Canadian Journal of Health Technologies

Canada's Drug Agency
L'Agence des médicaments du Canada

November 2024 Volume 4 Issue 11

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Clindamycin Plus Benzoyl Peroxide and Adapalene (Cabtreo)

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

Sponsor: Bausch Health, Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Cabtreo?

It is recommended that Cabtreo be reimbursed by public drug plans for the topical treatment of acne vulgaris in patients 12 years of age and older if certain conditions are met.

Which Patients Are Eligible for Coverage?

Cabtreo should only be covered to treat patients 12 years of age and older with acne vulgaris.

What Are the Conditions for Reimbursement?

Cabtreo should only be reimbursed if the price of Cabtreo is negotiated so that it does not exceed the drug program cost of treatment with topical therapy for acne vulgaris reimbursed by participating plans.

Why Did Canada's Drug Agency Make This Recommendation?

- Evidence from 2 clinical trials showed that treatment with Cabtreo increased the rate of treatment success (measured using an acne severity scale) and reduced the number of inflammatory and noninflammatory lesions after 12 weeks of treatment compared with its vehicle gel (without an active ingredient).
- The treatment effect of Cabtreo on acne, compared with topical treatments that are a combination of 2 active ingredients, was uncertain based on evidence from 1 indirect treatment comparison (ITC).
- Cabtreo may meet some of the unmet needs identified by patients, including access to effective and safe treatment options.
- Based on our assessment of the health economic evidence, Cabtreo does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Cabtreo than the topical therapies currently reimbursed by participating plans.
- Based on public list prices, Cabtreo is estimated to cost the public drug plans approximately $2,000,000 over the next 3 years.

Additional Information

What Is Acne Vulgaris?

Acne vulgaris (also called acne) is a skin condition characterized by noninflammatory lesions (open or closed comedones) and inflammatory lesions (papules, pustules, and nodules) that usually develop on the face,

Summary

neck, upper back, and chest. Acne affects 5,600,000 individuals living in Canada, nearly 20% of the population.

Unmet Needs in Acne Vulgaris

Patients identified a need for access to effective and safe treatment options. The clinical expert identified a need for treatment formulations that are more convenient by reducing the need for several products.

How Much Does Cabtreo Cost?

Treatment with Cabtreo is expected to cost approximately $1,616 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that clindamycin plus benzoyl peroxide and adapalene (IDP-126) gel be reimbursed for the topical treatment of acne vulgaris in patients 12 years of age and older only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, multicenter, double-blind, randomized controlled trials (RCTs) (Study 301 and Study 302) demonstrated that, compared with its vehicle gel, 12 weeks of treatment with IDP-126 gel applied once daily resulted in a benefit in treatment success based on the Evaluator's Global Severity Score (EGSS) and change in lesion count in patients aged 10 years and older with moderate to severe acne. In Study 301, the difference between IDP-126 and its vehicle gel in the proportion of patients with treatment success (defined as a ≥ 2-grade reduction from baseline in the EGSS and an EGSS of clear or almost clear) at week 12 was 24.7% (95% confidence interval [CI], 10.7% to 38.7%; P = 0.003), in favour of IDP-126 gel; in Study 302, the difference was 30.0% (95% CI, 16.4% to 43.6%; P = 0.001), also in favour of IDP-126 gel. In addition, IDP-126 gel resulted in a clinically meaningful reduction in inflammatory lesion count based on the percent change from baseline when compared with its vehicle gel (Study 301: between-group difference = –16.08% [95% CI, –23.72% to –8.44%; P < 0.001]; Study 302: between-group difference = –23.95% [95% CI, –31.73% to –16.16%; P < 0.001]).

In addition, the sponsor-conducted network meta-analysis (NMA) results showed a favourable treatment effect of IDP-126 gel versus vehicle or placebo, oral antibiotic, and topical monotherapies on treatment success and change in lesion counts. While the effect estimates are suggestive of a possible favourable treatment effect with IDP-126 gel versus topical fixed-dose combination dual therapies, there is some uncertainty as the 95% credible intervals (CrIs) included the null or were close to the null for some dual combination therapies. Due to possible exclusion of relevant studies, heterogeneity across trials in the networks, and omission of relevant comparators in Canada that suggest concerns for bias in the NMA estimates, the magnitude of effect associated with IDP-126 gel is uncertain.

Patients identified a need for access to effective and safe treatment options. Furthermore, the clinical expert identified a need for treatment formulations that may improve adherence by reducing the need for multiple products and the potential for cross-reactivity. CDEC concluded that IDP-126 gel may meet some of these needs as it is an effective and safe treatment option.

At the sponsor-submitted price for IDP-126 gel and publicly listed price for all other treatments, IDP-126 gel was more costly than all comparators apart from adapalene 0.3%. As there is uncertainty in the magnitude of benefit associated with IDP-126 gel compared with topical treatments, the total drug cost of IDP-126 gel should not exceed the total drug cost of other active treatments reimbursed by participating drug plans.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients 12 years of age and older with acne vulgaris	Studies 301 and 302 demonstrated that treatment with IDP-126 gel results in a clinical benefit in patients with moderate to severe acne vulgaris compared to its vehicle gel.	—
Pricing		
2. IDP-126 gel should be negotiated so that it does not exceed the drug program cost of treatment with topical therapies reimbursed by participating plans for the treatment of acne vulgaris.	While IDP-126 gel appears to have favourable effects on treatment success and change in lesion count when compared with other active therapies, based on indirect evidence; the magnitude of benefit associated with IDP-126 gel was uncertain. As such, there is insufficient evidence to justify a price premium for IDP-126 gel over topical therapies reimbursed by public drug plans for acne vulgaris.	—

IDP-126 = clindamycin plus benzoyl peroxide and adapalene.

Discussion Points

- **Certainty of the evidence:** CDEC noted that the evidence from Study 301 and Study 302 regarding acne severity, lesion counts, harms, and health-related quality of life (HRQoL) was of moderate to high certainty, per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments. It was of high certainty that IDP-126 gel results in a clinically meaningful increase in the proportion of patients with treatment success, reduction in the mean percent change in noninflammatory lesion count, and reduction in the mean percent change in inflammatory lesion count. While a statistically significant reduction in the absolute change in inflammatory lesion count was demonstrated in the trials, the GRADE assessment for this end point concluded that there is little to no clinically meaningful difference as the effect estimates for the absolute difference did not exceed the suggested threshold of importance. The results of the HRQoL outcomes at week 12 were suggestive of little to no clinically meaningful difference in the Acne-Specific Quality of Life (Acne-QoL) self-perfection and acne symptom domain scores (moderate and high certainty, respectively) with IDP-126 gel compared to its vehicle gel.
- **Adverse effects:** Patient groups concluded that patients weigh the side effects associated with treatment against effectiveness when deciding to start, stop, or continue their acne therapy. The clinical expert indicated there was no concern with the safety profile of IDP-126 gel based on the safety results from the reviewed phase II and phase III trials.
- **Additional indirect evidence:** The findings from an NMA by Huang et al. aligned with the sponsor-conducted NMA results as the estimates comparing triple therapy (i.e., topical antibiotic, retinoid, and benzoyl peroxide) to placebo were generally consistent with the sponsor-conducted ITC. However, this evidence as it relates to IDP-126 is limited primarily due to Huang et al. combining IDP-126

with other triple therapies and only reporting results comparing active treatments to placebo. Other limitations of the published NMA included the lack of prespecification of study methods through a review protocol, and notable heterogeneity in effect modifying factors across the studies included in the network. The exploration of between-study differences and potential biases was further limited by missing information on patient and study characteristics.

