CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

clascoterone (Winlevi)

(Sun Pharma Canada Inc.)

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

August 19, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Winlevi (clascoterone)
Indication: Acne vulgaris (first-line prescription topical treatment of moderate and severe acne vulgaris in patients 12 years of age and older)
Name of Patient Group: Acne and Rosacea Society of Canada (ARSC) and Canadian Skin Patient Alliance (CSPA)
Author of Submission: Sue Sherlock, Executive Director, ARSC and Sabrina Ribau, Programs Manager, CSPA

1. About Your Patient Group

The Acne and Rosacea Society of Canada (ARSC), a national, not for profit organization comprised of dermatologists, patients, educators and communicators, offers hope and help to sufferers by providing independent, reputable and current information on these conditions and raising awareness. For more information, please visit https://www.acneaction.ca.

The Canadian Skin Patient Alliance (CSPA) is a national non-profit organization with a mission to improve the health and wellbeing of people across Canada affected by skin, hair, and nail conditions, through collaboration, advocacy, and education. The CSPA also works with our network of Affiliate Members, including the Acne and Rosacea Society of Canada, to support the communities we both serve. For more information, please visit www.canadianskin.ca.

2. Information Gathering

1. In order to gather information for section 6, Experience with the Drug Under Review, ARSC and CSPA created a survey (Google Forms) for patients who have used the drug. We contacted dermatologist members of ARSC's and CSPA's medical advisory committees and we sent emails to a list provided by Sun Pharma Canada of 10 Canadian dermatologists known to have prescribed Winlevi with a request to all to email their patients who have used the drug and enquire if they would be interested in replying to a survey about their experiences with the drug. We received 3 responses from patients. These are detailed in section 6, Experience with the Drug Under Review.

2. In June of 2022, the Acne and Rosacea Society of Canada (ARSC) and the Canadian Skin Patient Alliance (CSPA) conducted a joint survey to understand patient experiences with acne, including onset, healthcare resource use, experiences with treatments and impact on quality of life. We included a 5-question scale called CompAQ-short form (SF) to understand how facial and torso / truncal acne affected respondents' quality of life.

The survey was created in Survey Monkey. Eligibility criteria was either diagnosed with acne by a healthcare provider or self-diagnosed with acne or acting as a caregiver to an individual with acne. Resides in Canada was the other eligibility criteria. We disseminated the survey link through CSPA's website, newsletter, social media channels and email lists and ARSC's social media channels and network of dermatologists. The survey was open from June 7-30, 2022.

We received 154 eligible respondents, 59% of whom acne were diagnosed by a dermatologist, 24% diagnosed by a healthcare provider and 14% self-diagnosed. Some 68% of respondents were female, 30% male and 2% identified as non-binary. Regarding age, 55% were 20-29 years old, some 23% were 30 to 39 and 12% were aged 16-19.

Some 28% of respondents first experienced pimples and breakouts at age 12 or younger. Almost half of respondents (47%) first developed acne symptoms between the ages of 13 and 19.

Some 62% were Caucasian, 15% Indigenous/Aboriginal, and 7% Black/African American while the remaining respondents came from a wide range of ethnic backgrounds. Respondents represented all provinces. Some 50% were from Ontario and British Columbia.

Respondents were provided with definitions and pictures of mild, moderate and severe acne and were asked to indicate the severity of their acne symptoms. Nearly half of all respondents (47%) reported symptoms consistent with moderate acne (blackheads, whiteheads and red pustules and papules on face),16% indicated severe acne (facial redness with numerous red papules and pustules and swollen lumps and bumps on face, chest and/or back) and 37% reported mild acne (blackheads, whiteheads and a few red pustules and papules intermittently).

Information gathered from the survey was analyzed and formed a report, "Breaking Out: A report on the acne patient experience in Canada".

3. Disease Experience

Acne is a common skin condition involving the oil (sebaceous) glands in the skin. The highest concentrations of oil glands are found in the skin on the face, neck, chest, shoulders and back – areas where acne appears.

Acne usually begins at the start of puberty when hormone levels, particularly testosterone, surge. These hormones cause many changes within our bodies. One of these is to disrupt the skin's normal processes. Dead skin cells in the pores are not shed as quickly as usual, stick together and pile up on the surface. Oil glands within the skin, stimulated by hormones, enlarge and become overactive, pumping out excess oil. This oily substance combines with dead skin cells to clog skin pores. The earliest stages of acne appear – blackheads, clogged but open pores and whiteheads, plugged, closed pores.

Bacteria naturally present in the skin thrive in these blocked, oily skin pores. The plugged pores may expand and break, and the bacteria may then add to the inflammatory reaction seen as redness and swelling. Papules - many, small red bumps with or without pus - appear and pustules (known as *pimples*), pus-filled spots can be seen. Some people develop deep acne nodules and boil-like lesions called acne cysts. Cysts and nodules are often painful, lodged deep and can cause considerable injury to the skin.

Acne affects 85% of people aged 12 to 24. The condition occurs in people of all ethnic groups. In the past, acne was seen as a mainly teenage skin problem. However, studies show it is prevalent in adults too, particularly women in their 20s and 30s. Adult acne causes frustration and emotional distress and can lead to anxiety and depression.

It is estimated that 70% of Canadians will get mild acne, a form that can be self-treated with good skincare and over-the-counter treatments. This is not the case for moderate and severe acne. Approximately 26-27% will get moderate acne. Moderate acne generally requires medical intervention to resolve the condition and limit the risk of scarring, pigmentation changes (brown or red stains left after acne) and emotional distress. An estimated 3-4% will get severe acne. **Medical help** is needed to bring severe acne under control and limit the risk of scarring, pigmentation changes and emotional distress.

Acne usually appears on the face and consequently affects appearance, self-esteem and self-confidence. It generally occurs during the teenage years and can affect the development of self-image and assertiveness – factors that are important in forming friendships and dating.

"In elementary school, I didn't really care much about having acne but it started to get to me once I hit high school. I was embarrassed and wanted to fix it. Acne impacted me during on-line school because you get up to take a break. While most people might check themselves in the mirror, I could not look at myself for the longest time. I'd turn off my camera most of the time too."

Acne is associated with various forms of emotional distress ranging from bad moods to anxiety, anger, poor self-image, loneliness, self-consciousness, shame, low self-esteem, depression, pain, anxiety in social situations, a feeling of overall poor health and unhappiness with appearance.

"Acne is much more than cosmetic. My pimples were itchy, uncomfortable, and even painful. They also did a serious number on my self-esteem. I have no pictures of my acne at its worst because I made a point of avoiding cameras. I also avoided mirrors and made excuses not to attend gatherings with friends and family. On good days, I felt ugly. On bad days, I felt worthless."

The prevalence of depression in acne patients is thought to be high. A survey of high school students in New Zealand with problem acne reported high rates of depressive symptoms (24%), anxiety (9%), and suicidal thoughts (34%)[(1)].

People with acne often feel ashamed and self-conscious and report that the condition impedes their ability to be social and conduct daily activities. They may avoid social interactions, use makeup to hide their acne or grow their hair or beard to hide their face. Some avoid sports such as swimming if they have acne on the body. Others may avoid using changerooms, which can negatively impact their interest and participation in sports and other activities.

Findings from our survey showed almost half of the respondents often or always feel self-conscious due to their acne. Most (87%) use strategies to hide their acne, with 63% using makeup and 59% avoiding social gatherings altogether.

"My way of coping was to put on lots of make-up. I would not leave the house without it. It was so embarrassing and affected my self-confidence in talking to people. The face is the first thing you see when you meet someone. I felt down, sometimes anxious, and even angry that I could not get rid of my acne."

