November 2015

Drug	ivermectin (Rosiver)
Indication	Treatment of inflammatory lesions (i.e., papules and pustules) of rosacea in adults 18 years of age or older
Listing request	As per Health Canada indication
Manufacturer	Galderma Canada Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TABLE OF CONTENTS

ABBREVIATIONS iii

EXECUTIVE SUMMARY 1

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION 3
1. Summary of the Manufacturer's Pharmacoeconomic Submission 3
2. Manufacturer's Base Case 4
3. Summary of Manufacturer's Sensitivity Analyses 4
4. Limitations of Manufacturer's Submission 5
5. CADTH Common Drug Review Analyses 6
5. CADTH Common Drug Review multi-way analysis 9
6. Issues for Consideration 10
7. Patient Input 10
8. Conclusions 10

APPENDIX 1: COST COMPARISON 11
APPENDIX 2: SUMMARY OF KEY OUTCOMES 13
APPENDIX 3: ADDITIONAL INFORMATION 15
APPENDIX 4: REVIEWER WORKSHEETS 16

REFERENCES 29

Tables

Table 1: Summary of the Manufacturer's Economic Submission iv
Table 2: Manufacturer's Base-Case Results Presented in a Sequential Analysis 4
Table 3: CADTH Common Drug Review Reanalysis #1: Equal Probability of Treatment Success in the Initial and Long-term Phase for All Comparisons 6
Table 4: CADTH Common Drug Review Reanalysis #2: Assumption of Maintenance Treatment 7
Table 5: CADTH Common Drug Review Reanalysis #3: Same Risk of Relapse 8
Table 6: CADTH Common Drug Review Reanalysis #4: Updated Weighted Average Cost of Systemic Antibiotics 8
Table 7: CADTH Common Drug Review Reanalysis Price Reduction Scenarios 9
Table 8: Cost Comparison Table for the Treatment of Inflammatory Lesions (Papules and Pustules) of Rosacea in Adults 18 Years of Age or Older — Topical Preparations 11
Table 9: Cost Comparison Table for the Treatment of Inflammatory Lesions (Papules and Pustules) of Rosacea in Adults 18 Years of Age or Older — Oral Antibiotics 12
Table 10: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Ivermectin 1% Cream Relative to Metronidazole 0.75% Cream? 13
Table 11: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Ivermectin 1% Cream Relative to Metronidazole 1% Gel? 13
Table 12: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Ivermectin 1% Cream Relative to Metronidazole 1% Cream? 13
Table 13: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Ivermectin 1% Cream Relative to Azelaic Acid 15% Gel? 14
Table 14: Submission Quality 15
Table 15: Author Information 15

Table 16: Data Sources 17
Table 17: Manufacturer's Key Assumptions 22
Table 18: Summary of the Results of the Manufacturer's Base Case, by Cost and Clinical Outcome (Per Patient) 23
Table 19: Summary of the Results of the Manufacturer's Base Case 23
Table 20: Market Share Data Distribution of Systemic Antibiotics 26
Table 21: Summary of CADTH Common Drug Review Reanalysis Scenarios, Based on Identified Limitations 26
Table 22: CADTH Common Drug Review Multi-way Analysis: Sequential Incremental Cost-utility Ratio 27
Table 23: CADTH Common Drug Review Multi-way Analysis: Incremental Costs per Patient Over Three Years 27
Table 24: Incremental Costs Using Only Approximate Daily Cost of Topical Drugs 28

Figure

Figure 1: Manufacturer's Model Structure, Used in Base-case Analysis 17

ABBREVIATIONS

CDR	CADTH Common Drug Review
ICUR	incremental cost-utility ratio
IGA	Investigator's Global Assessment
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Ivermectin 1% topical cream (Rosiver)
Study Question	"What is the incremental cost-effectiveness of ivermectin 1% cream compared to metronidazole 0.75% cream, metronidazole 1% cream/gel, and azelaic acid 15% gel in the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older?"
Type of Economic Evaluation	CUA, CEA
Target Population	Based on Study 40173 population: adult patients with moderate to severe papulopustular rosacea
Treatment	Ivermectin 1% topical cream q.d.
Outcome	QALYs
Comparators	• metronidazole 0.75% cream b.i.d. • metronidazole 1% cream b.i.d. • metronidazole 1% gel q.d. • azelaic acid 15% gel b.i.d.
Perspective	Canadian health care system
Time Horizon	3 years
Results for Base Case	When considering the manufacturer's results sequentially: • Metronidazole 1% gel resulted in the lowest total costs (reference case) • Ivermectin 1% was associated with an ICUR of $50,062 per QALY compared with metronidazole 1% gel Other topical 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).
Key Limitations	• As noted in the CDR clinical review report, it is unclear if the difference observed with ivermectin 1% cream versus metronidazole 0.75% cream in Study 40173 for the outcome of success rate is clinically meaningful. • Comparative efficacy results for ivermectin 1% cream versus metronidazole 0.75% cream, metronidazole 1% gel, and azelaic acid 15% gel were derived from the [redacted]. Other limitations with the pharmacoeconomic model included: • Lack of data to inform treatment success in the long-term phase (after 36 weeks for ivermectin 1% cream and metronidazole 0.75% cream and 12 weeks for others). • Assumption of no maintenance treatment for patients who succeed on treatment. • Inaccurate weighted average costs of systemic antibiotics. • Health care resource utilization probabilities obtained from data sources from the United States, which may not represent Canadian practice.
CDR Estimate(s)	CDR conducted a number of reanalyses to assess the impact of the key limitations identified. These included: • Due to the lack of availability of treatment success probabilities based on the [redacted], CDR assumed equal treatment success probabilities for ivermectin 1% cream, metronidazole 0.75% cream, metronidazole 1% gel, and azelaic acid 15% gel (both in the initial and post-initial treatment phase).

[redacted]	• Assumption of maintenance treatment after treatment success in both the initial and post-initial treatment phases, for up to 3 years. • Assumption of same risk of relapse for all topical drugs. • Updated weighted average costs of systemic antibiotics. • CDR assumed equal treatment success rates and risk of relapse for all topical drugs in multi-way analyses, which resulted in equal treatment efficacy and the comparison of drug costs only. Ivermectin 1% cream (approximate daily cost of $[redacted] is more expensive than metronidazole 1% gel ($0.45), azelaic acid 15% gel ($0.79), and metronidazole 0.75% cream ($0.86). • A price reduction of [redacted] to [redacted]% would be needed for ivermectin 1% cream to be similar in price to metronidazole and azelaic acid.

b.i.d. = twice daily; CDR = CADTH Common Drug Review; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; ICUR = incremental cost-utility ratio; [redacted]; QALY = quality-adjusted life-year; q.d. = once daily.

EXECUTIVE SUMMARY

Background

Ivermectin 1% cream is a macrocyclic lactone derivative belonging to the avermectin class of drugs. It is being reviewed for the topical treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients 18 years of age or older. The recommended dose is five pea-sized amounts to be applied once daily to five areas of the face: forehead, chin, nose, and each cheek.[1] The manufacturer submitted a confidential price of $[redacted] per 60 g tube, or $[redacted]/g, or an approximate daily cost of $[redacted] (assuming 0.72 g applied daily).[2] The manufacturer is seeking reimbursement in line with the Health Canada indication.[2]

A cost-utility analysis was submitted comparing 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, over a three-year time horizon, in adult patients with moderate to severe papulopustular rosacea, under the perspective of the Canadian health care system.[3] The economic submission was based on a Markov model with two health states, based on the Investigator's Global Assessment (IGA) score on a 5-point rosacea severity scale: the state of having rosacea (defined as an IGA score of ≥ 2 [mild, moderate, or severe]) and the state of not having rosacea (defined as an IGA score of 0 [clear] or 1 [almost clear]).[3] In the manufacturer's base-case analysis, the probability of treatment success (defined as an IGA score of 0 or 1) was informed [redacted],[2] and a phase 3 active-controlled superiority trial (Study 40173), which compared ivermectin 1% cream with metronidazole 0.75% cream.[2,4] In the absence of any clinical data, the manufacturer conducted a qualitative analysis to infer the relative cost-effectiveness of ivermectin 1% cream in the population of patients with mild papulopustular rosacea.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several limitations with the submitted pharmacoeconomic evaluation, the most important being the uncertain comparative clinical benefit of ivermectin 1% cream versus metronidazole 0.75% cream, metronidazole 1% gel, and azelaic acid 15% gel, due to uncertainty regarding what constitutes a clinically meaningful difference in success rate as well as substantial limitations with the network meta-analysis. [redacted]. Other limitations of the manufacturer's model included the lack of data to inform treatment success in the long-term phase, the assumption of no maintenance treatment for patients who succeed on treatment, inaccurate weighted average costs of systemic antibiotics, and the use of US-based data for the probabilities of health care resource utilization.

