Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.

Recommendation: Reimburse with Conditions

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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 **Error! Reference source not found.** are met.

Rationale for the Recommendation

Two phase 3, 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 results 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 EGSS of clear or almost clear) at week 12 was 24.7% (95% confidence interval [CI], 10.7% to 38.7%; P value = 0.003), in favour of IDP-126 gel; in Study 302, the difference was 30.0% (95% CI, 16.4% to 43.6%; P value = 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 value < 0.001]; Study 302: between-group difference – 23.95% [95% CI, –31.73% to –16.16%; P value < 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 certain 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 since 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 therapy 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 Studies 301 and 302 regarding acne severity, lesion counts, harms, and health-related quality of life (HRQoL) was of moderate to high certainty as per the 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. Results of the HRQoL outcomes at week 12 were suggestive of little-to-no clinically meaningful difference in the 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 therapy for acne. 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 2 and phase 3 trials.
- **Additional indirect evidence:** Findings from an NMA by Huang et al. aligned with the sponsor conducted NMA results as the estimates comparing triple therapy (topical antibiotic, retinoid, and benzoyl peroxide [BPO]) 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 pre-specification 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 2 trials (Studies 201 and 202) provided supportive evidence suggesting a possible favourable treatment effect with IDP-126 gel versus vehicle gel and topical dual combination therapies (fixed-dose combination of retinoid and BPO, antibiotic and BPO, and retinoid and antibiotic) based on treatment success and change in lesion counts at week 12. The results were consistent with the pivotal phase 3 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 5.6 million individuals living in Canada, nearly 20% of the population.

According to the 2016 Canadian clinical practice guideline in the management of acne, topical therapies are a reasonable first-line treatment option for comedonal and mild papulopustular acne, including topical retinoids, benzoyl peroxide (BPO), and fixed-dose combinations of retinoids with BPO 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 female patients. Systemic therapies are a reasonable treatment option for severe acne, including oral isotretinoin, oral antibiotics in combination with BPO, 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. It is available as a topical gel and the dosage recommended in the product monograph is 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 3, multicenter, randomized, double-blinded, vehicle-controlled, parallel-group clinical studies in patients aged 9 years and older with moderate to severe acne; 2 indirect treatment comparisons; and 2 phase 2, multicenter, randomized, double-blind, vehicle-controlled studies.
- patients' perspectives gathered by 2 patient groups, Acne and Rosacea Society of Canada and Canadian Skin Patient Alliance
- input from public drug plans that participate in the CADTH 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

Stakeholder Perspectives

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

Patient Input

The Acne and Rosacea Society of Canada (ARSC) and the Canadian Skin Patient Alliance (CSPA) submitted a joint input on the current review of IDP-126 gel. Patient input was gathered using an online survey that was conducted between June 7 to 30, 2022. A total of 154 responses were collected from patients with acne (either diagnosed by a dermatologist or healthcare provider or self-diagnosed) and their caregivers living in Canada. Most respondents (68%) were female, 30% were male, and 2% identified as non-binary. 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 to 5 healthcare visits before receiving their diagnosis and treatment for acne. Nearly 30% of survey respondents reported visiting a healthcare 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, 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 regime 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 (non-prescription 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 versus their previous therapies. Further, 2 of the three 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 their acne, identifying triggers, and coping with high out-of-pocket expenses on non-prescription acne products and treatments. 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 include 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 BPO 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 other therapies currently available and due to 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 patients 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 CADTH reimbursement review process. The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
In Studies 301 and 302, many patients 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 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, and 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. Further, 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.
Considerations for initiation of therapy	
Are the coprimary efficacy end points assessed in Studies 301 and 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 Studies 301 and 302, patients did not have to fail 1 or 2 topical products for acne before being 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 have to 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 Studies 301 and 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

Implementation issues	Response
	medication that is causing the acne, treating a congenital hormonal condition, etc.).
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).

IDP-126 = clindamycin plus benzoyl peroxide and adapalene.

Clinical Evidence

Systematic Review

Description of Studies

Two phase 3, multicenter, double-blind, randomized controlled trials (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 health-related quality of life (HRQoL) measured by the self-perception and symptom subscales of the Acne-Specific Quality of Life (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 Evaluator's Global Severity Score

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% confidence interval [CI], 10.7% to 38.7%; P value = 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 value = 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 value < 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 value < 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 value < 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 value < 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 value < 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 value < 0.001), also in favor 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 value < 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 value < 0.001), also in favor of IPD-126 gel.

