Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	apremilast (Otezla)
Indication	Indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
Listing request	For the treatment of adult patients with moderate to severe plaque psoriasis who have had an inadequate response, or are intolerant or contraindicated to a conventional systemic therapy.
Manufacturer	Celgene 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.

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ABBREVIATIONS

AE	adverse event
BSA	body surface area
BSC	best supportive care
CUA	cost-utility analysis
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire
HoDAR	health outcomes data repository
ICUR	incremental cost-utility ratio
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PSO	psoriasis
QALY	quality-adjusted life-year
SEB	subsequent entry biologic
sPGA	static Physician Global Assessment

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Apremilast (Otezla)
Study Question	Among patients with moderate to severe plaque PSO who are candidates for systemic therapy or phototherapy, what is the cost-effectiveness of apremilast compared with systemic therapies (methotrexate, cyclosporine), biologics (etanercept, ustekinumab, adalimumab, infliximab), or palliative care?
Type of Economic Evaluation	CUA
Target Population	Patients with plaque PSO who are eligible for systemic therapy or phototherapy.
Treatment	Apremilast
Outcome	QALYs
Comparators	• Palliative care, defined as 6 doctor visits per annum without active medication • Methotrexate • Cyclosporine • Adalimumab • Etanercept • Ustekinumab • Infliximab
Perspective	Canadian public payer
Time Horizon	10 years
Results for Base Case	The manufacturer reported the incremental cost per QALY for treatments compared with palliative care: • $7,262 for methotrexate • $97,607 for apremilast • $118,416 for cyclosporine • $134,325 for etanercept • $121,067 for adalimumab • $128,064 for ustekinumab • $197,337 for infliximab
Key Limitations	CDR noted several limitations: • Lack of information on the population for which the manufacturer is seeking listing • Lack of consideration for subsequent entry biologic price for infliximab • Assumptions around the use of and disutility associated with cyclosporine • Assumptions around the withdrawal rates and disutility associated with methotrexate.
CDR Estimates	• Based on the manufacturer's results, apremilast is ruled out by extended dominance by methotrexate and adalimumab — it does not represent the set of most efficient choices. • When considering SEB price for infliximab, apremilast is ruled out by extended dominance by methotrexate and SEB infliximab. • When using alternative assumptions around the use of cyclosporine, apremilast is further ruled out by extended dominance by cyclosporine and SEB infliximab. • When using alternative assumptions around the use of methotrexate, apremilast is dominated by methotrexate.

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; PSO = psoriasis; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.

EXECUTIVE SUMMARY

Background

Apremilast (Otezla) is an oral phosphodiesterase-4 inhibitor approved for the treatment of moderate to severe plaque psoriasis (PSO). The manufacturer requested listing of apremilast for patients with PSO with failure, intolerance, or contraindication to traditional systemic therapies (i.e., methotrexate or cyclosporine).[1] At a recommended dose of two 30 mg tablets daily and a submitted confidential price of [redacted] per tablet, apremilast costs [redacted] daily.

The manufacturer submitted a cost-utility analysis (CUA) based on a Markov model evaluating the cost-effectiveness of apremilast in patients with moderate to severe PSO (defined as a Psoriasis Area and Severity Index [PASI] score ≥ 12 with ≥ 10% of body surface area [BSA] affected, and static Physician Global Assessment [sPGA] ≥ 3) who are eligible for systemic therapy or phototherapy.[2] Comparators were systemic therapies (methotrexate, cyclosporine), biologics (etanercept, adalimumab, ustekinumab, and infliximab), and palliative care, defined as six physician visits per year without any active drug. Patients entered the model assigned to one of the seven treatments or palliative care (i.e., no pharmacologic treatment) and would be assessed for response (75% or greater reduction in PASI score, PASI 75) at the end of the cycle. Responders were assumed to continue treatment; once withdrawing from treatment, they would lose response and receive palliative care. Non-responders and those who withdrew from treatment entered the palliative care state. Treatment efficacy values were informed by a manufacturer-sponsored network meta-analysis (NMA). The association of PASI scores to utilities was based on a two-step approach: firstly, mapping PASI response to Dermatology Life Quality Index (DLQI) scores and then to EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) utilities. Patients who were non-responders or who withdrew from treatment to palliative care were assumed to experience baseline utility. The analysis was undertaken from the Canadian public payer perspective and used a horizon of 10 years.

Summary of Identified Limitations and Key Results

- **Sequential analysis:** The manufacturer reported the results compared with palliative care. Reporting the incremental cost-utility ratios (ICURs) sequentially provides a comparative assessment of treatments and allows an understanding of the most efficient (cost-effective) options. When considering the ICURs in a sequential manner, apremilast is extendedly dominated by methotrexate and adalimumab — it does not comprise the cost-effectiveness frontier.
- **Lack of information on the listing request:** The manufacturer is requesting listing for apremilast in patients who have failed, or are intolerant or have contraindications to, phototherapy or systemic therapy. No clinical (or economic) data were available on these patients. The listing request represents an intermediate treatment between systemic and biologic therapies, but there are no data to suggest that use of apremilast prior to biologics (delaying use of treatment with higher PASI response) represents a cost-effective strategy.
- **Lack of direct clinical evidence:** In the absence of direct active comparator studies, the manufacturer sponsored an NMA to inform clinical effectiveness in the economic model. The analysis presented by the manufacturer did not directly compare apremilast to other drugs, and instead compared each drug to placebo. Although there were 29 trials included in this NMA, these include eight different drugs; therefore, there were a relatively low number of included trials per drug, perhaps introducing uncertainty into the analysis. Of the 29 included studies, only 58% were rated as either “excellent” or “good” quality, and 28% were rated as “poor” quality (CADTH Common Drug Review [CDR] Otezla Clinical Report, Appendix 7).

