Common Drug Review
Pharmacoeconomic Review Report

December 2015

Drug	Apremilast (Otezla)
Indication	For use alone, or in combination with methotrexate, for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response, intolerance, or contraindication to a prior DMARD.
Listing request	As per indication
Dosage form(s)	10 mg, 20 mg, and 30 mg tablets for oral administration
NOC date	10 June 2015
Manufacturer	Celgene Inc.

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
BSC	best supportive care
CDR	CADTH Common Drug Review
DMARD	disease-modifying anti-rheumatic drug
EQ-5D	EuroQol 5-Dimensions Questionnaire
GOL	golimumab
HAQ-DI	Health Assessment Questionnaire–Disability Index
MCID	minimal clinically important difference
MTX	methotrexate
NMA	network meta-analysis
PASI	Psoriasis Area Severity Index
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
SC	subcutaneous
SEB	subsequent entry biologic
SMR	standardized mortality ratio

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	**Apremilast (Otezla)**
Study Question	"From the perspective of the publicly funded health care system, what is the cost-effectiveness and efficiency of apremilast for the treatment of adult patients with active PsA who are unresponsive, or intolerant or contraindicated to a DMARD, when compared to the conventional therapies?"
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with active PsA who have not responded to previous DMARD therapy.
Treatment	Apremilast 30 mg twice daily, following a one-week titration schedule
Outcome	QALYs
Comparator(s)	BSC (defined as use of conventional DMARDs: methotrexate, leflunomide or sulfasalazine) Certolizumab pegol SC 400 mg at weeks 0, 2, and 4, and then 200 mg every other week Adalimumab SC 40 mg every other week Etanercept SC 50 mg weekly Infliximab 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 Golimumab SC 50 mg monthly Ustekinumab SC 45 mg at weeks 0 and 4, and then every 12 weeks
Perspective	Canadian public payer
Time Horizon	40 years
Results for Base Case	• Compared with BSC, apremilast had an ICUR of $40,572 per QALY. • Based on sequential analysis, apremilast is associated with the lowest ICUR versus BSC, followed by golimumab ($50,630 per QALY versus apremilast) and SEB-infliximab ($150,378 per QALY versus golimumab). All other agents were either dominated[a] or extendedly dominated.[b]
Key Limitations	• Comparative efficacy of apremilast was based on an NMA that had several limitations. As such, the comparative efficacy of apremilast with BSC and biologics is uncertain • Uncertain assumptions regarding disease progression and quality of life (HAQ-DI score) upon treatment discontinuation • Overestimation of BSC costs and underestimation of total costs of apremilast treatment • Uncertain assumption regarding long-term maintenance of apremilast treatment effect • Use of differential treatment trial periods across agents (ranging from 12 to 16 weeks), which may have overestimated the cost-effectiveness value of apremilast
CDR Estimate(s)	• Considering alternative assumptions for quality of life upon treatment discontinuation and corrected treatment costs, the CDR base case, with a 40-year time horizon, resulted in apremilast being extendedly dominated by BSC and golimumab, with an ICUR of $63,071 per QALY compared with BSC. Under this scenario, a price reduction for apremilast of 5% per pill was necessary to bring apremilast onto the cost-effectiveness frontier and make it the most cost-effective option with an ICUR of $59,839 per QALY versus BSC (for reference, golimumab, the second most cost-

Drug Product	Apremilast (Otezla)
	effective option in this case, was $61,944 vs. BSC and had a sequential ICUR of $63,720 compared to apremilast with a 5% price reduction). • Using the CDR base case with a shortened time horizon of 10 years to account for uncertain long-term efficacy resulted in an ICUR of $81,572 for apremilast compared with BSC, with apremilast remaining extendedly dominated by BSC and golimumab. Under this scenario, a price reduction for apremilast of 10% per pill was necessary to bring apremilast onto the cost-effectiveness frontier and make it the most cost-effective option with an ICUR of $73,218 per QALY versus BSC (for reference, golimumab, the second most cost-effective option in this case, was $74,736 vs. BSC and had a sequential ICUR of $75,876 compared with apremilast with a 10% price reduction). • The manufacturer reported that the ICUR for apremilast vs. BSC was lower than that for golimumab, based on the list price of golimumab. Where price reductions of > 10% have been negotiated for golimumab, apremilast would be ruled out through extended dominance by BSC and golimumab.