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

[redacted]

Harms Results

The following summary of harms results from Studies 301 and 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 were reported with 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 were reported with a TEAE categorized as a skin and subcutaneous tissue disorder.

Critical Appraisal

Internal Validity

Studies 301 and 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 Food and Drug Administration (FDA) guidance 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 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 to consider both changes in lesion counts and treatment success in the assessment of treatment effect — this is reflected in Studies 301 and 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 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 Studies 301 and 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 12 years of age 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 Canadian clinical practice. 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 pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for 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 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.

For the GRADE assessments, 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

Error! Reference source not found. presents the GRADE summary of findings for IDP-126 gel versus IDP-126 vehicle gel.

Indirect Comparisons

Description of Indirect Treatment Comparisons

The sponsor conducted an indirect treatment comparison (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 network meta-analyses (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/BPO/retinoid, topical retinoid/BPO, topical antibiotic/BPO, or topical antibiotic/retinoid, topical monotherapies (i.e., antibiotic, retinoid, BPO, or other), combinations of topical treatments that includes oral antibiotic, oral antibiotic monotherapy, combinations of physical treatments with oral antibiotic, physical treatment only, other treatments, and vehicle/placebo. A Bayesian framework was used, employing 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 by using the Investigator's Global Assessment (IGA); and discontinuation due to any adverse events (AEs).

Efficacy Results

NMA on proportion of patients experiencing treatment success included 46 trials and 12 treatment groups. According to the estimated odds ratio (ORs), IDP-126 gel demonstrated higher efficacy compared to the vehicle/placebo comparison group (OR = 6.30; 95% credible interval [CrI], 3.90 to 9.87). Moreover, IDP-126 gel was favored in comparisons to other active treatments (oral antibiotic monotherapy, topical monotherapies, topical fixed-dose combinations of antibiotic/retinoid and antibiotic/BPO).

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 2813 per study for the two networks. 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 (-8.21; 95% CrI, -10.33 to -6.13 and -13.41; 95% CrI, -16.69 to -10.32), respectively). Comparisons with other active treatments (i.e., oral antibiotic, topical monotherapies, and topical antibiotic/retinoid - fixed-dose combinations) showed that IDP-126 gel was favored, both for the inflammatory and noninflammatory lesion count reduction.

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

Harms Results

[redacted]

Critical Appraisal

The sponsor conducted NMA used recommended methods for conduct and reporting of NMAs and demonstrated favorable 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. 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 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 Canadian clinical practice (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 included treatments. Considering all of the above, 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 pre-specification 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 issue (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 Canadian clinical context.

Studies Addressing Gaps in the Evidence From the Systematic Review

Study 201

Description of Study

One phase 2, 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 Studies 301 and 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 Studies 301 and 302. The comparators are IDP-126 Component A (BPO 3.1%/adapalene 0.15% gel), IDP-126 Component B (clindamycin phosphate 1.2%/BPO 3.1% gel), IDP-126 Component C (clindamycin phosphate 1.2%/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 Evaluator's Global Severity Score

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 Component A group, 30.5% in Component B group, 30.3% in Component C group, and 8.1% in the vehicle gel group. The treatment difference in treatment success based on the EGSS were not reported.

Lesion Count

Inflammatory Lesion Count

The LS mean change from baseline in inflammatory lesion count at week 12 were –29.9 (SD = 11.86) in the IDP-126 gel group, –26.7 (SD = 11.74) in Component A group, –24.8 (SD = 11.71) in Component B group, –26.8 (SD = 11.69) in Component C group, and –19.6 (SD = 12.12) in its vehicle gel group. The treatment difference in the mean absolute change from baseline in inflammatory lesion count at week 12 were not reported.

[redacted]

Noninflammatory Lesion Count

The LS mean change 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 Component A group, –27.8 (SD = 15.97) in Component B group, –30.0 (SD = 16.40) in Component C group, and –21.8 (SD = 16.58) in its vehicle gel group. The treatment difference in the mean absolute change from baseline in noninflammatory lesion count at week 12 were not reported.