- **Inclusion of subsequent entry biologic (SEB) price for infliximab:** A SEB for infliximab (Inflectra) was recently approved by Health Canada and reviewed by CADTH.[3] Where the manufacturer included this as a comparator in its analysis, the ICUR versus palliative care would be $129,917 (reduced from $197,337 for brand infliximab, Remicade). In terms of the rank order for comparators, apremilast would be ruled out by methotrexate and SEB infliximab (adalimumab and ustekinumab would also be ruled out).
- **Assumptions relating to cyclosporine*:*** While there were insufficient data to directly compare the effectiveness of apremilast and cyclosporine, cyclosporine was found to have a higher probability of PASI 75 and PASI 90 response compared with placebo than apremilast. Furthermore, cyclosporine is less expensive than apremilast. The manufacturer assumed that patients underwent only six months of treatment with cyclosporine and benefits of treatment accrued for only three months. No justification was provided for this assumption, which was not applied to other treatments. Furthermore, a disutility multiplier was applied to treatment with cyclosporine (and methotrexate) to account for side effects and toxicity, while adverse events (AEs) were not considered for other comparators. The use of alternative assumptions regarding cyclosporine found its ICUR to be lower than that of apremilast when compared with palliative care ($36,953 to $39,481 per quality-adjusted life-year [QALY]); as such, apremilast is subjected to extended dominance by cyclosporine and adalimumab.
- **Assumptions relating to methotrexate:** While there were insufficient data to directly compare the effectiveness of apremilast and methotrexate, methotrexate was found to have a higher probability of PASI 50, PASI 75, and PASI 90 response compared with placebo than apremilast. Methotrexate is less expensive than apremilast. The manufacturer assumed that the withdrawal rate with methotrexate and a disutility multiplier was applied to treatment with methotrexate to account for side effects and toxicity, while AEs were not considered for other comparators. The use of alternative assumptions regarding methotrexate resulted in methotrexate being less costly and more effective than apremilast (methotrexate dominant).
- **Uncertainty in reported QALYs:** The manufacturer used the two-step method of Woolacott et al. in which PASI response is initially mapped to a DLQI score according to values from etanercept trials included in the Woolacott systematic review.[4] DLQI scores are then mapped to EQ-5D utilities according to a linear regression developed by Woolacott et al. on the basis of patients in the Health Outcomes Data Repository (HoDAR) database with DLQI scores and EQ-5D utilities. The use of an indirect method based on non-Canadian values, the existence of multiple mappings, and doubts regarding the correlation between PASI and DLQI and between the DLQI and EQ-5D[5-7] introduces uncertainty around the manufacturer's calculated QALYs. Use of available utility mappings from recent publications led to ICURs for apremilast between $82,994 and $126,096 per QALY compared with palliative care.

Conclusions

The manufacturer reported that the incremental cost per QALY for apremilast is $97,607 compared with palliative care, which is more than methotrexate ($7,262 per QALY) but less than biologics ($121,067 [adalimumab] to $197,337 [infliximab]). However, when considering treatments comparatively, apremilast is ruled out (by extended dominance) by methotrexate and adalimumab, or methotrexate and SEB infliximab.

Based on CDR analyses considering more conservative assumptions regarding methotrexate and cyclosporine, apremilast is dominated by methotrexate, and ruled out by cyclosporine and SEB infliximab. For apremilast to be cost-effective based on a cost per QALY threshold of $50,000, the price would need to be reduced by 80% when compared with cyclosporine.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) using a Markov state-transition model comparing apremilast, systemic therapies (methotrexate, cyclosporine), and biologics (etanercept, adalimumab, ustekinumab, infliximab) with palliative care (routine physician visits, palliative care), in patients with moderate to severe plaque psoriasis (PSO) (defined as Psoriasis Area and Severity Index [PASI] ≥ 12, body surface area [BSA] ≥ 10%, and static Physician Global Assessment [sPGA] score ≥ 3) who are candidates for phototherapy or systemic therapy.[2] The manufacturer's model is based on the widely used York model of PSO developed by Woolacott et al.[4] Among patients receiving one of the active interventions, treatment response was assessed after a variable trial period (10 weeks for infliximab, 12 weeks for etanercept, and 16 weeks for apremilast, adalimumab, ustekinumab, and methotrexate) based on PASI 75 response. After the trial period, a two-state Markov model is used to follow patients through the rest of the study period, consisting of a "continued treatment" state and a "palliative care" state. Responders enter and remain in the continued treatment state until they withdraw (it was not specified whether this was due to loss of treatment response, discontinuation due to side effects, or both). Non-responders and patients who withdraw from the continued treatment state move to the palliative care state in which patients attend six doctor's visits per year with no active pharmacologic treatment. Among patients on cyclosporine, it is assumed that all patients remain on treatment for six months, at which point they enter the palliative care state. The manufacturer assumed that this was the case due to cumulative toxicity. Incremental cost-utility ratios (ICURs) for all treatments were calculated relative to palliative care. A 10-year horizon and public health care payer perspective were used.

The proportion of responders for each treatment was assessed by a manufacturer-sponsored network meta-analysis (NMA). The probability of PASI 75 and PASI 90 response relative to placebo were calculated for all treatments (
Table 13). There was no attempt to compare any of the active comparators. A total of 29 studies were assessed, including the pivotal phase 3, double-blind randomized controlled trials (RCTs) for apremilast (ESTEEM-1 and ESTEEM-2).[8,9] Among responders, withdrawal to palliative care was assumed to be 20% annually. This value was justified by noting that it is the most common figure encountered in recent pharmacoeconomic evaluations of psoriasis drugs. There was no indication of whether withdrawal was due to loss of treatment effectiveness, onset of side effects, or both. Patients who withdrew to palliative care returned to baseline utility. Among patients receiving palliative care alone, it was assumed that utility remained at its baseline value throughout the study period.

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 and higher) and change in utility from baseline associated with different PASI responses. The utility gain associated with PASI response was taken from Woolacott et al.'s study.[4] Woolacott et al. used a two-stage process. PASI responses were mapped to changes in DLQI scores according to values from the etanercept trials in Woolacott et al.'s systematic review. Then, values from patients in the Health Outcomes Data Repository (HoDAR) database who had completed both DLQI and EQ-5D were used to undertake an ordinary least squares linear regression to map DLQI scores to changes in EQ-5D utilities. Baseline utility was 0.7 as per Revicki et al.'s study.[10] For patients in palliative care, it was assumed that baseline utility was maintained over the entire period.

For patients who withdrew from treatment to palliative care, it was assumed that utilities returned for the remainder of the study period. A disutility multiplier of 0.97 was applied to patients on methotrexate or cyclosporine to account for possible side effects and toxicity. This value was obtained from a study of methotrexate and cyclosporine in rheumatoid arthritis. For cyclosporine, it was assumed that of the six months on treatment, benefits only accrued for months 4 to 6. The manufacturer did not justify this assumption. No adjustments for the potential side effects with the other comparators, including apremilast, were included.

Costs considered were drug acquisition costs and costs of monitoring and follow-up. Dosages were assumed to be the recommended doses from product monographs. The cost of apremilast was from the manufacturer's confidential submitted price, while the costs of all other medications were from the Ontario Drug Benefit (ODB) formulary (2014). Schedules of monitoring and follow-up were based on clinical expert input and comprised doctor's visits and laboratory testing. Drug administration costs were not considered as they were not relevant for apremilast, methotrexate, and cyclosporine. For biologics, the costs of injection were assumed to be covered by the manufacturer. The costs of physician visits were obtained from the Ontario Health Insurance Plan (OHIP) schedule of benefits (2012),[11] while the costs of laboratory tests were obtained from the 1999 Schedule of Benefits for Laboratory Services.

Costs of adverse events (AEs) were not considered for apremilast or biologics. The manufacturer justified this by pointing to a lack of long-term data on AEs associated with apremilast and biologics, as well as evidence of minimal AEs where data exist. However, side effects were considered for methotrexate and cyclosporine, reflected in the disutility multiplier, a more frequent schedule of follow-ups and testing.