BSC = best supportive care; CDR = CADTH Common Drug Review; DMARD = disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; ICUR = incremental cost-utility ratio; IV = intravenous; PsA = psoriatic arthritis; QALY = quality-adjusted life-year; SC = subcutaneous; SEB = subsequent entry biologic; vs. = versus.

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

[b] 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.

EXECUTIVE SUMMARY

Background

Apremilast (Otezla) is an oral phosphodiesterase-4 inhibitor approved for the treatment of psoriatic arthritis (PsA) in adult patients who have an inadequate response or intolerance to a disease-modifying anti-rheumatic drug (DMARD). The manufacturer is requesting listing of apremilast as per the indication.[1] The recommended dose of apremilast is 30 mg twice daily, following a one-week titration schedule. Apremilast is available in 10 mg, 20 mg, and 30 mg tablets, at a confidential price of [redacted] per tablet ([redacted] daily once titration completed).[2]

The CADTH Common Drug Review (CDR) previously reviewed apremilast for use in plaque psoriasis. 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 manufacturer submitted a cost-utility analysis comparing apremilast against best supportive care (BSC, defined as use of a conventional DMARD: methotrexate [MTX], leflunomide, or sulfasalazine) and biologics (etanercept, adalimumab, ustekinumab, infliximab, subsequent entry biologic [SEB] infliximab, golimumab SC, and certolizumab pegol) in the treatment of patients with active PsA who have previously failed, are intolerant to or have a contraindication to a conventional DMARD.[4] Patients on active treatment were assessed for achievement of Psoriatic Arthritis Response Criteria (PsARC) response after a treatment trial period ranging from 12 to 16 weeks. A PsARC response is defined as showing improvement in at least two of the following four measures: patient-self assessment, physician assessment, joint pain/tenderness score, and a joint swelling score, one of which is the joint pain/tenderness score or joint swelling score, with no worsening in any of these four measures. Responders were assumed to continue treatment until withdrawing to BSC (16.5% annual withdrawal rate applied to apremilast and biologics), while initial non-responders moved directly to BSC. The main clinical effectiveness data for apremilast were derived from three phase 3, placebo-controlled randomized clinical trials (PALACE-1, -2, and -3).[5-7]

Efficacy inputs to the economic model were informed by a manufacturer-sponsored network meta-analysis (NMA).[8] Treatment- and response-specific changes in Health Assessment Questionnaire–isability Index (HAQ-DI) and Psoriasis Area Severity Index (PASI) — representing effects on the arthritis and psoriasis components of PsA, respectively — were used to estimate EuroQol 5-Dimensions Questionnaire (EQ-5D) utilities through a previously published linear regression mapping.[9] Patients who failed to respond to BSC were assumed to experience disease progression, as reflected by an increasing HAQ-DI score. The analysis was undertaken from the Canadian public payer perspective and used a lifetime horizon (40 years).

The manufacturer reported that apremilast had an incremental cost-utility ratio (ICUR) of $40,572 per quality-adjusted life-year (QALY) when compared with BSC, while golimumab had a sequential ICUR of $50,630 per QALY compared with apremilast, and SEB-infliximab had a sequential ICUR of $150,378 per QALY compared with golimumab. Infliximab was dominated by SEB-infliximab (i.e., less effective while costing more), adalimumab was dominated by certolizumab pegol, and etanercept was dominated by golimumab. Ustekinumab and certolizumab pegol were ruled out through extended dominance by apremilast and golimumab.

Summary of Identified Limitations and Key Results

CDR identified several limitations with the submitted economic analysis. The key limitations were the uncertain clinical efficacy of apremilast compared with BSC and biologics; uncertain assumptions regarding disease progression and quality of life (reflected by HAQ-DI score) upon treatment discontinuation; and the assumption that the efficacy of apremilast was maintained throughout the model time horizon (40 years).