- **Supportive studies:** Two phase II trials (Study 201 and Study 202) provided supportive evidence suggesting a possible favourable treatment effect with IDP-126 gel versus vehicle gel and topical dual combination therapies (i.e., a fixed-dose combination of retinoid and benzoyl peroxide, antibiotic and benzoyl peroxide, and retinoid and antibiotic) based on treatment success and change in lesion counts at week 12. The results were consistent with the pivotal phase III trials and the sponsor-conducted NMA.
- **Relevant comparators:** According to feedback received from public drug plans, coverage of many of the topical treatments included in the pharmacoeconomic analysis is variable across jurisdictions. As such, relevant comparators to IDP-126 gel are likely to vary by public drug plan.

Background

Acne vulgaris (hereafter referred to as acne) is a chronic inflammatory skin condition of the pilosebaceous glands that typically begins at puberty and may continue through adulthood, with flares that are associated with an increase in androgen levels. Acne is characterized by noninflammatory lesions (open or closed comedones) and inflammatory lesions (papules, pustules, and nodules) that primarily develop on the face, neck, upper back, and chest. Acne affects 5,600,000 individuals living in Canada, nearly 20% of the population.

According to the 2016 *Management of acne: Canadian clinical practice guideline*, topical therapies are a reasonable first-line treatment option for comedonal and mild papulopustular acne, including topical retinoids, benzoyl peroxide, and fixed-dose combinations of retinoids with benzoyl peroxide or clindamycin. For more extensive moderate papulopustular acne, or areas not amenable to topical therapy, systemic therapies in addition to topical therapies are a reasonable treatment option, including oral antibiotics and combined oral contraceptives in some patients. Systemic therapies are a reasonable treatment option for severe acne, including oral isotretinoin and oral antibiotics in combination with benzoyl peroxide, with or without topical retinoids.

IDP-126 gel has been approved by Health Canada for the topical treatment of acne vulgaris in patients 12 years of age and older. Clindamycin phosphate, adapalene, and benzoyl peroxide are an antibiotic, retinoid, and antibacterial, respectively. IDP-126 gel is available as a topical gel and the dosage recommended in the product monograph is to apply a thin layer to the affected area once daily.

Sources of Information Used by the Committee

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

- a review of 2 phase III, multicenter, randomized, double-blinded, vehicle-controlled, parallel-group clinical studies in patients aged 9 years and older with moderate to severe acne; 2 ITCs; and 2 phase II, multicenter, randomized, double-blind, vehicle-controlled studies
- patients' perspectives gathered by 2 patient groups, the Acne and Rosacea Society of Canada (ARSC) and the Canadian Skin Patient Alliance (CSPA)
- input from public drug plans that participate in the CDA-AMC review process
- 1 clinical specialist with expertise diagnosing and treating patients with acne
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

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

Patient Input

The ARSC and the CSPA submitted joint input on the current review of IDP-126 gel. The patient input was gathered using an online survey that was conducted between June 7 and 30, 2022. A total of 154 responses were collected from patients with acne (either diagnosed by a dermatologist or health care provider or self-diagnosed) and their caregivers living in Canada. Most respondents (68%) were female, 30% were male, and 2% identified as nonbinary. The distribution of respondents by age ranges was 20 to 29 years (55% of respondents), 30 to 39 years (23%), and 16 to 19 years (12%). Additionally, CSPA and ARSC created a survey targeting participants in clinical trials of IDP-126 gel and received a total of 3 responses.

Almost half (47%) of the survey respondents reported moderate acne, while 16% reported severe acne. Almost half (42%) of the survey respondents indicated they had between 2 and 5 health care visits before receiving their diagnosis and treatment for acne. Nearly 30% of survey respondents reported visiting a health care provider more than 5 times. Almost half of survey respondents reported feeling self-conscious often or always due to acne. Most respondents (87%) reported using a strategy to hide their acne, with 63% using makeup and 59% avoiding social gatherings altogether. Most respondents reported acne scarring (87%) and changes in skin pigmentation due to acne (90%).

Overall, the survey respondents reported experience with various treatments with varying degrees of improvement (or sometimes worsening) in their acne and experience of associated side effects. The majority of respondents (89%) reported prior use of prescription gels or creams for acne, of which, 21% reported no change, 43% reported a little improvement, 13% reported a big improvement, and 12% reported worsening of their condition. Most (59%) survey respondents reported experience with isotretinoin therapy, of which 28% reported significant improvement and 43% reported slight improvement. Similarly, 59% of respondents

reported experience with hormone therapy, including birth control and spironolactone, of which 23% reported significant improvement and 36% reported minor improvement. Most (95%) respondents reported experiencing adverse effects associated with their treatment regimen for acne in the last year, with the most common adverse effect being skin irritation (64%), dry skin (62%), and skin flaking (55%). More specifically, 85% of respondents reported experiencing side effects associated with their current topical treatment regimen (nonprescription and prescription), most (70%) of which were reported as minor side effects. Most survey respondents indicated they were willing to accept these side effects because they thought the treatment was effective. Additionally, facials and peels were used by more than half of all respondents (53%), while 65% reported undergoing light or laser therapy.

All 3 patients with experience with IDP-126 gel reported manageable side effects. Two of the 3 patient respondents indicated treatment with IDP-126 gel was easier to use than their previous therapies. Furthermore, 2 of the 3 patient respondents indicated the value of IDP-126 gel is treatment effectiveness and time to improvement.

According to the survey respondents, common challenges in the management of acne include hiding the acne, identifying triggers, and coping with high out-of-pocket expenses for nonprescription acne products and treatments. The survey respondents identified the following goals for improved outcomes: ability to enjoy personal relationships, have less scarring, and have fewer changes in skin pigmentation. Other goals included clearer skin, improved mental health, increased self-confidence, and improved overall daily life.

Clinician Input

Input From Clinical Expert Consulted

The clinical expert expected a triple therapy, such as IDP-126 gel, to become widely adopted as first-line therapy in the treatment of acne. The clinical expert anticipated that the drug under review may cause a shift in the current treatment paradigm with topical combination (dual) therapies (e.g., adapalene and benzoyl peroxide topical gel, clindamycin phosphate and tretinoin gel) that have been widely adopted in clinical practice. The clinical expert does not expect IDP-126 gel to be used in combination with other therapies. The clinical expert advised that patients with acne should not have to be required to try other therapies before initiating treatment with IDP-126 gel due to overlap with the other therapies currently available and patients developing exhaustion and frustration from topical products. More specifically, the clinical expert indicated that if there was a requirement for prior treatment failure with other topical therapies before being able to access IDP-126 gel, patients are more likely to request a step up to oral therapies.

The clinical expert suggested that patients with moderate acne (i.e., numerous inflammatory papules and noninflammatory lesions) are most likely to respond to treatment with IDP-126 gel. In contrast, the clinical expert suggested that patients with nodulocystic acne or severe acne and those with scarring are less likely to respond to treatment with IDP-126 gel (nodulocystic acne, a severe form of acne, tends to require systemic medication). As such, the clinical expert would likely only use IDP-126 gel in patients who do not have nodules or cysts.