The manufacturer submitted a second CUA that compared a treatment sequence with apremilast to a comparator sequence without apremilast among PSO patients who had an inadequate response to, are contraindicated, or intolerant of systemic therapies (APPENDIX 5: MANUFACTURER'S COST-UTILITY ANALYSIS COMPARING TREATMENT SEQUENCES). However, given the limited clinical information on the effects of treatments at various sequence positions, the focus of CDR was on the analysis of individual treatments.

2. MANUFACTURER'S BASE CASE

The manufacturer reported in its base case that apremilast is associated with a cost of $22,159 and 5.82 QALYs. When compared with palliative care, apremilast was $19,753 more costly and associated with a gain of 0.20 QALYs, for an ICUR of $97,607 (see Table 16 for additional details). The manufacturer reported ICURs of other treatment compared with palliative care:

- $7,262 for methotrexate
- $118,416 for cyclosporine
- $134,325 for etanercept
- $121,067 for adalimumab
- $128,064 for ustekinumab
- $197,337 for infliximab.

Apremilast had a higher ICUR than methotrexate but a lower ICUR than cyclosporine or any of the biologics.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Among the manufacturer's sensitivity analyses, varying the utility gains associated with PASI scores had an impact on ICURs. Varying the utility values for response results in changes to the ICUR for apremilast compared with palliative care varying from $77,896 (high value for PASI 75 to PASI 90) to $130,672 (low value for PASI 75 to PASI 90).

While the manufacturer described methods for conducting its probabilistic sensitivity analysis (PSA), this was not presented for the analysis of individual treatments (only for its assessment of treatment sequences).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Sequential analysis. The manufacturer reported the results for all treatments compared with palliative care. Reporting the ICURs sequentially provides a comparative assessment of treatments and allows an understanding of the most efficient (cost-effective) options. When considering the ICURs in a sequential manner, apremilast is extendedly dominated by methotrexate and adalimumab — it does not comprise the cost-effectiveness frontier (Table 2).

Lack of information on the listing request. The manufacturer is requesting listing for apremilast in patients who have failed, or are intolerant or have contraindications to, phototherapy or systemic therapy. No clinical (or economic) data were available on these patients. The listing request represents an intermediate treatment between systemic and biologic therapies, but there are no data to suggest that use of apremilast prior to biologics (delaying use of treatment with higher PASI response) represents a cost-effective strategy. Given the limited clinical information on the effectiveness of drugs for subsequent lines of therapy, the manufacturer's analysis of treatment sequences was not the focus of the review.

Lack of direct clinical evidence. The NMA presented by the manufacturer did not directly compare apremilast to other drugs, and instead compared each drug to placebo. Although there were 29 trials included in this NMA, these include eight different drugs; therefore, there were a relatively low number of included trials per drug, perhaps introducing uncertainty into the analysis. Of the 29 included studies, only 58% were rated as either "excellent" or "good" quality, and 28% were rated as "poor" quality (CDR Otezla Clinical Report, Appendix 7).

Inclusion of subsequent entry biologic (SEB) price for infliximab. A SEB for infliximab (Inflectra) was recently approved by Health Canada and reviewed by CADTH.[3] Where the manufacturer included this as a comparator in its analysis, the ICUR versus palliative care would be $129,917 (reduced from $197,337 for brand infliximab, Remicade). In terms of the rank order for comparators, apremilast would be ruled out by methotrexate and SEB infliximab (ustekinumab would also be ruled out).

Manufacturer's assumptions for cyclosporine. As per the manufacturer's NMA, the PASI response observed for apremilast is similar to that of methotrexate and cyclosporine compared with biologics (Table 13). However, the manufacturer made a number of assumptions around the effects of cyclosporine. All patients were assumed to be on treatment for six months before discontinuing and transitioning to palliative care for the remaining 9.5 years of the model. In practice, patients may be on cyclosporine for up to and beyond two years, based on CDR clinical expert feedback. Also, while costs for cyclosporine accrued over the six months of administration, benefits in terms of PASI response only

accrued from months 4 to 6. No justification was provided for this, and the CDR clinical expert confirmed that there are no grounds for supposing that benefits from cyclosporine accrue later than for other treatments. While AEs were not considered in the model for apremilast or biologics, a disutility multiplier was applied to patients on cyclosporine to address concerns of toxicity. The CDR reanalysis incorporated a cyclosporine trial period of three months (as per clinical expert input) and maximal use of cyclosporine for up to one year or two years, with benefits accrued from the beginning of treatment.

Manufacturer's assumptions for methotrexate . As per the manufacturer's NMA, the PASI response observed for apremilast is closer to that of methotrexate and cyclosporine than biologics (Table 13). However, the manufacturer made a number of assumptions around the effects of methotrexate. The annual withdrawal rate for methotrexate was higher than for apremilast (25.4% versus 20.0%) and a disutility multiplier was applied to patients on methotrexate to address concerns of toxicity, yet no allowance for any potential side effects with apremilast were made. The CDR reanalysis incorporated the same withdrawal rates for methotrexate as for apremilast and excluded the disutility multiplier.

Uncertainty in utility values associated with PASI scores. As noted in the manufacturer's sensitivity analyses, the utility gains associated with PASI scores impact the ICURs. Previous pharmacoeconomic studies of treatments for PSO have used several different mappings between PASI scores and utilities. Furthermore, the mapping chosen by the manufacturer (based on that of Woolacott et al.) is indirect, initially associating PASI scores to DLQI values that are subsequently mapped to EQ-5D utilities. There are indications that the correlation between PASI and DLQI scores is poor.[5,6] Furthermore, the DLQI exhibits poor correlation with EQ-5D utilities.[7] CDR reanalysis used three additional PASI to utility mappings to assess their effects on the cost-effectiveness of apremilast.

Assumptions on post-treatment discontinuation. Patients were assumed to receive treatments (monotherapy) and discontinue upon treatment failure, proceeding to palliative care. In practice, there is likely to be switching of treatments as well as use of combination therapy.[12] The assumption of monotherapy and subsequent palliative care likely does not reflect clinical practice. However, CDR acknowledges limited clinical data in this area.

Assumption of continuation of treatment effect. Data are available up to 16 weeks for apremilast from the initial trials and for up to 52 weeks in an open-label extension study.[8,9] The assumption of constant effectiveness over 10 years is unsubstantiated. Biologic fatigue is a known phenomenon, and thus the assumption of constant treatment effect may not be warranted.[13] These concerns may be addressed by the manufacturer's 20% annual discontinuation rate, but it is not specified whether this figure is due to side effects, treatment failure, or both.

5. CADTH COMMON DRUG REVIEW ANALYSES

Sequential Analysis

CDR calculated sequential ICURs based on the manufacturer's base-case results (Table 2). When considering the results in this manner, the treatments that are on the cost-effectiveness frontier (representing the cost-effective treatments) are clearly identified. In this case, apremilast is ruled out by methotrexate and adalimumab.