Acne can last for several years with periods of breakouts and clear skin, adding to the emotional toll of the condition. Half of the respondents in our survey reported they were always or often concerned that their skin would never clear up.

Some acne sufferers say the psychological effects associated with this condition, such as hurt and shame, continue to be felt for many years. Experts call this "emotional scarring".

There are some upsetting myths about acne – that it is self-caused by eating fatty or high carb foods, or through being unhygienic in daily care, that stigmatize the condition. Another myth is that acne is "just pimples" offering little empathy or understanding of the emotional distress that can accompany the condition.

"Acne was just considered a part of growing up. And maybe my acne just wasn't as bad as other people's acne. It always affected me mentally; I hated my skin (and still do) and have always felt unattractive because of it."

Finally, the burden of acne is not only in the active lesions but also acne scars and pigmentation changes. These are significant, lasting and detrimental manifestations of acne. Visible scars can cause embarrassment, self-consciousness and are a risk factor for depression and anxiety.

Our survey of Canadian acne patients revealed a very high prevalence of acne scarring and pigmentation changes. The vast majority of respondents reported they had both scarring (87%) and pigmentation changes (90%) due to their acne.

In ARSC's and CSPA's 2022 collaborative report, *Breaking Out*, a correlation was seen between acne severity and both acne scarring and pigmentation changes with 100% of those with severe acne having both acne scarring and pigmentation changes. Of those reporting moderate acne, 84% had scarring and 94% pigmentation changes. Of those with mild acne, 71% had scarring and 86% pigmentation changes.

"Acne has left my face unrecognizable. My mental state is very depressed, prone to psychological disorders. This seriously affects my quality of life."

The high rate of acne scarring and hyperpigmentation among acne patients indicates a need for early, effective treatment to prevent these issues from developing. Many of our respondents reported moderate acne (47%) while 16% reported severe acne. Almost half of those surveyed (42%) said they had between 2-5 healthcare visits before being diagnosed and treated for acne. Nearly 30% visited a healthcare professional more than 5 times. Delay in the diagnosis and treatment of moderate and severe acne is a cause for concern given the risk of acne scarring, pigmentation changes and significant emotional effects.

(1) Sood S, Jafferany M, Vinaya kumar S, Depression, psychiatric comorbidities, and psychosocial implications associated with acne vulgaris. *J Cosmet Dermatol*. 2020;19:3177–3182. https://doi.org/10.1111/jocd.13753

4. Experiences With Currently Available Treatments

In our survey, we asked acne patients about their experiences with prescription medications. Respondents replied they have tried multiple prescriptions as well as skin procedures to try to gain control of their acne.

More than half (59%) of respondents reported that they had used isotretinoin pills to treat their acne, and it was the most effective treatment option seen in the survey, with 28% of individuals reporting significant improvement and 43% improving slightly.

Hormone pills (birth control and spironolactone) were the second most effective treatment option for those surveyed. Of the 59% who reported having used them, 23% had significant improvement and 36% had minor improvement.

It appears that prescription treatments may not be prescribed readily to those with acne, though future research is needed to understand whether this is due to physician perception that the patient may not be a good candidate for treatment benefits, patient hesitation, or lack of insurance coverage for the patient. There are also important barriers to accessing health care in Canada – particularly primary care and dermatology care – which may play a role as well.

The majority of respondents (95%) reported that they experienced acne treatment-related adverse effects in the last year, the most common being skin irritation (64%), dry skin (62%) and skin flaking (55%). When asked about current topical acne products (non-prescription and prescription), 85% of respondents reported that they were experiencing side effects due to their current regimen.

Minor side effects were reported by nearly 70% of respondents, and most were willing to accept them because the treatment was effective. Sixteen percent of individuals reported severe or very severe side effects, but their willingness to tolerate them was based on treatment effectiveness. Patients are clearly balancing out their desire to clear their skin - or at least improve it - with the harshness and discomfort of side effects, when deciding whether to start or continue their medications.

Looking at out-of-pocket monthly expenses due to prescription and non-prescription treatments for acne, nearly one-quarter of individuals indicated that they spend more than $50 every month on non-prescription acne products. When costs spent on acne products were compared based on respondents' acne severity, we found that a higher percentage

of individuals with severe acne paid $100/month or more on non-prescription acne products (14%) than those with mild (4%) or moderate acne (5%).

Between 15-20% of respondents reported that they spend more than $50 every month on each of the various prescription pills, gels and injection treatment options, providing evidence of a considerable financial burden that is not being covered by insurance. Respondents are also spending a considerable amount on prescribed gels and creams: 28% of those with severe acne and 17% of those with mild or moderate acne paid $50 or more every month.

Acne patients were also asked about specific skin procedures they had chosen to treat their acne. Facials and peels were used by more than half of all respondents (53%) while 65% underwent light or laser therapy. Individuals with moderate or severe acne were slightly more likely to undergo procedures to treat acne than those with mild acne.

Of all respondents, 12% reported paying more than $500 for each facial and peel, while 15% spent more than $500 for each light or laser therapy session. More than 30% of respondents of each severity spend more than $200 monthly on light or laser therapy while more than 28% of respondents of each severity spend that amount on facials and peels.

When asked about the challenges of managing acne, patients responded that the three most common areas of struggle were hiding acne, identifying triggers, and coping with mounting out-of-pocket expenses for treatments.

5. Improved Outcomes

Survey respondents were asked to rank the importance of various factors in deciding if their acne treatment had achieved their goals.

The three most prioritized goals were the ability to enjoy personal relationships, having less scarring, and having fewer changes in skin pigment. Other goals included clearer skin, better mental health, increased confidence, ability to be social and improved overall daily life.

More respondents reported satisfaction with prescription treatments (58%) than non-prescription treatments (44%). It is evident that treatment gaps exist for individuals with acne, and facilitation of access to effective and safe treatments is needed.

6. Experience With Drug Under Review

As mentioned at the beginning of this submission, we received three survey responses from individuals who have used Winlevi. Because there were so few responses, we have provided a snapshot of each of the survey respondents:

Respondent 1 is age 35–44 and first developed acne between the ages of 18 and 24. When asked to indicate the type of acne spots they had, the respondent reported "**pimples, whiteheads, red bumps and cysts**". The acne was located on the cheeks and jawline. According to the respondent, the most important aspects of acne to control are "**pimples, redness, red bumps, cysts and painful spots**." When asked how well their acne is controlled, they replied "**well controlled**".

Respondent 1 gained access to the drug via the self-paid route. In reply to the question - Compared to any other prescription treatments used, what were the benefits of the new treatment, they replied: "**When I stopped birth control, my acne came back with a vengeance. Antibiotics and prior creams don't clear my skin. This is the only topical that helps with my acne, I suspect because it works on hormones and the others don't. It's also not irritating, which must acne treatments are.**"

Respondent 1 was asked to compare the new treatment to any other prescription treatments used, and indicate the disadvantages of the new treatment. They replied: "**very expensive**".

Asked about the benefits/disadvantages of the new treatment on their daily life, respondent 1 said: "**Having acne at my age is embarrassing. This gives me confidence at work, social functions, even with my friends and family. I feel happier, don't avoid social functikns anymore. Sometimes I would wear a mask, not for Covid, but to hide my acne (Covid was a good excuse)**".

When questioned about the side effects experienced while using the new drug (choices were skin irritation, dry skin, redness, worsening of acne) respondent 1 said "**None of these**".

The respondent was asked if the drug easier to use than previous treatments and if so, how. They replied: "**Yes - not irritating**."

Respondent 1 was asked if the new treatment worked better or worse than previous treatments used. They replied: "**Better**".