The clinical expert indicated that family physicians, nurse practitioners, and other primary care providers can prescribe and monitor treatment with IDP-126 gel in any setting. In the assessment of treatment response in clinical practice, the clinical expert indicated that, in general, clinicians estimate the number of inflammatory and noninflammatory lesions (i.e., not counted) and carry out a global assessment (no acne; mild, moderate, or severe acne). The clinical expert indicated that patients using topical therapies are generally reassessed every 3 to 6 months. The clinical expert indicated the following would be considerations for discontinuation of IDP-126 gel: lack of response or minimal response (i.e., no improvement or minimal improvement from baseline as determined by examining the patient), severity of side effects, and disease progression (i.e., increase in the number of nodules or scar formation).

Drug Program Input

Input was obtained from the drug programs that participate in the CDA-AMC reimbursement review process. The clinical expert we consulted provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
In Study 301 and Study 302, many patient's acne appeared to respond to the vehicle gel. Is the magnitude of response to vehicle gel similar to other studies for topical treatments of acne? If so, what is the rationale for high response rates to the vehicle (e.g., do patients just require the use of a moisturizer)? If not, what study design characteristics could explain this?	The clinical expert advised that placebo (or vehicle) response rates in acne trials generally range from 20% to 25%. The clinical expert indicated that moisturizers alone have a clinically meaningful, beneficial effect on acne; the mechanism of action is thought to be related to improved water balance, decreased inflammation, improved keratinocyte differentiation, and sloughing of corneocytes.
In clinical practice, what type of patients significantly benefit from the use of combination topical therapies compared to the use of its active ingredients separately?	The clinical expert anticipated that monotherapy will still be used at times due to tolerability concerns or when specific treatment outcomes are targeted (i.e., comedonal acne or hormonal acne). The clinical expert suggested that combination therapies tend to improve patient adherence, while treatment regimens that are complicated (i.e., requiring ≥ 2 different products) tend to reduce adherence. Furthermore, the clinical expert advised that combining monotherapies introduces the potential for active ingredient cross-reactivity and reduced efficacy.
Most public drug plans in Canada do not cover any or most of the combination products for the treatment of acne. Specifying the failure of a dual combination product before being eligible for a triple combination product would not allow this triple therapy product to be listed in jurisdictions that do not cover dual combination products for the treatment of acne.	This is a comment from the drug plans to inform CDEC deliberations.

Implementation issues	Response
Considerations for initiation of therapy	
Are the coprimary efficacy end points assessed in Study 301 and Study 302 applicable to clinical practice? Could they be used as criteria for assessing continued reimbursement of the drug under review?	The clinical expert indicated that the assessment of treatment response in practice includes an estimate of the total number of inflammatory and noninflammatory lesions, which contributes to their global assessment (no acne; mild, moderate, or severe acne). Thus, requiring lesion counts as part of the initiation and renewal criteria would not be reflective of current practice.
In Study 301 and 302, there did not have to be treatment failure of 1 or 2 topical products for acne before the patient could be enrolled. Are there situations where you would start a patient on triple topical therapy for acne without trying mono- and/or combination therapy before? What is considered the minimum trial length of mono- and combination therapy? How is a lack of response determined?	The clinical expert expected a triple therapy, such as IDP-126 gel, to become widely adopted as first-line therapy in the treatment of acne. The clinical expert advised that patients with acne should not be required to try other treatments before initiating treatment with IDP-126 gel due to major overlap with other current treatment options. In general, the clinical expert indicated that any topical therapy should be used for 3 to 6 months before considering treatment failure. The clinical expert defined lack of response as no improvement or minimal improvement from baseline as determined by examining the patient.
Patients with secondary acne were excluded from Study 301 and Study 302. Could the drug under review be used to treat patients with secondary acne?	The clinical expert suggested that it is possible to consider using IDP-126 gel in secondary acne. However, the clinical expert advised that secondary acne would likely be more difficult to treat and may require other therapeutic manipulations (e.g., stopping a medication that is causing the acne, treating a congenital hormonal condition).
Considerations for discontinuation of therapy	
What parameters would you consider before discontinuing the drug under review due to ineffectiveness?	The clinical expert indicated the following are considerations for discontinuation of IDP-126 gel: lack of response or minimal response, severity of side effects, and disease progression (i.e., increase in the number of nodules or scar formation).

CDEC = Canadian Drug Expert Committee; IDP-126 = clindamycin plus benzoyl peroxide and adapalene.

Clinical Evidence

Systematic Review

Description of Studies

Two phase III, multicenter, double-blind RCTs (Study 301, N = 183; Study 302, N = 180) assessed whether there is a difference in the proportion of patients with treatment success (defined by ≥ 2-grade reduction from baseline in the EGSS and an EGSS of clear or almost clear) and change from baseline in inflammatory and noninflammatory lesion counts in patients aged 9 years and older with moderate to severe acne applying IDP-126 topical gel once daily for 12 weeks when compared to its vehicle gel. Other outcomes of interest include change in HRQoL measured by the self-perception and symptom subscales of the Acne-QoL questionnaire. Notable harms include general disorders and administration site conditions, skin and

subcutaneous tissue disorders, and serious adverse events (SAEs). The mean age of patients randomized to each study drug group was similar — approximately 20 years and ranged from 10 to 48 years across studies. The majority of patients in each study drug group had moderate acne, defined as a baseline EGSS of 3, ranging from 87.7% to 95.1% of patients across studies. The remainder of patients in each study drug group had severe acne, defined as a baseline EGSS of 4, ranging from 4.9% to 12.3% of patients across studies.

Efficacy Results

Treatment Success Based on the EGSS

Study 301: The treatment difference in treatment success based on the EGSS at week 12 between IDP-126 gel and its vehicle gel was 24.7% (95% CI, 10.7% to 38.7%; P = 0.003), in favour of IDP-126 gel.

Study 302: The treatment difference in treatment success based on the EGSS at week 12 between IDP-126 gel and its vehicle gel was 30.0% (95% CI, 16.4% to 43.6%; P = 0.001), also in favour of IDP-126 gel.

Inflammatory Lesion Count

Study 301: The treatment difference in the mean absolute change from baseline in inflammatory lesion count at week 12 between IDP-126 gel and its vehicle gel was –5.94 (95% CI, –8.73 to –3.14; P < 0.001), in favour of IDP-126 gel. The treatment difference in the mean percent change from baseline in inflammatory lesion count at week 12 between IDP-126 gel and its vehicle gel was –16.08% (95% CI, –23.72% to –8.44%; P < 0.001), also in favour of IDP-126 gel.

Study 302: The treatment difference in the mean absolute change from baseline in inflammatory lesion count at week 12 between IDP-126 gel and its vehicle gel was –9.30 (95% CI, –12.38 to –6.23; P < 0.001), also in favour of IDP-126 gel. The treatment difference in the mean percent change from baseline in inflammatory lesion count at week 12 between IDP-126 gel and its vehicle gel was – 23.95% (95% CI, –31.73% to –16.16%; P < 0.001), also in favour of IDP-126 gel.

Noninflammatory Lesion Count

Study 301: The treatment difference in the mean absolute change from baseline in noninflammatory lesion count at week 12 between IDP-126 gel and its vehicle gel was –11.85 (95% CI, –16.56 to –7.14; P < 0.001), in favour of IDP-126 gel. The treatment difference in the mean percent change from baseline in noninflammatory lesion count at week 12 between IDP-126 gel and its vehicle gel was –25.09% (95% CI, –34.96% to –15.22%; P < 0.001), also in favour of IPD-126 gel.