TABLE 2: MANUFACTURER'S BASE CASE — SEQUENTIAL INCREMENTAL COST-UTILITY RATIOS

Interventions	Total Costs ($)	Total QALYs	Sequential ICUR
Palliative care	2,405	5.62	–
Methotrexate	3,462	5.76	$7,262
Adalimumab	57,012	6.07	$172,741
Ustekinumab	69,608	6.14	$179,943
Infliximab	117,156	6.20	$792,467
Cyclosporine	5,154	5.64	Dominated by MTX
Apremilast	22,159	5.82	Extendedly dominated
Etanercept	55,986	6.02	Extendedly dominated

ICUR = incremental cost-utility ratio; MTX = methotrexate; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer's pharmacoeconomic submission.

Inclusion of Subsequent Entry Biologic Price for Infliximab

A SEB version of infliximab has recently been approved by Health Canada and reviewed by CADTH.[3] When considering the price of Inflectra in the analysis, instead of the price of brand infliximab (Remicade), the total cost of infliximab is reduced and the ICUR compared with methotrexate is $169,294 (Table 3).

TABLE 3: INCLUSION OF SUBSEQUENT ENTRY BIOLOGIC INFLIXIMAB PRICE — SEQUENTIAL INCREMENTAL COST-UTILITY RATIOS

Interventions	Total Costs ($)	Total QALYs	Sequential ICUR
Palliative care	2,405	5.62	–
Methotrexate	3,462	5.76	$7,262
SEB infliximab (Inflectra)	77,951	6.20	$169,294
Cyclosporine	5,154	5.64	Dominated by MTX
Infliximab	117,156	6.20	Dominated by SEB infliximab
Adalimumab	57,012	6.07	Extendedly dominated
Ustekinumab	69,608	6.14	Extendedly dominated
Apremilast	22,159	5.82	Extendedly dominated
Etanercept	55,986	6.02	Extendedly dominated

ICUR = incremental cost-utility ratio; MTX = methotrexate; QALYs = quality-adjusted life-years; SEB = subsequent entry biologic.

Alternate Cyclosporine Assumptions

Given the manufacturer's assumptions for cyclosporine, CDR considered alternative assumptions around the treatment period. Extending treatment to one year or two years with patients experiencing benefits from the start of treatment was considered. Total costs were $5,590 for one year and $7,868 for two years of treatment, with total QALYs at 5.71 and 5.77 respectively for cyclosporine. The resulting ICURs, when compared with palliative care, were $39,481 for one year of treatment and $36,953 per QALY for two years of treatment, which are lower than the ICUR for apremilast. However, cyclosporine remains dominated by methotrexate — it is more costly and less effective for one year of treatment, and more costly and similarly effective for two years of treatment.

Alternate Methotrexate Assumptions

Given the assumptions manufacturer's assumptions for methotrexate, CDR considered alternative assumptions relating to the annual withdrawal rates and the disutility on therapy. Under these assumptions, the total cost of methotrexate was $3,617 with total QALYs of 5.83. Thus, methotrexate dominated apremilast — it is less costly and more effective.

Psoriasis Area and Severity Index to Utility Mapping Algorithms

Given the sensitivity of the results to the choice of utility values, a search for mapping studies was conducted to identify other sources of information. Three studies were identified that used a similar approach (Table 4).[14-16]

TABLE 4: SOURCES OF UTILITY INFORMATION

	Base Case (Woolacott et al.)	Anis	Pan	Knight[b]
PASI 90	0.21	0.21	0.25	0.232
PASI 75 to 89	0.19	0.12[a]	0.20	0.232
PASI 50 to 74	0.17	0.12	0.17	0.201
PASI < 50	0.05	0.04	0.04	0.101

PASI = Psoriasis Area and Severity Index.
[a] PASI 50 to 89: 0.12.
[b] PASI ≥ 75: 0.232.

When using the values from these studies, the ICUR for apremilast increased ranged from $82,994 to $126,096 (Table 5).

TABLE 5: ALTERNATE UTILITY SOURCES

PASI/Utility Mapping Data Source	Incremental Cost Per QALY ($) for Apremilast vs. PC
Default (Woolacott)	$97,067
Anis	$126,096
Pan	$88,257
Knight	$82,994

PASI = Psoriasis Area and Severity Index; PC = palliative care; QALY = quality-adjusted life-years; vs. = versus.

Price Reduction Scenarios

When considering the manufacturer's results, when compared with palliative care, a 50% price reduction for apremilast would be required for the ICUR to fall below $50,000 per QALY. Alternatively, if compared with methotrexate, a price reduction of 80% would be required (
Table 18). Similarly, when compared with cyclosporine, considering more realistic scenarios of one- or two-year treatment, the price of apremilast would need to be reduced by 80% for the ICUR to fall below $50,000 per QALY.

6. PATIENT INPUT

Input was received from the Canadian Skin Patient Alliance (CSPA) and the Canadian Association of Psoriasis Patients (CAPP). In these inputs, patients noted that PSO symptoms have a significant impact on their quality of life and on their ability to function daily. Patients noted that, while biologics are effective, they generally experience "biologic fatigue" where treatment loses effectiveness. It is unclear whether apremilast would address this need as it would likely be used prior to biologics.
Patients also noted their concerns regarding adverse effects associated with methotrexate and cyclosporine, including fear of liver and kidney damage. Even accounting for the toxicity of methotrexate and cyclosporine (in terms of higher monitoring costs and disutility multiplier), apremilast fails to appear cost-effective.

Patients anticipated that apremilast would have the benefits of oral dosing and better adherence. This was not accounted for in the manufacturer's economic submission.

7. CONCLUSIONS

The manufacturer reported that the incremental cost per QALY for apremilast is $97,607 compared with palliative care, which is more than methotrexate ($7,262 per QALY) but less than biologics ($121,067 [adalimumab] to $197,337 [infliximab]). However, when considering treatments comparatively, apremilast is ruled out (by extended dominance) by methotrexate and adalimumab or methotrexate and SEB infliximab.

Based on CDR analyses considering more conservative assumptions around methotrexate and cyclosporine, apremilast is dominated by methotrexate, and ruled out by cyclosporine and SEB infliximab. For apremilast to be cost-effective based on a cost per QALY threshold of $50,000, the price would need to be reduced by 80% when compared with cyclosporine.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 6 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.