Given: (1) the [redacted], (2) the overall conclusions of the clinical review report around similar efficacy for all drugs, and (3) the lack of treatment success probabilities from the [redacted], CDR assumed ivermectin 1% cream had a similar probability of treatment success as other topical drugs. Further, assumptions that patients would be on maintenance treatment after succeeding on treatment for up to three years (resulting in lower and likely similar risk of relapse), and an updated

weight average cost of systemic antibiotics were made. This comprised the CDR multi-way analysis, where drug costs only were compared, reported as per patient over three years.

Assuming that 0.72 g of topical drugs are used if applied once daily and 1.31 g are used if applied twice daily (based on the number of grams used in Study 40173 and the manufacturer's submission), ivermectin 1% cream (approximate daily cost of $[redacted]) is more expensive than metronidazole 1% gel ($0.45), azelaic acid 15% gel ($0.79), and metronidazole 0.75% cream ($0.86).

Conclusions

The CDR clinical review concluded that the available evidence suggests that ivermectin is similar to metronidazole and azelaic acid with respect to efficacy and potential harms. Treatment success probabilities derived from the [redacted] were unavailable, and therefore, CDR reanalysis assumed equal efficacy among all topical drugs and focused on drug costs alone. Ivermectin 1% cream (approximate daily cost of $[redacted]) is more expensive than metronidazole 1% gel, azelaic acid 15% gel, and metronidazole 0.75% cream. A price reduction of [redacted] to [redacted]% would be needed for ivermectin to be equal in price with metronidazole and azelaic acid.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis using 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.[3] The manufacturer conducted a qualitative analysis to determine the relative cost-effectiveness of ivermectin 1% cream in patients with mild papulopustular rosacea, in order to address the broad population as per the Health Canada indication.[3]

The model comprised of two health states, based on the Investigator's Global Assessment (IGA) score: the state of having rosacea (defined as an IGA score ≥ 2) and the state of not having rosacea (defined as an IGA score of 0 or 1).[3] The model followed a cohort of 1,000 patients with moderate to severe papulopustular rosacea, based on observation at baseline in Study 40173, an active-controlled, phase 3 trial that compared ivermectin 1% cream with metronidazole 0.75% cream.[4] The model tracked this cohort for three years, with a cycle length of 12 to 16 weeks for the initial phase, followed by monthly cycles until the end of the time horizon. After the initial treatment period, patients who were successful on treatment (i.e., IGA score ≤ 1; in the health state of "no rosacea"), were assumed to stop treatment. All patients who stopped treatment were at the risk of experiencing a relapse (IGA score ≥ 2). If patients experienced a relapse (i.e., any time after the initial treatment phase), they were switched back to receive the same topical drug they were receiving initially. Alternatively, patients who failed initial treatment (i.e., IGA score > 1; in the health state of "rosacea") were assumed to switch to combination therapy, defined as the combination of a topical drug and a systemic antibiotic (e.g., tetracycline, doxycycline, and minocycline). Any subsequent treatment successes resulted in patients stopping treatment (and being at the risk of experiencing a relapse) and subsequent treatment failures resulted in patients switching (or continuing on) combination therapy. In the manufacturer's base-case analysis, treatment efficacy (i.e., success rate) during the initial treatment phase was informed [redacted].[2] Success rate after the post-initial treatment phase was informed by the results of the 36-week extension period of Study 40173 for comparison versus metronidazole 0.75% cream[4] and the [redacted].[2] Treatment efficacy with combination therapy was sourced from the literature. Relapse rates were also informed by the results of the extension period of Study 40173.[4]

Utility weights associated with both health states were based on pooled EuroQol 5-Dimensions Questionnaire (EQ-5D) data from Study 40173.[4] Resource utilization was based on literature and was confirmed with the input of Canadian clinicians. Costs were taken primarily from Ontario health care costs sources. The manufacturer obtained the number of grams per day of topical therapy for ivermectin 1% cream and metronidazole 0.75% cream from Study 40173, and for azelaic acid 15% gel from external literature, and from this inferred the number of grams per day for all comparators.

2. MANUFACTURER'S BASE CASE

The manufacturer reported that, over three years, compared with metronidazole 0.75% cream, metronidazole 1% gel or cream, and azelaic acid, ivermectin 1% cream was associated with the highest total costs ($812 per patient, the majority of which was attributed to medication costs), and the highest quality-adjusted life-years (QALYs) (2.2282 per patient). See Table 18 and Table 19, Appendix 4 for more details on the manufacturer's results.

The manufacturer's analyses presented only pairwise comparisons of ivermectin 1% cream versus comparators. However, it is optimal to consider all treatment options together to identify which treatment option is the most cost-effective (Table 2).

TABLE 2: MANUFACTURER'S BASE-CASE RESULTS PRESENTED IN A SEQUENTIAL ANALYSIS

Interventions	Total Costs ($) per Patient Over 3 Years	Total QALYs per Patient Over 3 Years	Sequential ICUR
Metronidazole 1% gel	$380	2.2195	Reference
Ivermectin 1% cream	$812	2.2282	$50,073
Azelaic acid 15% gel	$543	2.2169	Dominated by metronidazole 1% gel[a]
Metronidazole 0.75% cream	$538	2.2199	Dominated by metronidazole 1% cream[a]
Metronidazole 1% cream	$494	2.2199[b]	Extendedly dominated by metro 1% gel and ivermectin 1% cream[c]

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
[a] A dominated strategy is more costly and provides less QALY gains (i.e., is less effective) than an alternative strategy.
[b] The manufacturer assumed that metronidazole 1% cream would have the same efficacy as metronidazole 0.75% cream.
[c] There are combinations of metronidazole 1% gel and ivermectin 1% cream that are less costly and provide greater benefits (QALYs) than metronidazole 1% cream – metronidazole 1% cream is extendedly dominated.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

When considered in a sequential manner, the manufacturer's base-case results suggest that metronidazole 1% gel was associated with the lowest total costs.[3] Ivermectin 1% was associated with an incremental cost-utility ratio (ICUR) of $50,073 per QALY compared with metronidazole 1% gel, while other drugs were ruled out by dominance or extended dominance.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty around the parameters chosen for the base-case analysis was addressed by the manufacturer using one-way and multi-way deterministic sensitivity analyses and a probabilistic sensitivity analysis (PSA), except for the comparison with metronidazole 1% cream, for which a PSA could not be conducted. The following parameters had the greatest impact on ICUR (± 25%): time horizon; treatment switching; dosing of topical therapy (assuming lower and higher number of grams per day); and the health state utility inputs.

The PSA showed that, based on 10,000 iterations, in approximately 50% of iterations, the ICUR was below a willingness-to-pay threshold of $50,000 per QALY for ivermectin versus all comparators.