Study 302: The treatment difference in the mean absolute change from baseline in noninflammatory lesion count at week 12 between IDP-126 gel and its vehicle gel was –13.27 (95% CI, –17.74 to –8.80; P < 0.001), also in favour of IDP-126 gel. The treatment difference in the mean percent change from baseline in noninflammatory lesion count at week 12 between IDP-126 gel and its vehicle gel was – 24.27% (95% CI, –32.86% to –15.68%; P < 0.001), also in favour of IPD-126 gel.

Self-Perception and Symptom Domain Score on the Acne-Specific Quality of Life Questionnaire

Harms Results

The following summary of harms results from Study 301 and Study 302 are based on pooled data. There are no reports of patients with SAEs and no reports of deaths in either study.

Adverse Events

The proportion of patients with at least 1 treatment emergent adverse event (TEAE) was 21.9% of patients (53 of 242 patients) in the IDP-126 gel group and 7.4% of patients (9 of 121 patients) in its vehicle gel group. The most common TEAE reported was application site pain in 9.1% of patients (22 of 242 patients) in the IDP-126 gel group and 0.8% of patients (1 of 121 patients) in its vehicle gel group.

Withdrawals Due to Adverse Events

The proportion of patients who stopped their study drug and/or study due to any TEAE was 2.9% of patients (7 of 242 patients) in the IDP-126 gel group and no patients in its vehicle gel group. The most common TEAE reported to have led to discontinuation of study drug and/or study was application site pain and erythema — each TEAE was reported in 0.8% of patients (2 of 242 patients) in the IDP-126 gel group.

Notable Harms

A total of 9.1% of patients (22 of 242 patients) in the IDP-126 gel group and 0.8% of patients (1 of 121 patients) in its vehicle gel group reported a TEAE categorized as a general disorder and administrative site condition.

A total of 2.9% of patients (7 of 242 patients) in the IDP-126 gel group and 0.8% of patients (1 of 121 patients) in its vehicle gel group reported a TEAE categorized as a skin and subcutaneous tissue disorder.

Critical Appraisal

Internal Validity

Study 301 and Study 302 were generally appropriately designed and powered to evaluate the efficacy of IDP-126 gel relative to vehicle gel. Type I error was controlled in each study by requiring all 3 coprimary efficacy end points to be statistically significant to be able to draw a conclusion of superiority for IDP-126 gel relative to its vehicle gel and by testing the secondary efficacy end points using a gated, sequential process. No inferential statistics were conducted in the subgroup analyses and HRQoL outcomes; therefore, these results are considered as supportive evidence only.

The 2018 FDA guidance, *Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment*, suggested treatment success, defined by a score of 0 (clear) or 1 (almost clear), and at least a 2-grade improvement from baseline on the static Investigator's Global Assessment (IGA) scale (an ordinal scale of 5 severity grades, each defined by a distinct and clinically relevant morphologic description), is a clinically meaningful outcome in the treatment of acne. Recognizing that there is no standardized grading system for disease severity, the FDA guidance suggested considering both changes in lesion counts and treatment success in the assessment of treatment effect — this is reflected in Study 301 and Study 302. Additionally, there is evidence in the literature to support the validity, reliability, and responsiveness of the Acne-QoL questionnaire as a measure of HRQoL in patients with acne. Therefore, bias in the measurement of important outcomes is unlikely.

In consultation with the clinical expert, age, sex, and ethnicity or race were identified as possible effect modifiers in the treatment of acne. Although randomization was not stratified, the relevant patient demographic and disease characteristics at baseline were generally well-balanced between the study drug groups in each study. As such, it was concluded that any possible impact on the interpretation of the efficacy results due to baseline differences between study drug groups is unlikely.

External Validity

The inclusion criteria used in Study 301 and Study 302 — patients aged 9 years and older with moderate to severe acne — include the population of interest identified in the anticipated indication for IDP-126 gel, which is for the topical treatment of acne in patients aged 12 years and older. In consultation with the clinical expert, it was concluded that the inclusion criteria adequately capture (and consequently the study population from both studies is representative of) the patients who would be candidates for IDP-126 gel seen in practice.

In consideration of the goal to minimize confounders using exclusion criteria, it was concluded that no patient who would be a candidate for IDP-126 gel was missed as a result of any exclusion criterion. However, the clinical expert highlighted that patients with these exclusion criteria seen in practice may still have an indication for topical therapy and be considered for IDP-126 gel. The clinical expert provided such examples, including patients with polycystic ovarian disease, clinically significant menstrual irregularities, or secondary acne, and patients taking birth control.

In consultation with the clinical expert, it was concluded that the outcome measures of acne severity and lesion counts used in the trials are applicable to clinical practice in Canada. It was also concluded that a follow-up at 12 weeks after starting a topical therapy is appropriate for an assessment of effect in this therapeutic area.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For the 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 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 based on thresholds identified in the literature and/or informed by the clinical expert consulted for this review; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance was 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.

For the GRADE assessments, the findings from Study 301 and Study 302 were considered together and summarized narratively per outcome because these studies were similar 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 groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- acne severity (treatment success defined by using the EGSS)
- lesion counts (inflammatory and noninflammatory lesions)
- HRQoL (Acne-QoL self-perception and acne symptom subscale scores)
- notable harms (general disorders and administration site conditions, skin and subcutaneous tissue disorders, and SAEs).

Results of GRADE Assessments

Table 2 presents the GRADE summary of findings for IDP-126 gel versus IDP-126 vehicle gel.

Indirect Comparisons

Description of ITCs

The sponsor conducted an ITC designed to assess the efficacy of IDP-126 gel compared to other treatments available in Canada for patients with moderate to severe acne. The analyses included NMAs of 85 RCTs

identified from a systematic literature search that reported on percentage of patients with at least a 2-grade reduction from baseline and a score of clear or almost clear on the IGA or equivalent scales (treatment success) and changes in inflammatory lesion and noninflammatory lesion counts. The NMA incorporated the following 14 different treatment groups: fixed-dose combinations of topical antibiotic, benzoyl peroxide, and retinoid; topical retinoid and benzoyl peroxide; topical antibiotic and benzoyl peroxide, or topical antibiotic and retinoid; topical monotherapies (i.e., antibiotic, retinoid, benzoyl peroxide, or other); combinations of topical treatments that include an oral antibiotic; oral antibiotic monotherapy; combinations of physical treatments with oral antibiotic; physical treatment only; other treatments; and vehicle or placebo. A Bayesian framework was used that employes random study, fixed-class effect models to estimate treatment effects for each outcome as the primary analyses.

One published NMA of 221 trials conducted by Huang et al. was also submitted by the sponsor for this review. The analysis adopted a frequentist approach to assess the effect of different treatments for acne on outcomes of interest, including reductions in total, inflammatory, and noninflammatory lesions; treatment success defined using the IGA; and discontinuation due to any adverse events.

Efficacy Results

The NMA on proportion of patients experiencing treatment success included 46 trials and 12 treatment groups. According to the estimated odds ratio, IDP-126 gel demonstrated higher efficacy compared to the vehicle or placebo comparison group (odds ratio = 6.30; 95% CrI, 3.90 to 9.87). Moreover, IDP-126 gel was favoured in comparisons to other active treatments (oral antibiotic monotherapy, topical monotherapies, topical fixed-dose combinations of an antibiotic and a retinoid and an antibiotic and benzoyl peroxide).