TABLE 6: COST COMPARISON TABLE FOR PLAQUE PSORIASIS

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Cost ($)
Apremilast (Otezla)	**10 mg**[a] **20 mg**[a] **30 mg**	**Tab**	[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 initial dose, 40 mg every other week starting one week after initial dose	First year: $20,730 Subsequent years: $19,249
Etanercept (Enbrel)	50 mg/mL 25 mg/vial	Syringe or pen vial Vial	$390.7425 $195.3125	50 mg twice weekly for 12 weeks, then 25 mg twice weekly	First year: $25,000[c] Subsequent years: $20,313
Infliximab (Remicade)	100 mg/vial	Vial	$987.5600	5 mg/kg/dose, for 3 doses (0, 2, 6 weeks) then 5 mg/kg every 8 weeks	First year: $39,502[e] Subsequent years: $32,096
Infliximab (Inflectra)			$650,0000[d]		First year: $26,000 Subsequent years: $21,125
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/1 mL	Pre-filled syringe	$4,593.1400	< 100 kg patients — 45 mg at wks 0 and 4, followed by 45 mg every 12 weeks thereafter (same for > 100 kg, except 90 mg)	First year: $22,966 Subsequent years: $20,669[f]
Systemic Treatments					
Methotrexate	2.5 mg 10 mg 25 mg/mL	Tab Tab Inj	$0.6325 $2.4541[g] $8.9200/2 mL injection	10 mg to 25 mg by mouth or IM weekly	$132 to $329 $464

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Cost ($)
Cyclosporine (Neoral)	10 mg 25 mg 50 mg 100 mg	Cap	$0.6238 $0.9952 $1.9400 $3.8815	2.5 mg/kg daily (rounded to 200 mg/day) (max 5 mg/kg/day)	$1,304 to $1,578[h]
Acitretin (Soriatane)	25 mg	Cap	$3.7636	25 mg to 50 mg daily	$1,370 to $2,739

Cap = capsule; IM = intramuscularly; inj = injection; Tab = tablet, wks = weeks.
Note: Average weight was assumed to be 93 kg, as per manufacturer's trials and values used in models.
[a] Manufacturer's submitted confidential price. Note the 10 mg and 20 mg dose tablets are only available through the 27-count starter pack.
[b] First year includes titration period with equivalently priced 10 and 20 mg pills.
[c] $25,008 and $20,319 annually if 50 mg vials are used in place of 25 mg vials.
[d] Source: CADTH Canadian Drug Expert Committee Recommendation for Inflectra.[3]
[e] Assumes wastage of partially used vials occurs. Eight treatments first year, 6.5 average subsequent years.
[f] Five treatments first year, 4.5 average subsequent. Price for 45 mg and 90 mg is the same.
[g] Source: Saskatchewan formulary.
[h] Lower value assumes 200 mg/day, upper end assumes dosage for average body weight from apremilast trials. In all cases, assume 2.5 mg/kg/d on average, administer for six months.
Source: Ontario Drug Benefit (April 2014) except where noted.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

The following are based on the manufacturer's results.

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO PALLIATIVE CARE?

Apremilast vs. Palliative 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	$97,607 per QALY					

CE = cost-effectiveness; NA = not applicable; PC = palliative care; QALY = quality-adjusted life-year; vs. = versus.

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO METHOTREXATE?

Apremilast vs. Methotrexate	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	$311,622 per QALY					

CE = cost-effectiveness; NA = not applicable; PC = palliative care; QALY = quality-adjusted life-year; vs. = versus.

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO CYCLOSPORINE?

Apremilast vs. Cyclosporine	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	$94,472 per QALY					

CE = cost-effectiveness; NA = not applicable; PC = palliative care; QALY = quality-adjusted life-year; vs. = versus.

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO ETANERCEPT, ADALIMUMAB, USTEKINUMAB, AND INFLIXIMAB?

	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	$169,137 per QALY (vs. etanercept) $139,412 per QALY (vs. adalimumab) $148,278 per QALY (vs. ustekinumab) $249,992 per QALY (vs. infliximab)					

CE = cost-effectiveness; NA = not applicable; PC = palliative care; QALY = quality-adjusted life-year; vs. = versus.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 11: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 12: AUTHOR INFORMATION

Authors	Affiliations
Sandrine Cure, MSc Hélène Cawston, MSc	OptumInsight

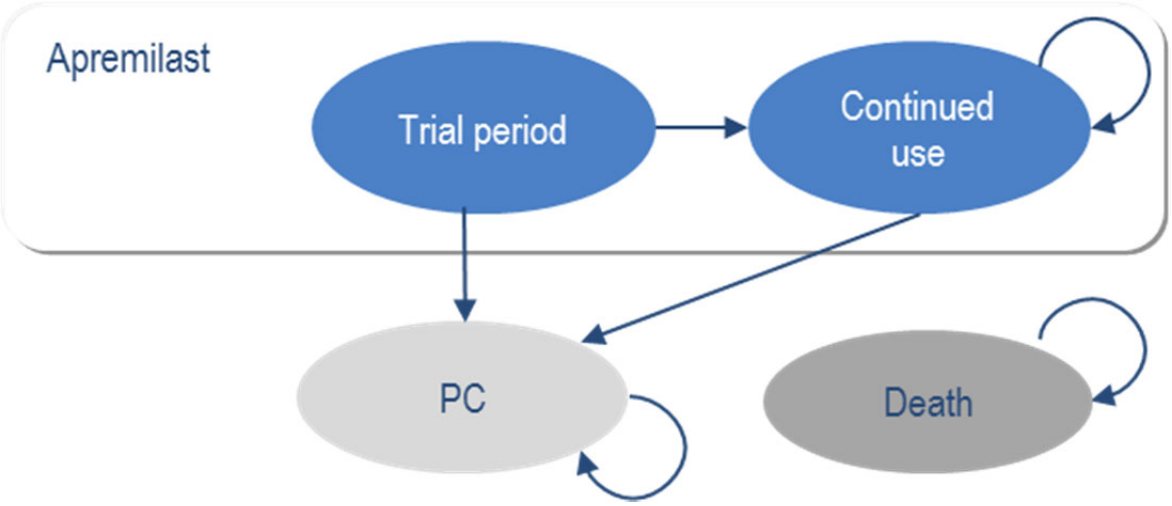
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis		X	

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis (CUA) using a Markov state-transition model comparing apremilast, systemic therapies (methotrexate, cyclosporine, and biologics (etanercept, adalimumab, ustekinumab, infliximab) to palliative care to assess their cost-effectiveness among patients with moderate to severe plaque psoriasis (PSO) (defined as Psoriasis Area and Severity Index (PASI) ≥ 12, body surface area (BSA) ≥ 10% and static Physician Global Assessment (sPGA) score ≥ 3) who are candidates for phototherapy or systemic therapy.[2] The manufacturer's model is based on the widely used York model of PSO developed by Woolacott et al.[4] Among patients receiving one of the active interventions, treatment response was assessed after a variable trial period (10 weeks for infliximab, 12 weeks for etanercept, and 16 weeks for apremilast, adalimumab, ustekinumab, and methotrexate) using achievement of PASI 75 as the response criterion. After the trial period, a two-state Markov model is used to follow patients through the rest of the study period, consisting of a "continued treatment" state and a "palliative care" state (Figure 1 shows the model structure for patients receiving active treatment using apremilast as an example). Responders enter and remain in the continued treatment state until they withdraw (it was not specified whether this was due to loss of treatment response, discontinuation due to side effects, or both). Non-responders and patients who withdraw from the continued treatment state move to the palliative care state in which patients receive palliative care (defined as six doctor's visits per year with no active treatment). Among patients on cyclosporine, it is assumed that all patients remain on treatment for six months, at which point they enter the palliative care state. The manufacturer assumed that this was the case due to cyclosporine's cumulative toxicity. Incremental cost-utility ratios (ICURs) for all treatments are calculated relative to a palliative care–alone strategy. A 10-year horizon and public health care payer perspective were used.