A key area of uncertainty pertains to the estimates of comparative clinical efficacy of apremilast with BSC and biologic treatment options based on the manufacturer's NMA. Furthermore, the listing indication for apremilast is for use in a post-DMARD population. This place in therapy is indicated for most of the biologic comparators, or this is the way in which it is used in clinical practice. In this context, the use of a potentially more cost-effective (less costly and with lower QALY gains) treatment option such as apremilast may be questionable in clinical practice, considering a potentially clinically desirable strategy of early and aggressive treatment of PsA to optimize patient improvement in terms of joint damage and minimizing disease activity).[10]

Other limitations include miscalculation of treatment costs and a questionable use of different treatment trial periods for different comparators. CDR reanalyses used alternate assumptions for quality of life values (HAQ-DI score) upon treatment discontinuation and adjustment of treatment costs where possible. Two base cases are presented: one with the original 40-year model horizon and one with a reduced 10-year time horizon to reflect uncertainty in the maintenance of long-term treatment efficacy. Based on CDR's reanalysis, apremilast was associated with an ICUR of $63,071 per QALY when compared with BSC and was extendedly dominated by BSC and golimumab. When the model horizon was reduced to 10 years, the ICUR for apremilast versus BSC increased to $81,572 per QALY, with apremilast still being extendedly dominated by BSC and golimumab.

Conclusions

Apremilast is indicated for the treatment of PsA among a post-DMARD population of patients, similar to biologic drug options. Under the manufacturer's base case, apremilast was the most cost-effective option compared with BSC. However, CDR identified several limitations that introduce uncertainty into the manufacturer's conclusions, most notably apremilast's uncertain efficacy compared with BSC and biologics, as well as the uncertain long-term efficacy of apremilast. It should be noted that with the manufacturer base case, a price reduction of > 10% to the publically listed price for golimumab would exclude apremilast as the most cost-effective option, favouring golimumab.

Based on CDR analyses amending costs, considering more conservative assumptions regarding quality of life (HAQ-DI score) after treatment discontinuation and an alternate time horizon, apremilast has an ICUR between $63,071 (40-year time horizon) and $81,572 (10-year time horizon) per QALY compared with BSC, and is extendedly dominated by BSC and golimumab, indicating that the use of BSC or golimumab represents more cost-effective options than apremilast for the treatment of PsA. In order for apremilast to not be any more extendedly dominated, price reductions of apremilast of 5% (40-year time horizon) and 10% (10-year time horizon) per pill were necessary to make apremilast the most cost-effective option under the CDR base case. However, this cost-effective superiority of apremilast was because it was less costly and less effective than biologic options, which may lead to questions about its place in therapy versus biologics — which are more effective recommended alternatives (in terms of QALY benefit).

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis using a Markov model comparing apremilast against BSC and biologics indicated for the treatment of psoriatic arthritis (PsA) (etanercept, infliximab, subsequent entry biologic [SEB] infliximab, ustekinumab, adalimumab, subcutaneous [SC] golimumab, and certolizumab pegol) among patients with active PsA who have previously failed on a conventional disease-modifying anti-rheumatic drug (DMARD).[4] Best supportive care (BSC) was defined as use of DMARDs ([redacted]% methotrexate [MTX], [redacted]% leflunomide, and [redacted]% sulfasalazine) based on the distribution observed at baseline among DMARD-users in the placebo arm of the PALACE trials.[5-7] The model population was assumed to have baseline characteristics similar to patients in the PALACE trials, with a mean age of 50.3 years and weight of 85.46 kg. A time horizon of 40 years was assessed using model cycles 28 days in length and a publicly funded health care system perspective.

