectiveness of clascoterone 1% cream seems to be maintained long-term, the long-term study was not randomized and no formal statistical testing for efficacy outcomes (which were not primary objectives) had been conducted. Furthermore, there was no true comparator tested during the LTE period. Also, there may be a selection bias as those who have benefitted from clascoterone treatment during the 12-week pivotal trials were more likely to continue and high adherence rate (greater than 80%) was an inclusion criterion for the LTE study, which could overestimate the treatment effect. Another concern is high attrition rate. For example, at 9 months, about 20% of patients remained in the LTE study. It is uncertain how this attrition rate affects the long-term results of safety and/or effectiveness of clascoterone treatment. Lastly, treatment effects on patients' HRQoL have not been assessed even though impact of acne on HRQoL seems to be significant based on patient group input. As for external validity, since patients were rolled over from the pivotal trials, the same generalizability concerns apply to the LTE study.

Indirect Comparisons

Description of Studies

CADTH appraised a systematic review and NMA submitted by the sponsor. The reference case NMAs compared clascoterone with benzoyl peroxide (2.5% cream/3.1% gel or 5% cream; applied once daily), tretinoin (0.025% cream, 0.04% gel/0.05% cream; once daily), tazarotene (0.045% gel/0.1% cream; once daily), adapalene (0.1% cream/0.15% gel or 0.3% cream; once daily), and

trifarotene (0.005%; once daily). Sensitivity and scenario analyses consider additional comparators (i.e., oral contraceptives, topical or oral spironolactone, clindamycin phosphate 1.2% gel and clindamycin 1% cream, erythromycin 1.5% cream, and combinations) in terms of effects at 12 weeks on inflammatory lesions, noninflammatory lesions and study discontinuations for any reason. Scenario analyses were also presented as sensitivity analyses that considered additional treatments (combination therapies, spironolactone, oral contraceptives).

Efficacy Results

Reference case NMAs for changes in ILCs and NILCs at 12 weeks consisted of 8 treatment nodes,19 RCTs and 12,226 patients. Findings from random effects (RE) Bayesian NMAs regarding inflammatory lesions found clascoterone (–5.2; 95% credible interval [CrI], –7.2 to –3.2) and all other active treatments in the network to be associated with a greater impact on reduction of inflammatory lesions compared to placebo, while comparisons between active treatments showed no treatment was favoured based on inspection of 95% CrIs. Interpretations from an RE NMA investigating changes in noninflammatory lesions were similar.

Harms Results

Comparison of study discontinuations for any reason at 12 weeks after randomization was also performed using RE Bayesian NMA. Clascoterone displayed a similar frequency of discontinuation compared to placebo (risk ratio [RR] = 0.90; 95% CrI, 0.72 to 1.10), as did most active treatments. Comparisons of clascoterone with other active treatments found no important differences, with the exception of a reduced frequency of discontinuation when compared to tazarotene 1% (RR = 0.71; 95% CrI, 0.53 to 0.94).

Critical Appraisal

The sponsor's submitted NMA used recommended methods for conducting and reporting of NMAs and demonstrated similar benefits relative to other available treatments, though certain limitations were noted. The NMAs appeared to include study populations that ranged broadly from mild to severe acne based on mean baseline lesion counts, which introduced challenges to interpretation of the findings from the NMA as well as concerns that the validity of treatment effects measuring absolute changes in lesion count could be impacted. Variability of placebo or vehicle group responses across trials was not described in detail, and thus the appropriateness of combining these groups for the purposes of NMA was unclear. Methods to identify effect modifiers of interest to judge appropriateness of the transitivity assumption were unclear, and the effects of differences between study populations between certain effect modifiers (duration of acne, severity of acne, previous treatments) could not be addressed due to limited reporting from the included trials. Input from the clinical content expert suggested that certain additional treatments (oral antibiotics, isotretinoin, topical dapsone, combination treatments) could have been included in reference case analyses. Findings from NMAs should thus be interpreted with some degree of caution.