Finally, respondent 1 was questioned about what was important and of value regarding the new drug. (choices were dosing regimen, ability to use a topical, coping with side effects, time it took for improvement, effectiveness of the drug, level of improvement). They replied: "**ability to use a topical, coping with side effects, time it took for improvement, effectiveness of the drug, level of improvement."**

Respondent 2 is age 25-34 and first developed acne under the age of 18. Their acne spots were identified as "**pimples, blackheads, whiteheads, red bumps, cysts**." The acne was located on the cheeks, nose, jawline and forehead. According to the respondent, the most important aspects of acne to control are: "**painful spots and scars**". When asked how well their acne is controlled, they replied: "**well controlled**".

Respondent 2 accessed the drug via private insurance. In reply to the question - Compared to any other prescription treatments used, what were the benefits of the new treatment, they replied: "**no irritation**".

They were asked to compare the new treatment to any other prescription treatments used, and indicate the disadvantages of the new treatment and replied: "**expensive**".

Asked about the benefits/disadvantages of the new treatment on their daily life, respondent 2 said: "**none**". When questioned about the side effects experienced while using the new drug (choices were skin irritation, dry skin, redness, worsening of acne) respondent 2 said "**None of these**".

The respondent was asked if the drug easier to use than previous treatments and if so, how. They replied: "**yes, i can use it every day without irritation**".

Respondent 2 was asked if the new treatment worked better or worse than previous treatments used. They replied: "**Better**".

Respondent 2 was questioned about what was important and of value regarding the new drug (choices were dosing regimen, ability to use a topical, coping with side effects, time it took for improvement, effectiveness of the drug, level of improvement). They replied: "**dosing regimen, ability to use a topical, coping with side effects, time it took for improvement, effectiveness of the drug, level of improvement**".

Respondent 3 is age under 18. They identified their acne spots as "**pimples**". The acne was located on the forehead. When asked what is the most important aspect of acne to control, they replied "**pimples**".

When asked how well their acne is controlled, they replied: "**somewhat controlled**". Respondent 3 gained access to the drug via private insurance. In reply to the question - Compared to any other prescription treatments used, what were the benefits of the new treatment, they replied: "**helps clear the skin**".

They were asked to compare the new treatment to any other prescription treatments used, and indicate the disadvantages of the new treatment and replied: "**it did not completely clear**".

Respondent 3 did not reply to the question about the benefits/disadvantages of the new treatment on their daily life. When questioned about the side effects experienced while using the new drug (choices were skin irritation, dry skin, worsening of acne) respondent 3 said "**None of these**".

The respondent was asked if the drug easier to use than previous treatments and if so, how. They replied: "**It was smooth and didn't make skin dry.**"

Respondent 3 was asked if the new treatment worked better or worse than previous treatments used. They replied: "**Better**".

Respondent 3 was questioned about what was important and of value regarding the new drug (choices were dosing regimen, ability to use a topical, coping with side effects, time it took for improvement, effectiveness of the drug, level of improvement). They replied: "**dosing regimen, coping with side effects, effectiveness of the drug**".

Despite the small group of respondents, we heard from 3 age groups – a person under the age of 18, another aged 25-34 and a third person aged 35-44. All respondents had acne on the face.

All three said the drug was easier to use than previous treatments since they did not experience side effects such as skin dryness and irritation. When asked what was important and of value regarding the new drug, they all indicated "**coping with side effects**" and "**effectiveness of the drug**".

7. Companion Diagnostic Test

There is no companion diagnostic test

8. Anything Else?

1. Acne is often disregarded as a cosmetic concern and the impacts of acne on patients' lives diminished. The driving mechanism of acne is rightly considered a medical issue and treatment approaches must be evidence-based.

2. There appears to be limited prescription treatment options for Canadians with moderate to severe acne as many respondents (59%) in our survey reported using only 2 treatments – isotretinoin and hormone pills (birth control and spironolactone). The side effects of isotretinion can be considerable and patients must be carefully monitored. Given that the hormone pills mentioned above cannot be used by males, treatment options for males are even more limited.

3. As we have seen in our survey, without access to safe, effective and affordable prescription treatment options, patients with moderate to severe acne are relying on a multitude of approaches that are not effective and may be expensive.

4. Not treating acne has its own consequences: Undertreated acne often results in scars and pigmentation changes which are each much more difficult to treat and can impact a patient for the rest of their lives. There is also the risk of negative psychosocial impacts when acne goes untreated.
5. Based on our survey findings, we have developed 3 stakeholder recommendations to improve the lives of individuals with acne:

    1. Increase access to new treatment options that are safe and effective.
    2. Ensure health care providers who see patients with acne are aware of all new and existing treatment options.
    3. Evaluate every patient with acne for depression and anxiety and connect them with support.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

    No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No. As mentioned above, the ARSC and CSPA collaborated to create the report, “Breaking Out: A report on the acne patient experience in Canada”. Sun Pharma, Bausch Health and L’Oreal Active Cosmetics provided financial support for the development of the report, including the survey that formed the basis of the report. No funders were involved in developing the content of the survey, which was led by consultant Jennifer Pereira, Dr Jerry Tan (President of the Acne and Rosacea Society of Canada), Sue Sherlock, Rachael Manion, Sabrina Ribau (Programs Manager, CSPA), an adult acne patient and a teenaged acne patient. The ARSC and CSPA are grateful to everyone who filled out the survey and shared their experiences with us.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bausch Health Canada		X		
Galderma Canada			X	
Sun Pharma Canada			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Sue Sherlock
Position: Executive Director
Patient Group: Acne and Rosacea Society of Canada
Date: **August 13, 2024**

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bausch Canada			X	
Galderma Canada			X	
L'Oréal Active Cosmetics		X		

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Sabrina Ribau
Position: Programs Manager
Patient Group: Canadian Skin Patient Alliance
Date: **August 13, 2024**

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0786
Generic Drug Name (Brand Name): Clascoterone (Winlevi™)
Indication: Acne Vulgaris
Name of Clinician Group: Dermatology Association of Ontario
Author of Submission: Dr. Maxwell Sauder, Secretary, Dermatology Association of Ontario

PLEASE NOTE: Section 6 is the only update from the previous submission. All other sections have remained the same.

1. About Your Clinician Group

The Dermatology Association of Ontario (DAO) (https://www.daontario.com) provides broad representation for dermatologists practicing in Ontario. Representing over half of the country's registered dermatologists, the DAO provides a unified voice for Ontario dermatologists in promoting better patient care, promoting dermatology in Ontario and supporting research and education within the community. The DAO membership consists of community dermatologists as well as national and internationally recognized experts in the treatment of acne.

2. Information Gathering

Information for this submission was gathered from clinical trial data, available literature retrieved through PubMed, and real-world evidence on clascoterone use in the United States. The clinical trial data includes information from the clascoterone Phase 3 pivotal trials, the Phase 3 long-term extension study, the Phase 2 safety study of high dose clascoterone use, and the Phase 2 clascoterone pharmacokinetics study. In areas where citable literature is scarce, we provided our expert opinion on the management approach, treatment landscape and available treatment options.

