Common Drug Review
Pharmacoeconomic Review Report

September 2017

Drug	Apremilast (Otezla)
Indication	For the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
Reimbursement Request	[redacted]
Dosage Form(s)	10 mg, 20 mg and 30 mg tablets
NOC Date	November 12, 2014
Manufacturer	Celgene Inc.

Apremilast (Otezla) CADTH Common Drug Review Pharmacoeconomic Report was prepared using DeltaPA data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in dermatology who provided input on the conduct of the review and the interpretation of findings.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary reimbursement recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

TABLE OF CONTENTS

ABBREVIATIONS II

EXECUTIVE SUMMARY V

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION 1
1. Summary of the Manufacturer's Pharmacoeconomic Submission 1
2. Manufacturer's Base Case 2
3. Limitations of Manufacturer's Submission 2
4. Issues for Consideration 6
5. Conclusions 7

APPENDIX 1: COST COMPARISON 8
APPENDIX 2: SUMMARY OF KEY OUTCOMES 10
APPENDIX 3: ADDITIONAL INFORMATION 11
APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG 12
APPENDIX 5: REVIEWER WORKSHEETS 14

REFERENCES 21

Tables

Table 1: Summary of the Manufacturer's Economic Submission iii
Table 2: CADTH Common Drug Review Base Case 5
Table 3: Cost Comparison Table for Plaque Psoriasis 8
Table 4: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Apremilast Relative to Standard of Care? 10
Table 5: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Apremilast Relative to Biologics (Adalimumab, Etanercept, Infliximab, Ustekinumab, SEB Infliximab, Secukinumab)? 10
Table 6: Submission Quality 11
Table 7: Authors' Information 11
Table 8: Summary of Other Health Technology Assessment Reviews of Apremilast 12
Table 9: Data Sources 14
Table 10: Manufacturer's Key Assumptions 16
Table 11: Summary of Results of the Manufacturer's Base Case 17
Table 12: The CADTH Common Drug Review's Base-Case Sequential Analysis (Standard of Care Utilities, Monitoring Costs, Five-Year Horizon) Interventions 17
Table 13: CADTH Common Drug Review Reanalysis Price Reduction Scenarios 18
Table 14: CADTH Common Drug Review Price Reduction Analysis — Price Analysis for Comparators 18
Table 15: CADTH Common Drug Review Conservative Scenario Analysis 20

Figure

Figure 1: Apremilast Model Structure 14

ABBREVIATIONS

CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
ICUR	incremental cost-utility ratio
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
SEB	subsequent entry biologic
SoC	standard of care

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Apremilast (Otezla)
Study Question	To compare the cost-effectiveness of apremilast and currently available therapies to SoC in adult patients with moderate-to-severe plaque psoriasis who have had an inadequate response, contraindication, or intolerance to prior conventional systemic therapies, by evaluating costs and benefits in a trial setting, from the perspective of the Canadian publicly funded health care system
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with moderate-to-severe plaque psoriasis who have had an inadequate response, intolerance, or contraindication to prior conventional systemic therapies
Treatment	Apremilast 30 mg twice daily, following a one-week titration schedule
Outcome	QALYs
Comparators	– SoC (consisting of topical agents, phototherapy and routine physician visits) – Adalimumab SC 40 mg every other week – Etanercept SC 50 mg weekly – Infliximab (branded) IV 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks – SEB infliximab IV 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks – Ustekinumab SC 45 mg at weeks 0 and 4, and then every 12 weeks
Perspective	Canadian publicly funded health care system
Time Horizon	10 years
Results for Base Case	– Compared with SoC, apremilast had an ICUR of $83,480 per QALY – Based on the sequential analysis, apremilast is associated with the lowest ICUR ($83,480 per QALY versus SoC), followed by SEB infliximab ($99,747 per QALY versus apremilast)

Key Limitations	– The manufacturer failed to include comparators relevant to the full population for the Health Canada indication. Available clinical information indicates that apremilast may be no more effective than methotrexate or cyclosporine, but is considerably more expensive. Consequently, when compared with conventional systemic therapies, apremilast is likely dominated by methotrexate (i.e., associated with less QALYs and more expensive).
	– The new clinical information submitted by the manufacturer failed to address concerns previously raised by CDEC regarding a lack of direct comparative clinical effectiveness information compared with other treatments. The manufacturer submitted indirect evidence that suggested apremilast is less effective than biologics considered.
	– A number of issues were identified with the manufacturer's modelling approach:
	  – Incorrect coding of the QALY gain among SoC patients biased the cost-effectiveness results in favour of apremilast.
	  – The manufacturer assumed that all treatments were subject to an equal rate of all-cause withdrawal, reflecting the onset of adverse events and loss of efficacy. However, this is of questionable appropriateness given that apremilast is less effective than the biologics and is associated with a statistically significantly higher likelihood of adverse events compared with all comparators, apart from secukinumab and infliximab.
	  – Assumptions regarding the schedule of monitoring and laboratory tests may not reflect clinical practice.
	  – The assumption that PASI response was maintained throughout the model time horizon does not reflect available evidence.

	– The use of a 10-year model horizon is likely too long, given uncertainty in the long-term maintenance of PASI response and observed times to treatment discontinuation in practice. – The assumption that patients on SoC achieve a PASI response of any magnitude (PASI 50, 75, or 90) is questionable among a population with psoriasis that is severe enough to have failed previous conventional therapy and a biologic or apremilast.
CDR Estimate(s)	– Based on CDR reanalyses accounting for some of the aforementioned limitations (i.e., correction of SoC utility coding error, alternative monitoring costs and use of a 5-year horizon), apremilast was associated with an ICUR of $105,935 per QALY versus SoC, and was extendedly dominated by SoC and SEB infliximab. – A price reduction of more than 50% would be necessary for apremilast to achieve an ICUR of less than $50,000 per QALY versus SoC in the CDR base case. – Based on available clinical evidence, apremilast is dominated by MTX. – The ordering of cost-effective treatments is sensitive to small changes in the price of comparators.

CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IV = intravenous; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life-year; SC = subcutaneous; SEB = subsequent entry biologic; SoC = standard of care.

EXECUTIVE SUMMARY

Background

Apremilast (Otezla) is an oral phosphodiesterase 4 inhibitor indicated for the treatment of moderate-to-severe plaque psoriasis among adult patients who are candidates for phototherapy or systemic therapy.[1] The manufacturer is requesting reimbursement of apremilast for patients with moderate-to-severe plaque psoriasis who have failed, or are contraindicated for or intolerant of conventional systemic therapy. The recommended dose of apremilast is 30 mg twice daily, following a one-week titration schedule.[2] Apremilast is available in 10 mg, 20 mg, and 30 mg tablets, at a confidential price of [redacted] per tablet. At a recommended dose of 30 mg twice daily, the daily cost of apremilast is [redacted] once titration is completed.

The CADTH Common Drug Review (CDR) previously reviewed apremilast for use in the same indication. The CADTH Canadian Drug Expert Committee (CDEC) recommended that apremilast not be listed on the basis of uncertain clinical benefit relative to other available therapies.[3] The current submission includes results from a new clinical study (LIBERATE)[4] and a pharmacoeconomic evaluation based on an updated network meta-analysis (NMA) with a different set of comparators, based on the same model with some of the same limitations. CDR further reviewed apremilast for use in psoriatic arthritis. CDEC recommended that apremilast be reimbursed for this indication, with the condition of a reduced price.[5]

The manufacturer submitted a cost-utility analysis comparing apremilast and biologics (adalimumab, etanercept, infliximab, subsequent entry biologic [SEB] infliximab, secukinumab, and ustekinumab) with standard of care (defined as topical agents, phototherapy, and physician visits) among adult patients with moderate-to-severe plaque psoriasis who are inadequately controlled on conventional systemic therapies.[6] The analysis used a 10-year time horizon and was undertaken from the perspective of the Canadian publicly funded health care system. The manufacturer reported that, when compared with treatment with standard of care (SoC), apremilast has an incremental cost-utility ratio (ICUR) of $83,480 per quality-adjusted life-year (QALY). When considering all comparators in a sequential analysis, apremilast is associated with the lowest ICUR versus SoC, followed by SEB infliximab ($99,747 per QALY versus apremilast). All other drugs were either dominated or extendedly dominated.