Among the interventions evaluated, treatment response was assessed after a variable treatment trial period (12 weeks for ustekinumab, certolizumab, etanercept, and adalimumab; 14 weeks for infliximab, SEB-infliximab, and golimumab; and 16 weeks for BSC and apremilast) based on Psoriatic Arthritis Response Criteria (PsARC) response (defined as showing improvement in at least two of the following four measures: patient-self assessment, physician assessment, joint pain/tenderness score, and a joint swelling score, one of which is the joint pain/tenderness score or joint swelling score, with no worsening in any of these four measures). After the treatment trial period, patients either entered the "continued use" or BSC state. Responders entered and remained in the continued use state until withdrawal due to loss of treatment efficacy or onset of adverse events. Non-responders and patients who withdrew from the continued treatment state moved to the BSC state. Patients in the BSC could either achieve PsARC response (according to the rate of response in the placebo arms of the PALACE trials) or fail to respond, in which case they experienced disease progression as reflected by an increment of their Health Assessment Questionnaire–Disability Index (HAQ-DI) score (constant increment of 0.006 per cycle, based on Rodgers et al.[9]). Among responders, withdrawal to BSC was assumed to be 16.5% annually (same for other treatment options), based on the figure derived in Rodgers et al.'s meta-analysis of withdrawal rates.[9] Patients could die at any time, according to age-specific Canadian mortality tables corrected for a PsA standardized mortality ratio (SMR) based on Canadian data of 1.36, per Ali et al.[11]

Clinical effectiveness data for apremilast were derived from three placebo-controlled randomized clinical trials (PALACE-1, -2, and -3).[5-7] Efficacy inputs to the economic model were obtained from the manufacturer's network meta-analysis (NMA). Treatment- and response-specific changes in HAQ-DI and Psoriasis Area and Severity Index (PASI) scores were associated with the continued use and BSC states based on the NMA. The utilities associated with treatment were based on changes in HAQ-DI and PASI scores, which were mapped to EuroQol 5-Dimensions Questionnaire (EQ-5D) utilities based on a linear regression used by Rodgers et al.[9] Responders experienced a decrease in HAQ-DI and PASI score. While patients remained in the continued use state, it was assumed that there was no progression in HAQ-DI scores, reflecting arrest of disease progression. Non-responders to active treatment experienced an increased HAQ-DI score equal to the initial decrement, while non-responders to BSC experienced a constant-over-time increase in HAQ-DI score.

Costs considered were for drug acquisition and monitoring and follow-up. Dosages were the recommended dosages 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).[12] Schedules of monitoring and follow-up were based on clinical expert input and consisted of doctors' visits and laboratory testing. Drug administration costs were not considered as they were not relevant for apremilast or BSC. For biologics, the infusion costs were assumed to be covered by the manufacturers. The costs of physician visits were obtained from the Ontario Health Insurance Plan (OHIP) schedule of benefits (2014),[13] while the costs of laboratory tests were obtained from the 1999 Schedule of Benefits for Laboratory Services.[14]

Costs and disutilities associated with adverse events (AEs) were not considered. The manufacturer stated that the effects of AEs on outcomes were partially accounted for by the all-cause withdrawal from active treatment to BSC. Further, it noted the lack of long-term data on AEs associated with apremilast and biologics.

2. MANUFACTURER'S BASE CASE

In its base case, the manufacturer reported that apremilast is associated with a total cost of $52,895 and 5.28 quality-adjusted life-years (QALYs) over 40 years. When compared with BSC, apremilast was $36,035 more costly and was associated with a gain of 0.89 QALYs, leading to an incremental cost-utility ratio (ICUR) of $40,572 per QALY. Sequential analysis revealed that the efficiency frontier comprised BSC, apremilast, golimumab, and SEB-infliximab with sequential ICURs of $40,572 (apremilast versus BSC), $50,630 (golimumab versus apremilast), and $150,378 (SEB-infliximab versus golimumab). All other comparators were extendedly dominated by apremilast and golimumab, apart from infliximab (Remicade), which was dominated by SEB-infliximab; adalimumab, which was dominated by certolizumab pegol; and etanercept, which was dominated by golimumab (Table 2).

TABLE 2: MANUFACTURER'S BASE CASE

Intervention	Total Costs ($)	Total QALYs	Compared with BSC			Sequential ICUR ($)
			Incremental Costs ($)	Incremental QALYs	ICUR ($)	
BSC	16,860	4.39	Reference	Reference	Reference	Reference
Apremilast	**52,895**	**5.28**	**36,035**	**0.89**	**40,572**	**40,572**
Golimumab	94,753	6.11	77,893	1.72	45,421	50,630
SEB-Infliximab	111,025	6.22	94,165	1.83	51,650	150,378
Dominated and extendedly dominated options						
Ustekinumab	77,997	5.52	61,137	1.13	54,221	Extendedly dominated by apremilast and golimumab
Adalimumab	82,138	5.65	65,278	1.26	51,875	Dominated
Certolizumab Pegol	78,557	5.76	61,697	1.37	45,201	Extendedly dominated by apremilast and golimumab
Etanercept	97,065	6.01	80,205	1.62	49,509	Dominated
Infliximab - Remicade	161,137	6.22	144,277	1.83	79,137	Dominated