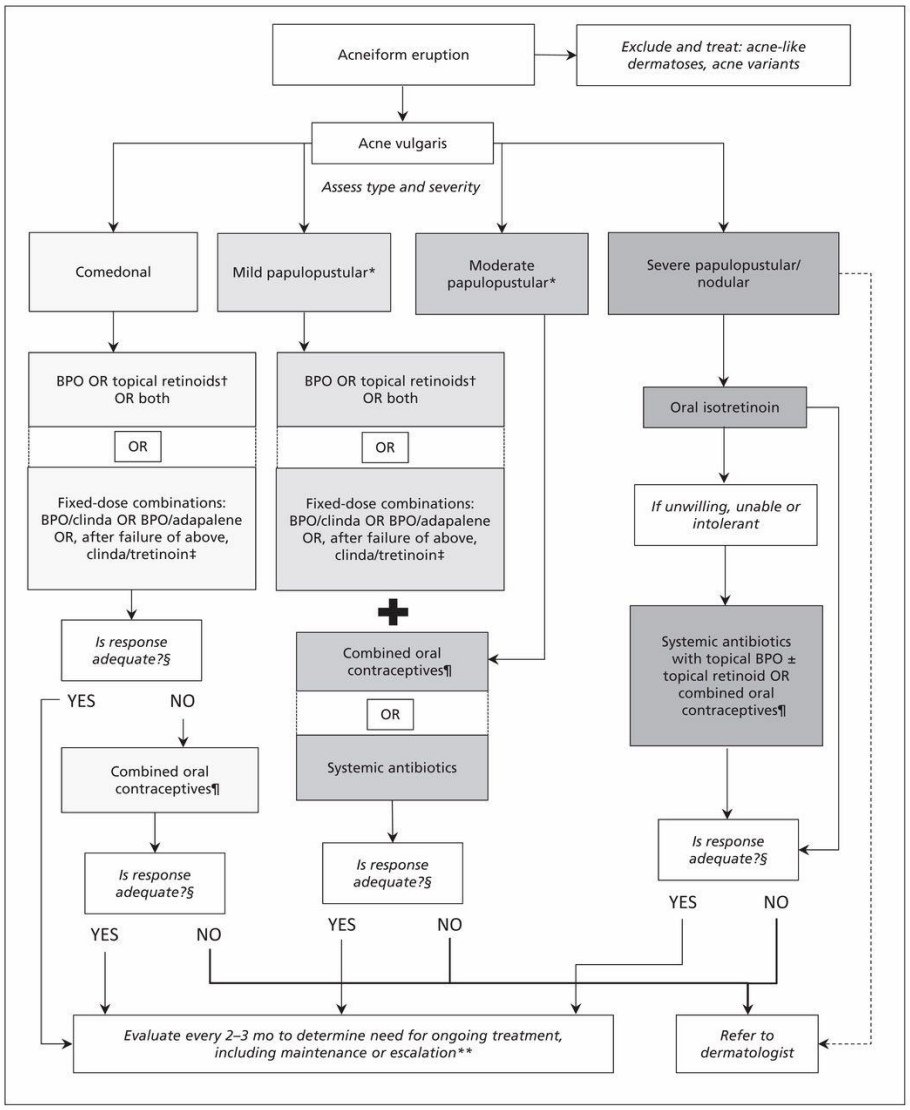
3. Current Treatments and Treatment Goals

2016 Canadian Treatment Algorithm

- The current algorithm for acne management in Canada was published in 2016 (Figure 1 below) *[Asai Y et al. 2016]*

- These guidelines recommend a general approach to selecting treatment options based on an assessment of acne type and severity *[Asai Y et al. 2016]*:
  - Comedonal acne (mild)
  - Papular acne (mild-to-moderate)
  - Pustular acne (moderate-to-severe)
  - Nodulocystic acne (severe)
- A Canadian working group is currently working on an update focusing on a multidisciplinary approach to acne management

Figure 1: 2016 Canadian Acne Treatment Algorithm *[Asai Y et al. 2016]*



Non-Prescription Treatment Options in Canada *[CDA website; AAD Acne Clinical Guidelines]*

- OTC medications are commonly used to treat mild acne and are readily available in Canada
- OTC products are generally milder forms of prescription-strength products and include cleansers, topical creams and gels
- Active ingredients include salicylic acid and benzoyl peroxide (BPO) in various strengths
- Salicylic acid boosts anti-inflammatory and peeling action, while BPO reduces bacteria involved in pathogenesis
- BPO is known to cause drying and slight peeling
- BPO cleansers and creams are available OTC in lower concentrations than are available with prescription treatments
- Patients need to routinely use these products for a couple of months before noticing a difference
- Physical modalities (e.g., laser therapy, photodynamic therapy, etc.) are also available, but can be cost-prohibitive, inaccessible and ineffective for many patients
- Patients may also seek alternative/complementary medicine approaches (e.g., tea tree oil, ayurvedic compounds, etc.) at their own discretion. While these approaches are often well tolerated, data supporting their safety and effectiveness are limited.

Prescription Acne Treatments in Canada

- Topical prescription acne treatments can include antibiotics, retinoids (vitamin A derivatives), benzoyl peroxide, anti-inflammatory medications and fixed dose combinations
- Oral (systemic) medication can include antibiotics, retinoids or hormonal agents (i.e., birth control pills, spironolactone)
- Current prescription treatment options in Canada are shown in Table 1

Table 1: Currently Available Prescription Pharmacotherapies in Canada

Class of Therapy	Generic Name	Trade Name
Topical Treatments		
Topical Retinoids	• Tretinoin • Adapalene • Tazarotene • Trifarotene	• Retin-A Micro™ • Differin™, Differin™ XP • Arazlo™ • Aklief™

Topical Antimicrobials	• Antibiotics
	  • Erythromycin
	  • Clindamycin
	• Benzoyl peroxide (BPO)
		
		eg. Staticin™
		eg. Clindasol™
		eg. Benzagel™

Topical Anti-inflammatories	• Dapsone	eg. Aczone™

Topical Combination Therapies	• Antibiotic + BPO
	  • Clindoxyl™ gel
	  • Clindoxyl™ gel ADV
	  • BenzaClin™ gel
	  • Benzamycin™ gel
		• Clindamycin 1% + BPO 5%
		• Clindamycin 1% + BPO 3%
		• Clindamycin 1% + BPO 5%
		• Erythromycin 3% + BPO 5%

	• Antibiotic + Retinoid • Biacna™ gel • Stievamycin™ gel • Retinoid + BPO •TactuPump™ gel •TactuPump™ FORTE gel	• Clindamycin 1% + tretinoin 0.025% • Erythromycin 4% + tretinoin 0.01%/0.025%/0.05% • Adapalene 0.1% + BPO 2.5% • Adapalene 0.3% + BPO 2.5%
Oral Therapies		
Oral Antibiotics	• Tetracycline • Doxycycline • Minocycline • Azithromycin • Erythromycin • Clindamycin • Trimethoprim/sulfamethoxazole	
Oral Retinoids	• Isotretinoin	• Accutane™ • Clarus™ • Epuris™ (lipid-encapsulated isotretinoin)
Oral anti-androgens	• Spironolactone (off-label) • Oral contraceptive (females only) • Cyproterone acetate/ethinyl estradiol • Norgestimate/ethinyl estradiol • Levonorgestrel/ethinyl estradiol • Ethinyl estradiol/drospirenone	Diane®-35/ CyEstra™-35/Cleo™-35 Tri-Cyclen® Alesse®/Aviane™ Yasmin®/Yaz®

Impact of Treatments on Underlying Disease Mechanism

- The main goals of acne treatment are to control or reduce existing acne lesions, prevent new lesions, prevent permanent scarring, limit the duration of the disorder and minimize morbidity [*Fox L et al. 2016*]
- In general, acne treatments aim to normalize follicular desquamation, decrease sebum production, reduce both *C. acnes* bacteria and inflammation
- Inhibition of hormone production is also a key factor in acne treatment, since hormones play an important role in regulating sebum production. Androgens, such as testosterone and dihydrotestosterone (DHT), are the most important hormones regulating sebum production and androgen effects on sebaceous gland activity contribute to acne vulgaris in both females and males. [*Elsaie ML. 2016; Del Rosso JQ et al. 2020*]
- Table 2 below summarizes how current topical therapies and clascoterone (anti-androgen) target different aspects of the underlying disease mechanism
- Of note, none of the currently available topical therapies target androgen binding that regulates sebum production
- Clascoterone is the only topical therapy that inhibits androgen binding, while also reducing sebum production and the inflammatory response