The model did not allow for a PSA that would include all comparators simultaneously and therefore identify the probability for ivermectin 1% to be the most cost-effective option, which is a limitation.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Uncertain comparative clinical efficacy of ivermectin 1% cream versus metronidazole 0.75% cream, metronidazole 1% gel, metronidazole 1% cream, and azelaic acid 15% gel.** The CADTH Common Drug Review (CDR) *Clinical Review Report* concludes that ivermectin 1% cream is likely similar to metronidazole and azelaic acid in terms of efficacy and potential harms. Based on the results of the direct trial (Study 40173), ivermectin 1% cream was shown to be statistically significantly superior to metronidazole 0.75% cream for the outcome of success rate, among others. However, as stated in the CDR clinical report, the clinical significance of this finding is uncertain. Further, the [redacted] Using the credible interval from the [redacted] in a sensitivity analyses would have provided a better assessment of the uncertainty surrounding the comparative effectiveness. CDR could not assess the impact of this in the model as [redacted] were not provided. Additionally, the CDR reviewer noticed some discrepancies and abnormalities between what the manufacturer reported and what was done in the pharmacoeconomic model. These could not be verified as data were not available.
- **Lack of data to inform treatment success in long-term phase.** The manufacturer used the outcome of "median time to success" from the extension phase of Study 40173 (Part B) to inform the probability of treatment success in the long-term phase (from week 16 to end of year 3) (in patients who succeed initially, relapse, and then receive a topical drug again) for the ivermectin 1% cream and metronidazole 0.75% cream treatment groups. However, it is uncertain whether this difference would sustain past 36 weeks (length of Study 40173 [Part B]). For the other comparators, the manufacturer used the relative effect of treatment success of ivermectin 1% cream versus metronidazole 1% gel and azelaic acid 15% gel [redacted]. This assumption is not valid, as the relative effect would likely not sustain past the initial phase. This was also apparent in [redacted] (i.e., potential treatment waning).
- **Assumption of no maintenance treatment for patients who succeed on treatment.** As indicated by the clinical expert involved in the review, it is a very common occurrence in clinical practice that patients who succeed on treatment with a topical drug or combination therapy (either patients who succeed initially or subsequently) will continue treatment for an extended period of time (can be a

number of years) in order to prevent relapse of rosacea. Further, in the pharmacoeconomic model, the relapse rates were based on patients not receiving treatment (as per Part B of Study 40173). Thus, with maintenance treatment, the risk of relapse would be expected to decrease and a more conservative scenario would be to assume that the risk of relapse is the same for all topical drugs.

- **Weighted average cost of systemic antibiotics.** The manufacturer reported that the market share data and distribution for the systemic antibiotics (that are used as part of combination therapy in the base-case analysis) were provided by Canadian clinicians based in Ontario. This included tetracycline (40%), minocycline (20%), generic doxycycline (30%), and branded doxycycline (Apprilon), which the manufacturer reported approximately 10% of patients were prescribed. Based on IMS Brogan Pharmastat data, CDR reviewers determined that this distribution was not accurate. Further, Apprilon received a "do not list" recommendation by the Canadian Drug Expert Committee (CDEC) in 2013[5] and there were no public claims found. Modifying the distribution and costs (as per CDR cost comparison table) associated with systemic antibiotics will reduce the weighted market share costs of systemic antibiotics and thus, overall costs associated with combination therapy in the model. The new distribution is reported later in this report (see Table 20).
- **Probabilities of health care resource utilization.** The resource use per month pertaining to physician visits for patients with rosacea was based on US data, determined from the study by Romanowicz et al. (2008).[6] Clinical practices may differ between the two countries, which may alter the total costs associated with having rosacea.

5. CADTH COMMON DRUG REVIEW ANALYSES

CDR reviewers conducted a number of reanalyses, addressing several of the key limitations. Key results are presented here:

1. Equal probability of treatment success rate in the initial and long-term phase for all comparisons:

This was done by applying the same probability of treatment success in first the initial treatment phase (success rate = 0.630) and then in the initial and post-initial treatment phases (success rates = 0.630 and 0.222).

TABLE 3: CADTH COMMON DRUG REVIEW REANALYSIS #1: EQUAL PROBABILITY OF TREATMENT SUCCESS IN THE INITIAL AND LONG-TERM PHASE FOR ALL COMPARISONS

Interventions	Total Costs ($) per Patient Over 3 years	Total QALYs per Patient Over 3 Years	Sequential ICUR
Metronidazole 1% gel	$317	2.2266	Reference
Ivermectin 1% cream	$812	2.2282[a]	$323,688
Metronidazole 0.75% cream	$463	2.2266	Dominated by metronidazole 1% gel[b]
Azelaic acid 15% gel	$436	2.2266	

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year.

[a] The manufacturer assumed differential relapse rates for ivermectin 1% cream versus all comparators, explaining the difference in QALYs observed.

[b] A dominated strategy is more costly and provides less QALY gains (i.e., is less effective) than an alternative strategy.

As shown in Table 3, equating the probabilities of treatment success resulted in all drugs being equal in terms of benefits (expressed as QALYs), except ivermectin 1% cream (higher number of QALYs). This difference was due to a difference in relapse rate assumed by the manufacturer. Ivermectin 1% has an ICUR of $323,688 per QALY compared with metronidazole 1% gel, while other drugs were ruled out by dominance.

2. Assuming all patients stay on treatment after treatment success for three years, at full dose:

This was done by changing the values for treatment switching from "no treatment" to "treatment" for those who initially and subsequently succeeded on treatment. The number of months until patients who are on maintenance treatment stop treatment was changed to 32 months.

TABLE 4: CADTH COMMON DRUG REVIEW REANALYSIS #2: ASSUMPTION OF MAINTENANCE TREATMENT

Interventions	Total Costs ($) per Patient Over 3 Years	Total QALYs per Patient Over 3 Years	Sequential ICUR
Metronidazole 1% gel	$612	2.2301	Reference
Ivermectin 1% cream	$1,850	2.2385	$146,946
Azelaic acid 15% gel	$921	2.2274	Dominated by metronidazole 1% gel[a]
Metronidazole 0.75% cream	$971	2.2304	Extendedly dominated by metronidazole 1% gel and ivermectin 1% cream[b]

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year.
[a] A dominated strategy is more costly and provides less QALY gains (i.e., is less effective) than an alternative strategy.
[b] There are combinations of metronidazole 1% gel and ivermectin 1% cream that are less costly and provide greater benefits (QALYs) than metronidazole 0.75% cream – metronidazole 0.75% cream is extendedly dominated.

As shown in Table 4, assuming patients will stay on treatment after treatment success resulted in ivermectin 1% having an ICUR of $146,946 per QALY compared with metronidazole 1% gel, while other drugs were ruled out by dominance or extended dominance.

3. Assuming the same risk of relapse among patients on various topical drugs:

This was done by changing the risk of relapse in the model to a pooled risk from the ivermectin 1% cream and metronidazole 0.75% cream treatment groups from Part B of Study 40173, using the same distribution used by the manufacturer in its base-case analysis (i.e., "full trial" results using a generalized gamma survival curve distribution).

TABLE 5: CADTH COMMON DRUG REVIEW REANALYSIS #3: SAME RISK OF RELAPSE

Interventions	Total Costs ($) per Patient Over 3 Years	Total QALYs per Patient Over 3 Years	Sequential ICUR
Metronidazole 1% gel	$375	2.2202	Reference
Ivermectin 1% cream	$825	2.2274	$62,681
Azelaic acid 15% gel	$537	2.2176	Dominated by metronidazole 1% gel[a]
Metronidazole 0.75% cream	$531	2.2206	Extendedly dominated by metronidazole 1% gel and ivermectin 1% cream[b]

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year.
[a] A dominated strategy is more costly and provides less QALY gains (i.e., is less effective) than an alternative strategy.
[b] There are combinations of metronidazole 1% gel and ivermectin 1% cream that are less costly and provide greater benefits (QALYs) than metronidazole 0.75% cream – metronidazole 0.75% cream is extendedly dominated.

As shown in Table 5, assuming the same risk of relapse for topical drugs resulted in ivermectin 1% having an ICUR of $62,681 per QALY compared with metronidazole 1% gel, while other drugs were ruled out by dominance or extended dominance.

4. Alteration of the attributed weight (based on per cent claims) and price of systemic antibiotics to get a revised weighted average cost of systemic antibiotics:

This was done by altering the distribution of market shares for each antibiotic, based on IMS Brogan Pharmastat claims data for 2014 (full year), and updating the prices listed as per the CDR cost comparison table.

TABLE 6: CADTH COMMON DRUG REVIEW REANALYSIS #4: UPDATED WEIGHTED AVERAGE COST OF SYSTEMIC ANTIBIOTICS

Interventions	Total Costs ($) per Patient Over 3 Years	Total QALYs per Patient Over 3 Years	Sequential ICUR
Metronidazole 1% gel	$342	2.2195	Reference
Ivermectin 1% cream	$786	2.2282	$51,410
Azelaic acid 15% gel	$501	2.2169	Dominated by metronidazole 1% gel[a]
Metronidazole 0.75% cream	$501	2.2199	Extendedly dominated by metronidazole 1% gel and ivermectin 1% cream[b]

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year.
[a] A dominated strategy is more costly and provides less QALY gains (i.e., is less effective) than an alternative strategy.
[b] There are combinations of metronidazole 1% gel and ivermectin 1% cream that are less costly and provide greater benefits (QALYs) than metronidazole 0.75% cream – metronidazole 0.75% cream is extendedly dominated.

