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Reimbursement Recommendation

Clascoterone (Winlevi)

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

Sponsor: Sun Pharma Canada Inc.

Final recommendation: Do not reimburse

Summary

What Is the Reimbursement Recommendation for Winlevi?

Canada's Drug Agency (CDA-AMC) recommends that Winlevi not be reimbursed by public drug plans for the topical treatment of acne vulgaris in patients aged 12 years and older.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Winlevi increased the rate of treatment success (assessed using a measure of overall acne severity) compared with its vehicle cream (without active ingredient).
- Patients identified a need for treatments that improve skin clearance (i.e., reduce the number of acne lesions and prevent scarring) and health-related quality of life (HRQoL). However, based on the evidence reviewed in the initial meeting and the reconsideration meeting, the Canadian Drug Expert Committee (CDEC) could not determine if Winlevi would address the unmet needs relative to other active treatments. This uncertainty stems from missing data, a lack of HRQoL data, and uncertainty about whether the results were clinically meaningful. There were limitations in the submitted indirect evidence that also made it uncertain how Winlevi compares to other acne treatments in terms of efficacy and tolerability.

Additional Information

What Is Acne Vulgaris?

Acne vulgaris is a skin condition characterized by noninflammatory lesions (e.g., blackheads and whiteheads) and inflammatory lesions (e.g., pimples and nodules) that usually appear on the face, neck, upper back, and chest. Acne affects about 5.6 million people in Canada.

Unmet Needs in Acne Vulgaris

Patients and clinicians identified a need for access to effective and safe treatment options that improve skin clearance, prevent acne scarring and pigmentation, are nonirritating, work quickly, and improve quality of life.

How Much Does Winlevi Cost?

Treatment with Winlevi is expected to cost up to $5,899 per patient per year.

Recommendation

CDEC recommends that clascoterone not be reimbursed for the topical treatment of acne vulgaris in patients aged 12 years 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 HRQoL. CDEC noted that, compared to vehicle cream, clascoterone could provide an additional treatment option that may reduce acne lesions and reduce irritative side effects. However, CDEC could not substantiate that clascoterone meets many of the unmet needs relative to other acne treatments, including improving skin clearance, reducing 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 OR = 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 noninflammatory lesion counts (NILCs), inflammatory lesion counts (ILCs), and total lesion counts (TLCs) — were statistically significant in the pivotal trials compared to the vehicle cream, the evidence was uncertain because of a high level of missing data, and the results did not reach the threshold for a minimally clinical important difference compared to the 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-analysis (NMA), namely heterogeneous populations and missing comparators, which prevented CDEC from drawing firm conclusions on the comparative efficacy and tolerability of clascoterone versus other active treatments.

Discussion Points

- **Reconsideration request:** The sponsor requested a reconsideration of the initial draft recommendation to not reimburse clascoterone for the topical treatment of acne vulgaris in patients

aged 12 years and older. The 5 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC included reconsidering the Grading of Recommendations Assessment, Development and Evaluation (GRADE) of evidence based on the GRADE results by the American Academy of Dermatology (AAD) working group, the variability in what constitutes a clinically important difference in acne treatment, engagement of clinical expertise for the refiled submission, addressing the variability in assessment criteria between acne reviews with regards to generalizability concerns specifically related to the appropriateness of a 12-week time frame for outcomes and the recognition of lesion counts as a valid measure in current clinical practice in Canada, as well as consideration for the real-world experience of clascoterone, as described in the clinician group input.