[redacted]

Quality of Life

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

The mean change 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 Component A group, 7.5 (SD = 7.22) in Component B group, 8.5 (SD = 8.22) in Component C group, and 5.9 (SD = 7.99) in its vehicle gel group. The treatment difference in the absolute change from baseline in the Acne-QoL self-perception domain score at week 12 were not reported.

The mean change 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 Component A group, 6.9 (SD = 5.63) in Component B group, 6.6 (SD = 6.07) in Component C group, and 4.9 (SD = 5.53) in its vehicle gel group. The treatment difference 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 that reported at least one TEAE were similar in the IDP-126 gel and IDP-126 Component A groups (36.2% and 35.6%, respectively), while the proportion of patients that 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 Component A group, 0.7% in Component B group, 3.4% in Component C group, and 0.7% in its vehicle gel group), application site dryness (6.4% of patients in the IDP-126 gel group, 5.5% in Component A group, 1.4% in Component B group, 6.1% in Component C group, and 0.7% in its vehicle gel group), and application site exfoliation (3.5% of patients in the IDP-126 gel group, 2.1% in Component A group, 0.0% in Component B group, 1.4% in Component C group, and 0.7% in its vehicle gel group).

Serious Adverse Events

A total of 4 patients were reported with SAEs – one patient in the IDP-126 gel group experienced sickle cell anaemia with crisis, and 3 patients in the Component C group (hyperbilirubinaemia, enteritis, and abortion induced; n = 1 each).

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 vel 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 one 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. Since it was a phase 2 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 and therefore there is a greater likelihood of type 1 error. For the outcomes on quality of life (Acne-QoL self-perception and symptom domains), no inferential analyses or multiplicity adjustments were conducted as per the statistical analysis plan, so this data is 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, the 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 2 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/BPO, antibiotic/BPO, and retinoid/antibiotic) are relevant comparators to IDP-126 gel in the Canadian practice setting. 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 Canadian clinical practice. Overall, no notable concerns on the generalizability of results to the population of interest in the Canadian setting was identified in the appraisal of Study 201.

Study 202

Description of Study

One additional phase 2, 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 Studies 301 and 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%/BPO 2.5% gel. Other efficacy and safety outcomes assessed are similar to those assessed in Studies 301 and 302. The mean age of patients randomized to each study drug group was similar— approximately 20 years and ranged 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]

[redacted]

Critical Appraisal

The randomization and masking procedures in Study 202 were considered appropriate. The coprimary and secondary endpoints were controlled for multiplicity. Type I error was controlled by requiring all the coprimary efficacy endpoints to be statistically significant, and failure of any one of the coprimary efficacy end points invalidated the statistical significance of all secondary efficacy end points. Since it was a phase 2 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 seven 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 as 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 prior to 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/BPO, are relevant comparators to IDP-126 gel in the Canadian practice setting. 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 Canadian clinical practice. 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 Canadian setting 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.
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.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
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.
Health-related Quality of Life				
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 (95% CI) Follow-up: Week 12	183 (Study 301) 180 (Study 302)	Study 301 • IDP-126 gel: 7.6 (NA) • IDP-126 vehicle gel: 5.5 (NA) • Difference: [redacted] Study 302 • IDP-126 gel: 7.6 (NA) • IDP-126 vehicle gel: 4.1 (NA) • Difference: [redacted]	High[g]	Once daily topical application of IDP-126 gel results in little to no clinically meaningful 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]	

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
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; EGSS = Evaluator's Global Severity Score; LS = least squares; NA = not available; RCT = randomized controlled trial; SAE = serious adverse event.

Note: 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 table 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 Studies 301 and 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] –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, results are considered supportive evidence. –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, 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] –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 and 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 9 years of age 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/retinoid fixed dose combinations • Topical retinoid/BPO fixed dose combinations • Topical antibiotic/BPO 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, 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/BPO 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 versus 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 versus 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/ 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 versus 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 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 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 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.

Component	Description
	• Treatments that represent current management of acne vulgaris (such as hormone therapies, oral antibiotic monotherapy, combinations of double-agent 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.
CADTH reanalysis results	• CADTH was unable to address the identified limitations of the submitted economic evaluation through reanalysis and, a CADTH reanalysis could not be specified. As a result, the cost-effectiveness of IDP-126 gel for the treatment of acne vulgaris in patients 9 years of age and older is highly uncertain.

BPO = benzoyl peroxide; 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.

Budget Impact

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

CADTH was 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 three-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