BSC = best supportive care; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.
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: Adapted from manufacturer's pharmacoeconomic submission.[4]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer performed a number of deterministic sensitivity analyses, scenario analyses, and a probabilistic sensitivity analysis. Among the manufacturer's reported sensitivity analyses, varying the per-cycle HAQ-DI score progression of BSC non-responders (reflecting the rate of disease progression and quality of life deterioration) had the most notable impact on the ICUR for apremilast compared with BSC, varying from $84,341 per QALY (low rate of HAQ-DI progression) to $33,518 per QALY (high rate of HAQ-DI progression).

Other parameters that were found to substantially alter results were the following:

- Allowing quality of life (HAQ-DI score) to rebound to natural history instead of to initial gain resulted in apremilast being extendedly dominated by BSC and golimumab. The ICUR of apremilast compared with BSC becomes $66,201 per QALY.
- The use of a 10-year model horizon in place of a 40-year horizon resulted in apremilast being extendedly dominated by BSC and golimumab. The ICUR of apremilast compared with BSC becomes $73,043 per QALY.
- The use of non-linear mappings from HAQ-DI and PASI scores to EQ-5D utilities had the potential to change model results. The use of a regression equation from Abbott did not substantially change the ICUR ($40,701 per QALY compared with BSC), but the use of Schering-Plough's regression equation increased the ICUR to $69,239 per QALY. The relative rankings of ICURs remained unchanged.

The manufacturer also conducted a probabilistic sensitivity analysis using 5,000 iterations. Under the manufacturer's base case, apremilast had a 0.99 probability of being cost-effective versus BSC at a willingness-to-pay threshold of $43,000.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Uncertain comparative effectiveness of apremilast with BSC and biologics: The efficacy of the model's compared arms was based on the manufacturer's NMA, which is associated with non-negligible limitations undermining the certainty of its assessment of the comparative efficacy of treatment options (refer to Clinical Report) and associated cost-effectiveness results and conclusions. The placebo arms of the clinical trials included in the NMA (representing the BSC arm of the model) included patients with baseline DMARD use ranging from 21% to 79%,[8] a feature that may have biased the efficacy results used for the BSC arm of the model. From a costing point of view, 100% of BSC patients in the model incurred the costs of DMARD therapy, but only 65% of placebo patients had baseline DMARD use in the pooled PALACE-1, -2, and -3 trials.[5-7] As a result, the cost of BSC was artificially inflated. Finally, while the average dose of concurrent methotrexate (MTX) was 15 mg weekly in all three PALACE trials, the model included the costs for 20 mg MTX use in the BSC arm. The costs of BSC were adjusted in the reanalyses by the CADTH Common Drug Review (CDR) to reflect 65% DMARD use in the placebo arms of the PALACE trials and the costs of 15 mg MTX in BSC patients were used in place of 20 mg.

Uncertain assumptions regarding disease progression and quality of life: The model assumed that quality of life (HAQ-DI score) would rebound to a baseline once patients withdrew from treatment. Limited information exists to inform how patients will progress once treatment is discontinued.[9] CDR considered the manufacturer's alternative scenario analysis — in which patients entering the BSC health state were directly assigned a HAQ-DI score that would have been expected if they had never received any treatment — to be more conservative.

Miscalculation of treatment costs: While half of apremilast patients in the PALACE-1, -2, and -3 trials had baseline MTX use (range 49.7% to 56.2%)[5-7] and the product monograph indicates that apremilast may be used with concurrent MTX,[2] the costs of concurrent MTX and associated additional monitoring costs were not considered. CDR attempted to rectify this, but found the model resistant to changing treatment costs appropriately for all comparators; thus, costs of concurrent MTX and appropriate monitoring in the apremilast and biologics arms were excluded from CDR's base case. These costs were found to have a negligible influence on the ICUR of apremilast relative to BSC, changing the ICUR from $63,071 to $64,655 and from $81,572 to $83,633 for a 40- and 10-year horizon, respectively. Further, inclusion of these costs did not appear to change the relative rankings of ICURs. Finally, the manufacturer included pharmacy markup and dispensing fees. CDR removed the markup but found the model resistant to changes in dispensing fees.