- **Unmet needs:** During the initial meeting and the reconsideration meeting, CDEC discussed the 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 because of 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 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 end points in the CB-03-01/25 and CB-03-01/26 trials. During the reconsideration meeting, CDEC discussed the feedback on the draft recommendation from the sponsor and clinician groups that emphasized improvements in HRQoL and self-confidence based on experience; however, CDEC maintained that there were no data to support these claims as these outcomes were not evaluated in the submitted evidence package provided by the sponsor. CDEC, as well as the patient and clinician group 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. These issues were also discussed at the reconsideration meeting and CDEC upheld its initial conclusion that it is uncertain whether clascoterone addressed the unmet needs identified within this review.
- **Certainty of evidence:** During the initial meeting and the reconsideration meeting, CDEC discussed the GRADE assessment of outcomes selected for the review of clascoterone, particularly for treatment success and lesion count outcomes. The committee acknowledged that IGA may be a more clinically relevant outcome compared to lesion counts; however, clinical expert input indicated that neither measure is typically used in practice. While the results for IGA were statistically significant in favour of clascoterone over the 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% versus 8.9%; OR = 2.36 [95% CI, 1.4 to 3.9] and 20.8% versus 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. CDEC also discussed the certainty of the evidence for changes in lesion counts (NILC, ILC, and TLC) in the CB-03-01/25 and

CB-03-01/26 trials, which was considered very low or low due to high levels of missing data (ranging from 18% to 22%), and the inability of clascoterone to consistently reach the identified threshold of minimally clinically important difference of 10% (percent change in NILC, ILC, and TILC of –8.8%, –8.3%, and –8.7% in the CB-03-01/25 trial and –13.5%, –17.2%, and –15.6% in the CB-03-01/26 trial, respectively) defined in the GRADE assessment. During the reconsideration meeting, CDEC and the clinical expert discussed minimally important difference thresholds for treatment success and lesion count outcomes. The clinical expert noted that minimally important differences are patient-specific and may be closer to 20% or 30% (something that was also cited by the clinician group input), which were not achieved by clascoterone over the vehicle cream for these outcomes. During the reconsideration meeting, CDEC also discussed the GRADE assessments conducted by AAD — which recently added a conditional recommendation for the use of clascoterone based on a high certainty of evidence rating, but conditional given the high cost of the drug — however, CDEC noted that the reason for any differences in GRADE assessments between CDA-AMC and AAD were unclear as no rationale supporting the certainty of evidence was provided by the AAD guidelines.

- **Indirect evidence:** CDEC noted that there are many effective treatment options available for patients with acne vulgaris. The committee discussed the uncertainty with the comparative efficacy of clascoterone due to the absence of direct comparative evidence. CDEC discussed the sponsor-submitted NMA 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 noted that patients weigh the adverse effects associated with treatment against effectiveness when deciding to start, stop, or continue their acne therapy. The clinical expert consulted on this review noted that, based on their clinical experience with clascoterone, the drug is well tolerated and reduces dryness, which is likely due to it having a cream base. During the reconsideration meeting, CDEC also discussed the clinician group feedback on the draft recommendation that also supported claims of the drug's tolerability. The 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 its comparative safety versus other acne treatments.
- **Generalizability:** During the initial meeting and the reconsideration meeting, CDEC discussed the generalizability concerns associated with clascoterone. CDEC and the clinical expert consulted for this review discussed the treatment duration of 12 weeks; the clinical expert noted that some improvements may be observed at 3 months, but a clinically meaningful change in outcomes is unlikely until 6 months (based on clascoterone's mechanism of action), particularly for NILC. However, any potential benefits of clascoterone over the vehicle cream beyond 12 weeks were not evaluated in the sponsor-submitted evidence. With respect to clinical trial duration, and in terms of

harms (i.e., localized skin reactions, the mechanism of action, and the cream base were highlighted), the 12-week duration was considered reasonable to align with other trials of acne therapies. Further, at both the initial and reconsideration meetings, CDEC discussed the impracticality of absolute lesion counts in real-world clinical practice, citing the clinical expert consulted for this review, who emphasized that overall improvement (i.e., treatment success) is more accepted in clinical practice.