Studies Addressing Gaps in the Systematic Review Evidence

No other studies addressing gaps in the systematic review evidence were submitted for this review.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target populations	Health Canada indication: Topical treatment of acne vulgaris in patients 12 years of age and older Reimbursement request: First-line prescription topical treatment of moderate and severe acne vulgaris in patients 12 years of age and older.
Treatment	Clascoterone 1% cream
Dose regimen	The recommended dose per application is up to approximately 1 gram, applied in a thin uniform layer twice per day

Component	Description
Submitted price	30g tube: $242.42
Submitted treatment cost	Incorporating a prescription refill rate, the sponsor's estimated cost was $584 per patient per year

Comparators	• Topical monotherapies
	  ○ Benzoyl peroxide 5%
	  ○ Tazarotene 0.1%
	  ○ Tretinoin 0.025%, 0.05%, and 0.04%
	  ○ Adapaline 0.1% and 0.3%
	• Oral contraceptives
	  ○ Cyproterone acetate and ethinyl estradiol
	  ○ Desogestrel and ethinyl estradiol
	  ○ Drospirenone and ethinyl estradiol
	  ○ Levonorgestrel and ethinyl estradiol
	  ○ Norgestimate and ethinyl estradiol
	• Spironolactone 100 mg

Perspective	Canadian publicly funded health care payer
Time horizon	One year
Key data source	CB-03-01/25 and CB-03-01/26 pivotal randomized controlled trials comparing clascoterone cream to vehicle. One sponsor-commissioned network meta-analysis report, consisting of indirect treatment comparisons exploring 12 analyses in total.
Costs considered	Drug acquisition costs
Key limitations	• The place in therapy for clascoterone cream is uncertain. The sponsor requested reimbursement as first line monotherapy of moderate and severe acne vulgaris, while clinical expert input suggests its appropriate use would be as monotherapy in mild acne or as part of combination therapy with a variety of other treatments for moderate acne. As a result, there is uncertainty regarding the most appropriate comparators for clascoterone cream. • The assumption of clinical similarity between clascoterone cream, topical monotherapies, oral contraceptives, and spironolactone is uncertain due to heterogeneity identified in patient populations, response rates to placebo or vehicle, and baseline disease severity in the sponsor-conducted ITCs. No trials directly comparing clascoterone cream to active therapies were available. • The annual costs of clascoterone cream and its comparators as estimated by the sponsor are based on usage ratios inconsistent with the clinical trials in the ITC, and thus inconsistent with the evidence underlying the assumption of clinical similarity. • Some comparators were incorrectly priced given the availability of generic products or being from a source including markups. Some list prices had changed since the sponsor's submission. Additionally, the sponsor's analysis used a 60% adherence rate for oral contraceptives and spironolactone, which was inconsistent with clinical expert opinion obtained by CADTH.
CADTH reanalysis results	• CADTH revised the annual usage of clascoterone cream to be consistent with a 60% adherence to clinical trial dosing as assumed for all other topical comparators, revised the adherence rate of oral contraceptives and spironolactone to be 100%, and updated the unit costs of several comparators. CADTH was unable to address uncertainty in the clinical efficacy and safety of clascoterone cream relative to its comparators, nor the uncertainty in the place in therapy of clascoterone cream. • At an average annual cost of $3,539 per patient, clascoterone cream is more costly than treatment with any of the included topical monotherapies (incremental costs ranged from $2,862 to $3,492 per patient), and also more costly than oral contraceptives or spironolactone (incremental costs ranged from $3,235 to $3,525 per patient). At the submitted price, and based

Component	Description
	on public list prices for all comparators, the price of clascoterone cream would need to be reduced by 98.7% to equal that of the least expensive topical comparator.

Budget Impact

CADTH identified several limitations with the sponsor's analysis: there was uncertainty with the claims-based approach and the sponsor's methodology for assessing the budget impact; the annual cost and market uptake of clascoterone cream were inappropriately estimated; the full costs associated unfunded comparators were inappropriately included from a public drug plan payer perspective; some comparators were inappropriately priced; there was ucertainty in the market share and displacement of hormone therapies; and there was uncertainty in the applicability of the included comparators and their market share to the reimbursement request population.

CADTH reanalyses included correcting the assumed adherence rate for hormone therapies to be 100%, adjusting the annual per patient cost of clascoterone cream, adjusting the average costs paid by public plans for comparators rarely publicly reimbursed, and adjusting the unit costs of some comparators to reflect updated costs paid by public plans.

CADTH reanalyses suggest that for the Health Canada indicated population of patients with acne vulgaris aged 12 years and older, the reimbursement of clascoterone cream would be associated with an incremental cost of $5,338,439 in Year 1, $17,540,587 in Year 2, and $26,692,197 in Year 3, for a three-year budget impact of $49,571,223. When considering only patients with moderate and severe acne, CADTH reanalyses estimates a potential three-year budgetary impact of $31,229,870.

CADTH was unable to address limitations with the sponsor's claims-based approach, and thus the resulting budgetary impact is considered uncertain.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: September 25, 2024

Regrets:

2 expert committee members did not attend.

Conflicts of interest:

None