FIGURE 1: MODEL STRUCTURE FOR PATIENTS RECEIVING ACTIVE TREATMENT



PC = palliative care.
Source: Manufacturer's pharmacoeconomic submission[2]

The proportion of responders for each treatment was assessed by a manufacturer-commissioned network meta-analysis (NMA). The probability of PASI 75 and PASI 90 response relative to placebo were calculated for all treatments (Table 7). There was no attempt to compare any of the active comparators, just each comparator to placebo. A total of 29 studies were assessed, including the pivotal phase 3 double-blind randomized controlled trials (RCTs) for apremilast (ESTEEM-1 and ESTEEM-2) (detailed description in CDR Otezla Clinical Report, Appendix 7). Among responders, withdrawal to palliative care was assumed to be 20% annually. This value was justified by noting that it is the most common figure encountered in recent pharmacoeconomic evaluations of psoriasis drugs. There was no indication of whether withdrawal was due to loss of treatment effectiveness, onset of side effects, or both. Patients who withdrew to palliative care returned to baseline utility. Among patients receiving palliative care alone, it was assumed that utility remained at its baseline value throughout the study period.

TABLE 13: EFFECTIVENESS VALUES FROM MANUFACTURER'S NETWORK META-ANALYSIS

	Probability of PASI 75 (SD)	Probability of PASI 90 (SD)
Placebo	[redacted]	[redacted]
Apremilast 30 mg BID	[redacted]	[redacted]
Methotrexate 10 to 25 mg every week	[redacted]	[redacted]
Cyclosporine 1.5 to 5 mg/kg/day	[redacted]	[redacted]
Etanercept 50 mg twice weekly for 3 months, then 50 mg weekly	[redacted]	[redacted]
Adalimumab 40 mg EOW with 80 mg loading	[redacted]	[redacted]
Ustekinumab 45 mg at wks 0, 4, and Q12W	[redacted]	[redacted]
Ustekinumab 90 mg at wks 0, 4, and Q12W	[redacted]	[redacted]
Infliximab 5 mg/kg at wks 0, 2, 6, then every 8 weeks	[redacted]	[redacted]

BID = twice daily; EOW = every other week; PASI = Psoriasis Area and Severity Index; Q12W = every 12 weeks; SD = standard deviation; wks = weeks.

The utilities associated with treatment were based on the proportion of patients in different PASI response categories (i.e., 75 to 90, 90 or greater) and change in utility from baseline associated with different PASI responses. The utility gain associated with PASI response was taken from Woolacott et al.'s study. Woolacott et al. used a two-stage process. Firstly, PASI responses were mapped to changes in DLQI scores according to values from the etanercept trials in Woolacott et al.'s systematic review. Secondly, values from patients in the Health Outcomes Database Repository (HoDAR) database who had completed both DLQI and EQ-5D were used to undertake an ordinary least squares linear regression to map DLQI scores to changes in EQ-5D utilities. Baseline utility was 0.7 as per Revicki et al.'s study.[10] For patients in palliative care, it was assumed that baseline utility was maintained over the entire period. For patients who withdrew from treatment to palliative care, it was assumed that utilities returned for the remainder of the study period. A disutility multiplier of 0.97 was applied to patients on methotrexate or cyclosporine to account for possible side effects and toxicity. This value was obtained from a study of methotrexate and cyclosporine in rheumatoid arthritis. For cyclosporine, it was assumed that of the six months on treatment, benefits only accrued for months 4 to 6. The manufacturer did not justify this assumption. No considerations for the potential side effects for other comparators were included.

TABLE 14: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy (probability of PASI 50/PASI 75/PASI 90 for each treatment relative to palliative care)	The efficacy of apremilast in PSO was established in two phase 3, pivotal, double-blind, placebo-controlled RCTs — ESTEEM-1 and ESTEEM-2. The manufacturer commissioned an NMA to determine efficacy inputs to the economic model for all relevant comparators (systemic therapy [CYC, MTX] and biologics [ETN, ADA, UST, IFX]).	The methodology was transparent, reasonable inclusion/exclusion criteria were used, and recommended doses of medications were assessed, but no active comparison studies were included. A high percentage of studies of poor quality — 30%. The population of interest was not analyzed (i.e., those who had failed systemic therapy).
Baseline cohort characteristics	The baseline patient characteristics were obtained from ESTEEM-1 and ESTEEM-2 trials (46 years old and weighed 93 kg). Literature values were used to estimate baseline utility at 0.7[10]	Baseline patient characteristics deemed appropriate by clinical expert. Varying baseline utility made no difference.
Utilities	The utility gain associated with PASI response was taken from Woolacott et al.'s study.[4]	Results are sensitive to utility gains associated with PASI scores. Alternate values were considered in CDR reanalysis.
Mortality	Background mortality made use of age-specific Canadian mortality figures.	Appropriate.
Resource use	Drug acquisition costs, costs of monitoring, and follow-up. Largely based on expert opinion.	
Adverse events	Adverse events were not considered.	The manufacturer's NMA did not consider safety outcomes.
Discontinuation rates, disutility multipliers	Annual withdrawal probabilities for apremilast and biologics were based on assumptions and published economic evaluations. Withdrawal rates for methotrexate were assumed to be higher based on a retrospective study[17] and claims data. Disutility associated with MTX and CYC were based on a rheumatoid arthritis study.[18]	No evidence to suggest that the discontinuation rate for MTX differs from that of apremilast. Disutility multiplier was not assessed in the disease area of interest.
Costs		
Drugs	• Apremilast — manufacturer's confidential submitted price • Comparators — from the Ontario Drug Benefit Formulary (2014)	

Data Input	Description of Data Source	Comment
Administration	• Costs of injections were not considered separately, but were included in administration fee of injections themselves • Frequency of administration from expert opinion • Cost of administration from Ontario Schedule of Benefits (2013) • Cost of lab tests from Ontario 1999	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.

ADA = adalimumab; CDR = CADTH Common Drug Review; CYC = cyclosporine; ETN = etanercept; IFX = infliximab; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PC = palliative care; PSO = plaque psoriasis; UST = ustekinumab.