- **Supportive studies:** CDEC also discussed 1 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 (e.g., back, chest, upper arms), type and number of lesions (e.g., 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 1 of the most common dermatological disorders worldwide and affects 5.6 million people living in Canada. Although it predominantly affects the adolescent population (approximately 80%), it can also affect preadolescents (aged 7 to 12 years) and postadolescents. 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 for acne vulgaris 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 antiandrogen for females (e.g., combined oral contraceptive or spironolactone). According to the updated 2024 AAD 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, while hormonal drugs (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 treatment-resistant recalcitrant acne), 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 postinflammatory hyperpigmentation and scarring. The main therapies currently used for acne are aimed at reducing the 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 aged 12 years and older. Clascoterone is an androgen receptor inhibitor that is available as a 10 mg/g cream and the dosage recommended per application in the product monograph is approximately 1 g 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 the public drug plans that participate in the CDA-AMC 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
- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups that responded to the CDA-AMC call for input and from the clinical expert consulted by CDA-AMC 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 and diagnosed with acne. ARSC comprises dermatologists, patients, educators, and communicators who provide information and raise awareness about the disease. CSPA strives to improve the lives of people affected by skin, hair, and nail conditions through collaboration, advocacy, and education.

The 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. The 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 people with acne feel they have poor health overall. Furthermore, the patient groups said these factors impede their ability to be social and conduct daily activities (e.g., forming friendship and dating, avoiding social interaction, and being seen on camera, swimming, and in changerooms where patients must 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 makeup, which increase with acne severity (i.e., 4% of patients with mild acne, 5% of patients with moderate acne, and 14% of overall respondents were 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 the financial burden. 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, the ability to be social, and improved overall quality of daily life.

To improve their lives, respondents want increased access to new treatments that are safe and effective, health care providers to be aware of all the new and existing treatment options for acne, and evaluations for depression and anxiety that could help them get support.

Three individuals who had experience with clascoterone felt that their acne was well controlled with the drug (also resulting in greater confidence) and noted that they did not experience the typical side effects associated with topical treatments for acne with clascoterone. 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 CDA-AMC

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 poor treatment adherence. 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 for 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 as 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 for severe acne. The clinical expert noted that clascoterone could potentially be used in combination with oral contraceptives or spironolactone in females 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 who are receiving monthly isotretinoin treatment. 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 vary, 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 are 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 CDA-AMC 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 CDA-AMC 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 CDA-AMC. 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 the input received

from the clinical expert consulted by CDA-AMC, 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 a 2-point (or even 1-point) reduction in IGA score. Additionally, DAO suggested that transmasculine, gender minority, and mature patient (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 regards to 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 CDA-AMC reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CDA-AMC 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.

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.

The CB-03-01/25 trial was conducted primarily in the US and the CB-03-01/26 trial was conducted primarily in Europe. Neither trial had any study sites in Canada. In the CB-03-01/25 trial, 708 patients were randomized to treatment with either clascoterone 1% cream (N = 353) or the vehicle cream (N = 355). In the CB-03-01/26 trial, 732 patients were randomized to treatment with either clascoterone 1% cream (N = 369) or the vehicle cream (N = 363). In the CB-03-01/25 trial, the median age for both treatment groups was 18 years (range, 9 to 58 years) and in the CB-03-01/26 trial, the median age for both treatment groups was 18 years (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; they consisted of the following study periods:

- Screening phase: visit 1
- Treatment phase: 12 weeks (with 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 (i.e., papules, pustules, and nodules), and at least 30 to a maximum of 100 noninflammatory lesions (i.e., 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; if were planning to be or needed to be exposed to artificial tanning devices or excessive sunlight during the trial; or 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 the CB-03-01/25 trial 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 the vehicle cream (range, 30 to 83), mean NILC was 59.1 lesions for clascoterone and 60.7 lesions for the vehicle cream (range, 30 to 144), and mean TLC was 101.5 lesions for clascoterone and 103.6 lesions for the vehicle cream (range, 60 to 196). In the CB-03-01/26 trial, 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 the clascoterone group and 41.3 lesions in the 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 the CB-03-01/25 trial, 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 the CB-03-01/26 trial, 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. The results of the last observation carried forward and baseline outcome carried forward analyses confirmed the robustness of the results obtained from the ITT set for the primary efficacy end points.