Note that the manufacturer provided an updated economic model outside of the CDR process, which allowed for better control of cost variables. Use of the updated model and testing the variation of additional cost components did not change the conclusions of CDR's analyses.

Uncertain long-term efficacy profile: The submitted model projected the analysis to a 40-year time horizon and assumed maintenance of treatment effect over time. However, the available evidence of efficacy is limited to 24 weeks of double-blinded duration (with early escape possible at 16 weeks). Furthermore, the assumption of lifetime BSC after failure of a single therapy does not reflect clinical

practice, according to CDR's clinical expert, as patients are likely to be switched to another biologic after failure of an initial one. CDR addressed these concerns by considering a time horizon of 10 years in addition to the original 40-year horizon.

Different treatment trial periods: CDR had concerns about the use of differential treatment trial periods for apremilast (16 weeks) and biologics (12 to 14 weeks) and the possible effects of this on estimates of clinical efficacy and subsequent cost-effectiveness. It is unknown whether the use of a longer trial period for biologics would result in an increase in observed response rate for biologics. Because neither 12-week response rates for apremilast nor 16-week response rates for biologics were available, CDR was unable to assess this limitation.

Use of mapped utility values instead of directly measured EQ-5D utilities: The manufacturer used a regression based on Rodgers et al. to inform EQ-5D utilities in the model. However, EQ-5D utilities were also directly recorded in the PALACE trials, where there were inconsistent results regarding differences between apremilast and placebo. There is uncertainty on the EQ-5D utilities benefit. Given that the EQ-5D has been shown to be responsive and valid in PsA,[15] any mapped utility differences from placebo must be interpreted with caution.

Note that the manufacturer provided an updated economic model outside of the CDR process, which allowed use of the directly measured EQ-5D utilities. Analyses by CDR found that use of these utilities would not result in any changes to its conclusions. However, it is worth noting that use of directly measured values raises the ICUR estimate of apremilast relative to BSC by more than $10,000 for the CDR base case.

4. CADTH COMMON DRUG REVIEW ANALYSES

To account for the limitations identified above, CDR undertook several analyses. Note that all reanalyses used the updated list price for etanercept (from $390.74 to $395.39 per 50 mg dose), as presented in Table 4. Analyses are presented for both a 40-year horizon and a 10-year horizon, to account for uncertainty concerning the long-term efficacy profile of apremilast.

4.1 Corrected Costs

Costs in the BSC arm were set at 65% of the original drug costs in the model to account for efficacy based on 65% baseline DMARD use in the PALACE trials. The costs of MTX were changed from a 20 mg dose to a 15 mg dose in accordance with the average dose in the PALACE trials. Note that the ICUR for apremilast compared with BSC decreased due to removal of the 8% pharmacy markup, resulting in decreased relative costs for the apremilast treatment.

4.2 HAQ-DI Rebound in Patients Withdrawing From Active Treatment

Patients who withdrew from active treatment to BSC (with subsequent non-response to BSC) were assumed to have a HAQ-DI score that rebounded to natural history (i.e., what the HAQ-DI score would have been in the absence of any treatment). This approach is consistent with CDR's analysis of ustekinumab for PsA.[16]

a) CADTH Common Drug Review Base Case

CDR's base case consisted of revised HAQ-DI rebound assumptions and correction of costs, finding that apremilast had ICURs of $63,071 and $81,572 compared with BSC when considering a 40- and 10-year time horizon, respectively. In both cases, apremilast was extendedly dominated by BSC and golimumab (Table 3).

