CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

IVERMECTIN
(Rosiver — Galderma Canada Inc.)
Indication: Rosacea

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ivermectin 1% be listed for the treatment of inflammatory lesions of rosacea in adults aged 18 years or older, if the following clinical criterion and condition are met:

Clinical criterion:
- For the treatment of moderate to severe papulopustular rosacea.

Condition:
- Drug plan cost for ivermectin 1% should not exceed the drug plan cost of other topical treatments for rosacea that are currently reimbursed by the jurisdiction.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) (Studies 18170 [N = 683] and 18171 [N = 688]) demonstrated that ivermectin 1% once daily was associated with a statistically significantly greater reduction in the number of inflammatory lesions and a statistically significantly higher success rate than vehicle-treated patients.
2. One RCT (Study 40173 [N = 962]) demonstrated that ivermectin 1% was associated with a statistically significantly greater percentage reduction in the number of inflammatory lesions (−83.0% versus −73.7%) and a statistically significantly higher success rate (84.9% versus 75.4%) compared with metronidazole (0.75% cream applied twice daily); however, the clinical relevance of these differences is uncertain.
3. At the submitted price, the daily cost of treatment with ivermectin 1% ([redacted]) is greater than the daily cost of treatment with metronidazole 1% gel ($0.45), azelaic acid 15% gel ($0.79), and metronidazole 0.75% cream ($0.86).

Background:
Ivermectin has a Health Canada indication for the topical treatment of inflammatory lesions (i.e., papules and pustules) of rosacea in adults aged 18 years or older. Ivermectin is a broad-

spectrum anti-parasitic drug with anti-inflammatory properties. Ivermectin is available as a 1% (10 mg/g) cream.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of ivermectin for the treatment of rosacea, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group – submitted information about outcomes and issues important to patients living with rosacea.

Patient Input Information
One patient group, the Canadian Skin Patient Alliance, responded to the CDR call for patient input. Information was gathered from a questionnaire distributed through social media and dermatologists. The following is a summary of key information provided by the patient group:

- Rosacea is a common, poorly understood disease that causes redness, flushing, and inflammation of the skin. While usually affecting the face, it can extend to the full body and cause vascular dysfunction in the face, extremities, and bowels. Other symptoms can include dry, thick, or scaling skin, knobby bumps on the nose, enlargement of the nose, and inflammation of the eyes.
- The noticeable skin changes on the face can have a profound long-term effect on a person's quality of life by causing low self-esteem, embarrassment, and frustration. Many respondents reported shame, depression, and inability to participate in day-to-day activities. Existing therapies for rosacea have limited efficacy in improving symptoms.
- Patients reported experience with a range of treatment options including metronidazole, azelaic acid, laser therapy, and other prescription and over-the-counter therapies. They noted that there remains an unmet therapeutic need because existing treatments can be associated with limited effectiveness, adverse events, and high cost.

Clinical Trials
The CDR systematic review included three multi-centre RCTs that enrolled adult patients with moderate to severe rosacea (i.e., Investigator's Global Assessment [IGA] ≥ 3; 15 to 70 facial inflammatory lesions).

- Studies 18170 (N = 683) and 18171 (N = 688) included a 12-week, double-blind, vehicle-controlled phase that evaluated efficacy and safety, followed by a 40-week investigator-blind phase to evaluate long-term safety. Patients were initially randomized to either ivermectin 1% once daily or vehicle for 12 weeks and, during the long-term safety phase, patients continued on ivermectin or were switched to azelaic acid 15% gel twice daily if they were originally treated with vehicle.
- Study 40173 (N = 962) was an investigator-blind trial that randomized patients to either ivermectin 1% once daily or metronidazole 0.75% cream twice daily. At 16 weeks, those who had responded to treatment discontinued and were followed up for 36 weeks, with treatment resuming upon relapse.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Lesion count — the sum of papules and pustules on each of the five facial regions (forehead, chin, nose, and right and left cheeks).