As shown in Table 6, updating the weighted average cost of systemic antibiotics resulted in ivermectin 1% having an ICUR of $51,410 per QALY compared with metronidazole 1% gel, while other drugs were ruled out by dominance or extended dominance.

For more detailed CDR reanalyses, see Table 21 in Appendix 4.

5. CADTH COMMON DRUG REVIEW MULTI-WAY ANALYSIS

CDR multi-way analysis assumed ivermectin 1% cream would have the probability of treatment success, given the conclusions of the CDR clinical review report and the absence of treatment success probabilities based on the [redacted]. Further, it was assumed patients would receive maintenance treatment after treatment success for the duration of the time horizon. As maintenance therapy would likely decrease the risk of relapse, a more conservative scenario assumed that the risk of relapse would be the same for all drugs. Lastly, the multi-way analysis considered an updated weighted average cost of systemic antibiotics, based on an updated market share distribution and costs.

Given equal treatment success probabilities and same relapse rates, only drug costs differed between topical drugs. Ivermectin 1% cream was associated with an incremental drug cost of $[redacted] per patient over three years versus metronidazole 1% gel. Detailed results are reported in Appendix 4 (see Table 23). When looking at the approximate daily costs only, ivermectin 1% cream ($[redacted] if dosed as per manufacturer's submission), is associated with an incremental daily cost of $[redacted] per patient versus metronidazole 1% gel (see Table 24).

Price reduction analysis

As shown in Table 7, the price of ivermectin 1% cream would need to be reduced by [redacted]% to be equivalent to the price of metronidazole 1% gel, when both are dosed once daily at the same number of grams. The price of ivermectin 1% cream would need to be reduced by [redacted] and [redacted]% to be equivalent to the price of metronidazole 0.75% cream and azelaic acid 15% gel, respectively, if the drugs are dosed based on the number of grams used in Study 40173 and the manufacturer's submission (0.72 g if used once daily and 1.31 g if used twice daily).

TABLE 7: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

Current Price[a]	Scenario	Reduced Price	% Price Reduction[b]
$[redacted] per gram[a]	Price reduction needed to equal the price of metronidazole 1% gel (based on an approximate daily cost of $0.4527)	$0.6287	[redacted]%
	Price reduction needed to equal the price of azelaic acid 15% gel (based on an approximate daily cost of $0.7860)	$0.6000	[redacted]%
	Price reduction needed to equal the price of metronidazole 0.75% cream (based on an approximate daily cost of $0.8646)	$0.6600	[redacted]%

[a] Approximate daily cost $[redacted] (see cost comparison table).

[b] All price reductions are calculated based on the assumption of 0.72 g are used if dosed once daily and 1.31 g used if dosed twice daily, as per the number of grams used in Study 40173 and the manufacturer's pharmacoeconomic submission.[3]

6. ISSUES FOR CONSIDERATION

- Current clinical evidence around the efficacy and safety of ivermectin 1% cream has been studied only in patients with moderate to severe papulopustular rosacea.
- As noted by the CDR clinical expert, there is potential for ivermectin 1% cream to be used in other subtypes of rosacea (i.e., off-label).
- Although ivermectin 1% cream is indicated for use as a first-line topical drug in the treatment of inflammatory lesions of rosacea, the clinical expert indicated that in clinical practice in Canada, it may be used as a second-line drug, after failing initial treatment with metronidazole 0.75% cream or 1% cream. However, there is no clinical evidence to support the use of ivermectin 1% cream as a second-line drug.
- An IMS Brogan Pharmastat search indicated that the three most common topical drugs used are metronidazole 1% gel (37%), metronidazole 0.75% cream (36%), and metronidazole 1% cream (23%). Note that these may include use for other indications than rosacea.

7. PATIENT INPUT

Input was received from one patient group, the Canadian Skin Patient Alliance. Patients reported that rosacea causes noticeable skin changes on the face, which have long-term effects on a quality of life. This included low self-esteem, embarrassment, frustration, sadness, shame, depression, and inability to participate in day-to-day activities. Patients expressed that the most important symptoms to control were redness and bumps. The most common therapies patients were on included 1% metronidazole gel and azelaic acid 15% gel, in addition to a variety of prescription creams and over-the-counter acne medications. Several patients also stated concerns about the high expenses associated with treatment, and that they were open to trying different therapies to find relief of their rosacea symptoms.

8. CONCLUSIONS

The CDR clinical review concluded that the available evidence suggests that ivermectin is similar to metronidazole and azelaic acid with respect to efficacy and potential harms. Treatment success probabilities derived from the [redacted] were unavailable, and therefore, CDR reanalysis assumed equal efficacy among all topical drugs and focused on drug costs alone. Ivermectin 1% cream (approximate daily cost of $[redacted]) is more expensive than metronidazole 1% gel, azelaic acid 15% gel, and metronidazole 0.75% cream. A price reduction of [redacted] to [redacted]% would be needed for ivermectin to be equal in price with metronidazole and azelaic acid.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 8 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 8: COST COMPARISON TABLE FOR THE TREATMENT OF INFLAMMATORY LESIONS (PAPULES AND PUSTULES) OF ROSACEA IN ADULTS 18 YEARS OF AGE OR OLDER — TOPICAL PREPARATIONS

Comparators	Strength	Dose Form	Recommended Dose	Price per Gram ($)	Approximate Daily Cost[a] ($)
Ivermectin (Rosiver)	**1%**	**Cream**	**Apply thin layer once daily**	[redacted][b]	[redacted]
Azelaic acid (Finacea)	15%	Gel	Apply thin layer twice daily	0.6000	0.60 to 0.79
Metronidazole (MetroGel)	0.75% 1%	Gel	Apply and rub in a thin film twice daily Apply and rub in a thin film once daily	1.2855[c] 0.6287	1.29 to 1.68 0.31 to 0.45
Metronidazole (MetroCream)	0.75%	Cream	Apply and rub in a thin film twice daily	0.6600	0.66 to 0.86
Metronidazole (MetroLotion)	0.75%	Lotion	Apply and rub in a thin film twice daily	0.6600	0.66 to 0.86
Metronidazole (Noritate)	1%	Cream	Apply and rub ½ cm of cream twice daily	0.5789	0.58 to 0.76[d]

[a] Range of costs is based on 0.5 g to 0.72 g if applied once daily and 1.0 g to 1.31 g if applied twice daily. The lower dose in the range is based on the product monograph for azelaic acid 15% gel, which states that one thin layer application consists of 0.5 g (and thus 1 g if applied twice daily).[7] The higher dose in the range is based on the number of grams used in Study 40173 and the manufacturer's pharmacoeconomic submission.[3]

[b] Manufacturer's confidential submitted price.

[c] Not reimbursed under any public drug plan in Canada. Price per gram was estimated using data for private plans in Ontario from IMS PharmaStat, using cost per unit and removing the current Ontario Drug Benefit (ODB) dispensing fee and mark-up rates.

[d] Calculated based on the number of grams per day, not the centimetres recommended.

Note: All prices are from the ODB Formulary (accessed August 2015), unless otherwise indicated, and do not include dispensing fees.

TABLE 9: COST COMPARISON TABLE FOR THE TREATMENT OF INFLAMMATORY LESIONS (PAPULES AND PUSTULES) OF ROSACEA IN ADULTS 18 YEARS OF AGE OR OLDER — ORAL ANTIBIOTICS

Drug / Comparator	Strength	Form	Price	Recommended Daily Dose	Daily Cost ($)
Doxycycline monohydrate (Apprilon)	40 mg	Modified-release capsule	NA	40 mg daily	2.55[a]
Other drugs that may be used (not indicated for rosacea)					
Doxycycline hyclate (generics)	100 mg 100 mg	Capsule; tablet	0.5860	200 mg initially, followed by 100 mg once daily	0.59 to 1.17
Minocycline HCL (generics)	50 mg 100 mg	Capsule	0.3064 0.5912	100 mg to 200 mg initially, followed by 100 mg every 12 hours	0.59 to 1.23
Tetracycline HCL (generics)	250 mg	Capsule	0.0670	500 mg b.i.d. for 2 weeks followed by 500 mg daily until controlled, then 250 mg daily for 3 to 4 weeks	0.07 to 0.27

b.i.d. = twice daily; NA = not available.