TABLE 3: CADTH COMMON DRUG REVIEW BASE CASE

Scenario		40-Year Horizon		10-Year Horizon	
		ICUR ($ per QALY) for apremilast vs. BSC	Comparison with other treatments	ICUR ($ per QALY) for apremilast vs. BSC	Comparison with other treatments
	Manufacturer's base case	$40,572	$40,572 vs. BSC	$73,043	Extendedly dominated by BSC and GOL
1	Costs corrected	$38,654	$38,654 vs. BSC	$69,589	Extendedly dominated by BSC and GOL
2	HAQ-DI rebound to natural history	$66,201	Extendedly dominated by BSC and GOL.	$85,621	Extendedly dominated by BSC and GOL
1-2	**CDR base case**	**$63,071**	**Extendedly dominated by BSC and GOL.**	**$81,572**	Extendedly dominated by BSC and GOL

BSC = best supportive care; CDR = CADTH Common Drug Review; GOL = golimumab; HAQ-DI = Health Assessment Questionnaire–Disability Index; ICUR = incremental cost-utility ratio; vs. = versus.

4.3 CADTH Common Drug Review Scenario Analyses

4.3.1 Price Reduction Analysis — Golimumab

Under the manufacturer's base case, apremilast is a more cost-effective option than golimumab, as it has a lower ICUR when compared with BSC. However, this assumes that the list price of golimumab represents the price actually paid by drug plans and does not represent existing Product Listing Agreements. CDR found that price reductions of > 10% for golimumab resulted in apremilast being extendedly dominated by BSC and golimumab (Table 24).

4.3.2 Price Reduction Analysis — Apremilast

Under CDR's base case, apremilast is extendedly dominated by BSC and golimumab. CDR undertook price reduction analyses on the submitted price of apremilast, finding that reductions of 5% and 10% per pill were necessary to bring apremilast onto the cost-effectiveness frontier for 40- and 10-year horizons, respectively (and to make apremilast the most cost-effective option):

- 40-year horizon, 5% reduction in price of apremilast ICUR of $59,839 per QALY (versus $63,071 originally — for reference, golimumab, the second most cost-effective option in this context, is $61,944 versus BSC and has a sequential ICUR of $63,720 compared with apremilast at a 5% price reduction).
- 10-year horizon, 10% reduction in price of apremilast ICUR of $73,218 per QALY (versus $81,572 originally — for reference, golimumab, the second most cost-effective option in this context, is $74,736 versus BSC and has a sequential ICUR of $75,876 compared with apremilast at a 10% price reduction).

5. ISSUES FOR CONSIDERATION

5.1 Unclear place in therapy

The listing indication for apremilast is for use as a post-DMARD treatment, similar to biologics. However, based on the results of the manufacturer's cost-utility base case, apremilast is less effective (in terms of QALYs) and less costly than biologic drugs. Further, it has been noted that early, aggressive treatment of PsA may lead to improved patient outcomes in terms of joint damage and minimizing disease activity.[10] As such, the benefit of offering a less efficacious option prior to biologics is unclear. The clinical expert noted that apremilast may represent a useful option for patients with concerns regarding immunosuppression, intolerance to biologics, and aversion to needles. Outside of these subgroups, it is unclear who would benefit from using apremilast in place of biologics, given its lower relative efficacy versus biologics in terms of QALY gained.

5.2 Assumptions regarding infliximab dosing and average patient body weight

One of the three CDR-participating drug plans that reimburse infliximab for PsA (British Columbia Pharmacare Formulary)[17] indicates that lower doses of infliximab may be used (3 mg/kg). If patients incur the cost of 3 mg/kg infliximab, then BSC and SEB-infliximab extendedly dominate all other options regardless of horizon in both the manufacturer's and CDR's base case. This analysis is exploratory, as it assumes that the efficacy of 3 mg/kg infliximab is the same as that of 5 mg/kg infliximab (there is, however, evidence that the two dosing regimens are similarly effective in PsA; e.g., Glintborg et al.[18]).

Considering that many of the manufacturer's assumptions were based on the Rodgers et al. study,[9] it may have been appropriate to consider a body weight of 70 kg, as considered in Rodgers et al. If the average patient weight is 70 kg, then BSC and SEB-infliximab extendedly dominate all other options, regardless of horizon in CDR's base case and under a 10-year horizon for the manufacturer's base case.