- IGA — scale ranging from 0 (clear) to 4 (very severe) based on the number of papules/ pustules and the severity of erythema. Success was defined as an IGA score ≤ 1.
- Patient's assessment of rosacea improvement — assessment of symptom improvement from baseline; ranging from 1 (excellent improvement) to 5 (worse).
- Dermatology Life Quality Index (DLQI) — a generic quality-of-life measure applicable to all dermatological conditions concerning the impact of dermatological disease on feelings, daily activities, work, school, leisure, and personal relationships. Scored from 0 (no impairment) to 30 (maximum impairment).
- Rosacea Quality of Life Index (RosaQoL) — disease-specific quality-of-life instrument focusing on symptoms, function, and emotions, with higher scores representing greater impact of rosacea on patient's quality of life.

The co-primary end points in Studies 18170 and 18171 were the absolute change in total inflammatory lesion count and success rate based on the IGA score, both at 12 weeks. The co-primary end points in Study 40173 were the percentage change in inflammatory lesion counts at 16 weeks and time to the onset of efficacy.

Efficacy

Vehicle-Controlled Studies (18170 and 18171)

- The absolute improvement in inflammatory lesion counts was greater in the ivermectin groups compared with the vehicle-control groups. The differences in mean inflammatory lesion counts for ivermectin versus vehicle were (Studies 18170 and 18171, respectively):
  - Difference in absolute change from baseline: −8.13 lesions (95% confidence interval [CI]: −10.12 to −6.13) and −8.22 lesions (95% CI: −10.18 to −6.25)
  - Percentage change from baseline: −64.9% versus −41.6% and −65.7% versus −43.4% ($P < 0.001$ for both).
- The proportion of patients achieving success (IGA ≤ 1) was greater in the ivermectin groups compared with the vehicle-controlled groups at week 12.
  - Study 18170: 38.4% versus 11.6%; $P < 0.001$
  - Study 18171: 40.1% versus 18.8%; $P < 0.001$.
- The proportion of patients who rated their improvement on the patient assessment of rosacea improvement scale as "excellent" was statistically significantly greater in the ivermectin groups compared with the vehicle-controlled groups.
  - Study 18170: 34.3% versus 9.5%; $P < 0.001$
  - Study 18171: 32.0% versus 7.3%; $P < 0.001$.
- Improvement in all quality-of-life measures was statistically significantly greater with ivermectin compared with vehicle at 12 weeks. Mean absolute changes from baseline for ivermectin versus vehicle were (Studies 18170 and 18171, respectively):
  - RosaQoL: –0.64 versus –0.35 and –0.60 versus –0.35 ($P < 0.001$ for both)
  - DLQI: –3.5 versus –2.2 and –3.2 versus –2.0 ($P < 0.001$ for both).

Active-Controlled Study (40173)

- There was a statistically significantly greater percentage reduction in lesion count with ivermectin compared with metronidazole cream after 16 weeks of treatment (–83.0% versus –73.7%; $P < 0.001$). A statistically significant difference between treatments ($P < 0.05$) in the

percentage change in inflammatory lesion count was observed as early as three weeks and was maintained until the end of treatment at 16 weeks.
- The rate of success (IGA ≤ 1) was greater for ivermectin 1% (84.9%) compared with metronidazole cream (75.4%) at week 16 ($P < 0.001$).
- In the 36-week extension phase, the relapse rate was 62.7% and 68.4% in the ivermectin and metronidazole cream groups, respectively ($P = 0.10$). The median time to first relapse was significantly greater in the ivermectin 1% group (115 days; 95% CI, 113 to 165) compared with the metronidazole group (85 days; 95% CI, 85 to 113).
- Quality of life improved in both the ivermectin and metronidazole groups (mean absolute change in DLQI: 5.2 versus 3.9) and there was no statistical analysis conducted between the two groups.
- The proportion of patients who rated their improvement on the patient assessment of rosacea improvement scale as "excellent" was statistically significantly greater in the ivermectin group compared with the metronidazole group (52.3% versus 37.0%; $P < 0.002$).