NMAs for changes in inflammatory and noninflammatory lesion counts consisted of 50 and 46 trials, respectively. There were 12 treatment nodes available in the networks for both outcomes. The number of patients ranged from 107 to 2,813 per study for the 2 networks. The findings regarding inflammatory and noninflammatory lesion counts revealed IDP-126 gel to be associated with a greater impact on reduction of lesions compared to placebo (IDP-126 gel = −8.21; 95% CrI, −10.33 to −6.13; placebo = −13.41; 95% CrI, −16.69 to −10.32). Comparisons with other active treatments (i.e., oral antibiotic, topical monotherapies, and topical antibiotic and retinoid fixed-dose combinations) showed that IDP-126 gel was favoured, both for the inflammatory and noninflammatory lesion count reduction.

The findings from the published NMA reporting efficacy outcomes on the comparison of triple therapy (i.e., topical antibiotic, a topical retinoid, and benzoyl peroxide) to placebo were aligned with the sponsor-conducted ITC.

Harms Results

Critical Appraisal

The sponsor-conducted NMA used recommended methods for conduct and reporting of NMAs and demonstrated favourable benefits relative to other available treatments, though important limitations were noted. Restrictive exclusion criteria were applied in the literature review, prohibiting the inclusion of single RCTs and studies with small sample sizes. The NMAs appeared to include study populations that varied greatly in terms of their disease severity and sex distributions, which raise concerns for heterogeneity across studies in the network that may bias the comparison. Even though a literature review and meta-regression were performed to identify and assess the influence of effect modifying variables (i.e., duration of treatment, severity of acne, diverse treatments), their impact on overall NMA estimates could not be properly addressed due to limited reporting by the included trials. Input from the clinical expert suggested that certain treatments of interest for clinical practice in Canada (e.g., oral isotretinoin, azelaic acid, topical dapsone) were missing in the NMA network. Moreover, treatment group nodes incorporated some mono- and combination therapies unavailable in Canada, limiting the generalizability of the included treatments. Considering all of this, it is likely that the NMA estimates are subject to an unknown amount and direction of bias.

Limitations of the published ITC included the lack of prespecification of study methods through a review protocol and notable heterogeneity in prognostic and effect modifying factors across the studies included in the network. The exploration of between-study differences and potential biases was further limited by missing information on patient and study characteristics. Notable generalizability issues (i.e., NMA estimates coming from comparisons to placebo only and presence of treatments without market approval in Canada in the network) further limit the applicability of this analyses to the clinical context in Canada.

Studies Addressing Gaps in the Evidence From the Systematic Review

Study 201

Description of Study

One phase II, multicenter, double-blind RCT, Study 201 (N = 741) was submitted by the sponsor to further address the evidence gap on direct comparative evidence of IDP-126 gel to other relevant comparators. Study 201 also assessed whether there is a difference in the proportion of patients with treatment success (same definition used in Study 301 and Study 302) and change from baseline in inflammatory and noninflammatory lesion counts in patients aged 9 years and older with moderate to severe acne applying IDP-126 topical gel once daily for 12 weeks. Other efficacy and safety outcomes assessed are similar to those assessed in Study 301 and Study 302. The comparators are IDP-126 Component A (benzoyl peroxide 3.1% and adapalene 0.15% gel), IDP-126 Component B (clindamycin phosphate 1.2% and benzoyl peroxide 3.1% gel), IDP-126 Component C (clindamycin phosphate 1.2% and adapalene 0.15% gel), and IDP-126 vehicle gel. The mean age of patients randomized to each study drug group was similar, approximately 20 years and ranged from 10 to 60 years. The majority of patients in each study drug group had moderate acne, ranging from 79.3% to 86.0%. The remainder of patients had severe acne, ranging from 14.0% to 20.7%.

Efficacy Results

Acne Severity

Treatment success based on the EGSS: The percentage of patients with at least a 2-grade reduction from baseline in the EGSS and an EGSS of clear or almost clear (i.e., treatment success) at week 12 were 52.5% in the IDP-126 gel group, 27.8% in the Component A group, 30.5% in the Component B group, 30.3% in the Component C group, and 8.1% in the vehicle gel group. The treatment differences in treatment success based on the EGSS were not reported.

Lesion Count

Inflammatory lesion count: The least squares mean changes from baseline in inflammatory lesion count at week 12 were –29.9 (standard deviation [SD] = 11.86) in the IDP-126 gel group, –26.7 (SD = 11.74) in the Component A group, –24.8 (SD = 11.71) in the Component B group, –26.8 (SD = 11.69) in the Component C group, and –19.6 (SD = 12.12) in the vehicle gel group. The treatment differences in the mean absolute change from baseline in inflammatory lesion count at week 12 were not reported.

Noninflammatory lesion count: The least squares mean changes from baseline in noninflammatory lesion count at week 12 were –35.5 (SD = 16.25) in the IDP-126 gel group, –29.9 (SD = 16.40) in the Component A group, –27.8 (SD = 15.97) in the Component B group, –30.0 (SD = 16.40) in the Component C group, and –21.8 (SD = 16.58) in the vehicle gel group. The treatment differences in the mean absolute change from baseline in noninflammatory lesion count at week 12 were not reported.

Quality of Life

Self-perception and symptom domain score on the Acne-QoL: The mean changes from baseline in the Acne-QoL self-perception domain score at week 12 were 9.8 (SD = 8.80) in the IDP-126 gel group, 7.3 (SD = 8.34) in the Component A group, 7.5 (SD = 7.22) in the Component B group, 8.5 (SD = 8.22) in the

Component C group, and 5.9 (SD = 7.99) in the vehicle gel group. The treatment differences in the absolute change from baseline in the Acne-QoL self-perception domain score at week 12 were not reported.

The mean changes from baseline in the Acne-QoL symptoms domain score at week 12 were 7.4 (SD = 6.19) in the IDP-126 gel group, 7.3 (SD = 6.52) in the Component A group, 6.9 (SD = 5.63) in the Component B group, 6.6 (SD = 6.07) in the Component C group, and 4.9 (SD = 5.53) in the vehicle gel group. The treatment differences in the absolute change from baseline in the Acne-QoL symptoms domain score at week 12 were not reported.

Harms Results

Adverse Events

The proportion of patients who reported at least 1 TEAE was similar in the IDP-126 gel and IDP-126 Component A groups (36.2% and 35.6%, respectively), while the proportion of patients who reported a TEAE in the IDP-126 Component B, IDP-126 Component C, and IDP-126 vehicle gel groups was 18.1%, 27.0%, and 15.1%, respectively. The most common TEAEs reported were application site pain (7.8% of patients in the IDP-126 gel group, 11.0% in the Component A group, 0.7% in the Component B group, 3.4% in the Component C group, and 0.7% in the vehicle gel group), application site dryness (6.4% of patients in the IDP-126 gel group, 5.5% in the Component A group, 1.4% in the Component B group, 6.1% in the Component C group, and 0.7% in the vehicle gel group), and application site exfoliation (3.5% of patients in the IDP-126 gel group, 2.1% in the Component A group, 0.0% in the Component B group, 1.4% in the Component C group, and 0.7% in the vehicle gel group).

Serious Adverse Events

A total of 4 patients reported SAEs — 1 patient in the IDP-126 gel group experienced sickle cell anemia with crisis and 3 patients in the Component C group experiences 1 each of hyperbilirubinemia, enteritis, and induced abortion.

Withdrawals Due to Adverse Events

A total of 17 patients, 4 in the IDP-126 gel group, 8 in the IDP-126 Component A group, 3 in the IDP-126 Component C group, and 2 in the IDP-126 vehicle gel group, had their study drug withdrawn due to TEAEs. A total of 16 patients (4 in the IDP-126 gel group, 8 in the IDP-126 Component A group, 3 in the IDP-126 Component C group, and 1 in the IDP-126 vehicle gel group) discontinued the study due to TEAEs.