Summary of Identified Limitations and Key Results

CDR identified several limitations of the manufacturer's submission. Most notably, the manufacturer failed to include information on comparators reflecting the full Health Canada indication as required by CDR submission guidelines.[7] In particular, no information was included on methotrexate and cyclosporine. Available clinical evidence suggests that apremilast is no more effective than methotrexate or cyclosporine in terms of Psoriasis Area and Severity Index 75 (PASI 75) response rates (defined as achieving a 75% or greater reduction in the PASI score), but is considerably more expensive.[3,8]

The resubmission material does not address CDEC's concern regarding the lack of direct comparative clinical effectiveness information.[3] The LIBERATE study, which was provided as new clinical information in the resubmission material, is a 16-week double-blind randomized controlled trial that compared apremilast with placebo and etanercept (using a 50 mg weekly dose, which is lower than that recommended by the product monograph[9]) with placebo; no comparisons were planned that directly compared apremilast with etanercept.[4] The manufacturer submitted an NMA that provided indirect comparative efficacy results. As noted in CDR's Clinical Review, the NMA was of generally sound quality and indicated that apremilast is significantly less effective than all biologics considered.

The manufacturer's economic evaluation specifically considered a patient population who had failed, or are contraindicated for or intolerant to, conventional systemic therapy. A number of issues were noted with the manufacturer's economic model:

- the presence of a coding error that affected QALY calculations for SoC patients and that served to bias cost-effectiveness results in favour of apremilast
- inappropriate assumptions regarding equal withdrawal from treatment for all comparators
- assumptions regarding monitoring schedule and laboratory tests that may not reflect clinical practice
- use of an overly long time horizon
- assumptions regarding PASI response among SoC patients
- assumptions regarding constancy of PASI response over the model duration.

Conclusions

The manufacturer's resubmission had several limitations, most notably the failure to consider comparators relevant to the full Health Canada indication and a lack of direct comparative clinical information for apremilast conventional therapy or biologics. Based on clinical information from the original submission, apremilast does not appear to be more effective than methotrexate or cyclosporine, while being considerably more expensive (apremilast costs [redacted] per patient annually compared with methotrexate, which costs $132 to $329 annually). Based on the manufacturer's NMA, apremilast appears to be associated with lower rates of PASI response compared with biologics, with potentially similar or higher rates of adverse events, which raises questions regarding apremilast's potential place in therapy.

When correcting coding errors in the manufacturer's model, and considering alternative assumptions regarding model time horizon and monitoring costs, CDR found the ICUR for apremilast was $105,935 per QALY compared with SoC. A price reduction of more than 50% would be required to lower the ICUR to less than $50,000. When considering comparators for the full Health Canada indication, available clinical evidence suggests that apremilast is strictly dominated by methotrexate (i.e., methotrexate is less costly and more effective). The ordering of cost-effective treatments, and whether apremilast is a potentially efficient option, is sensitive to small changes in the price of comparators.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) comparing apremilast and biologics (adalimumab, etanercept, infliximab, subsequent entry biologic [SEB] infliximab, secukinumab, ustekinumab) with standard of care (SoC) (defined as receiving topical agents, phototherapy, and routine physician visits), in patients with moderate-to-severe plaque psoriasis (defined as having PASI ≥ 12, body surface area ≥ 10%, and Static Physician Global Assessment [sPGA] ≥ 3) who have had an inadequate response, or an intolerance or contraindication to, prior conventional systemic therapies.[6] The model population was assumed to have characteristics similar to patients included in the LIBERATE trial, with a mean age of 45 and a weight of 89 kg.[4] The CUA was based on a Markov state transition model using a 10-year horizon and 28-day cycle length. All costs and outcomes were discounted at a rate of 5% annually, and the analysis was undertaken from the perspective of the Canadian publicly funded health care system.

The health states in the model comprised an initial "trial period," a long-term "continued use" period, SoC and death (Figure 1). Among patients receiving apremilast or a biologic, response to treatment (defined as achieving PASI 75) was assessed at the end of a variable trial period of 10 to 16 weeks, depending on the drug used and the trial period recommended in its product monograph (10 weeks for infliximab and SEB infliximab; 12 weeks for etanercept and secukinumab; and 16 weeks for apremilast, adalimumab, and ustekinumab). Patients who achieved a PASI 75 response transitioned to the "continued use" state, while non-responders moved to SoC. Patients who moved to SoC remained in this state for the rest of the analysis or until they died. Estimates of response to treatment were based on probabilities of achieving PASI 75 derived from a manufacturer-commissioned network meta-analysis (NMA).[10]

Patients in the "continued use" state were subject to an annual 20% all-cause withdrawal from treatment, which accounted for loss of efficacy or the onset of adverse events; this value was based on previously used literature values. Patients who withdrew from the "continued use" state moved to the SoC health state. It was assumed that patients in the SoC state underwent a trial period of 12 weeks, similar to active treatment, during which patients could achieve a PASI response according to rates seen in the placebo groups of the manufacturer-commissioned NMA.[10] Non-responders to SoC were assumed to experience baseline utility. Patients could die in any health state according to age-specific mortality rates from Statistics Canada data; it was assumed psoriasis had no effect on mortality.

The utilities associated with treatment were based on the proportion of patients in different PASI response categories (i.e., PASI 75 to PASI 90, PASI 90 to PASI 100). Each PASI response category was associated with a change in utility from baseline; values were based on Short Form (36) Health Survey (SF-36) utilities collected at baseline and week 16 during the apremilast trials (ESTEEM-1, ESTEEM-2, and LIBERATE).[4,11,12] The baseline utility value of 0.7 was taken from literature sources.[13]

Costs considered were drug acquisition costs and costs of monitoring and follow-up. Dosages were assumed from the product monographs. The cost of apremilast was obtained from the manufacturer's submission, while the costs of all other medications were obtained from the Ontario Drug Benefit formulary (2016).[14] Schedules of monitoring and follow-up were based on clinical expert input and

consisted of doctor's visits and laboratory testing. Drug administration costs were not considered. The costs of physician visits were obtained from the Ontario Health Insurance Plan schedule of benefits (2016),[15] while the costs of laboratory tests were taken from the 1999 Schedule of Benefits for Laboratory Services for Ontario.[16] The costs of adverse events were not considered for apremilast or biologics.

2. MANUFACTURER'S BASE CASE

The manufacturer reported in its base case that apremilast was associated with a cost of $24,101 and 5.62 QALYs. When compared with SoC, apremilast was $17,823 more costly and associated with a gain of 0.21 QALYs, for an ICUR of $83,480 per QALY compared with SoC (Table 11).

When compared sequentially, the most cost-effective options were: SoC, apremilast, and SEB infliximab. Sequential ICURs for apremilast compared with SoC were $83,480 per QALY and $99,747 per QALY for SEB infliximab compared with apremilast.

2.1 Summary of Manufacturer's Sensitivity Analyses

Based on the manufacturer's reported one-way deterministic sensitivity analyses, results were sensitive to changes in utilities associated with PASI 75 response (ICUR of apremilast increased to $98,122 per QALY) and PASI 90 response ($98,138 per QALY). The rank order of comparators did not change in these sensitivity analyses.