[a] Received a "do not list" recommendation by the Canadian Drug Expert Committee (CDEC) in 2013.[5] Not reimbursed under any public drug plan in Canada. Price per gram was estimated using data for private plans in Ontario from IMS PharmaStat, using cost per unit and removing the current Ontario Drug Benefit dispensing fee and mark-up rates.

Note: All prices are from the Saskatchewan Drug Benefit Formulary (accessed August 2015), unless otherwise indicated, and do not include dispensing fees.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS IVERMECTIN 1% CREAM RELATIVE TO METRONIDAZOLE 0.75% CREAM?

Ivermectin 1% Cream Versus Metronidazole 0.75% Cream	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
ICUR	$33,245 per QALY (manufacturer's base-case analysis) Incremental cost of ivermectin 1% cream: $927 per patient, over 3 years					

ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

TABLE 11: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS IVERMECTIN 1% CREAM RELATIVE TO METRONIDAZOLE 1% GEL?

Ivermectin 1% Cream Versus Metronidazole 1% Gel	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
ICUR	$38,677 per QALY (manufacturer's base-case analysis) Incremental cost of ivermectin 1% cream: $[redacted] per patient, over 3 years					

ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS IVERMECTIN 1% CREAM RELATIVE TO METRONIDAZOLE 1% CREAM?

Ivermectin 1% Cream Versus Metronidazole 1% Cream	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
ICUR	$50,062 per QALY (manufacturer's base-case analysis) Could not conduct CDR reanalysis (comparator not included in PE model)					

CDR = CADTH Common Drug Report; ICUR = incremental cost-utility ratio; NA = not applicable; PE = pharmacoeconomic; QALY = quality-adjusted life-year.

TABLE 13: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS IVERMECTIN 1% CREAM RELATIVE TO AZELAIC ACID 15% GEL?

Ivermectin 1% Cream Versus Azelaic Acid 15% Gel	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
ICUR	$23,831 per QALY (manufacturer's base-case analysis) Incremental cost of ivermectin 1% cream: $996 per patient, over 3 years					

ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 14: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments *Reviewer to provide comments if checking "no"*	Lack of clarity on how certain values very derived and calculated (i.e., [redacted], combination therapy — which was explained upon request, etc.). The comparison of ivermectin 1% cream versus metronidazole 1% cream was missing from the PE model.		
Was the material included (content) sufficient?			X
Comments *Reviewer to provide comments if checking "poor"*	The manufacturer did not include treatment success probabilities obtained from [redacted] in the economic model or report ([redacted]). It was impossible for CDR reviewer to run reanalyses using these values.		
Was the submission well organized and was information easy to locate?			X
Comments *Reviewer to provide comments if checking "poor"*	Confusion in the written PE report in terms of what was done in base-case analysis and what did not apply to the base-case analysis (and was included as part of the larger, complex model).		

CDR = CADTH Common Drug Review; PE = pharmacoeconomic.

TABLE 15: AUTHOR INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review			
☐ Adaptation of global model/Canadian model done by the manufacturer			
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer			
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer			
☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

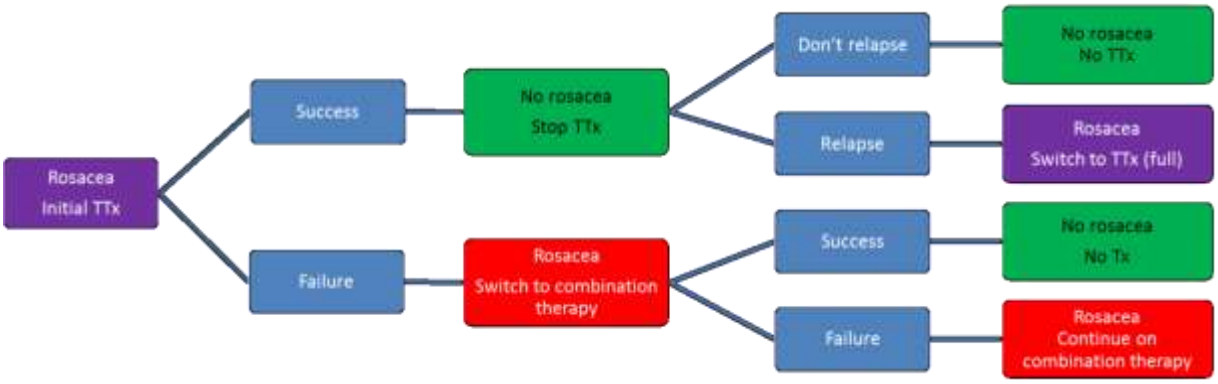
The manufacturer submitted a cost-utility analysis based on a decision analytic Markov model where adult patients with inflammatory lesions (i.e., papules and pustules) of rosacea transitioned between two health states, defined by their Investigator's Global Assessment (IGA) score, over a three-year time horizon.[3] Patients were assumed to have moderate to severe papulopustular rosacea at the start of the model, based on the baseline distribution of patients observed in three phase 3 studies (two vehicle-controlled, one active-controlled).[4,8,9] The health states were defined as follows:

- No rosacea: IGA score of 0 (clear; no inflammatory lesions present, no erythema) or an IGA score of 1 (almost clear; very few small papules/pustules, very mild erythema present)
- Rosacea: IGA score of 2 (mild; few small papules/pustules, mild erythema), 3 (moderate; several small or large papules/pustules, moderate erythema) or 4 (severe; numerous small and/or large papules/pustules, severe erythema)

The manufacturer's model followed a cohort of 1,000 patients. In the base-case analysis, all patients received treatment with a topical drug during an initial period of 12 weeks, and treatment efficacy was assumed to be sustained until 16 weeks (i.e., no treatment during weeks 12 to 16). After this initial period, treatment success (i.e., IGA score ≤ 1; in the health state of "no rosacea") or treatment failure (i.e., IGA score > 1, in the health state of "rosacea") was assessed every month. Patients who were successful after initial treatment were assumed to stop treatment entirely (i.e., no maintenance treatment assumed), with the only risk being that of relapse (IGA score ≥ 2) for the duration of the time horizon. If patients did not experience relapse, they remained in the state of "no rosacea". If they did experience a relapse, patients were switched back to receiving the topical drug (at the full dose), at which point treatment success was assessed again at every cycle. Alternatively, patients who failed after the initial treatment period were switched to combination therapy right away, defined as the combination of the topical drug and systemic antibiotics. If patients were deemed as successful on treatment, they were taken off treatment. If they continued to fail on treatment, they were assumed to continue on combination therapy. In the model, patients who had initially failed were only switched between therapies after three months' time. For the duration of the time horizon, any subsequent treatment successes with a topical drug or combination therapy resulted in patients stopping treatment. Any subsequent treatment failures resulted in patients switching to combination therapy.

It should be noted that the manufacturer's base-case model structure was based on the application of a number of simplifying assumptions to a larger, more complex model structure. This larger model allowed for all patients who experienced treatment success, treatment failure, or a relapse to either: stop treatment, start maintenance treatment, or switch to another treatment. In this model, patients were able to switch between topical treatment (full dose), topical treatment (reduced dose), systemic antibiotic treatment (full dose), systemic antibiotic (reduced dose), or combination therapy (full dose topical treatment plus full dose systemic antibiotic treatment).

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE, USED IN BASE-CASE ANALYSIS



TTx = topical treatment; Tx = treatment.
Source: Manufacturer's pharmacoeconomic submission.[3]

The manufacturer stated that the model was validated by both internal and external members. This included checking the model structure, data, and coding in addition to verifying model calculations and assumptions.