Mortality

There were no reports of patients who died in Study 201.

Notable Harms

[redacted]

Critical Appraisal

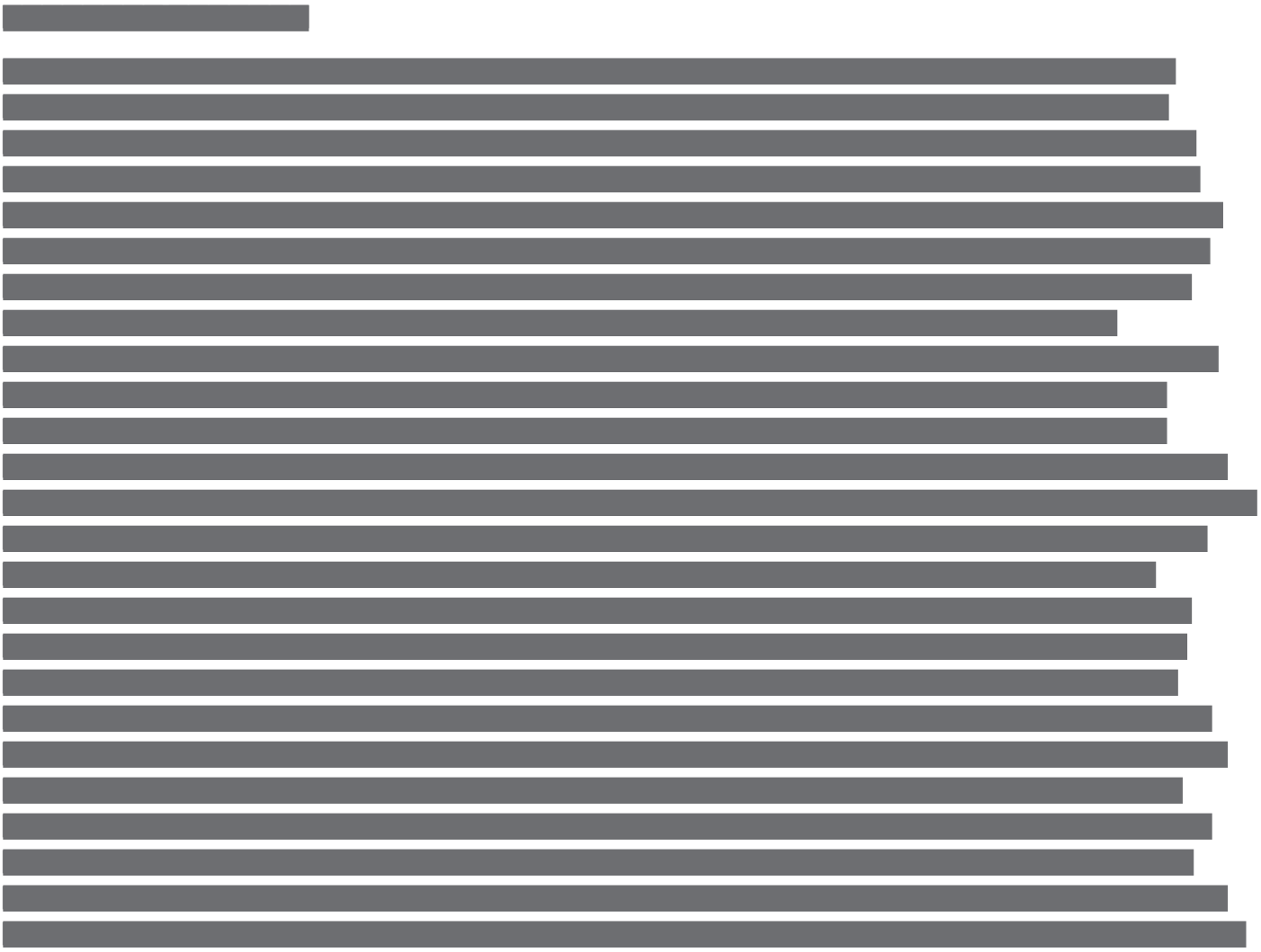
The randomization and masking procedures in Study 201 were considered appropriate. As it was a phase II trial aiming to provide preliminary evidence about the efficacy and harms of the study drug, the results cannot be considered confirmatory. Relevant patient demographic characteristics at baseline appeared to be well-balanced between the study drug groups. No notable differences in the baseline EGSS and lesion counts between study drug groups were identified. Similar to the pivotal trial, the washout periods used in the studies were considered adequate and the list of prohibited treatments for acne was considered comprehensive by the clinical expert. No adjustments were made for multiple comparisons for primary and secondary outcomes; therefore, there is a greater likelihood of type I error. For the outcomes on quality of life (Acne-QoL self-perception and symptom domains), no inferential analyses or multiplicity adjustments were conducted, per the statistical analysis plan, so these data are considered supportive and no definitive conclusions could be drawn. Study discontinuation rates were similar between the pivotal trials and Study 201 (i.e., not high in the context of this patient population and rates are similar between groups for overall study discontinuation and by reasons for study discontinuation). Similar to the pivotal trials, in consultation with the clinical expert, it was concluded that the study discontinuation rates are reasonable in the context of the therapeutic area and as such, risk of attrition bias and possible unblinding are unlikely. Overall, no major concern for bias in the results were identified; however, the results cannot be interpreted as conclusive evidence due to the phase II trial design.

The inclusion criteria used in Study 201 include the population of interest identified in the anticipated indication for IDP-126 gel — patients aged 9 years and older with a clinical diagnosis of moderate to severe acne vulgaris, defined as a baseline of EGSS of 3 (moderate) or 4 (severe) for facial acne. In consultation with the clinical expert, it was concluded that the inclusion criteria adequately capture (and consequently the study population is representative of) the patients who would be candidates for IDP-126 gel seen in practice. Similar to the pivotal trials, the majority of patients from each study (approximately ≥ 79.3% of patients in each study drug group) had moderate acne. On the lack of enrolment of patients aged 9 years, the clinical expert advised there is no clinically meaningful difference between patients with acne aged 9 years versus 10 years. In consultation with the clinical expert, it was concluded that topical fixed-dose combination therapies (i.e., retinoid and benzoyl peroxide, an antibiotic and benzoyl peroxide, and retinoid and an antibiotic) are relevant comparators to IDP-126 gel in practice settings in Canada. Similar to the pivotal trials, in consultation with the clinical expert, it was concluded that the outcome measures of acne severity and lesion counts used in Study 201 are applicable to clinical practice in Canada. Overall, no notable concerns on the generalizability of the results to the population of interest in the setting in Canada was identified in the appraisal of Study 201.

Study 202

Description of Study

One additional phase II, multicenter, double-blind, RCT, Study 202 (N = 686), was submitted by the sponsor to further address the evidence gap on direct comparative evidence of IDP-126 gel to other relevant comparators. Study 202 also assessed whether there is a difference in the proportion of patients with treatment success (same definition used in Study 301 and Study 302) and change from baseline in inflammatory and noninflammatory lesion counts in patients aged 12 years and older with moderate to severe acne applying IDP-126 topical gel once daily for 12 weeks when compared with adapalene 0.3% and benzoyl peroxide 2.5% gel. Other efficacy and safety outcomes assessed are similar to those assessed in Study 301 and Study 302. The mean age of patients randomized to each study drug group was similar—approximately 20 years and ranged from 12 to 56 years. The majority of patients in each study drug group had moderate acne — ranging from 87.4% to 89.5%. The remainder of patients had severe acne — ranging from 10.5% to 12.6%.