The manufacturer also reported the results of a probabilistic sensitivity analysis (PSA) using 1,000 iterations in which the majority of simulations appeared in the northeastern quadrant of the cost-effectiveness plane (indicating that apremilast is more costly and produces more QALYs than SoC). A cost-effectiveness acceptability curve indicates that apremilast has an 84% probability of being cost-effective at a willingness-to-pay threshold of $100,000, and a 0% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

Of note, the manufacturer's model does not permit running a PSA with greater than 1,000 iterations. Further, the design of the model did not allow for a PSA that would allow comparison of all comparators simultaneously. The inability to assess all options concurrently is a major weakness of the PSA.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

3.1 Failure to Consider the Full Indicated Population

As per CDR submission guidelines,[7] the manufacturer is to provide information on the full Health Canada–approved indication (i.e., moderate-to-severe plaque psoriasis patients who are eligible for systemic therapies or phototherapy). The manufacturer's resubmission includes only information related to the reimbursement request population, which consists of patients who have failed or are intolerant or contraindicated to conventional systemic therapies. The resubmission material does not provide information on the comparative efficacy or cost-effectiveness of apremilast compared with systemic therapies (e.g., methotrexate and cyclosporine). Based on the information included in the manufacturer's previous submission for this indication,[3,8] apremilast was no more effective than methotrexate or cyclosporine in terms of PASI 50, 75, or 90 response rates. In the absence of any new information, apremilast remains more expensive compared with methotrexate or cyclosporine ([redacted]

per patient annually, compared with methotrexate [$132 to $329] and cyclosporine [$2,833]), and does not provide additional clinical benefits compared with methotrexate.

3.2 Clinical Information Submitted for Resubmission Did Not Address CDEC's Previous Concerns

Among CDEC's reasons for issuing a "do not list" recommendation in the previous submission was "insufficient evidence to evaluate the comparative clinical benefit of apremilast relative to other available therapies, including oral therapies with demonstrated effectiveness in moderate-to-severe plaque psoriasis, due to the absence of direct comparisons."[3] The new study (LIBERATE)[4] submitted by the manufacturer was not designed to allow a direct comparison between apremilast and etanercept. As noted in the CDR clinical report, there are numerical differences in the proportion of patients achieving PASI 75 with etanercept (48%) and apremilast (40%) when compared with placebo. Of note, the dosage of etanercept used in the LIBERATE study (50 mg once weekly) was less than the recommended dose in the product monograph (50 mg twice weekly for three months followed by 50 mg once weekly[9]); as a result, the effectiveness of etanercept compared with placebo is likely underestimated.

A number of issues were noted with the model and assumptions, which impacted the results:

- **Incorrect coding of utility gain among SoC patients in the model biased the results in favour of apremilast.**
  In its base case, the manufacturer stated that responders in the SoC group would accrue utilities according to the PASI response rates from the placebo groups of included trials in the NMA. However, this was found to be incorrectly coded in the model such that SoC patients all experienced baseline utility regardless of response; SoC responders in the apremilast group did, however, experience utility according to response. This biased incremental QALYs in favour of apremilast.
- **The assumptions regarding withdrawal from treatment were uncertain.**
  The manufacturer assumed that all treatments were subject to a 20% annual all-cause withdrawal after completion of the trial period, based on assumptions and previously published economic evaluations. Based on the results of the manufacturer's NMA, it suggests that efficacy in terms of PASI response may be lower with apremilast compared with other biologics, and rates of adverse events may be higher for apremilast (with potential exceptions when compared with secukinumab and infliximab). As withdrawals may be linked with lack of response or the emergence of adverse events, given the differences among treatments, withdrawals may vary by treatment. This is supported by a manufacturer-commissioned analysis of persistence for apremilast and biologics, which found biologics have higher rates of persistence than apremilast for both treatment-naive patients and patients with prior exposure to biologic or non-biologic therapies.[17] Further, a recent review by Bartos et al.[18] examining maintenance of response to psoriasis treatment found that apremilast had the lowest rate of initial responders who maintained response at one year, and lowest rates of maintenance among all patients initially exposed to treatment. As such, the assumption that apremilast has withdrawal rates comparable with biologics is not supported.
- **The monitoring schedule was uncertain.**
  The manufacturer assumed that biologics would have a more intensive schedule of monitoring than apremilast, both at baseline (incurring a more extensive set of tests) and during follow-up. The clinical expert consulted for this review noted that the proposed monitoring schedule may not reflect clinical practice. In particular, there may be no differences in initial assessment between apremilast patients and patients receiving a biologic, especially given that patients who have failed conventional systemic therapies would have exposure to small-molecule drugs (methotrexate, cyclosporine) with immunosuppressive properties similar to biologics. Follow-up monitoring of

patients on biologics would likely be done annually (rather than twice annually, as in the manufacturer's base case).

- **It was assumed that the PASI response would be maintained over the model horizon.**
  The manufacturer assumed there was no loss of PASI response over the model time horizon. That is, after the induction period, patients either remained in their PASI health state (accruing the costs and benefits of that health state) or transitioned to best supportive care. This does not account for deterioration in the condition or for any attenuation of treatment effect. However, loss of treatment efficacy with prolonged use has been noted in biologics[19] and with apremilast (the long-term extension of LIBERATE found that nearly half of patients did not maintain PASI 75 response at week 52)[20]; consequently, QALYs may be overestimated in the model. While the manufacturer included an option to adjust utilities in the model for observed long-term PASI response for apremilast (from the LIBERATE trial), there was no option available to account for long-term PASI response for other comparators.
- **The time horizon of the model may not be appropriate.**
  The manufacturer considered a 10-year time horizon in the base case. However, this may be longer than appropriate for several reasons:
  - Uncertainty in maintenance of PASI response over the horizon
  - In Levin et al.'s study, infliximab had the longest average time until treatment discontinuation at 292 days (i.e., less than one year.[21] Further, in a retrospective chart review of Canadian patients, the longest median duration of therapy until discontinuation due to adverse events was 27.2 months with ustekinumab.[22] Of note, biologics had a longer time to discontinuation (mean: 242 days) than the less effective and more adverse event–inducing systemic therapies (141 days).[21] These suggest that shorter time horizons are appropriate when considering monotherapy followed by SoC.

  CDR considered a shorter time horizon of five years in its base case, also reporting results for one-year and 10-year horizons.
- **There were assumptions regarding PASI response among patients on SoC.**
  The manufacturer used PASI response observed among the placebo groups of the trials included in the NMA to inform PASI response among SoC patients in the model. However, patients in the model represent a population that has failed both conventional therapy and a second-line, more intensive therapy. The trials included in the NMA considered a more heterogeneous group of patients, including some patients who were treatment-naive, or who were a post-conventional population who were biologic-naive. It is unclear whether the more severe patients considered in the manufacturer's model would respond to the same extent to topical agents and phototherapy. CDR assessed a more conservative scenario in which SoC functioned as palliative care and patients experienced baseline utility (i.e., derived no benefit in terms of PASI response) as a sensitivity analysis. Of note, placebo response was excluded among SoC patients in the manufacturer's first submission.

3.3 CADTH Common Drug Review Reanalyses

To account for the limitations identified earlier, the following analyses were undertaken:

1. **Correction of utility gain among SoC responders**
   The manufacturer stated that responders in the SoC group accrued utilities based on PASI response among placebo patients in the NMA; however, the model did not reflect this approach. The model was updated accordingly, resulting in an increased ICUR of $98,147 compared with SoC.

2. **Use of an alternative monitoring schedule**
   Based on feedback from the clinical expert consulted by CDR, the set of monitoring and follow-up tests was revised, assuming similar tests were conducted regardless of treatment; patients on biologics were assumed to receive tests once yearly instead of twice yearly. This had a minimal impact on the ICUR.
3. **Use of a five-year horizon**
   Given the uncertainty in terms of long-term response to treatments, and the lack of the exploration of this in the manufacturer's model, CDR considered a horizon of five years in its base case. This had a minimal impact on the ICUR. A one-year time horizon was also considered for the CDR base case.