Table 2: Impact of Current Treatment and Clascoterone on Underlying Disease [*Williams HC et al. 2012; Rosette C et al. 2019*]

Factors contributing to pathogenesis	Currently Available Prescription Topical Therapies				Clascoterone (anti-androgen)
	Retinoids	BPO	Antibiotics	Dapsone	
Normalize follicular desquamation	**Yes**	**Yes**	**-**	**-**	**-**
Reduce inflammatory response	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Reduce sebum produce	**-**	**-**	**-**	**-**	**Yes**
Reduce *C. Acnes*	**-**	**Yes**	**Yes**	**Yes**	**-**
Inhibit androgen binding	**-**	**-**	**-**	**-**	**Yes**

Treatment Goals of an Ideal Treatment

- Overall, an ideal treatment (oral or topical) would aim to correct each of the primary factors that contribute to acne pathogenesis, including:
  - Normalizing follicular desquamation
  - Reducing inflammatory response
  - Reducing sebum productions
  - Reducing *C. acnes*
  - Inhibiting androgen binding
- In the case of topical therapies, an ideal treatment would have the following characteristics:
  - No systemic side effects
  - Minimal local skin reactions
  - Side effect profile that does not limit adherence
  - Side effect profile similar to vehicle or placebo

References:

Asai Y, et al. *CMAJ*. 2016;188(2):118-126

Acne Clinical Guideline. American Academy of Dermatology Association website. Accessed June 15, 2023. https://www.aad.org/member/clinical-quality/guidelines/acne

Canadian Dermatology Association website. Accessed June 17, 2023. https://dermatology.ca/

Del Rosso JQ, et al. *J Clin Aesthet Dermatol*. 2020;13(6 Suppl):S17-S24

Elsaie ML. *Clin Cosmet Investig Dermatol*. 2016;9:241-48

Fox L, et al. *Molecules*. 2016;21(8):1063

Rosette C, et al. *J Drugs Dermatol*. 2019;18(5):412–418

Williams HC, et al. *The Lancet*. 2012;379:361-372

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Needs Not Currently Met by Current Therapies

Patient Satisfaction

- Approximately 85% of teenagers are affected by acne at some point during their teenage years, and acne can cause permanent scarring, poor self-image, depression, and anxiety in patients of all ages *[AAD Acne Clinical Guideline]*
- A 2022 survey from the CSPA of Canadian patients with acne found that ~25% were dissatisfied or strongly dissatisfied with the medical care that they received for acne *[Canadian Skin Patient Alliance]*

Acne Pathogenesis

- Although topical medications are the mainstay of acne treatment, none of those currently recommended by the guidelines address all 4 key factors of acne pathogenesis *[Baldwin H et al. 2023]*
- There is currently no recommended topical therapy that decreases sebum production or especially inhibit androgen binding *[Haider A et al. 2004; Lucky AW et al. 1997; Redmond GP et al. 1997; Thiboutot D et al. 2001; Leyden JJ et al. 2002; Van Vloten WA et al. 2002; Jones DH et al. 1983; Strauss JS et al. 1984; Strauss JS et al. 2001]*

Limitations of Current Oral Therapies

- There are several limitations with oral therapies that target sebum production and androgen binding, including:
  - Inability to use these agents (e.g., oral contraceptives) in males
  - Lack of an approved indication for use in acne (e.g., spironolactone) *[Peterson H et al. 2023]*
- Treatment alternatives for women on oral spironolactone treatment experiencing side effects, including breast tenderness and potassium alterations, are also needed and may help minimize the need for blood test monitoring
- In general, safe and effective alternatives to oral isotretinoin are needed
- There is increasing resistance to antibiotics used in the treatment of acne *[Dessinioti C et al. 2022]*
- Oral treatments targeting androgens or sebum production are frequently not suitable for all patients, due to systemic side effects, *[Haider A et al. 2004; Baldwin H et al. 2023]*

Limitations of Current Topical Therapies

- Compliance to treatments can be diminished due to side effects, such as dry skin, peeling and irritation *[AAD Acne Clinical Guideline]*
- In practice, these side effects are generally managed by reducing application frequency, which compromises effectiveness
- Therapies without significant irritation are needed to increase compliance, and are especially important for patients with sensitive and eczema-prone skin, where irritation is of particular concern for patients and clinicians *[AAD Acne Clinical Guideline]*

- Effective topicals may also be essential for maintenance following or with the concurrent use of oral antibiotics *[AAD Acne Clinical Guideline]*
- Currently, there is a lack of topical hormonal options and a need for additional topical options for those who cannot tolerate, or fail, retinoids or BPO
- There is also a need for additional options for patients with contraindications to systemic agents (e.g., migraine with aura prohibiting COC use, depression/suicidal thoughts prohibiting isotretinoin use)
- Overall, safe and reliable control of androgenic influences on acne development are needed

Additional Limitations of Current Hormonal Therapies:

- Currently hormonal therapies are not recommended for men, pregnant or lactating patients, and woman older than 35 years who are heavy smokers, nor are they advisable in patients receiving testosterone *[Baldwin H et al. 2023]*
- Spironolactone is associated with adverse effects including diuresis, menstrual irregularities, breast tenderness, and gynecomastia, and may block the effects of testosterone therapy *[Baldwin H et al. 2023]*

References:

Acne Clinical Guideline. American Academy of Dermatology Association website. Accessed June 15, 2023. https://www.aad.org/member/clinical-quality/guidelines/acne

Baldwin, H, et al. *J Drugs in Dermatol*. 2023;22(6):582-587.

Canadian Skin Patient Alliance. A report on the acne patient experience in Canada. September 2022. Accessed on May 25 2023: https://skinpatientalliance.ca/advocacy/advocacyreports/acne-report

Dessinioti C, et al. *Yale J Biol Med*. 2022;95(4):429-443

Haider A, et al. *JAMA*. 2004;292:726–735

Jones DH, et al. *Br J Dermatol*. 1983;108:333–343

Leyden JJ, et al. *J Am Acad Dermatol*. 2002;47:399–409

Lucky AW, et al. *J Am Acad Dermatol*. 1997;31:746–754

Peterson, H, et al. *J Drugs Dermatol*. 2023;22:56(Suppl 1):s7-14

Redmond GP, et al. *Obstet Gynecol*. 1997;89:615–622

Strauss JS, et al. *J Am Acad Dermatol*. 1984;10:490–496

Strauss JS, et al. *J Am Acad Dermatol*. 2001:45:187–195

Thiboutot D, et al. *Fertil Steril*. 2001;76:461–468

Van Vloten WA, et al. *Cutis*. 2002;69(suppl 4);3–15

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Treatment MOA

- While the exact mechanism of action is unknown, clascoterone is hypothesized to exert its effect by antagonistically binding to androgen receptors, thereby influencing androgen-regulated lipid and inflammatory cytokine production *[Ferraboschi P et al. 2014; Rosette C et al. 2019]*
- *In vitro* studies show that clascoterone competes with dihydrotestosterone (DHT) for binding to the androgen receptor, inhibiting downstream signaling leading to inhibited sebum production, reduced secretion of inflammatory cytokines, and inhibition of inflammatory pathways *[Ferraboschi P et al. 2014; Rosette C et al. 2019]*
- Clascoterone has been studied as a monotherapy in acne and not in combination with other therapies