Harms (Safety and Tolerability)
- Adverse events in patients treated with ivermectin 1% were similar compared with patients treated with vehicle or metronidazole 0.75% cream. Reports of dermatological adverse events, such as skin irritation, skin burning, dermatitis, pain of skin or pruritus were low in frequency and balanced between treatment groups. The proportions of patients who experienced at least one adverse event were:
  - Study 18170: ivermectin (40.5%) and vehicle (39.4%)
  - Study 18171: ivermectin (36.5%) and vehicle (36.5%)
  - Study 40173: ivermectin (32.4%) and metronidazole (33.1%).
- The proportions of patients with at least one serious adverse event were:
  - Study 18170: ivermectin (0.7%) and vehicle (0.4%)
  - Study 18171: ivermectin (1.5%) and vehicle (1.7%)
  - Study 40173: ivermectin (1.7%) and metronidazole (1.0%).
- The proportions of patients who withdrew as a result of adverse events were:
  - Study 18170: ivermectin (1.5%) and vehicle (2.6%)
  - Study 18171: ivermectin (1.3%) and vehicle (2.6%)
  - Study 40173: ivermectin (1.3%) and metronidazole (2.7%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis based on a Markov model comparing topical application of ivermectin 1% cream (once daily) with metronidazole 0.75% cream (twice daily), metronidazole 1% gel (once daily), metronidazole 1% cream (twice daily), and azelaic acid 15% gel (twice daily) for the treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients with moderate to severe papulopustular rosacea. The model was based on a three-year time horizon, under a Canadian health care system perspective.

The model comprised two health states, based on the IGA score: the state of having rosacea (defined as an IGA score of ≥ 2) and the state of not having rosacea (defined as an IGA score of 0 or 1). Efficacy data were primarily obtained from Study 40173 and a [redacted], while utility values were based on pooled EuroQol 5-Dimensions Questionnaire (EQ-5D) data from Study 40173. The manufacturer included combination therapy, which included the use of systemic antibiotics, in addition to the utilization of other

health care resources. The manufacturer's base-case analysis, when considered in a sequential manner, resulted in an incremental cost-utility ratio of $50,073 per quality-adjusted life-year for the comparison of ivermectin 1% cream versus metronidazole 1% gel. All other drugs were ruled out by dominance (more costly and less effective) or extended dominance (combinations of metronidazole 1% gel and ivermectin 1% cream are less costly and more effective than other comparators).

CDR identified a number of limitations with the manufacturer's economic evaluation:

- Uncertain comparative clinical benefit of ivermectin versus other drugs, due to uncertainty in what constitutes a clinically meaningful difference for the outcome of success rate, as well as the lack of statistical significance observed in the random effects model of the NMA
- Lack of data to inform treatment success in the long-term phase
- Assumption of no maintenance treatment for patients who succeed on treatment
- Inaccurate weighted average costs of systemic antibiotics
- Health care resource utilization probabilities based on data from the United States.

Based on the results of the manufacturer's NMA and given the limitations with the manufacturer's pharmacoeconomic analyses, CDR assumed equal efficacy among topical drugs and considered comparative drug costs. At the submitted price of $[redacted], assuming that 0.72 g is used if applied once daily and 1.31 g is used if applied twice daily (based on the number of grams used in Study 40173 and manufacturer's assumptions), the daily cost of ivermectin 1% cream ([redacted]) is more than metronidazole 1% gel ($0.45), azelaic acid 15% gel ($0.79), and metronidazole 0.75% cream ($0.86).

Other Discussion Points:

CDEC noted the following:

- A minimal clinically important difference has not been established for the end points that were evaluated in the included studies and, with the exception of RosaQoL, these outcome measures have not been validated in patients with rosacea.
- Patients enrolled in the included studies had moderate to severe rosacea, but the Health Canada–approved indication is not limited based on disease severity.
- The majority of patients in the included trials were treatment-naive and there is uncertainty regarding the efficacy of ivermectin in patients who have experienced an inadequate response to alternative therapies (e.g., metronidazole).

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Direct comparisons with topical treatments for rosacea other than metronidazole 0.75% cream.
- The long-term safety and efficacy profile of ivermectin for the treatment of rosacea requires further evaluation.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

October 21, 2015 Meeting

Regrets:
None.

Conflicts of Interest:
None.

About this Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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