When considering all three limitations together for the CDR base case, apremilast could be ruled out as a cost-effective treatment compared with SoC and SEB infliximab (i.e., apremilast was extendedly dominated by SoC and SEB infliximab (Table 2, Table 12). CDR was unable to assess limitations relating to withdrawal rates or long-term response adjustment, as the model did not permit such analyses.

TABLE 2: CADTH COMMON DRUG REVIEW BASE CASE

Scenario		ICUR ($ per QALY) for Apremilast Versus SoC	Sequential ICUR of Apremilast
	Manufacturer's base case	**$83,480**	**$83,840 vs. SoC**
1	SoC responder utilities corrected	$98,147	$98,147 vs. SoC
2	Monitoring costs corrected	$83,848	$83,848 vs. SoC
3	5-year time horizon	$89,453	$89,453 vs. SoC
1 to 3	**CDR base case**	**$105,935**	**Extendedly dominated by SoC and SEB infliximab**
	CDR base case: one-year horizon	$188,124	Extendedly dominated by SoC and SEB infliximab

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SoC = standard of care; vs. = versus.

3.4 Price Reduction Scenarios

When considering the CDR base case, a price reduction of more than 50% for apremilast would be required for the ICUR of apremilast to fall below $50,000 per QALY compared with SoC (Table 13).

Note that the manufacturer's base case assumes that the list prices of drugs reflect the prices paid by drug plans under product reimbursement agreements. CDR considered the effects of reduced costs of biologics and the impact on the results in Table 14.

4. ISSUES FOR CONSIDERATION

- **Potential for indication creep**
  The manufacturer is requesting reimbursement following the failure of conventional systemic therapy; it is likely that this may be used earlier in the management of patients. Additionally, the use in patients with milder forms of psoriasis would increase the overall cost of care.
- **Introduction of SEB etanercept**
  SEB etanercept is currently under review by CDR for rheumatoid arthritis and ankylosing spondylitis, given that etanercept is approved for the treatment of plaque psoriasis, it is anticipated that SEB etanercept may become available for the same indication. As per the analysis of comparators, price reductions of 27% to 32% for etanercept would exclude apremilast as a cost-effective treatment option (Table 14). Given that SEB infliximab is nearly 50% the cost of branded infliximab (Table 3), this is not an unlikely price reduction.
- **Place in therapy for apremilast**
  As per the manufacturer's current NMA, apremilast is less effective than biologics in terms of PASI response.[10] Further, apremilast is associated with statistically significantly higher rates of adverse events compared with all biologics, with the exception of secukinumab and infliximab. Given that the use of more aggressive and effective treatment earlier on may lead to improved patient outcomes,[23] it is unclear that the use of apremilast rather than biologics among eligible patients represents a clinically or economically desirable option. As per CDR's consulting clinical expert, conventional systemic therapies and biologics serve patients' needs, and very few patients would be refractory to these therapies. Apremilast may be considered for patients who are intolerant of traditional systemic therapies or who do not want to take biologics; this is expected to be a minority (< 5%) of patients. Most patients would opt for higher efficacy treatments where available, as per the clinical expert and surveys cited in Winterfield et al.[23] As apremilast is not immunosuppressive, it may be preferred for immunocompromised patients. However, biologics are not absolutely contraindicated and may be used in these patients with proper monitoring.

4.1 Patient Input

Input was received from the Canadian Skin Patient Alliance. Patients noted that plaque psoriasis symptoms have a significant impact on their quality of life and psychosocial functioning, and on their ability to undertake the activities of daily living. This was accounted for in the model by including utility gains associated with improvements in disease status, as measured by PASI response. Patients also noted there is a substantial burden on caregivers, including an increased need for cleaning due to skin flaking, time needed to take patients to phototherapy and infusion clinics, and overall negative emotional burden. Caregiver burden was not accounted for in the model.

Current therapies include topical agents, phototherapy, conventional systemic therapies, and biologics. Notable concerns included treatment costs, time commitments, and the presence of side effects. Patients also noted concerns surrounding "biologic fatigue," where a treatment loses effectiveness with continued use. It is unclear whether apremilast would address this need, as it is expected to be used prior to biologics. Patients welcomed the addition of effective treatments that did not require phototherapy or infusion visits. This was reflected in the cost of treatments in the manufacturer's economic model.

5. CONCLUSIONS

The manufacturer's resubmission had several limitations, most notably a failure to consider clinical or economic evidence relating to indication-appropriate comparators such as methotrexate and cyclosporine. Consideration of this larger set of treatments casts doubt on the appropriateness of the manufacturer's reimbursement request, as apremilast does not appear to be any more effective than methotrexate or cyclosporine, while being considerably more expensive (the annual costs of apremilast are 30 to 100 times the costs of methotrexate). Its significantly lower efficacy compared with biologics also raises questions regarding its potential place in therapy. The manufacturer's resubmission fails to address the concerns of the previous submission and the conclusions do not differ.

When correcting coding errors in the manufacturer's model, and considering alternative assumptions regarding model time horizon and monitoring costs, CDR found apremilast to be extendedly dominated by SoC and SEB infliximab. When considering comparators for the full Health Canada indication, available clinical evidence indicates that apremilast is strictly dominated by methotrexate. When considering only the corrected version of the manufacturer's model, a 2% reduction in the price of SEB infliximab is sufficient to exclude apremilast from the set of economically desirable options, and reductions of less than 20% in the price of adalimumab or secukinumab is sufficient to produce the same result.

APPENDIX 1: COST COMPARISON

TABLE 3: COST COMPARISON TABLE FOR PLAQUE PSORIASIS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Cost ($)
Apremilast (Otezla)[a]	**10 mg 20 mg 30 mg**	**Tablet**	[redacted][a]	**30 mg twice daily**	**First year:** [redacted][b] **Subsequent years:** [redacted]
Biologics					
Adalimumab (Humira)	40 mg/0.8 mL	Syringe or pen	$740.3600	80 mg first dose, 40 mg every other week starting one week after first dose	First year: $20,730 Year 2 onwards: $19,249
Etanercept (Enbrel)	50 mg/mL 25 mg/vial	Syringe or pen Vial	$395.3900 $197.6350	50 mg twice weekly for 12 weeks, then 25 mg twice weekly	First year: $25,300[c] Year 2 onwards: $20,554
Infliximab (Remicade)	100 mg/vial	Vial	$962.6800[d]	5 mg/kg/dose, for 3 doses (0, 2, 6 weeks) then 5 mg/kg every 8 weeks	First year: $38,507[e] Year 2 onwards: $31,287
Infliximab (Inflectra)			$525.0000		First year: $21,000 Year 2 onwards: $17,063
Secukinumab (Cosentyx)	150 mg/mL	Pre-filled syringe	$1,645.0000 per 300 mg dose[f] (2 × 150 mg syringes/pkg)	300 mg SC injection at weeks 0, 1, 2, and 3, then monthly starting week 4	First year: $26,320 Year 2 onwards: $19,740
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/1 mL	Pre-filled syringe	$4,593.1400	– < 100 kg pts: 45 mg at weeks 0 and 4, then 45 mg every 12 weeks – > 100 kg pts: same schedule at 90 mg	First year: $22,966 Year 2 onwards: $20,669[g]
Systemic treatments					
Methotrexate	2.5 mg 10 mg 10 mg/mL 25 mg/mL	Tab Tab Vial/inj Vial/inj	$0.6325 $2.7000[h] $12.5000/2 mL $8.9200/2 mL	10 mg to 25 mg by mouth **or** IM weekly	$132 to $329 $232 to $325

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Cost ($)
Cyclosporine (Neoral)	10 mg 25 mg 50 mg 100 mg	Capsule	$0.6238 $0.9952 $1.9400 $3.8815	2.5 mg/kg daily (rounded to 200 mg/day) (max 5 mg/kg/day)	**$2,833i**
Acitretin (Soriatane)	10 mg 25 mg	Capsule	$2.3573 $4.1400	25 mg to 50 mg daily	$1,507 to $3,014