Treatment Paradigm

- Clascoterone is the first topical therapy that directly reduces sebum production and inhibits pro-inflammatory cytokine production and is the only anti-androgenic topical therapy [*Rosette C et al. 2019]*
- Clascoterone is one of only a few newly approved acne drugs on the market in Canada
- Oral isotretinoin has remained the gold standard for treating severe acne over the last 20+ years and the addition of a new topical therapy targeting hormonal pathways represents a significant and welcomed advance in acne management
- Clascoterone provides an option for general practitioners to use as an effective monotherapy in uncomplicated patients prior to referral to a dermatologist
- Clascoterone is a well-tolerated topical treatment option as demonstrated by the low frequency of treatment-emergent adverse events in the phase 3 clinical and long-term extension study *[Eichenfield L et al. 2020; Herbert A et al. 2020*]
- Clascoterone also provides an additional option for dermatologists to use in both uncomplicated and complex patients

Place in Treatment Algorithm

- Patients suitable for clascoterone therapy will be similar to the patients enrolled in the pivotal clinical trials
- The phase 3 pivotal trials, studied clascoterone as a monotherapy in acne in males and non-pregnant females 9 years and older with moderate-to-severe facial acne scores on the Investigators Global Assessment scale *[Herbert A et al. 2020]*
- Patients were excluded from the phase 3 clinical trials if they were using other topical or systemic antiacne medications [*Herbert A et al. 2020]*
- The Health Canada approved indication for clascoterone is for patients who are 12 years of age and up
- A US consensus statement identifies clascoterone as a foundational treatment for moderate-to-severe comendonal and inflammatory acne in patients ≥12 of age of any sex [*Baldwin et al. 2023*]
- In real-world practice, it is likely that clascoterone will be used as monotherapy for uncomplicated cases of moderate to severe acne managed by general practitioners and dermatologists
- For more complex cases in dermatology practices, clascoterone may be trialed in combination with other topical or oral treatments to address the different components of acne pathogenesis *[AAD Acne Clinical Guidelines]*
- In some cases, dermatologists may also consider clascoterone use of adjunct or maintenance therapy following isotretinoin

Reserved Use in Patients who are Intolerant to Other Treatments

- Clascoterone is likely to be used as a monotherapy in patients with moderate-to-severe acne

- Clascoterone may be used in those who are intolerant to other treatments or in whom other treatments are contraindicated, due its locally acting mechanism of action and favourable safety profile
- Specific patient populations are outlined in the responses below

Impact on Current Treatment Paradigm

- Availability of clascoterone may shift or delay the use of oral isotretinoin due to the limitations noted above
- Availability of clascoterone will allow males to benefit from a topical anti-androgen treatment without systemic effects

Treatment Prior to Clascoterone Prescription

- Patients may try personal hygiene and dietary changes prior to seeking a prescription
- Patients may begin with over-the-counter available options before trying prescription
- Subsequently prescription topicals, including clascoterone, would be indicated

References:

Acne Clinical Guideline. American Academy of Dermatology Association website. Accessed June 15, 2023. https://www.aad.org/member/clinical-quality/guidelines/acne

Baldwin H, et al. *J Drugs Dermatol*. 2023; 22(6):582-587

Eichenfield L, et al. *J Am Acad Dermatol*. 2020;83(2):477–485.

Hebert A, et al. *JAMA Dermatol*. 2020;156(6):621–630

Ferraboschi P, et al. *Med Chem Commun.* 2014;5:904–914

Peterson H, et al. *J Drugs Dermatol*. 2023:56(Suppl 1):s7-14 (did not cite sources within)

Rosette C, et al. *J Drugs Dermatol*. 2019;18(5):412–418

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients Best Suited for Treatment

- Clascoterone may be an appropriate topical prescription option in patients (12 years or older) with moderate to severe acne who failed to be controlled with the available OTC products
- More specifically, clascoterone may be used:
    - As an alternative to antibiotics in patients who are not good candidates for oral tetracycline therapy or when concern for resistance to topical antibiotics exists *[Peterson H et al. 2023]*
    - In place of tretinoin given its greater tolerability and the lower incidence of dermatitis associated with its use *[Peterson H et al. 2023]*
    - As an option for mixed comedonal and papulopustular acne that does not respond to other medications such as topical retinoids, benzoyl peroxide, topical antibiotics, or topical dapsone *[Peterson H et al. 2023]*
    - In patients in which other hormonal therapies are unsafe (e.g., male patients)
    - In patients for facial and truncal acne
- Clascoterone could also be suitable in the following specific populations *[Baldwin H et al. 2023]*:

- Patients with moderate to severe acne who do not wish to take antibiotics
- Transmasculine patients for whom medications such as spironolactone could interfere with their gender-affirming care
- Gender minority patients
- Patients receiving androgen therapy
- Mature patients of any gender with acne (ages 29-40 years) including males
- Patients for whom isotretinoin is not indicated
- Patients who do not wish to use oral medications
- Patients with sensitive, eczema-prone skin; those who fail or cannot tolerate retinoids/BPO

Patients Least Suitable for Treatment

- Clascoterone is contraindicated in patients who have a hypersensitivity to the product ingredients
- Clascoterone was not studied in the elderly population (>65 years old)
- The efficacy and safety clascoterone has not been established in the pediatric population (<12 years old)
- The drug product was also not studied in patients who were pregnant or breastfeeding

Likely Responders

- There are limited data available identifying potential responders to clascoterone

Patients Most in Need of an Intervention

- Eligible patient populations have been outlined above
- Based on the US experience, clascoterone is viewed as a foundational treatment for moderate to severe comedonal and inflammatory acne in patients ≥12 of age of any sex at any level of acne severity [*Baldwin H et al. 2023*]
- Patients who are most in need are those who have tried and failed other OTC and prescription medications or who are intolerant or ineligible for other prescription options

Patient Identification

- Identification of appropriate patients would be based on clinical examination of the patient, assessment of acne severity/subtype, and review of use and response to prior therapies
- There is no companion diagnostic required for this treatment

Diagnosis and Misdiagnosis

- No issues related to diagnosis or misdiagnosis/underdiagnosis are noted

References:

Baldwin H, et al. *J Drugs Dermatol*. 2023;22(6):582-587

Peterson H, et al. *J Drugs Dermatol*. 2023;56(Suppl 1):s7-14

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Outcomes in Clinical Practice versus Real-World *[Expert Opinion]*

- The outcome most commonly used in routine clinical practice is physician or investigator global assessment.
- Approximately a 30% reduction in lesions is noticeable by eye to clinicians and is often used as a metric of success
- Investigator's Global Assessment (IGA) definitions (e.g. clear, almost clear, etc.) is preferred over IGA numerical values
- IGA numerical values are often used to quantify clearance in trials, e.g. a 2 point reduction in score in the clascoterone trials; however, even a 1 point reduction may still be a meaningful improvement for patients depending on severity
- Time to assess treatment response may vary from clinician to clinician, but typically occurs between 4-6 months following initiation of treatment
- The clascoterone phase 3 trial data include percent reduction measures for total lesion count, specifically non-inflammatory and inflammatory lesion counts, which provides a relatable outcome for comparison in real-world practice

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Factors for Discontinuing Clascoterone:

Poor Adherence:

- Overall, an estimated 30-40% of patients do not adhere to topical treatments *[Purvis CG et al. 2021]*
- Topical therapies require prolonged and consistent application to be effective, which can be demanding for patients
- Most topical acne therapies are irritating and may produce an irritant contact dermatitis that reduces adherence.
- Adolescents especially struggle with adherence, due to emotional, developmental, and family challenges *[Purvis CG et al. 2021]*
- Some acne treatment regimens are complex, involving multiple topical medications and combinations with other products
- These complicated regimens can be confusing to patients and may lead to poor adherence *[Expert Opinion]*
- Clascoterone is a relatively straightforward product to use and apply; however, adherence in the real-world setting may differ from clinical trials, since follow-up visits are less frequent and accountability for maintaining treatment is not as strong *[Purvis CG et al. 2021]*
- Discontinuation rates due to adverse events in the clascoterone clinical trials were low

References:

Purvis CG, et al. *Ann Pharmaco*. 2021;1-3

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Clinical Settings

- Clascoterone is appropriate for use in community GP and dermatology settings *[Expert Opinion]*
- A dermatologist is not generally required to diagnose, treat or monitor patients undergoing acne treatment, although many cases are diagnosed and managed in dermatology practices
- General practitioners are well-suited to manage uncomplicated patients and refer refractory or complex cases to community dermatologists
- Given the safety profile, general practitioners are likely to prescribe clascoterone as a first-line option in uncomplicated patients who are eligible for treatment *[Expert Opinion]*

6. Additional Information

Now that Clascoterone (Winlevi™) cream has been available in Canada for almost 1 year, our collective clinical experience has reinforced the clinical trial data as well as highlighted:

- **Improvement in Acne Symptoms:** Winlevi cream has shown significant efficacy in reducing acne lesions, both inflammatory and non-inflammatory, leading to clearer skin and improved complexion for patients.
- **Well-Tolerated Treatment Option:** Winlevi cream is an extremely well-tolerated treatment as compared to most other anti-acne topical prescriptions that more frequently cause irritant contact dermatitis. This is especially important as it addresses an unmet need in our patients with “sensitive skin” as well as atopic dermatitis where retinoids and benzyl peroxide topical treatments often are not tolerated. Further, it is a topical that can be used in conjunction with oral isotretinoin without exacerbating the xerosis caused by isotretinoin and achieving quicker clinical than isotretinoin monotherapy. Finally, since it is very well tolerated this has led to enhanced adherence and overall satisfaction compared with other topicals currently available.
- **Unique mechanism of action:** By topically targeting androgen receptors in the skin, Winlevi has been particularly effective in managing hormonal acne, offering relief to patients who may not respond well to other treatments. Our experience has shown that Winlevi can often eliminate the need to use off-label systemic medication such as spironolactone. As well, oral Spironolactone is not used in males; however, Winlevi is safely used in males allowing them to access a safe anti-androgen acne mechanism of action that previously was not available for them.
- **Boost in Self-Confidence:** Due to all of the points above and especially the clinical response, we have found that patients using Winlevi have experienced a noticeable boost in self-esteem and confidence due to the visible improvement in their skin’s appearance.

Overall, this has been a hugely beneficial topical treatment for acne that unfortunately is currently only accessible to those with private drug plans. We would welcome universal access to this medication to better control acne, prevent scarring and permeant morbidity from acne.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

NO

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

NO

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single documen**

Declaration for Clinician 1

Name: Dr. Maxwell Sauder, MD, FRCPC
Position: Dermatologist; Secretary, Dermatology Association of Ontario
Date: 19 Aug 2024

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sun Pharma Canada		X		
Bausch Health	X			
Galderma Canada			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Carrie Lynde, MD, FRCPC

Position: Dermatologist
Date: 9 Aug 2024

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sun Pharma Canada		X		
Bausch Health		X		
Galderma Canada		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. John Kraft, MD, FRCPC
Position: Dermatologist
Date: 9 Aug 2024

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sun Pharma Canada		X		
Bausch Health		X		
Galderma Canada		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. David Adam, MD, FRCPC
Position: Dermatologist; President, Dermatology Association of Ontario
Date: 10 Aug 2024

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sun Pharma Canada	X			
Bausch Health			X	
Galderma Canada			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Lyne Giroux, MD, FRCPC
Position: Dermatologist
Date: 14 Aug 2024

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sun Pharma Canada	X			
Bausch Health	X			
Galderma Canada	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Jennifer Lipson, MD, FRCPC
Position: Dermatologist
Date: 15 Aug 2024

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Sun Pharma Canada		X		
Bausch Health		X		
Galderma Canada		X		

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: **SR0863-000**
Generic Drug Name (Brand Name): **Clascoterone (WINLEVI)**
Indication: **For the topical treatment of acne vulgaris in patients 12 years of age and older.**
Name of Clinician Group: Primary Care Dermatology Society of Canada, Board of Directors
Author of Submission: Dr. Yana Simice

1. About Your Clinician Group

We are the Board of Directors of the Primary Care Dermatology Society of Canada (PCDSC). We represent a society of Family Physicians who practice in the field of dermatology. Our society's mission is to educate and connect Family Physicians who have an added focus or interest in dermatology. We have an annual educational conference as well as webinars and workshops which are all carefully curated by the members of our Board of Directors.

PCDSC website link.

2. Information Gathering

Information included in this submission was gathered via the following methods and sources:

a. Acne vulgaris society guidelines

b. Literature review

c. Clinical discussion via Zoom and BaseCamp (project management software tool). Within our group, we have a vast shared experience of treating acne.

3. Current Treatments and Treatment Goals

Acne is a disease of inflammation of the pilosebaceous unit (sebaceous gland and hair follicle) and the subsequent local and secondary sequelae. Acne pathogenesis consists of complex local interactions comprising of increased androgens, increased sebum production, microbiome dysbiosis (Cutibacterium acnes proliferation), increased inflammation and follicular hyperkeratinization. Therapeutic interventions target different aspects of acne pathogenesis.

The Canadian current treatment paradigm for acne vulgaris is comprised of the following:

a. Topical and systemic medication recommendations described in the Management of Acne: Canadian Practice Guideline published in the Canadian Medicine Association Journal in 2016.

   Approved topical therapies are antibiotics, benzoyl peroxide, retinoids and azelaic acid. Approved systemic therapies are oral contraceptives (women only), oral antibiotics, and oral isotretinoin. Oral isotretinoin is the only treatment that permanently clears or reduces acne and is indicated for severe and treatment-resistant acne.

b. Counseling and life-style recommendations

Patients are encouraged to avoid traumatizing their acne lesions to prevent further scarring and inflammation. Some patients benefit from decreasing their dairy intake. Furthermore, diets with a high glycemic load can trigger acne in some people. Patients who smoke are advised to stop.

c. Additional “off label” prescribing (not reviewed or authorized by Health Canada for the indication of acne) of oral spironolactone for women for its anti-androgen properties.

d. Over-the-counter therapies such as benzoyl peroxide, salicylic acid, alpha-hydroxy acids, and beta-hydroxy acids. Less effective as monotherapy but may be helpful in mild acne or as adjunctive therapy.

e. Office-based private procedures such as light therapies, lasers, chemical peels, dermabrasion, and skin needling. Depending on the therapy, intended to target inflammation and/or scarring of acne. Costly to patient. Varying degrees of evidence for effectiveness.

f. Clascoterone cream, a topical androgen receptor inhibitor, approved for sale by prescription in Canada in August 2023.

The ideal treatment of acne would result in the resolution of acne to alleviate pain, scarring, post-inflammatory pigmentation, and psychological morbidity. Since only systemic isotretinoin can provide a “cure” in about a third of patients treated, realistic ideal treatment of acne with our currently available medications is the following:

- Minimize or remove reliance on antibiotics in the treatment paradigm of acne. Emerging bacterial resistance is a significant issue. Currently, the only alternative oral therapy to isotretinoin available to males are oral antibiotics.
- Treatments that are simple for patients to apply or ingest with minimal or no adverse effects.
- Treatments that prevent further acne and secondary scarring.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Considering that acne is self-reported in 35-90% of adolescents and can continue through to old age in 15% of adults, we can extrapolate that patients are not being treated effectively for several reasons.