Lesion Counts

Absolute Change From Baseline in NILC at Week 12

In the CB-03-01/25 trial, a greater absolute decrease from baseline in NILC was seen in patients treated with clascoterone (–19.4 lesions) compared to patients treated with the vehicle cream (–13.1 lesions) at week 12 (–6.3 lesion difference between treatment groups; 95% CI, –10.2 to –2.4 lesions; P = 0.0016). Similarly, in the CB-03-01/26 trial, 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 lesion 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, the results of the worst-value and worst-case analysis were inconsistent with the results obtained on the ITT set for this outcome. The results of the last observation carried forward and baseline outcome carried forward analyses confirm the robustness of the results obtained from the ITT set for the primary efficacy end points.

Percent Change in NILC From Baseline at Week 12

In the CB-03-01/25 trial, 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 the CB-03-01/26 trial, the percent change from baseline to week 12 was greater in the clascoterone group than in 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 the CB-03-01/25 trial, 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 the CB-03-01/26 trial, 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, the results of the worst-value and worst-case analysis were inconsistent with the results obtained from the ITT set for this outcome in the CB-03-01/25 trial and the results of the worst-case analysis were inconsistent with the results obtained from the ITT set for this outcome in the CB-03-01/26 trial.

Percent Change in ILC From Baseline at Week 12

In the CB-03-01/25 trial, the percent change from baseline to week 12 was greater in the clascoterone group than in 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 the CB-03-01/26 trial, the percent change from baseline to week 12 was greater in the clascoterone group than in 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 the CB-03-01/25 trial, the absolute change from baseline to week 12 was greater in the clascoterone group than in 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 the CB-03-01/26 trial, the absolute change from baseline to week 12 was greater in the clascoterone group than in 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 the CB-03-01/25 trial, the percent change from baseline to week 12 was greater in the clascoterone group than in 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 the CB-03-01/26 trial, the percent change from baseline to week 12 was greater in the clascoterone group than in 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 the CB-03-01/25 and CB-03-01/26 trials.

Harms Results

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

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

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

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

In the CB-03-01/25 and CB-03-01/26 trials, incidence of local skin reactions (LSRs) (i.e., telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling or dryness, stinging or burning, and pruritus) was

similar across treatment groups. In the CB-03-01/25 trial, 52.6% of patients in the clascoterone group and 54.0% of patients in the vehicle group experienced an LSR. In the CB-03-01/26 trial, 55.3% of patients in the clascoterone group and 53.3% of patients in the vehicle group experienced an LSR. 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 groups 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; as patient dropout was likely driven by a 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 the results from the 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 aged 12 years and older, though the data reported in the clinical review report are for patients aged 9 years and older. When comparing the 2 datasets (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 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 there are no limitations 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. 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 noted 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 the outcomes considered most relevant to inform the CDA-AMC 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, the findings from the CB-03-01/25 and CB-03-01/26 trials 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 the patient and clinician groups and the public drug plans. The following list of outcomes was finalized in consultation with the expert committee members:

- global success as measured by the proportion of patients aged 12 years or older who achieved 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 the 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 the vehicle cream.