TABLE 16: DATA SOURCES

Data Input	Description of Data Source	Comment
Natural history	Adult patients with moderate to severe papulopustular rosacea, based on the baseline distribution of patients enrolled in Study 40173.[4] Study 40173 was a phase 3, active-controlled study comparing the efficacy and safety of ivermectin 1% cream versus metronidazole 0.75% cream over 16 weeks of treatment (Part A), followed by a 36-week extension phase (Part B).	
Efficacy		
Treatment success with topical drug during the initial treatment phase	[redacted] Although not used in the base-case analysis, the model included the option to use the results of Study 40173.	There were a number of limitations [redacted]. Uncertain comparative clinical benefit of ivermectin 1% cream versus all comparators, due to [redacted] and uncertainty regarding what constitutes an MCID. Could not be reanalyzed as manufacturer did not provide

Data Input	Description of Data Source	Comment
	Treatment efficacy of metronidazole 1% cream was assumed to be the same as metronidazole 0.75% cream.	treatment success probabilities with the [redacted] There was one discrepancy found between the results of the [redacted] than the direct trial (Study 40173) results. However, for the same comparison, when looking at the [redacted] in the PE model.
Treatment success with topical drug during the post-initial/long-term treatment phase (i.e., patients who switch back to treatment with a topical drug after experiencing a relapse)	Part B results from Study 40173 were used to inform treatment success probabilities for ivermectin 1% cream and metronidazole 0.75% cream.[4] The outcome of "median time to success" was used, where the number of days to treatment success was converted to monthly probabilities. [redacted][2]	A relative effect of treatment would likely not sustain past the initial phase of 12 weeks. This was also apparent in [redacted]
Treatment success with combination therapy	The manufacturer obtained risk ratios of treatment success for combination therapy (with antibiotics) versus monotherapy (only topical drug) from external literature.[10] This study compared metronidazole 1% gel plus doxycycline with metronidazole 1% gel plus placebo. The relative effect of combination therapy versus monotherapy was applied to all comparators in the model, to determine treatment success with combination therapy.	
Relapse rate	For patients who were successful during the initial treatment phase, the manufacturer extrapolated out "time-to-relapse" data	

Data Input	Description of Data Source	Comment
	from the results of Part B of Study 40173,[4] using a generalized gamma distribution for the survival curve for both ivermectin 1% cream and metronidazole 0.75% cream. Thus, applying time-dependent monthly probabilities. In the absence of data, the relapse rates for metronidazole 1% gel and azelaic acid 15% gel were assumed to be the same as metronidazole 0.75% cream. To determine the risk of relapse for patients who succeed after a failed treatment or who succeed after a relapse, relapse data from Part B of Study 40173 was used to apply a constant monthly probability of relapse.[4] The same probability was assumed for all topical drugs.	
Maintenance treatment	Treatment success for patients on maintenance treatment was assumed to be the same as treatment success during the post-initial treatment phase (for patients who switch back to treatment with a topical drug after experiencing a relapse), as described above. In order to account for the impact of maintenance treatment on the relapse rate for those who succeeded initially, the manufacturer included a hazard ratio, to be applied to the extrapolated "time-to-relapse" data, derived from the study by Dahl et al. (1998).[11] The same hazard ratio was applied to all treatment groups. In order to account for the impact of maintenance treatment on the relapse rate for patients who succeeded after a failed treatment or who succeeded after a relapse, the manufacturer included an average relative risk of relapse, also based on data from Dahl et al. (1998).[11] The same relative risk was applied to all treatment groups.	Manufacturer did not include maintenance treatment in their base-case analysis. As mentioned by the CDR clinical expert, most patients continue on treatment after succeeding in order to prevent relapse.
Utilities	QoL was measured through the EQ-5D (in all domains including anxiety/depression, mobility, pain/discomfort, self-care, and usual activities) from Study 40173,[4] where patient-level data were collected at baseline and weeks 16, 32, and 52. The mean EQ-5D index score was calculated per visit and as a total mean score across all visits, for the	

Data Input	Description of Data Source	Comment
	health states of no rosacea (IGA = 0 or 1) and rosacea (IGA ≥ 2).	
Resource use		
Systemic antibiotics	The manufacturer reported that market share data for each of the antibiotics was provided by Canadian clinicians based in Ontario.[3] The antibiotics included tetracycline, doxycycline (generic and brand, Apprilon), and minocycline.	Upon verifying using IMS Brogan Pharmastat data, CDR determined that this distribution was not accurate. Further, Apprilon received a "do not list" recommendation by CDEC in 2013[5] and there were no public claims found.
Physician visit(s)	A US-based study on health care utilization and costs of patients with rosacea was used to determine the number of general practitioner and specialist (dermatologist) visits per cycle for patients with rosacea.[6] The manufacturer reported that this was in line with the Canadian setting.	Clinical practices may differ between the two countries. Also, resource use per month is not in line with the information provided by the CDR clinical expert. According to the expert, patients with rosacea would likely see a physician every 8 to 12 weeks.
Costs		
Topical drugs	The unit drug cost per gram for ivermectin 1% cream was obtained from the manufacturer. The unit drug costs per gram for metronidazole 0.75% cream, 1% gel, and azelaic acid 15% gel were obtained from ODB, based on prices listed in January 2015. The number of grams used per day for ivermectin 1% q.d. cream and metronidazole 0.75% b.i.d. cream were obtained from Study 40173. This was based on the quantity of product used, which was derived from tube weight data, over the number of days it was used.[4] The number of grams used per day for azelaic acid 15% gel b.i.d. was obtained from another trial,[3] which the manufacturer reported was similar to the metronidazole 0.75% cream b.i.d. dose reported in Study 40173. Based on these studies, the manufacturer assumed that the two q.d. topical drugs (ivermectin 1% cream and metronidazole 1% gel) and the two b.i.d. topical drugs (metronidazole 0.75% cream and azelaic acid 15% gel) had the same daily doses. The cost per gram and the grams per day were used to calculate the cost per day for each topical drug. In the model, the manufacturer also included the cost of reduced dose, which	The number of grams per day for azelaic acid 15% gel b.i.d., obtained from the other trial, was not similar to that of metronidazole 0.75% cream b.i.d. dose reported in Study 40173. However, the manufacturer's base-case grams per day estimates seem conservative.

Data Input	Description of Data Source	Comment
	was assumed to be half the full dose. Reduced doses were not used in the base-case analysis.	
Systemic antibiotics	The unit drug cost per gram for generic tetracycline, doxycycline, and minocycline were obtained from the ODB, based on prices listed in January 2015. The unit drug cost per gram for brand doxycycline (Apprilon) was sourced from the AQPP, based on the price listed in February 2015.[3] The cost per day (based on recommended dosing) and weighted average cost per day (based on market share data) were calculated for each antibiotic. From this, an average cost of systemic antibiotic treatment per day was determined. The cost of combination therapy was assumed to be the total costs of the topical treatment plus this cost.	The price of generic minocycline could not be verified. CDR reanalysis will use the prices listed in the cost comparison table (see Appendix 1). The recommended dosing the manufacturer used in its analysis to determine the cost per day varies (see cost comparison table). CDR assumed the most frequent dose used.
Physician visit(s)	The unit cost for visits to the general practitioner and a dermatologist were obtained from the Ontario Schedule of Benefits. This included the unit costs for the first visit and unit costs for subsequent visits.[3]	
Societal costs	The manufacturer conducted a sensitivity analysis to explore the impact of societal costs on the model. This included: the costs associated with productivity lost associated with workdays lost for GP and specialist appointments.	

AQPP = Association québécoise des pharmaciens proprietaries; b.i.d. = twice daily; CDEC = Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; EQ-5D = EuroQol 5-Dimensions Questionnaire; GP = general practitioner; IGA = Investigator's Global Assessment; MCID = minimal clinically important difference; ODB = Ontario Drug Benefit; PE = pharmacoeconomic; q.d. = once daily; QoL = quality of life.