TABLE 15: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Monotherapy followed by PC	While this reflects a minority of cases,[12] there are no data available to assess more ecologically valid scenarios.
CYC is used for 6 months of treatment with only 3 months of benefits	Inappropriate; reanalyzed by CDR. Clinical expert confirmed that treatment may continue up to 2 years.
For analysis of treatment sequences (see Appendix 5), that response to biologic is the same regardless of drug positioning	May not be appropriate. A recent study by Mauskopf et al.[19] notes both a paucity of data on this point and the potential for effects of drug placement in the sequence, as well as the structure of the sequence.
A set of assumptions around PASI to utility mappings: • correlation of PASI and DLQI scores • linear relationship between DLQI scores and EQ-5D utilities • values can be generalized to Canadian context.	These assumptions may be inappropriate but there is a lack of better sources. • Regarding PASI/DLQI correlation, studies differ on how well they correlate.[5,6,20] • Regarding linearity of the DLQI and EQ-5D, in different disease areas, non-linear mappings have been employed to derive utilities from disease-specific measures.[21] Furthermore, correlation between DLQI and EQ-5D has been found to be poor.[7] • While it would have been optimal to have Canadian values for apremilast, the initial PASI/DLQI values were primarily from US studies of ETN and the DLQI/EQ-5D mapping made use of values from the UK. There have been concerns noted about the appropriateness of using UK and US EQ-5D values in Canadian contexts.[22]
Cohort is 46 years old and weighs 93 kg	Appropriate. Confirmed appropriateness with clinical expert.
Adverse events are not considered	Has precedent in other models, which note that biologics don't produce enough adverse events of note to warrant modelling them. Unknown how appropriate.
Baseline utilities hold across analysis horizon	Has precedent in other models; unknown how appropriate it is.
PC/BSC has same utility as baseline	The clinical expert noted it may not be the case but there are insufficient data to model alternatively.

Assumption	Comment
Assume return to baseline after treatment withdrawal	There may be protracted remission (e.g., some cycles without medication but with PASI response), but in the absence of information, this is a conservative assumption.
Schedule of follow-up and monitoring	The CDR clinical expert noted that different follow-up and monitoring schedules are possible, although this made little impact on resulting ICURs.
20% annual discontinuation rate: • A higher annual dropout rate for MTX was assumed (25.4%) due to toxicity, justified with reference to a study that found the same and Canadian Claims data • 100% of patients on CYC adhere to treatment for 6 months followed by PC	Unclear. Has precedent in other studies[4,15,16] and was deemed appropriate by CDR clinical expert. • Assumptions for CYC not appropriate, and tested by CDR.
No mortality attributable to psoriasis or drugs specifically, considered only age-specific Canadian background mortality rates	Appropriate.
Response to apremilast is same in treatment naive and treatment experience	Unclear how appropriate this is. There is a lack of data on the population for the requested listing.
Discontinuation rate of MTX higher than other comparators	There is insufficient evidence to suggest that MTX discontinuation rates are higher than those of apremilast.
There is additional disutility associated with MTX and CYC	The disutility multiplier is questionable as it originates from a rheumatoid arthritis trial.

BSC = best supportive care; CDR = CADTH Common Drug Review; CYC = cyclosporine; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions Questionnaire; ETN = etanercept; ICURs = incremental cost-utility ratios; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PC = palliative care; PSO = plaque psoriasis; UST = ustekinumab.

Manufacturer's Results

The manufacturer's base case found apremilast to have an ICUR of $97,607 per QALY compared with palliative care (Table 16).

TABLE 16: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

Interventions	Total Costs ($)	Total QALYs	Incremental Costs ($)	Incremental QALYs	ICUR ($) vs. PC
Palliative care	2,405	5.62	–	–	–
Methotrexate	3,462	5.76	1,056	0.15	7,262
Cyclosporine	5,154	5.64	2,748	0.02	118,416
Apremilast	22,159	5.82	19,753	0.20	97,607
Etanercept	55,986	6.02	53,581	0.40	134,325
Adalimumab	57,012	6.07	54,607	0.45	121,067
Ustekinumab	69,608	6.14	67,203	0.52	128,064
Infliximab	117,156	6.20	114,750	0.58	197,337

ICUR = incremental cost-utility ratio; PC = palliative care; QALYs: quality-adjusted life-years; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission.

TABLE 17: CADTH COMMON DRUG REVIEW REANALYSIS

The following scenarios were explored by CADTH to assess limitations identified:

Analysis	Scenario	Results
Cyclosporine	Allowed benefits to accrue from the beginning, used a 12-week trial period, allowed treatment to continue to 1 year or 2 years, at which time treatment was discontinued.	CYC was associated with an ICUR of $37,000 to $40,000 per QALY compared with PC, which is less than apremilast vs. PC ($97,607). However, both remain extendedly dominated by MTX and ADA.
Methotrexate	Assumed same annual withdrawal rates as apremilast and excluded the disutility multiplier.	Apremilast was dominated by MTX.
Utility mappings	Using alternate sources for utility mappings (from Anis, Knight, and Pan).	ICUR for apremilast vs. PC varied from $80,000 to $126,000 per QALY; however, this did not affect the rank order of treatments.
Inclusion of SEB IFX pricing	Considering the cost of SEB IFX (Inflectra): $650 (vs. $987) per 100 mg vial.	ICUR for IFX (SEB) vs. PC was reduced to $129,917 (from $197,337). Only MTX and SEB IFX would be cost-effective options.

ADA = adalimumab; CYC = cyclosporine; ICUR = incremental cost-utility ratio; IFX = infliximab; MTX = methotrexate; PC = palliative care; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; vs. = versus.

In addition, CADTH conducted price reduction analyses for apremilast to determine what reduction would be required such that apremilast would not be ruled out by extended dominance. A more than 40% reduction would be required.

Further price reduction scenarios comparing apremilast to palliative care, methotrexate, and cyclosporine (under CADTH reanalysis scenarios) were undertaken (
Table 18). In the manufacturer's base case, a 50% reduction would be required for apremilast to achieve an ICUR of less than $50,000 compared with palliative care, or an 80% price reduction compared with methotrexate. When considering longer treatment durations with cyclosporine, a 60% price reduction would be required.

TABLE 18: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

Price of Apremilast	ICUR Compared With PC	Compared to MTX	Compared With CYC — 1 Year	Compared With CYC — 2 Years
Submitted ($18.90/tablet)	97,607	311,622	150,627	285,816
10% reduction ($17.01/tablet)	87,823	278,622	132,627	246,215
20% reduction ($15.12/tablet)	78,039	245,621	114,627	206,615
30% reduction ($13.23/tablet)	68,255	212,621	96,626	167,014
40% reduction ($11.34/tablet)	58,472	179,620	78,626	127,413
50% reduction ($9.45/tablet)	48,688	146,620	60,626	87,813
60% reduction ($7.56/tablet)	38,904	113,619	42,626	48,212
70% reduction ($5.67/tablet)	29,120	80,619	24,625	8,612
80% reduction ($3.78/tablet)	19,336	47,618	6,625	Apremilast dominates
90% reduction ($1.89/tablet)	9,552	14,618	Apremilast dominates	Apremilast dominates

CYC = cyclosporine; ICUR = incremental cost-utility ratio; MTX = methotrexate; PC = palliative care.