IM = intramuscular; inj = injection; max = maximum; pkg = package; pt = patient; SC = subcutaneous.
[a] Manufacturer's submitted confidential price. Notes: the 10 mg and 20 mg dose tablets are available only in a starter pack; manufacturer's submitted price is [redacted] more expensive than the currently listed price per tablet under the Régie de l'Assurance Maladie du Québec formulary.[24]
[b] First year includes titration period with equivalently priced 10 mg and 20 mg pills.
[c] First-year cost includes use of 50 mg syringe for the first 12 weeks, followed by use of 25 mg vials. In subsequent years, patients are assumed to use 25 mg vials exclusively; costs are $20,560 if 50 mg syringes are used.
[d] Source: Alberta formulary (April 2016).[25]
[e] Assumes wastage of partially used vials occurs. Eight treatments first year, 6.5 average subsequent years. Note: Average weight was assumed to be 88.67 kg, as per manufacturer's trials and values used in models.
[f] Source: IMS Brogan DeltaPA.[26]
[g] Five treatments first year, 4.5 average subsequent. Price for 45 mg and 90 mg is the same.
[h] Source: Saskatchewan formulary (April 2016).[27]
[i] Lower value assumes 200 mg/day; upper end assumes dosage for average body weight from PSOR-010 (LIBERATE) trial.
Source: Ontario Drug Benefit (April 2016),[14] except where noted.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO STANDARD OF CARE?

Apremilast Versus Standard of Care	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$83,480 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
Source: Based on the manufacturer's results.

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO BIOLOGICS (ADALIMUMAB, ETANERCEPT, INFLIXIMAB, USTEKINUMAB, SEB INFLIXIMAB, SECUKINUMAB)?

Apremilast Versus Biologics	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)	X					
Drug treatment costs alone	X					
Clinical outcomes					X	
Quality of life					X	
Incremental CE ratio or net benefit calculation	$99,747 to $231,359 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: 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"*	There was a coding error affecting QALY gain among SoC responders that biased results in favour of apremilast. The probabilistic sensitivity analysis did not allow for simultaneous comparison of all interventions. When including utilities adjusted for long-term response, all comparators were constrained to have the same 16-week PASI response profile as apremilast which necessitated undertaking analyses manually.		
Was the material included (content) sufficient?			X
Comments *Reviewer to provide comments if checking "poor"*	Exclusion of information relating to methotrexate and cyclosporine did not accord with CDR submission guidelines stating that the full Health Canada–approved indication should be assessed.[7]		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*			

CDR = CADTH Common Drug Review; PASI = Psoriasis Area Severity Index; QALY = quality-adjusted life-year; SoC = standard of care.

TABLE 7: AUTHORS' INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CDR			
☐ 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	

CDR = CADTH Common Drug Review.

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

TABLE 8: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF APREMILAST

	NICE (November 2015)[28]	SMC (May 2015)[29]
Treatment	Apremilast 30 mg twice daily	
Price	£550 per 28-day pack (56 × 30 mg tablets) (exchange rate: £1 = C$1.954)[30]	£550 per 28-day pack (56 × 30 mg tablets) £1 = C$1.954)
Similarities With CDR Submission	– Model structure based on York model (initial trial period and continued use or supportive care based on PASI 75 response) – Use of 28-day cycles, 10-year horizon, public payer perspective – 20% annual all-cause withdrawal probability for all treatments – Costs and disutilities of AEs were not included	Model structure based on York model
Differences With CDR Submission	– Evaluated apremilast as additional line of therapy (before biologics and BSC) vs. sequence of biologics and BSC without apremilast – While LIBERATE data were available, not included in NMA – Psoriasis defined by PASI and DLQI rather than PASI, sPGA, and BSA. Patients stratified by DLQI – Manufacturer did not define BSC – Use of 3.5% discount rate – Utilities based on Woolacott mapping of PASI to EQ-5D utilities rather than clinical trial – No PASI response associated with BSC	• Evaluated apremilast as additional line of therapy (before biologics and BSC) compared with a sequence of biologics and BSC without apremilast, rather than considering apremilast and biologics as monotherapy followed by BSC • Psoriasis population was defined by PASI and DLQI rather than PASI, sPGA, and BSA • Data from LIBERATE were not included • Utility values were from published literature rather than trial values
Manufacturer's Results	– Apremilast sequence dominated non-apremilast sequence among patients with DLQI > 10 – Among patients with DLQI ≤ 10, apremilast dominated BSC	Apremilast sequence dominated non-apremilast sequence (i.e., produced additional QALYs while reducing costs)
Issues Noted by the Review Group	– Costs of BSC overestimated – Exclusion of placebo response from BSC arm questionable – Equal withdrawal for treatments uncertain – Use of mapped utility values vs. trial values (issues regarding mapping algorithm used) – Exclusion of LIBERATE trial data	• The cost of BSC was noted to be high (£887.90 per monthly cycle or £11,543 per year) • Infliximab was not included in any treatment sequences considered, despite being a treatment of interest

	NICE (November 2015)[28]	SMC (May 2015)[29]
Results of Reanalyses by the Review Group (If Any)	– Reanalysis was based on use of an updated NMA, including PSOR-010; altering costs of BSC; inclusion of PASI response for BSC; use of directly measured EQ-5D values for patients with a DLQI > 10 (and use of UK rather than US tariffs for utility calculation) – The base-case results were £28,574 per QALY comparing sequences with and without apremilast among patients with DLQI > 10 and £89,374 per QALY among patients with DLQI ≤ 10	– When BSC costs reduced to alternative literature-based values, apremilast sequence had ICUR of £15,92 QALY vs. non-apremilast sequence; for patients with DLQI ≤ 10, not eligible for biologics, reduced BSC cost leads to an ICUR of £22,824/QALY for apremilast vs. BSC – Inclusion of infliximab did not change results, apremilast sequence remained dominant – Despite similarities in submissions to SMC and NICE, SMC did not consider some of the limitations noted by NICE
Recommendation	"Apremilast is not recommended within its marketing authorization for treating psoriasis"	"Apremilast is accepted for use within NHS Scotland"

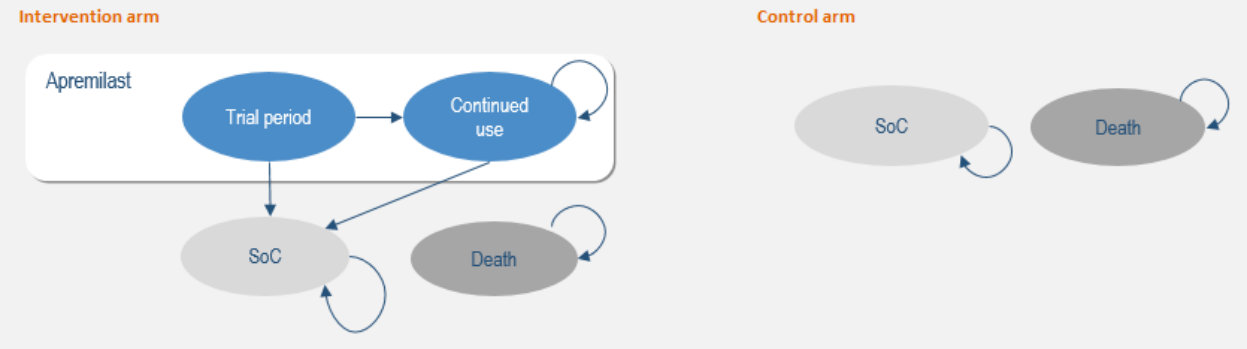
AE = adverse event; BSA = body surface area; BSC = best supportive care; CDR = CADTH Common Drug Review; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; ICUR = incremental cost-utility ratio; NHS = National Health Service; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SMC = Scottish Medicines Consortium; SoC = standard of care; sPGA = Static Physician Global Assessment; vs. = versus.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis comparing apremilast and biologics in patients with moderate-to-severe plaque psoriasis (defined as having Psoriasis Area Severity Index [PASI] ≥ 12, body surface area ≥ 10% and Static Physician Global Assessment [sPGA] ≥ 3) who have had an inadequate response, or are intolerant or contraindicated to prior conventional systemic therapies.[6] The health states in the model comprised an initial "trial period," a long-term "continued use" period, standard of care (SoC), and death (Figure 1). Among patients receiving apremilast or a biologic, response to treatment (defined as achieving PASI 75) was assessed at the end of a variable trial period of 10 to 16 weeks, depending on the drug used and the trial period recommended in its product. Patients who achieved a PASI 75 response transitioned to the "continued use" state, while non-responders moved to SoC. Patients who moved to SoC remained in this state for the rest of the analysis or until they died. Estimates of response to treatment were based on probabilities of achieving PASI 75 derived from a manufacturer-commissioned network meta-analysis.[10]