Even with full compliance, not all patients respond to currently available treatments. Although isotretinoin can provide the most definitive results, it is intolerable and/or contraindicated in some patients. The same statement can be made for other systemic therapies (antibiotics, spironolactone, combined oral contraceptives). Furthermore, access to isotretinoin is an issue for Canadians due to many primary care providers not being comfortable with prescribing, lack of primary care providers, and a lack of dermatologists.

From our use of spironolactone and combined oral contraceptives, we know that targeting androgen inhibition is effective treatment for acne vulgaris. These systemic therapies cannot be used in males. Clascoterone cream is the only topical anti-androgen therapy available and can be used for both males or females.

Topical retinoids are considered an essential component of most acne therapy regimens. However, they have a high rate of patient discontinuation due to local irritation. Patients being prescribed these medications require initial counselling on use and often need subsequent supportive counselling to continue. Some patients remain intolerant of this class of acne therapies. Many patients experience photosensitivity with these medication formulations affecting outdoor activities and occupations. The required sunscreen use can exacerbate their acne and may not be adequate to prevent sunburns and more serious long-term consequences.

Cost-effective and accessible therapies are needed to address acneiform scarring.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Clascoterone 1% cream is a novel new topical therapy for acne. The exact mechanism of action is thought to decrease local androgens by binding and inhibiting the dihydrotestosterone (DHT) receptor resulting in decreased sebum production, reduced secretion of inflammatory cytokines, and inhibition of inflammatory pathways. Clascoterone cream is the first topical treatment approved to address the local effect of androgens on acne pathogenesis and the only treatment with this mechanism for males.

Clascoterone cream works as a topical monotherapy option for acne. However, it can also be used in conjunction with acne therapies that target other points of the acne pathogenesis pathway.

Because of clascoterone's safety profile and high tolerability, this medication can be used a first-line treatment, in combination with other treatments, or as a later line of treatment.

Clascoterone is particularly useful in patients intolerant to other treatments and in whom treatments are contraindicated.

Clascoterone may shift the current treatment paradigm (e.g., Decrease antibiotic prescribing for acne). The true influence is yet to be determined as prescribers and patients become familiar with this medication.

Considering the cost of clascoterone, it may be appropriate for patients to try currently recommended first-line cost-effective topical treatments.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All patients seeking treatment of their acne need an intervention. Degrees of acne severity as assessed by a medical provider do not always correlate with the subjective distress the patient is experiencing and the impact on their quality of life.

Patients with severe acne and/or who meet the recommendations for systemic isotretinoin as per the Management of Acne: Canadian Practice Guideline should be treated with isotretinoin. Although most patients with acne are likely to respond clascoterone, patients with severe acne are less likely to achieve a satisfactory result with any monotherapy.

For patients who seek faster clearance of their acne, monotherapy with clascoterone is not a suitable first-line choice. Patients need to be counseled that results are not immediate and several months of treatment may be necessary before they are satisfied with effect. A safety and efficacy study from September of 2023 demonstrated that roughly 50% of patients with moderate-to-severe acne achieved clear or almost clear skin after nine months of twice daily application (see website link to noted study). Although the benefits of using clascoterone cream may not be fully realized for many patients after just three months of use, a recent meta-analysis shows that clascoterone, trifarotene, and tazarotene (the latter two being topical retinoids) have similar efficacy when used for this duration (see website link to noted study).

Patients best suited for treatment with clascoterone would be identified by the following:

a. HISTORY

- Presence of sensitive skin
- Intolerance or noncompliance with other topical acne therapies
- Individuals who spend significant time outdoors for work or recreation, where the use of topical retinoids is not recommended.

b. ON EXAM

- Displaying mild to moderate acne
- Severe acne cases where isotretinoin is contraindicated, intolerable, or inadequate.

For clinicians who regularly see acne in their practice, there should be no issues related to diagnosis. No companion diagnostic test is indicated.

Given the prevalence of acne in our population and our resource-stressed health-care system, acne is likely underdiagnosed despite the adverse impact of acne on patient well-being.

With the current available data, it is not possible to identify patients who are most likely to exhibit a response to treatment of clascoterone. One can postulate that in patients where hormones play a dominant role in acne pathogenesis (e.g., teenagers, perimenopausal acne, patients with metabolic syndromes), benefit could be predicted.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

In the clinical setting, a patient's acne is typically not assessed with same stringent lesion counts and grading scales used in a clinical trial setting. Some clinicians may use grading scales such as the Investigator's Global Assessment (IGA) scale for acne. Many will classify acne as per the Management of Acne: Canadian Practice Guideline as comedonal, mild papulopustular, moderate papulopustular, moderate papulopustular, and severe papulopustular/nodular. Patient subjective impression of their acne is likely considered more in clinical practice. Patient photos before and after treatment can be very beneficial in clinical practice.

A clinically meaningful response to treatment is a combination of the following outcomes:

- Patient satisfaction
- Visible improvement on photos before and after treatment
- Obvious decrease in number of lesions. Optimally, clear to almost clear skin.
- Patient's improvement in function (e.g., Resolution of pain and/or psychological impact)

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Stopping clascoterone should be considered in the following circumstances:

- No response or progression of acne despite an adequate trial of 3-6 months.
- A person with a uterus of child-bearing years becomes pregnant or is planning pregnancy.
- Patient reports intolerable side effects of treatment.

In patients with partial but not satisfactory response, it would be up to the clinician to consider adjunctive or alterative therapy.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Clascoterone is appropriate for prescribing in all clinical settings for primary care providers (e.g., Family Physicians and Nurse Practitioners), Pediatricians, Dermatologists.

6. Additional Information

Access to dermatologic care is a serious issue for Canadians. There are not enough dermatologists or other medical specialists in Canada providing medical dermatologic care. Many primary care providers do not feel comfortable prescribing isotretinoin or off-label spironolactone. Furthermore, encouraging patient compliance and maintenance with the approved topical retinoids, requires patient counseling from a provider experienced with the effect and expected outcomes with these treatments. With the rise of virtual walk-in clinics and the decline of longitudinal primary care, effective acne therapies with high patient treatment tolerability and compliance are needed.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Yana Simice
Position: Past-President, Board of Directors, Primary Care Dermatology Society of Canada
Date: 07-07-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
L'Oreal	X			
Bausch Health	X			
Pfizer	X			
Abbvie	X			
Arcutis	X			
Novartis	X			
Sanofi	X			
SunPharma		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Natalie Skinner
Position: President, Board of Directors, Primary Care Dermatology Society of Canada
Date: 07-07-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
L'Oreal	X			
SunPharma	X			
Arcutis	X			

Declaration for Clinician 3

Name: Monica Bertolo
Position: Treasurer, Board of Directors, Primary Care Dermatology Society of Canada
Date: 07/07/2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Pfizer	X			
Bausch Health	X			
Arcutis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Danielle Roy
Position: Member, Board of Directors, Primary Care Dermatology Society of Canada
Date: 07/07/2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Arcutis	X			
Pfizer	X			
Bausch Health	X			
Abbvie	X			
Celgene	X			
Dermacon Day of Derm	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Mamdouh Andrawis
Position: Member, Board of Directors, Primary Care Dermatology Society of Canada Date: 07-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Arcutis	X			

Declaration for Clinician 6

Name: Lana Wicentovich
Position: Member, Board of Directors, Primary Care Dermatology Society of Canada
Date: 07-07-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bausch Health	X			
Galaderma	X			
Arcutis	X			