Table 1: Summary of Findings for Clascoterone vs. Vehicle for Patients With Acne

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects	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 score 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-03-1/25:** • Clascoterone = 188 per 1,000 • Vehicle = 89 per 1,000 • Difference = 99 more per 1,000 (95% CI, 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 (95% CI, 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 the 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 (95% CI, 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 (95% CI, 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 the 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% (95% CI, −15.9% to −1.8%)[c] **CB-03-01/26:** • Clascoterone = −29.3%	Very low[b]	The evidence is very uncertain about the effect of clascoterone on percent change in NILC when compared with the vehicle cream.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects	Certainty	What happens
			• Vehicle = −15.8% • Difference = −13.5% (95% CI, −19.8% to −7.1%)[c]		
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 (95% CI, 6.5 fewer to 1.3 fewer) **CB-03-01/26:** • Clascoterone = 20.0 fewer lesions • Vehicle = 12.6 fewer lesions • Difference = 7.4 fewer lesions (95% CI, 9.8 fewer to 5.0 fewer)	Low[d]	Clascoterone may result in little to no difference in absolute change in ILC when compared with the vehicle cream.
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% (95% CI, −14.3% to −2.3%)[c] **CB-03-01/26:** • Clascoterone = −47.0% • Vehicle = −29.8% • Difference = −17.2% (95% CI, −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 the vehicle cream.
Absolute change in TLC 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 (95% CI, 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 (95% CI, 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 TLC when compared with the vehicle cream.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects	Certainty	What happens
Percent change in TLC Follow-up: 12 weeks	N = 1,440 (2 RCTs)	NR	**CB-03-01/25:** • Clascoterone = −37.1% • Vehicle = −28.5% • Difference = −8.7% (95% CI, −14.0% to −3.3%)[c] **CB-03-01/26:** • Clascoterone = −37.7% • Vehicle = −22.2% • Difference = −15.6% (95% CI, −20.9% to −10.3%)[c]	Very low[d]	The evidence is very uncertain about the effect of clascoterone on percent change in TLC when compared with the 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 an LSR. Difference = 1.4% in favour of clascoterone (95% CI, −8.8% to 6.1%) **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 an LSR. Difference = 2.0% in favour of vehicle cream (95% CI, −5.2% to 9.2%)	Moderate[e]	Clascoterone likely results in little to no difference in LSRs when compared with the vehicle cream.

CI = confidence interval; DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; ILC = inflammatory lesion count; LSR = local skin reaction; MID = minimal important difference; NA = not applicable; NILC = noninflammatory lesion count; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; TLC = total lesion count; vs. = versus.

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 following footnotes.

[a]Rated down 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]Rated down 1 level for serious study limitations. This is due to high rates of missing data with insufficient accounting for the likely missing data mechanism. Rated down 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. Rated down 1 level for serious imprecision. The clinical expert–identified MID (10 lesions) threshold was not met; the CI for difference between groups includes the possibility of no difference.

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

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

Sources: Clinical Study Reports for the CB-03-01/25 and CB-03-01/26 trials 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 the CB-03-01/25 and CB-03-01/26 studies. 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 III 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 (i.e., 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 with an IGA score of clear (0) or almost clear (1) increased over time being greatest (ITT = 181 of 609; 29.7%) at the end of the study (day 274). The proportion of patients with an IGA score of clear (0) or almost clear (1) increased over time with clascoterone, from 9.9% at baseline to 29.7% at day 274. A similar proportion of patients originally assigned to the vehicle cream (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 were treated with clascoterone during the LTE period.

Harms Results

Of 607 patients in the safety set, 110 patients (18.1%) 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 the 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 CDA-AMC, 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 CDA-AMC, 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) was conducted. Furthermore, there was no true comparator tested during the LTE period. Also,

there may have been a selection bias as those who benefited 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 the high attrition rate as, 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. Finally, treatment effects on patients' HRQoL have not been assessed even though the impact of acne on HRQoL seems to be significant based on the patient group input. As for external validity, as patients were rolled over from the pivotal trials, the same generalizability concerns apply to the LTE study.

Indirect Comparisons

Description of Studies

CDA-AMC appraised a systematic review and NMA submitted by the sponsor. The reference case NMA compared clascoterone with benzoyl peroxide (2.5% cream/3.1% gel or 5% cream applied once daily), tretinoin (0.025% cream or 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% cream once daily). Sensitivity and scenario analyses considered 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 (i.e., combination therapies, spironolactone, oral contraceptives).

Efficacy Results

Reference case networks 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. The interpretations from an RE NMA investigating changes in noninflammatory lesions were similar.

Harms Results

A comparison of study discontinuations for any reason at 12 weeks after randomization was also performed using an RE Bayesian NMA. Clascoterone displayed a similar frequency of discontinuation compared to placebo (risk ratio = 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% (risk ratio = 0.71; 95% CrI, 0.53 to 0.94).