FIGURE 1: APREMILAST MODEL STRUCTURE



SoC = standard of care.
Source: Manufacturer's pharmacoeconomic submission.[6]

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Efficacy inputs to the economic model were from a manufacturer-commissioned NMA. Results from a Bayesian random-effects analysis were used to derive distributions of PASI scores for comparators at the end of their respective trial periods. The efficacy of SoC was based on PASI response in the placebo groups of trials in the NMA. Efficacy of apremilast versus placebo was based on the post–conventional treatment subgroups of ESTEEM-1 and ESTEEM-2 trials,[11,12] as well as the newly submitted PSOR-010 LIBERATE trial.[4]	As noted in the CDR clinical report, there are strong concerns regarding the exclusion of methotrexate and cyclosporine from the manufacturer's NMA. The methodology was otherwise reasonable, although 27% of included studies were of "poor" or "satisfactory" quality. Notably, the LIBERATE trial failed to address CDEC's previous concerns regarding the lack of head-to-head comparisons of apremilast to active comparators.

Data Input	Description of Data Source	Comment
Baseline cohort characteristics	Baseline patient age is 45 years old, based on the pooled results of the phase 3 trials for secukinumab. Average weight (as required for weight-based dosing for infliximab) is 89 kg, based on values from the LIBERATE trial. Literature values were used to estimate baseline utility at 0.7.[13]	Baseline patient characteristics were deemed appropriate by the clinical expert. While the manufacturer's pharmacoeconomic report states that characteristics were based on LIBERATE, the model states they were based on "pooled apremilast trials." Baseline utility was appropriate.
Utilities	The utility gain associated with PASI response was taken from pooled values from the apremilast trials (ESTEEM-1, ESTEEM-2, and LIBERATE) using directly measured SF-36 values.	Appropriate
Discontinuation rates	An annual all-cause withdrawal probability of 20% was applied to all biologics and apremilast, reflecting both onset of adverse events and loss of treatment efficacy. This value was based on assumptions and as conducted in previously published economic evaluations.	Unclear whether appropriate; varying discontinuation rates did not impact ICURs substantially
Resource use	Drug acquisition costs, costs of monitoring, and follow-up; largely based on expert opinion	Appropriate
Adverse events	Adverse events were not considered	Unclear; all comparators in the manufacturer's NMA had lower odds of overall adverse events compared with apremilast except for infliximab and secukinumab
Mortality	Background mortality made use of age-specific Canadian mortality figures	Appropriate
Costs		
Drug	• Apremilast: manufacturer's confidential submitted price • Comparators: from the Ontario Drug Benefit Formulary (2016)[14]	Appropriate
Administration	• Costs of injections were not considered separately; instead, they were included in administration fees of drugs themselves • Components of SoC, schedule of follow-ups, and laboratory tests were based on expert opinion; costs of physician visits and laboratory tests were based on the Ontario Schedule of Benefits[15] and Schedule of Benefits for Laboratory Services.[16]	The CDR clinical expert noted that frequency of follow-up for apremilast may be more frequent given the lack of data on long-term safety and effectiveness. Furthermore, follow-up for MTX and CYC would likely decrease after 6 months. In practice, there is little impact on ICURs from the use of different follow-up schedules.

CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; CYC =cyclosporine; ICUR = incremental cost-utility ratio; MTX = methotrexate; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; SF-36 = Short Form (36) Health Survey; SoC = standard of care.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Patients who withdraw to SoC experience PASI response according to rates in the placebo groups of trials in the manufacturer's NMA	Unclear whether appropriate; the clinical expert consulted by CDR noted that patients who had failed conventional therapies and biologics or apremilast would be expected to respond minimally to topical therapies and phototherapy. SoC in this case would function more as palliative care where patients would continue to experience baseline utility. This was assessed in CDR's reanalyses as a more conservative assumption.
Assumption that there is no worsening of disease on SoC	Unclear whether appropriate; the course of psoriasis is highly variable and some patients experience progressive disease.[31] CDR acknowledges a paucity of data to adequately model this.
Withdrawal from apremilast and biologics was equal, at 20% annual probability	Likely inappropriate; all-cause withdrawal reflects both loss of efficacy and onset of adverse events. As per the manufacturer's NMA, apremilast has significantly higher odds of inducing overall adverse events compared with all comparators, apart from infliximab and secukinumab (the latter only because the upper bound of the 95% credible interval is 1). A manufacturer-commissioned analysis of persistence with biologics or apremilast found that patients receiving biologics were more likely to persist with treatment than those receiving apremilast, for all patient subgroups (treatment-naive and treatment-experienced with biologics, non-biologics, or both).[17] Further, a 2016 review by Bartos et al.[18] examining maintenance of response to psoriasis treatment (biologics and apremilast) found that apremilast had the lowest rate of initial responders who maintained response at one year (61%, compared with 72.3% to 95.2% for all other drugs at Health Canada–approved doses), and lowest rates of maintenance among all patients initially exposed to treatment (18.7%, compared with 37.2% to 65.2%).
Patients moved from monotherapy to SoC	The clinical expert confirmed that this does not reflect clinical practice: failure on one active medication is generally followed by treatment with another. Further, combinational or rotational therapy is often used.[32] However, CDR acknowledges a paucity of efficacy data on treatment sequences.
No mortality attributable to psoriasis or drugs specifically; considered only age-specific Canadian background mortality rates	Appropriate
Cohort composition reflected clinical practice	Confirmed as appropriate by clinical expert
PASI response is constant across the model horizon	Likely inappropriate, as biologic fatigue[19] and loss of efficacy with apremilast[20] have both been observed. While the manufacturer included an option to model long-term adjustment of PASI response, there were severe limitations with this analysis. CDR acknowledges a paucity of other relevant data to model this.
Adverse events are not considered	Likely inappropriate, given the results of the manufacturer's NMA.

CDR = CADTH Common Drug Review; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; SoC = standard of care.

Manufacturer's Results

The manufacturer reported in its base case that apremilast was associated with an ICUR of $83,480 per QALY compared with SoC (Table 11). When comparing comparators sequentially, the most cost-effective options were SoC, apremilast, and SEB infliximab.

TABLE 11: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

Interventions	Total Costs	Total QALYs	Compared With SoC			Sequential ICUR ($/QALY)
			Incremental Cost	Incremental QALYs	ICUR ($/QALY)	
SoC	$6,278	5.62	Reference			
Apremilast	$24,101	5.83	$17,823	0.21	$83,480	$83,480
Adalimumab	$56,509	6.07	$50,331	0.45	$110,662	Extendedly dominated by apremilast and SEB infliximab
Etanercept	$57,646	6.03	$51,368	0.41	$124,066	Dominated by adalimumab[a]
SEB infliximab	$63,740	6.23	$57,462	0.61	$94,062	$99,747
Ustekinumab	$68,986	6.15	$62,708	0.53	$117,253	Dominated by SEB infliximab
Secukinumab	$73,657	6.22	$67,379	0.60	$112,900	Dominated by SEB infliximab
Infliximab	$116,042	6.23	$109,764	0.61	$179,676	Dominated by SEB infliximab

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; SEB = subsequent entry biologic; SoC = standard of care.
[a] Incorrectly stated to be extendedly dominated by SoC and apremilast in the manufacturer's report.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.
Source: Manufacturer's pharmacoeconomic submission.[6]

CADTH Common Drug Review Reanalyses

Full details of the CDR base case (Table 2) are provided subsequently.