TABLE 17: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Assumptions in the base-case model	
Relative effect of treatment success of ivermectin 1% cream versus metronidazole 0.75% cream, metronidazole 1% gel, and azelaic acid 15% gel at 12 weeks maintains at 16 weeks, and beyond (for metronidazole 1% gel and azelaic acid 15% gel).	Not appropriate. The relative effect would likely not sustain past the initial phase as was apparent in [redacted]
Metronidazole 1% cream has the same treatment efficacy as metronidazole 0.75% cream.	Likely appropriate.
The risk of relapse for metronidazole 1% gel and azelaic acid 15% gel is the same as the risk of relapse of metronidazole 0.75% cream.	Likely appropriate.
The risk of relapse in patients who succeed after failing initial treatment or for those who relapse is the same as the risk of relapse for those who succeed on initial treatment.	Likely appropriate.
All patients stop treatment after successful treatment of rosacea (i.e., no maintenance therapy).	Not appropriate. As identified by the CDR clinical expert, patients who succeed on initial treatment will continue on maintenance therapy to prevent relapse.
All patients switch to (or continue on) combination treatment after failed treatment of rosacea.	Likely appropriate.
All patients who were successful on initial treatment will switch back to topical treatment if they experience a relapse.	Appropriate assumption. Successful patients would likely be on maintenance treatment, however.
Approximately 10% of public claims are for brand doxycycline (Apprilon).	Not appropriate. CDR verified using IMS Brogan Pharmastat data for the year 2014. Apprilon received a "do not list" recommendation by CDEC in 2013[5] and additionally, there were no public claims found.
The probability of physician and specialist visits for rosacea in Canada are similar to that of the US.	Not appropriate. Clinical practices may differ between the two countries.

CDEC = Canadian Drug Expert Committee; CDR = CADTH Common Drug Review.

Manufacturer's Results

The manufacturer reported total costs, by medication and health care resources used, in addition to clinical outcomes for ivermectin 1% cream, metronidazole 0.75% cream, metronidazole 1% cream, metronidazole 1% gel, and azelaic acid 15% gel. Ivermectin 1% cream was associated with the highest total costs ($812 per patient) and highest total benefits (2.2282 quality-adjusted life-years [QALYs] per patient), over a three-year time horizon. Metronidazole 1% gel was associated with the lowest total costs ($380 per patient), while azelaic acid 15% gel was associated with the lowest total benefits (2.2169 QALYs per patient). When considered in a sequential manner, the manufacturer's base-case results suggest that metronidazole 1% gel was associated with the lowest total costs.[3] Ivermectin 1% was associated with an incremental cost-utility ratio (ICUR) of $50,073 per QALY, while other drugs were ruled out by dominance or extended dominance. All total costs and benefits associated with the comparators, in addition to the manufacturer's base-case ICURs, can be found in Table 18 and Table 19.

TABLE 18: SUMMARY OF THE RESULTS OF THE MANUFACTURER'S BASE CASE, BY COST AND CLINICAL OUTCOME (PER PATIENT)

Model Parameters	Ivermectin 1% Cream	Metronidazole			Azelaic Acid 15% Gel
		0.75% cream	1% cream[c]	1% gel	
Costs[a]					
Medication costs[b]	$748	$464	$419	$305	$465
Health care costs	$64	$75	$75	$75	$79
Total costs	$812	$538	$494	$380	$543
Clinical outcomes[a]					
QALYs	2.2282	2.2199	2.2199	2.2195	2.2169
Disease-free days	570	511	511	508	489

QALY = quality-adjusted life-year.
[a] The manufacturer reports both undiscounted and discounted costs and clinical outcomes in its pharmacoeconomic report. Only discounted results are presented here.
[b] Includes the cost of systemic antibiotics.
[c] The comparison with metronidazole 1% cream was performed as a scenario analysis.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

TABLE 19: SUMMARY OF THE RESULTS OF THE MANUFACTURER'S BASE CASE

Comparator		Incremental (Ivermectin Versus Comparator)			ICUR	ICER
		Total Costs[a]	Total QALYs[a]	Disease-Free Days		
Metronidazole	**0.75% cream**	$274	0.0082	73	$33,245	$4
	1% cream[b]	$318	0.0082	73	$38,677	$4
	1% gel	$432	0.0086	77	$50,062	$6
Azelaic Acid 15% gel		$269	0.0113	100	$23,831	$3

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
[a] The manufacturer reports both undiscounted and discounted costs and clinical outcomes in its pharmacoeconomic report. Only discounted data are presented here.
[b] Ivermectin 1% cream versus metronidazole 1% cream was performed as a scenario analysis.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

Summary of Manufacturer's Sensitivity Analysis

Uncertainty around the parameters chosen for the base-case analysis was addressed by the manufacturer using a one-way deterministic sensitivity analysis and a Monte Carlo simulation probabilistic sensitivity analysis (PSA), with 10,000 iterations. The manufacturer illustrated the cost-effectiveness on a plane, in addition to providing cost-effectiveness acceptability curves at various willingness-to-pay thresholds. Sensitivity analyses were conducted separately for metronidazole 0.75% cream, metronidazole 1% gel, and azelaic acid 15% gel. As the comparison to metronidazole 1% cream was performed as a scenario analysis, the manufacturer did not include it in the PSA.

Deterministic Sensitivity Analysis

The parameters varied individually in each of the scenarios by the manufacturer included:

- Time horizon (one year, five years)
- Relative risk for combination therapy (1.000)
- Treatment switching (UK database, UK database assuming 75% of patients stop maintenance therapy after three months, US database, US database assuming 75% of patients stop maintenance therapy after three months)
- Survival curve distribution (log normal)
- Initial treatment period (whole period 16 weeks, monthly cycle 12 weeks)
- Dosing of topical therapy (0.36 g once daily/0.66 g for twice daily, 1.08 g for once daily/1.97 g for twice daily)
- Discount rate (0%, 3%)
- Productivity costs (included)
- Health care resource use probabilities (0.11 general practitioner visits/0.075 specialist visits, 0.037 general practitioner visits/0.025 specialist visits)
- Health state utility inputs (no rosacea = 0.976, rosacea = 0.924; no rosacea = 0.0976/ rosacea = 0.924)

The parameters with the greatest impact on ICUR (± 25%) included: the time horizon, treatment switching, dosing of topical therapy, and the health state utility inputs. When these parameters were varied individually, the ICUR ranged from $13,827 to $77,947 per QALY for metronidazole 0.75% cream. For metronidazole 1% cream and 1% gel, the ICUR ranged from $16,543 to $90,684 and $22,186 to $117,377 per QALY, respectively. For azelaic acid, the ICUR ranged from $8,981 to $55,976 per QALY.

Probabilistic Sensitivity Analysis

The variables considered in the PSA included: the probability of treatment success; relative risk of treatment success; probability of relapse; relative risk of relapse; drugs costs — grams per dose; health care costs — number of visits; and health state utility inputs. Following 10,000 iterations, the ICUR was calculated to be $32,757 per QALY for metronidazole 0.75% cream. For metronidazole 1% gel and azelaic acid 15% gel, the ICUR was calculated to be $45,969 and $23,232 per QALY, respectively.

At a willingness-to-pay threshold of $50,000, ivermectin 1% cream has an approximately 50% probability of being cost-effective when compared with metronidazole 0.75% cream, metronidazole 1% gel, and azelaic acid 15% gel.

CADTH Common Drug Review Reanalysis

CADTH Common Drug Review (CDR) conducted a number of reanalyses, addressing several of the limitations:

1. **Probability of treatment success:** equal probability of treatment success was assumed for ivermectin 1% cream versus metronidazole 0.75% cream, due to the [redacted] and the overall conclusions of the CDR clinical review report. This was done by applying the same probability of treatment success in (1) the initial treatment phase (success rate = 0.630) and (2) the initial and post-initial treatment phase (success rates = 0.630 and 0.222).
2. **Maintenance treatment after initial treatment success (reported as duration)**: CDR reanalysis looked at how the ICUR varies when different durations of maintenance treatment are assumed for patients who succeed after initial treatment. This was done by changing the values for treatment switching from "no treatment" to "treatment" for those who initially succeed on treatment. Durations were increased by six-month intervals, up to a total duration of 32 months (three years of treatment total), which is equivalent to the time horizon of the model. The CDR clinical expert also noted that maintenance treatment is typically dosed at once daily, regardless of the recommended dose. Thus, CDR looked at how the ICUR varies using both full dose (recommend dose of topical drug) and reduced dose (assuming all drugs are dosed once daily).
3. **Maintenance treatment after initial and post-initial treatment success**: CDR reanalysis looked at how the ICUR varies when maintenance treatment is assumed for patients who succeed after initial treatment and post-initial treatment. This was done by changing the values for treatment switching from "no treatment" to "treatment" for those who initially and subsequently succeed on treatment. As the duration of this could not be varied in the model, CDR only reported the ICUR when maintenance treatment is assumed for all treatment successes for the duration of the time horizon (32 months, or three years).
4. **Risk of relapse and survival curve distribution to extrapolate relapse data**: CDR looked at how the ICUR varies when a different distribution is used from the manufacturer's base-case analysis (i.e., log normal instead of generalized gamma) for ivermectin 1% cream and metronidazole 0.75% cream (which also applied to the other comparators). Additionally, CDR looked at how the ICUR changes when the same risk of relapse is assumed regardless of treatment (i.e., pooling from the ivermectin 1% cream and metronidazole 0.75% cream treatment groups from Part B of Study 40173; i.e., "full trial"). This was assessed using both the generalized gamma survival curve distribution and the log normal distribution.
5. **Weighted average cost of systemic antibiotics**: CDR conducted reanalyses using prices listed in the CDR cost comparison table (see Appendix 1), which were based on the Saskatchewan drug formulary. Further, CDR assumed the most frequently used recommended daily dose for each antibiotic, based on their respective product monographs and the CDR cost comparison table. Lastly, CDR altered the distribution of market shares for each antibiotic, based on IMS Brogan Pharmastat claims data for 2014 (full year). This included assuming 0% of patients would receive Apprilon, as it received a "do not list" recommendation by the Canadian Drug Expert Committee (CDEC) in 2013[5] and there were no public claims found.

TABLE 20: MARKET SHARE DATA DISTRIBUTION OF SYSTEMIC ANTIBIOTICS

Oral Antibiotic	Manufacturer's Base-Case, Based on Clinical Expert Opinion	CDR Reanalysis, Based on Pharmastat Claims Data for 2014 (Full Year)
Doxycycline, generic	30.0%	63.9%
Doxycycline, brand	10.0%	0.0%
Minocycline	20.0%	9.2%
Tetracycline	40.0%	26.9%

CDR = CADTH Common Drug Review.

TABLE 21: SUMMARY OF CADTH COMMON DRUG REVIEW REANALYSIS SCENARIOS, BASED ON IDENTIFIED LIMITATIONS

		Metronidazole 0.75% Cream b.i.d.	Metronidazole 1% Gel q.d.	Azelaic Acid 15% Gel b.i.d.
Manufacturer's base-case		$33,245	$50,062	$23,831
CDR Reanalysis				
Probability of treatment success				
Equal during the initial treatment phase		$50,600	$323,688[a]	$246,166[a]
Equal during the initial treatment and post-initial treatment phase		$227,886		
Maintenance treatment after initial treatment success; reported as duration				
6 months	Full dose	$39,025	$56,690	$28,832
	Reduced dose (q.d.)	$41,916		$30,624
12 months	Full dose	$45,879	$64,691	$34,352
	Reduced dose (q.d.)	$50,655		$37,318
18 months	Full dose	$52,073	$71,924	$39,294
	Reduced dose (q.d.)	$58,369		$43,208
24 months	Full dose	$57,657	$78,435	$43,726
	Reduced dose (q.d.)	$65,242		$48,443
30 months	Full dose	$62,736	$84,346	$47,741
	Reduced dose (q.d.)	$71,447		$53,159
32 months (for a total of 3 years of treatment)	Full dose	$64,360	$86,239	$49,022
	Reduced dose (q.d.)	$73,419		$54,656
Maintenance treatment after initial and post-initial treatment success				
32 months (for a total of 3 years of treatment)	Full dose	$108,155	$146,946	$83,164
	Reduced dose (q.d.)	$118,148		$89,285
Risk of relapse and survival curve distribution to extrapolate relapse data				
Log normal for ivermectin 1% and log normal for metronidazole 0.7% cream (and other comparators)		$39,458	$57,685	$27,868
Generalized gamma for all, full trial results[b]		$43,195	$62,681	$29,252
Log normal for all, full trial results[b]		$48,033	$68,383	$32,395
Weighted average cost of systemic antibiotics				
		$34,564	$51,410	$25,235

b.i.d. = twice daily; CDR = CADTH Common Drug Review; q.d. = once daily.

[a] Treatment efficacy during the post-initial treatment phase for metronidazole 1% gel and azelaic acid 15% gel is driven by treatment efficacy during initial phase. Assuming equal efficacy in the initial phase automatically assumes equal efficacy in the post-initial treatment phase. This is not the case for metronidazole 0.75% cream, where treatment efficacy during the post-initial treatment phase is based on the results of Part B of Study 40173.

[b] Assumes the same relapse rate for ivermectin 1% cream and all comparators.

CADTH Common Drug Review multi-way analysis

CDR multi-way analysis assumed ivermectin 1% cream would have the probability of treatment success during the initial and post-initial (long-term) phases. Further, it was assumed patients would receive maintenance treatment after any treatment success for the duration of the time horizon. As maintenance therapy would likely decrease the risk of relapse, a more conservative scenario assumed that the risk of relapse would be the same for all drugs (generalized gamma survival curve distribution assumed using full Study 40173 trial results). Lastly, the multi-way analysis considered an updated weighted average cost of systemic antibiotics, based on an updated market share distribution and costs.

Given equal treatment success probabilities and same relapse rates (i.e., equal QALYs), only drug costs were compared between topical drugs (see Table 22).

TABLE 22: CADTH COMMON DRUG REVIEW MULTI-WAY ANALYSIS: SEQUENTIAL INCREMENTAL COST-UTILITY RATIO

Interventions	Total Costs ($) per Patient Over 3 Years	Incremental Costs	Total QALYs per Patient Over 3 Years	Incremental QALYs	Sequential ICUR
Metronidazole 1% gel	$530	Reference	2.2380	Reference	Reference
Azelaic acid 15% gel	$823	$293	2.2380	0	NA
Metronidazole 0.75% cream	$892	$362	2.2380	0	NA
Ivermectin 1% cream	$[redacted]	$[redacted]	2.2380	0	NA

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Note: It should be noted that CDR could not re-run analyses on the ivermectin 1% cream versus metronidazole 1% cream comparison, as metronidazole 1% cream was not included in the pharmacoeconomic model.

As summarized in Table 23, ivermectin 1% cream is associated with an incremental total cost of $[redacted] per patient versus the lowest cost comparator, metronidazole 1% gel over a three-year time horizon.

TABLE 23: CADTH COMMON DRUG REVIEW MULTI-WAY ANALYSIS: INCREMENTAL COSTS PER PATIENT OVER THREE YEARS

Interventions	Costs per Patient, Over 3 Years			Incremental Cost
	Medication costs ($)	Health care costs[a] ($)	Total costs ($)	
Metronidazole 1% gel	$478	$51	$530	Reference
Azelaic acid 15% gel	$771	$51	$823	$293
Metronidazole 0.75% cream	$840	$51	$892	$362
Ivermectin 1% cream	$[redacted]	$51	$[redacted]	$[redacted]

CDR = CADTH Common Drug Review.
[a] Health care costs assumed to be the same for all comparators as equal efficacy is assumed.
Note: It should be noted that CDR could not re-run analyses on the ivermectin 1% cream versus metronidazole 1% cream comparison, as metronidazole 1% cream was not included in the pharmacoeconomic model.

When looking at approximate daily costs only, ivermectin 1% cream is associated with an incremental total cost of $[redacted] versus the lowest cost comparator, metronidazole 1% (see Table 24).

TABLE 24: INCREMENTAL COSTS USING ONLY APPROXIMATE DAILY COST OF TOPICAL DRUGS

Interventions	Approximate Daily Cost[a] ($)	Incremental Cost
Metronidazole 1% gel	$0.45	Reference
Azelaic acid 15% gel	$0.79	$0.34
Metronidazole 0.75% cream	$0.86	$0.41
Ivermectin 1% cream	$[redacted]	$[redacted]

CDR = CADTH Common Drug Review.

[a] Based on the assumption of 0.72 g used if dosed once daily and 1.31 g used if dosed twice daily, as per the number of grams used in Study 40173 and the manufacturer's pharmacoeconomic submission.[3]

Note: It should be noted that CDR could not re-run analyses on the ivermectin 1% cream versus metronidazole 1% cream comparison, as metronidazole 1% cream was not included in the pharmacoeconomic model.

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