APPENDIX 5: MANUFACTURER'S COST-UTILITY ANALYSIS COMPARING TREATMENT SEQUENCES

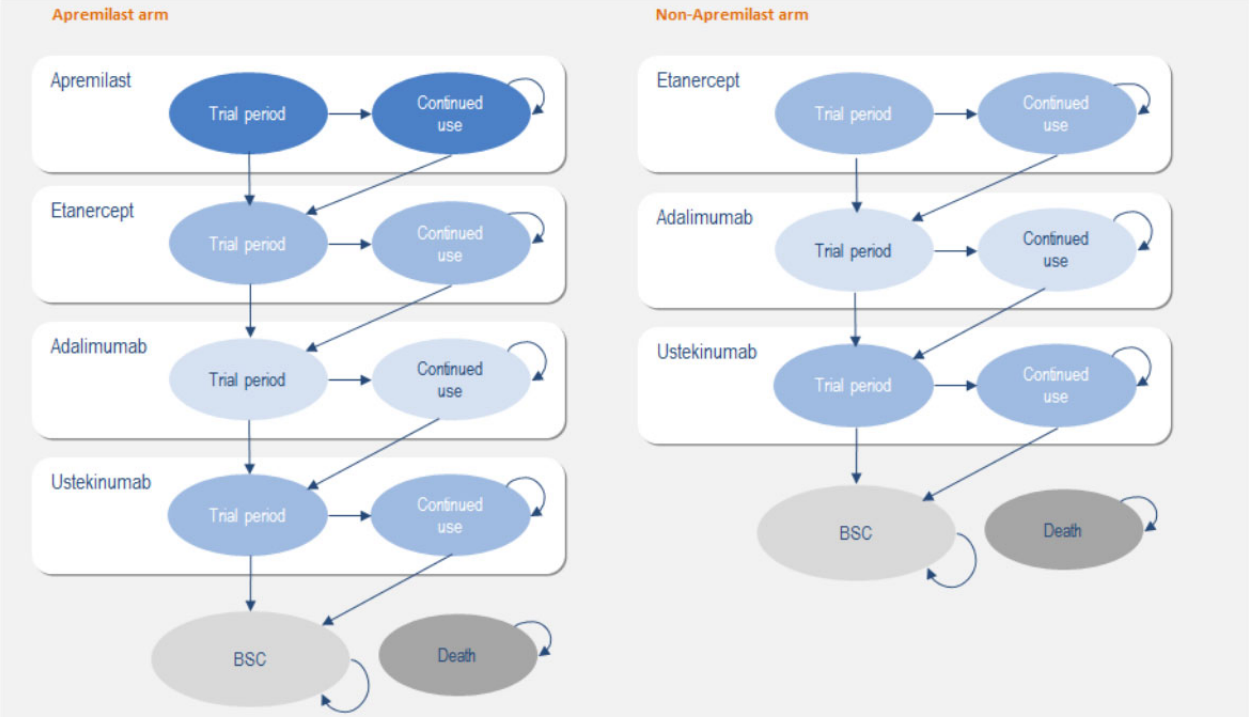
Summary

The manufacturer submitted a second cost-utility analysis (CUA) that compared a treatment sequence with apremilast to a comparator sequence without apremilast in patients with plaque psoriasis (PSO), who had an inadequate response, were contraindicated, or intolerant of systemic therapies. This population reflects the manufacturer's requested listing criteria. Patients entered the model receiving either the apremilast or non-apremilast group (Figure 2). In the apremilast group, patients began on apremilast and proceeded to etanercept, adalimumab, ustekinumab, and finally best supportive care (BSC). In the non-apremilast group, patients underwent the same sequence of biologics and BSC without initial apremilast. The objective was to assess whether — among PSO patients who have failed or are unable to undergo systemic therapy or phototherapy — the use of apremilast prior to biologics is cost-effective compared with using biologics alone. The analysis was undertaken from the Canadian public payer perspective and used a horizon of 10 years.

The model was an adaptation of Woolacott et al.'s York model. Patient response was assessed after a trial period at which point patients either entered the continued use state (where they remained until withdrawal) or moved to the trial period of the next drug in the sequence, where response was again assessed (Figure 2). Transition probabilities were derived from the network meta-analysis (NMA) that informed the first analysis. Notably, there was an assumption that effectiveness did not depend on drug positioning. Withdrawal probabilities were as the same as in the first analysis, as were assumptions regarding schedules of monitoring and follow-up for those on active treatment.

The costs and utilities of BSC were a weighted average of individual palliative strategies proposed by the manufacturer's clinical expert, comprising methotrexate (either alone, with a biologic, or phototherapy) or Acitretin plus phototherapy.

FIGURE 2: MODEL STRUCTURE FOR MODEL OF TREATMENT SEQUENCES



BSC = best supportive care.

Source: Manufacturer's pharmacoeconomic submission[2]

Results

In the base-case analysis, the apremilast group was dominant, producing more quality-adjusted life-years (QALYs) and costing less than the non-apremilast group (QALYs – 6.76 and 6.69, respectively; costs – $149,293 and $151,681, respectively). As assessed by sensitivity analysis, the main drivers of cost were costs of BSC, Psoriasis Area and Severity Index (PASI) to utility mappings, and number of biologics in the sequence. These drive the apremilast group from dominant to having an incremental cost-utility ratio (ICUR) (i.e., costs more and produces more QALYs).

Limitations

- No information to support the assumption that drug efficacy is independent of placement in the sequence. Mauskopf et al.'s recent systematic review[19] notes that results of such sequence comparisons may be sensitive to assumptions regarding treatment sequencing, and the choice and efficacy of biologics. Changes in the number, placement, and efficacy of drugs in the manufacturer's analysis are associated with changing the apremilast group from being dominant to being both more costly and effective than biologics alone.
- Among the potential palliative strategies considered under BSC is inclusion of a biologic. It is unclear that this would constitute BSC in actual practice. BSC has baseline utility while incorporating several active treatments. The inclusion of a biologic serves to inflate the price of BSC while accruing no benefits above baseline. Sensitivity analyses where the price of BSC is reduced render the apremilast group no longer dominant.

- Patients who fail systemic therapy comprise the population referred to in the manufacturer's listing request. However, there were no data included in the original submission indicating the apremilast response is the same in this population and the general PSO population assessed in the manufacturer's pivotal phase 3 trials (ESTEEM-1 and ESTEEM-2) or in the manufacturer's first analysis.

While the manufacturer provided subgroup data for a systemic failure population in its opportunity to comment, there are concerns regarding the uncertainty of this post-hoc subgroup analysis. For these reasons, the CADTH Common Drug Review (CDR) Pharmacoeconomic review focused on the appraisal of the CUA assessing individual treatments.

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