TABLE 12: THE CADTH COMMON DRUG REVIEW'S BASE-CASE SEQUENTIAL ANALYSIS (STANDARD OF CARE UTILITIES, MONITORING COSTS, FIVE-YEAR HORIZON) INTERVENTIONS

	Total Costs	Total QALYs	Compared With SoC			Sequential ICUR ($/QALY)
			Incremental Cost (CAD)	Incremental QALYs	ICUR ($/QALY)	
SoC	$3,539	3.19	Reference			
Apremilast	$18,422	3.33	$14,883	0.14	$105,935	Extendedly dominated by SoC and SEB infliximab
Adalimumab	$44,302	3.52	$40,763	0.33	$125,136	Extendedly dominated by SoC and SEB infliximab
Etanercept	$45,795	3.49	$42,255.76	0.3	$142,518	Dominated by adalimumab
SEB infliximab	$50,083	3.64	$46,543.76	0.45	$103,762	$103,762
Ustekinumab	$54,664	3.58	$51,124.76	0.39	$132,062	Dominated by SEB infliximab
Secukinumab	$58,271	3.63	$54,732.52	0.45	$125,056	Dominated by SEB infliximab
Infliximab	$92,474	3.64	$88,934.76	0.45	$198,267	Dominated by SEB infliximab

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SoC = standard of care.

Price Reduction Scenarios

When considering the CDR base case, a price reduction of more than 50% would be necessary for the ICUR of apremilast to fall below $50,000 per QALY compared with SoC (Table 13). When considering the manufacturer's base case, a price reduction of 40% would be necessary for the ICUR of apremilast to fall below $50,000 per QALY when compared with SoC. Of note, this is based on the submitted ICUR and is not corrected for the incorrectly coded utility response among SoC responders. When corrected, a price reduction of 47% ([redacted]/tablet) is required to achieve an ICUR of $50,000 per QALY compared with SoC.

TABLE 13: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of Apremilast Versus SoC		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR**
Submitted ([redacted]/tablet)	$83,480	$105,935
10% reduction ([redacted]/tablet)	$74,740	$94,914
15% reduction ([redacted]/tablet)	$70,370	$89,403
20% reduction ([redacted]/tablet)	$66,000	$83,893
25% reduction ([redacted]/tablet)	$61,631	$78,382
30% reduction ([redacted]/tablet)	$57,261	$72,871
35% reduction ([redacted]/tablet)	$52,891	$67,361
40% reduction ([redacted]/tablet)	$48,521	$61,850
45% reduction ([redacted]/tablet)	$44,151	$56,340
50% reduction ([redacted]/tablet)	$39,781	$50,829
55% reduction ([redacted]/tablet)	$35,411	$45,318

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; SoC = standard of care.

Note that the manufacturer's base case assumes that the list prices of drugs reflect the prices paid by drug plans under product reimbursement agreements. Where participating drug plans pay less than the list price for comparators, the overall findings may change. For example, if drug plans paid 11% less than the list price of SEB infliximab, apremilast would be extendedly dominated by SoC and SEB infliximab, based on the manufacturer's base case. When the coding error in SoC responder utilities is corrected, only a 2% reduction in the price of SEB infliximab is sufficient to extendedly dominate apremilast. Reductions of less than 20% in the prices of adalimumab and secukinumab are also sufficient to extendedly dominate apremilast (Table 14).

TABLE 14: CADTH COMMON DRUG REVIEW PRICE REDUCTION ANALYSIS — PRICE ANALYSIS FOR COMPARATORS

Percentage Price Reduction Necessary to Exclude Apremilast Through Extended Dominance		
Comparator	**Manufacturer's Base Case**	**Manufacturer's Base Case Corrected for SoC Utility Coding Error**
SEB infliximab	11% price reduction	2% price reduction
Adalimumab	24% price reduction	18% price reduction
Secukinumab	26% price reduction	18% price reduction
Ustekinumab	29% price reduction	21% price reduction
Etanercept	32% price reduction	27% price reduction

CDR = CADTH Common Drug Review; SEB = subsequent entry biologic; SoC = standard of care.

CADTH Common Drug Review Scenario Analyses

CDR explored a set of more conservative assumptions based on utility response among patients not achieving PASI 75, exclusion of placebo response on SoC, and long-term adjustment utilities. All analyses used a five-year horizon; a one-year horizon was also considered, due to limitations in the manufacturer's model relating to long-term utility adjustment. CDR found that apremilast would be associated with an ICUR of $131,662 per QALY compared with SoC, and would be extendedly dominated by SoC and SEB infliximab.

Correction of the manufacturer's coding error was not applied, as the original error (i.e., no accrual of utilities among SoC responders) was appropriate for assessing exclusion of PASI response among SoC responders. Corrected monitoring costs were not considered, as these affected ICURs minimally.

A. No utility gain among patients failing to achieve a PASI 75 response: CDR's consulting clinical expert noted that the availability of efficacious biologic treatments means that high levels of PASI response are expected by both patients and clinicians. Further, the 2015 update to the *European S3-Guidelines on the Systemic Treatment of Psoriasis Vulgaris* suggests that PASI 90 can be considered the new treatment goal, given the availability of highly effective newer anti-interleukin biologics.[33] Given these updates in the expectations of psoriasis treatment, CDR explored a scenario where patients who achieved responses lower than PASI 75 experienced no gain in utility (i.e., continued to accrue baseline utility).

B. Exclusion of placebo response in SoC: All patients who went to SoC accrued baseline utilities. The achievement of PASI response on topical agents and phototherapy among a post-conventional population of patients who have further failed a subsequent line of treatment was thought to be unlikely, and SoC was thought to function more as palliative care at best.

C. Long-term utility adjustment: In the manufacturer's base case, PASI response was maintained over time (i.e., there was no progression of disease). In practice, loss of efficacy for both biologics[19] and apremilast[20] has been noted. CDR applied the manufacturer's model option of including utilities adjusted for observed PASI response at 16 weeks, 32 weeks, and 52 weeks to account for loss of efficacy over time. Of note, this biases results against biologics as they are assumed to have the same long-term PASI response as apremilast, whereas they likely have a more favourable PASI distribution in practice.

D. Use of a five-year horizon: To account for uncertainty in long-term maintenance of PASI response and observed treatment durations in clinical practice, CDR considered a horizon of five years in its base case. Values are also reported for a one-year horizon.

TABLE 15: CADTH COMMON DRUG REVIEW CONSERVATIVE SCENARIO ANALYSIS

Scenario		ICUR ($ per QALY) for Apremilast Versus SoC	Sequential ICUR of Apremilast
	Manufacturer's base case	**$83,480**	**$83,840 versus SoC**
A	No utility gain for patients with < PASI 75	$95,553	$95,553 versus SoC
B	No PASI response among SoC patients	$100,557	Apremilast extendedly dominated by SoC and SEB infliximab
C	Long-term utility adjustment	$93,401	$93,401 versus SoC
D	Five-year time horizon	$89,453	$89,453 versus SoC
A to D	**CDR conservative scenario analysis**	**$131,662**	**Extendedly dominated by SoC and SEB infliximab**
	CDR conservative scenario: one-year horizon	$216,213	Extendedly dominated by SoC and SEB infliximab

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SoC = standard of care.