[redacted]

Critical Appraisal

The randomization and masking procedures in Study 202 were considered appropriate. The coprimary and secondary end points were controlled for multiplicity. Type I error was controlled by requiring all the coprimary efficacy end points to be statistically significant, and failure of any 1 of the coprimary efficacy end points invalidated the statistical significance of all secondary efficacy end points. As it was a phase II trial aiming to provide preliminary evidence about the efficacy and harms of the study drug, the results cannot be considered confirmatory. Relevant patient demographic characteristics at baseline appeared to be balanced among the study drug groups. No notable differences in the baseline EGSS and lesion counts among study drug groups were identified. Similar to the pivotal trial, the washout periods used in the studies were considered adequate and the list of prohibited treatments for acne was considered comprehensive by the clinical expert. A total of 7 patients had protocol deviations regarding the specified washout period for prior medications. For the outcomes on quality of life (Acne-QoL self-perception and symptom domains), no inferential analyses were conducted, per the statistical analysis plan, so no conclusions could be drawn from these data. Of note, while all data were summarized in listings presented by patient, data collected at early discontinuation and unscheduled visits occurring before study day 8 were not included in the analyses of efficacy and safety, except for baseline values.

The inclusion criteria used in Study 202 included the population of interest identified in the anticipated indication for IDP-126 gel, except those patients in Study 202 had to be at least 12 years of age, which differed from the anticipated indication (patients aged 9 years and older with acne vulgaris). In consultation with the clinical expert, it was concluded that the inclusion criteria adequately capture (and consequently the study population is representative of) the patients who would be candidates for IDP-126 gel seen in practice. In consultation with the clinical expert, it was concluded that topical fixed-dose combination therapies, including retinoid and benzoyl peroxide, are relevant comparators to IDP-126 gel in the practice settings in Canada. Similar to the pivotal trial and Study 201, in consultation with the clinical expert, it was concluded that the outcome measures of acne severity and lesion counts used in Study 202 are applicable to clinical practice in Canada. Similar to the pivotal trial, the majority of patients from each study (approximately ≥ 87.4% of patients in each study drug group) had moderate acne.

Overall, no notable concerns on the generalizability of results to the population of interest in the setting in Canada was identified in the appraisal of Study 202.

Table 3: Summary of Findings for IDP-126 Gel Versus IDP-126 Vehicle Gel for Patients With Acne

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Acne severity				
Treatment success, percentage of patients with ≥ 2-grade reduction from baseline in the EGSS and an EGSS of clear or almost clear (95% CI) Follow-up: week 12	183 (Study 301) 180 (Study 302)	Study 301 • IDP-126 gel: 496 per 1,000 (403 to 581 per 1,000) • IDP-126 vehicle gel: 249 per 1,000 (138 to 354 per 1,000) • Difference: 247 more per 1,000 (107 more to 387 more per 1,000) Study 302 • IDP-126 gel: 505 per 1,000 (411 to 589 per 1,000) • IDP-126 vehicle gel: 205 per 1,000 (99 to 301 per 1,000) • Difference: 300 more per 1,000 (164 more to 436 more per 1,000)	High[a]	Once-daily topical application of IDP-126 gel results in a clinically meaningful increase in the proportion of patients with treatment success when compared with its vehicle gel.
Lesion count				
Inflammatory lesion count, LS mean absolute change from baseline (95% CI) Follow-up: week 12	183 (Study 301) 180 (Study 302)	Study 301 • IDP-126 gel: –27.7 (–29.4 to –26.0) • IDP-126 vehicle gel: –21.7 (–23.9 to –19.5) • Difference: –5.94 (–8.73 to –3.14) Study 302 • IDP-126 gel: –30.1 (–31.8 to 28.4) • IDP-126 vehicle gel: –20.8 (–23.3 to –18.3) • Difference: –9.30 (–12.38 to –6.23)	High[b]	Once-daily topical application of IPD-126 gel results in little to no clinically meaningful difference in inflammatory lesion count when compared with its vehicle gel.
Inflammatory lesion count, LS mean percent change from baseline (95% CI) Follow-up: week 12	183 (Study 301) 180 (Study 302)	Study 301 • IDP-126 gel: –75.70 (NA) • IDP-126 vehicle gel: –59.62 (NA) • Difference: –16.08 (–23.72 to –8.44) Study 302 • IDP-126 gel: –80.13 (NA) • IDP-126 vehicle gel: –56.18 (NA) • Difference: –23.95 (–31.73 to –16.16)	High[c]	Once-daily topical application of IDP-126 gel results in a clinically meaningful reduction in inflammatory lesion count when compared with its vehicle gel.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Noninflammatory lesion count, LS mean absolute change from baseline (95% CI) Follow-up: week 12	183 (Study 301) 180 (Study 302)	Study 301 • IDP-126 gel: –35.4 (–38.2 to –32.6) • IDP-126 vehicle gel: –23.5 (–27.2 to –19.8) • Difference: –11.85 (–16.56 to –7.14) Study 302 • IDP-126 gel: –35.2 (–37.8 to –32.6) • IDP-126 vehicle gel: –22.0 (–25.6 to –18.4) • Difference: –13.27 (–17.74 to –8.80)	Moderate[d]	Once-daily topical application of IDP-126 gel likely results in a clinically meaningful reduction in noninflammatory lesion count when compared with its vehicle gel.
Noninflammatory lesion count, LS mean percent change from baseline (95% CI) Follow-up: week 12	183 (Study 301) 180 (Study 302)	Study 301 • IDP-126 gel: –72.70 (NA) • IDP-126 vehicle gel: –47.61 (NA) • Difference: –25.09 (–34.96 to –15.22) Study 302 • IDP-126 gel: –73.26 (NA) • IDP-126 vehicle gel: –48.99 (NA) • Difference: –24.27 (–32.86 to –15.68)	High[e]	Once-daily topical application of IDP-126 gel results in a clinically meaningful reduction in noninflammatory lesion count when compared with its vehicle gel.
HRQoL				
Acne-QoL self-perception domain score, mean absolute change from baseline (95% CI) Follow-up: week 12	183 (Study 301) 180 (Study 302)	Study 301 • IDP-126 gel: 8.3 (NA) • IDP-126 vehicle gel: 5.9 (NA) • Difference: [redacted] Study 302 • IDP-126 gel: 9.1 (NA) • IDP-126 vehicle gel: 5.0 (NA) • Difference: [redacted]	Moderate[f]	Once-daily topical application of IDP-126 gel likely results in little to no clinically meaningful difference in Acne-QoL self-perception domain score when compared with its vehicle gel.
Acne-QoL acne symptom domain score, mean absolute change from baseline	183 (Study 301) 180 (Study 302)	Study 301 • IDP-126 gel: 7.6 (NA) • IDP-126 vehicle gel: 5.5 (NA)	High[g]	Once-daily topical application of IDP-126 gel results in little to no clinically meaningful

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
(95% CI) Follow-up: week 12		• Difference: [redacted] Study 302 • IDP-126 gel: 7.6 (NA) • IDP-126 vehicle gel: 4.1 (NA) • Difference: [redacted]		difference in Acne-QoL acne symptom domain score when compared with its vehicle gel.
Harms				
General disorders and administration site conditions, n (95% CI) Follow-up: week 12	363 (2 RCTs)	Study 301 and Study 302 pooled • IDP-126 gel: 136 per 1,000 • IDP-126 vehicle gel: 8 per 1,000	Moderate[h]	Once-daily topical application of IDP-126 gel likely results in an increase in general disorders and administration site conditions, and skin and subcutaneous tissue disorders when compared with its vehicle gel.
Skin and subcutaneous tissue disorders, n (95% CI) Follow-up: week 12	363 (2 RCTs)	Study 301 and Study 302 pooled • IDP-126 gel: 29 per 1,000 • IDP-126 vehicle gel: 8 per 1,000	Moderate[h]	
SAEs, n (95% CI) Follow-up: week 12	363 (2 RCTs)	Study 301 and Study 302 pooled • IDP-126 gel: 0 per 1,000 • IDP-126 vehicle gel: 0 per 1,000	Moderate[h]	Once-daily topical application of IDP-126 gel likely results in little to no difference in SAEs when compared with its vehicle gel.