Critical Appraisal

The sponsor's submitted indirect treatment comparison used recommended methods for conducting and reporting of NMAs and demonstrated similar benefits relative to other available treatments, though certain limitations were noted. The NMA appeared to include study populations that ranged broadly from having 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; thus, the appropriateness of combining these groups for the purposes of the 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 (i.e., 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 (e.g., oral antibiotics, isotretinoin, topical dapsone, combination treatments) could have been included in reference case analyses. Findings from the NMA 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 aged 12 years and older
Treatment	Clascoterone 1% cream
Dose regimen	The recommended dose per application is up to approximately 1 g, applied in a thin uniform layer twice per day
Submitted price	30 g 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

Component	Description
	◦ 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 are 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 that included 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 CDA-AMC.
CDA-AMC reanalysis results	• CDA-AMC 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. CDA-AMC 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 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.

CDA-AMC = Canada's Drug Agency.

Budget Impact

CDA-AMC 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 uncertainty 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.

CDA-AMC 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 that are rarely publicly reimbursed, and adjusting the unit costs of some comparators to reflect updated costs paid by public plans.

CDA-AMC 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 3-year budget impact of $49,571,223. When considering only patients with moderate and severe acne, CDA-AMC reanalyses estimate a potential 3-year budgetary impact of $31,229,870.

CDA-AMC was unable to address limitations with the sponsor's claims-based approach; thus, the resulting budget impact is considered uncertain.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for clascoterone for the topical treatment of acne vulgaris in patients aged 12 years and older. In their request, the sponsor identified the following issues:

- The sponsor requested that CDEC reconsider the GRADE evaluation of evidence conducted by the AAD working group, comprised of qualified dermatologists and clinical experts (including dermatologists from Canada and the US, key opinion leaders, and clinical experts), and strongly encouraged CDA-AMC to reconsider the GRADE evaluations on the current CDEC recommendation to align with the AAD guidelines.
- The sponsor stated that there is significant variability in what constitutes a clinically important difference in acne treatment and that clinicians' subjective judgments in interpreting outcomes can lead to differing perspectives on the significance of results, influenced by their individual experiences and patients' specific situations. As such, the sponsor requested revisions to the certainty of evidence statements regarding Winlevi not meeting clinical importance thresholds. Additionally, the sponsor requested acknowledgement of the variability that may exist between different clinical perspectives on these thresholds and their implications for treatment.
- The sponsor requested that CDA-AMC engage a clinical expert to independently review the refiled submission for Winlevi separate from the original withdrawn submission. The sponsor viewed this as essential to accurately reflect practical experiences with prescribing Winlevi and the impacts observed in patients. Additionally, the sponsor noted that it is crucial to re-engage a clinical expert because the AAD guidelines in effect during the original submission were from 2016 and did not

include Winlevi. The updated guidelines, now in effect, contain recommendations for Winlevi, which are reflected in the refiled submission.

- The sponsor emphasized that there are notable variabilities in the assessment criteria between the evaluation of Winlevi and the recently reviewed Cabtreo, highlighting potential inconsistencies in the evaluation process for these treatments. As such, the sponsor requested a reassessment of the generalizability concerns for Winlevi, specifically regarding the appropriateness of a 12-week time frame for outcomes and the recognition of lesion counts as a valid measure in current clinical practice in Canada, consistent with the Cabtreo assessment.
- The sponsor requested that the reconsideration consider the positive feedback from the clinician group during the refiling of Winlevi, as it highlights the favourable real-world experiences of clinicians prescribing Winlevi to patients with acne over the past year and reflects on the treatment's positive impacts on patients. Additionally, the sponsor requested that key messages highlighting Winlevi's benefits be included in the recommendation to ensure the report's messaging is unbiased and accurately reflects its advantages.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 1 clinical specialist with expertise diagnosing and treating patients with acne
- feedback on the draft recommendation from 1 clinician group, DAO
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process
- feedback on the draft recommendation from the sponsor.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Members of the Committee (Initial Meeting)

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.

Initial meeting date: September 25, 2024

Regrets: Two expert committee members did not attend.

Members of the Committee (Reconsideration Meeting)

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Reconsideration meeting date: January 22, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.