REFERENCES

1. CDR submission: Otezla® (apremilast), 10mg, 20mg, 30 mg tablets. Company: Celgene Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Celgene Inc.; 2014 Oct.
2. Otezla® (apremilast) 10 mg, 20 mg, 30 mg tablets [product monograph]. Mississauga (ON): Celgene Inc.; 2015.
3. CADTH Canadian Drug Expert Committee (CDEC) final recommendation. Apremilast (Otezla - Celgene). Indication: moderate to severe plaque psoriasis. [Internet]. Ottawa: CADTH; 2015. [cited 2016 Apr 26]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0400-Otezla-Aug-10-15-e.pdf
4. Clinical Study Report: CC-10004-PSOR-010. A phase 3b, multicenter, randomized, placebo-controlled, double-blind, double-dummy, study of the efficacy and safety of apremilast (cc-10004), etanercept, and placebo, in subjects with moderate to severe plaque psoriasis [**CONFIDENTIAL** internal manufacturer's report]. Summit (NJ): Celgene Corporation; 2014 Oct 13.
5. Common Drug Review. CADTH Canadian Drug Expert Committee (CDEC) final recommendation. Apremilast (Otezla - Celgene). Indication: psoriatic arthritis [Internet]. Ottawa: CADTH; 2015. [cited 2016 Apr 29]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0437_complete_Otezla_PsA-Dec-21-15_e.pdf
6. Pharmacoeconomic evaluation. In: CDR submission: Otezla® (apremilast), 10mg, 20mg, 30 mg tablets. Company: Celgene Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Celgene Inc.; 2014 Oct.
7. Submission guidelines for the CADTH Common Drug Review [Internet]. Ottawa: CADTH; 2014. [cited 2016 May 16]. Available from: https://www.cadth.ca/media/cdr/process/CDR_Submission_Guidelines.pdf
8. PSO network meta-analysis report - a supplemental document to the Otezla® (apremilast) pharmacoeconomic evaluation report. In: CDR submission: Otezla® (apremilast), 10mg, 20mg, 30 mg tablets. Company: Celgene Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Celgene Inc.; 2014 Oct.
9. Enbrel® (etanercept) solution for injection in a prefilled syringe 50 mg/mL and lyophilized powder for reconstitution in a vial 25 mg/vial [product monograph] [Internet]. Thousand Oaks (CA): Immunex Corporation; 2015. [cited 2016 May 16]. Available from: https://www.amgen.ca/Enbrel_PM.pdf
10. PSO network meta-analysis report - a supplemental document to the Otezla® (apremilast) pharmacoeconomic evaluation report. In: CDR submission: Otezla® (apremilast) for the treatment of moderate to severe plaque psoriasis, 10 mg, 20 mg, and 30 mg oral tablets [Resubmission]. Company: Celgene Inc. 2016 Mar 3 [**CONFIDENTIAL** manufacturer's submission]. 2016 Feb.
11. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015 Jul;73(1):37-49.
12. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol [Internet]. 2015 Dec

[cited 2016 Apr 14];173(6):1387-99. Available from: http://onlinelibrary.wiley.com/doi/10.1111/bjd.14164/epdf

13. Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. Br J Dermatol. 2008 Mar;158(3):549-57.
14. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto: Queen's Printer of Ontario; 2016. [cited 2016 May 18]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary/
15. Ontario Ministry of Health and Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective May 1, 2015 [Internet]. Toronto: The Ministry; 2015. [cited 2016 May 18]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/sob_master11062015.pdf
16. Ontario Ministry of Health and Long-Term Care. Ontario Health Insurance (OHIP) schedule of benefits and fees. Schedule of benefits for laboratory services [Internet].Toronto; 1999. Queen's Printer for Ontario. [cited 2016 May 18]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/lab/lab_mn.html
17. Analysis Group, Inc. Analysis memo: description of the persistence analysis of patients using biologic, and non-biologic conventional systemic therapy for psoriasis before apremilast launch and persistence analysis of patients using apremilast, biologic, and non-biologic conventional systemic therapy for psoriasis after apremilast launch. In: CDR submission: Otezla® (apremilast) for the treatment of moderate to severe plaque psoriasis, 10 mg, 20 mg, and 30 mg oral tablets [Resubmission]. Company: Celgene Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Celgene Inc.; 2016 Mar 3. 2016.
18. Bartos S, Hill D, Feldman SR. Review of maintenance of response to psoriasis treatments. J Dermatolog Treat. 2016 Aug;27(4):293-7.
19. Levin EC, Gupta R, Brown G, Malakouti M, Koo J. Biologic fatigue in psoriasis. J Dermatolog Treat. 2014 Feb;25(1):78-82.
20. Celgene Corporation response to April 12, 2016 CDR request for additional information regarding the Otezla resubmission CDR review: LIBERATE study [**CONFIDENTIAL** additional manufacturer's information]. Summit (NJ): Celgene Corporation; 2016 Apr 25.
21. Levin AA, Gottlieb AB, Au SC. A comparison of psoriasis drug failure rates and reasons for discontinuation in biologics vs conventional systemic therapies. J Drugs Dermatol. 2014 Jul;13(7):848-53.
22. Kim WB, Marinas JE, Qiang J, Shahbaz A, Greaves S, Yeung J. Adverse events resulting in withdrawal of biologic therapy for psoriasis in real-world clinical practice: a Canadian multicenter retrospective study. J Am Acad Dermatol. 2015 Aug;73(2):237-41.
23. Winterfield LS, Menter A, Gordon K, Gottlieb A. Psoriasis treatment: current and emerging directed therapies. Ann Rheum Dis [Internet]. 2005 Mar [cited 2016 May 18];64(Suppl 2):ii87-ii90. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766866
24. List of medications [Internet]. Quebec (QC): Régie de l'assurance maladie du Québec (RAMQ); 2016 May 2. [cited 2016 May 18; last updated 2016 May 4]. Available from:

https://www.prod.ramq.gouv.qc.ca/DPI/PO/Commun/PDF/Liste_Med/Liste_Med/liste_med_2016_05_04_en.pdf

25. Interactive drug benefit list [Internet]. Edmonton (AB): Alberta Health; 2016. [cited 2016 May 18]. Available from: https://idbl.ab.bluecross.ca/idbl/load.do
26. DeltaPA [database on the Internet]. Ottawa: IMS Brogan; 2016 [cited 2016 May 18]. Available from: http://www.imsbrogancapabilities.com/en/market-insights/delta-pa.html Subscription required.
27. Saskatchewan online formulary database [Internet]. Regina (SK): Government of Saskatchewan; 2016. [cited 2016 May 18]. Available from: http://formulary.drugplan.health.gov.sk.ca/
28. Apremilast for treating moderate to severe plaque psoriasis [Internet]. London: National Institute for Health and Care Excellence; 2015 Nov 25. [cited 2016 May 18]. (Technology appraisal guidance 368). Available from: https://www.nice.org.uk/guidance/ta368/resources/apremilast-for-treating-moderate-to-severe-plaque-psoriasis-82602735492805
29. Apremilast 10mg, 20mg and 30mg film-coated tablets (Otezla®) [Internet]. Glasgow: Scottish Medicines Consortium; 2015 May 8. [cited 2016 May 18]. (SMC no 1052/15). Available from: https://www.scottishmedicines.org.uk/files/advice/apremilast__Otezla__plaque_psoriasis_FINAL_May_2015_REVISED_010615_for_website.pdf
30. Bank of Canada. Financial markets Canada: year average of exchange rates [Internet]. Ottawa (ON): Bank of Canada; 2015. [cited 2016 Jun 1]. Available from: http://www.bankofcanada.ca/stats/assets/pdf/nraa-2015-en.pdf
31. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis [Internet]. 2005 Mar [cited 2016 May 18];64 Suppl 2:ii18-ii23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766861
32. Lebwohl M, Menter A, Koo J, Feldman SR. Combination therapy to treat moderate to severe psoriasis. J Am Acad Dermatol. 2004 Mar;50(3):416-30.
33. Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris--update 2015--short version--EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015 Dec;29(12):2277-94.