Acne-QoL = Acne-specific Quality of Life; CI = confidence interval; EGSS = Evaluator's Global Severity Score; HRQoL = health-related quality of life; IDP-126 = clindamycin plus benzoyl peroxide and adapalene; LS = least squares; NA = not available; RCT = randomized controlled trial; SAE = serious adverse event.

Notes: Study limitations (which refers 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. Overall, no serious risk of bias concern and no serious concern about the generalizability of results to the population of interest was identified in the review and appraisal of Study 301 and Study 302. In consultation with 1 clinical expert consulted for the purpose of this review, the following thresholds of importance (i.e., a clinically meaningful difference) were determined for the assessment of outcomes on acne severity and lesion counts. The thresholds of importance (MID) used in the assessment of HRQoL outcomes are based on findings in the literature.

[a]Data from both trials show IDP-126 gel may provide benefit based on a clinically meaningful difference of at least 100 more patients with treatment success per 1,000 patients.

[b]Data from the trials show IDP-126 gel may provide little to no benefit based on a clinically meaningful difference of at least 10 lesions.

[c]Data from the trials show IDP-126 gel may provide benefit based on a clinically meaningful difference of at least 10% of lesions.

[d]Rated down 1 level for serious imprecision; data from both trials show IDP-126 may provide benefit or little to no benefit based on a clinically meaningful difference of at least 10 lesions.

[e]Data from both trials show IDP-126 gel may provide benefit based on a clinically meaningful difference of at least 10% of lesions.

[f]Analysis of this HRQoL outcome was not adjusted for multiplicity and as such, the results are considered supportive evidence. Rated down 1 level for serious imprecision; data from both trials show IDP-126 gel may provide benefit or little to no benefit based on a clinically meaningful difference of 5.15 points.

[g]Analysis of this HRQoL outcome was not adjusted for multiplicity and as such, the results are considered supportive evidence. Data from the trials show IDP-126 gel may provide little to no benefit based on a clinically meaningful difference of 4.62 points.

[h]Rated down 1 level for serious imprecision; total sample size and number of events did not reach the optimal information size.

Sources: Study V01-126A-301 Clinical Study Report, Study V01-126A-302 Clinical Study Report, and Common Technical Document section 2.7.4: summary of clinical safety. Details included in the table are from the sponsor's Summary of Clinical Evidence and sponsor response to April 8, 2024, request for additional information regarding IDP-126 gel review.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients aged 9 years and older with acne vulgaris
Treatment	Clindamycin 1.2%, benzoyl peroxide 3.1% and adapalene 0.15% topical gel (IDP-126)
Dose regimen	A pea-sized amount of gel (1.5 g) once daily
Submitted price	IDP-126 gel: $147.42 per 50 g pump
Submitted treatment cost	$1,614 per year
Comparators	• Topical retinoid monotherapy • Topical antibiotic monotherapy • Topical antibiotic and retinoid fixed-dose combinations • Topical retinoid and benzoyl peroxide fixed-dose combinations • Topical antibiotic and benzoyl peroxide fixed-dose combinations
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	60 weeks (1.15 years)
Key data source	Pivotal trials: Study 301 and Study 302 comparing IDP-126 gel to vehicle Sponsor-submitted indirect treatment comparison
Submitted results	Among the optimal treatments (on the efficiency frontier): IDP-126 gel was the most costly and most effective — with an ICER of $62,967 per QALY gained (incremental costs = $1,133; incremental QALYs = 0.02) compared to topical antibiotic and benzoyl peroxide fixed-dose combinations.
Key limitations	• The comparative efficacy of IDP-126 gel relative to other acne treatments is uncertain owing to a lack of robust comparative data. Indirect evidence submitted by the sponsor suggested that IDP-126 gel demonstrated a favourable treatment effect vs. topical monotherapies on change in lesion count reductions. Additionally, while the effect estimates are suggestive of a possible favourable treatment effect with IDP-126 gel vs. topical fixed-dose combination dual therapies, there is some uncertainty with this finding. Limitations with the NMA render the magnitude of benefit associated with IDP-126 gel to be uncertain. As well, comparisons between multiple topical treatments (for example, between topical antibiotic and benzoyl peroxide fixed-dose combinations used with a topical retinoid monotherapy) were not included in the submitted NMA. As such, the efficacy of the individual components of IDP-126 gel vs. the fixed-dose combination product is unknown. • The submitted model structure, based on lesion counts, does not reasonably reflect the disease area and current management of acne vulgaris. The model structure assumes that number of lesions is the only outcome of importance to patients — that patients would value any increase or decrease in any number of lesions — which contradicts the patient and clinical expert input received for this review. As well, the approach heavily relied on the number of lesions patients have at baseline, meaning the cost-effectiveness results were highly influenced by baseline lesion counts. This approach, combined with a number of additional simplifying assumptions made by the sponsor, meant that IDP-126 was certain to lead to an incremental clinical benefit, regardless

Component	Description
	of alternative inputs, apart from baseline lesion count. Due to limitations in the submitted model structure, the relative cost-effectiveness of IDP-126 gel for the treatment of acne vulgaris is highly uncertain. • Treatments that represent the current management of acne vulgaris (such as hormone therapies, oral antibiotic monotherapy, combinations of double-drug fixed-dose topical treatments with oral antibiotics, and combinations of different topical treatments) were identified as relevant comparators but were not included in the analysis. As some of the comparators were included in the sponsor's NMA, they could have been included in the economic evaluation. • The impact of IDP-126 on patient HRQoL is highly uncertain as the sponsor assumed a perfectly linear relationship between lesion count and utility values. This approached required that utilities be capped to avoid producing implausible utility values at lesion counts of 71 or greater.
CDA-AMC reanalysis results	• We were unable to address the identified limitations of the submitted economic evaluation through reanalysis and a CDA-AMC reanalysis could not be specified. As a result, the cost-effectiveness of IDP-126 gel for the treatment of acne vulgaris in patients aged 9 years and older is highly uncertain.

CDA-AMC = Canada's Drug Agency; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; IDP-126 = clindamycin, benzoyl peroxide, and adapalene; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; vs. = versus.

Budget Impact

We identified the following limitations in the sponsor's base case: uncertainty in the estimates of the market size and uncertainty in market uptake.

We were unable to address these limitations through reanalyses. In the submitted base case, the budget impact from the introduction of IDP-126 gel was estimated to be $444,986 in year 1, $712,533 in year 2, and $1,072,908 in year 3. The 3-year net budget impact of IDP-126 gel was estimated to be $2,230,428.

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: August 28, 2024

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.

ISSN: 2563-6596

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

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