5.3 Dactylitis and enthesitis

Dactylitis and enthesitis are hallmark features of PsA.[19] As noted in CDR's Clinical Report, it was unclear that apremilast offered any advantages compared with placebo for enthesitis and dactylitis in the PALACE trials. This is in contrast to golimumab (the next most cost-effective option in the manufacturer's base case, and the most cost-effective option in CDR's base case), which demonstrated clear efficacy on dactylitis and enthesitis end points.[20] It was further noted by the clinical expert that treatment with apremilast may not be suitable for patients with prominent dactylitis and enthesitis.

5.4 Biologic-Naive treatments

Given its indicated post-DMARD place in therapy, the biologic-naive population is a relevant subgroup. Subgroup analyses on biologic-naive patients did not reveal substantial differences in ICURs for apremilast versus BSC (reduction from $40,572 per QALY to $39,847 per QALY in the manufacturer's base case, and from $63,071 to $61,864 per QALY in CDR's base case), nor did it change the results of sequential analyses.

6. PATIENT INPUT

Input was received from the Arthritis Consumer Experts and Canadian Arthritis Patient Alliance. Patients noted that PsA symptoms have a significant impact on the activities of daily living, as well as quality of life. These were accounted for by inclusion of PsARC and PASI responses. Patients noted that current treatments include biologic drugs, DMARDs, and nonsteroidal anti-inflammatory drugs. Among issues noted were the need for additional therapeutic options, given the variability in disease presentation and unpredictability of who will be helped by a given drug. Patients also noted concerns regarding the loss of treatment effectiveness over time. Concerns were also noted over adverse effects with prolonged use, costs, scheduling for infusions, and need to take time off work. There were further concerns regarding immunosuppression, gastrointestinal side effects, and scarring from infusions, as well as burden on caregivers due to provision of care and travelling to infusion appointments. However, AEs were not considered in the manufacturer's model.

None of the interviewed patients had experience with using apremilast for PsA. Anticipated advantages include elimination of vein scarring and decreased time commitments for injections and infusions, the ease of oral medication, extension of range of available options when other drugs are ineffective, and lower immunosuppression and susceptibility to infection.

7. CONCLUSIONS

Considering alternative assumptions for quality of life upon treatment discontinuation and corrected treatment costs, the CDR base case, with a 40-year time horizon, resulted in apremilast being extendedly dominated by BSC and golimumab, with an ICUR of $63,071 per QALY compared with BSC. Under this scenario, a price reduction for apremilast of 5% per pill was necessary to bring it onto the cost-effectiveness frontier and make it the most cost-effective option with an ICUR of $59,839 per QALY versus BSC (for reference, golimumab, the second most cost-effective option in this case, was $61,944 versus BSC and had a sequential ICUR of $63,720 compared with apremilast at a 5% price reduction).

Using the CDR base case with a shortened time horizon of 10 years to account for uncertain long-term efficacy resulted in an ICUR of $81,572 for apremilast compared with BSC, with apremilast remaining extendedly dominated by BSC and golimumab. Under this scenario, a price reduction for apremilast of 10% per pill was necessary to bring apremilast onto the cost-effectiveness frontier and make it the most cost-effective option with an ICUR of $73,218 per QALY versus BSC (for reference, golimumab, the second most cost-effective option in this case, was $74,736 versus BSC and had a sequential ICUR of $75,876 compared with apremilast at a 10% price reduction).

The manufacturer reported that the ICUR for apremilast versus BSC was lower than that for golimumab, based on the list price of golimumab. Where price reductions of > 10% have been negotiated for golimumab, apremilast would be ruled out through extended dominance by BSC and golimumab.
The potential cost-effective superiority of apremilast versus biologics lies in its being less costly and less effective than these options, which may lead to questions regarding its place in therapy versus biologics — which are more effective alternatives (in terms of QALY benefit).

APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 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. Product Listing Agreements are not reflected in the table and therefore costs may not represent the actual costs to public drug plans.

TABLE 4: COST COMPARISON TABLE FOR PSORIATIC ARTHRITIS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Apremilast (Otezla)	**10 mg[a] 20 mg[a] 30 mg**	**Tablet**	[redacted][a]	**30 mg twice daily, following titration period**	**First year: $[redacted][b] Subsequent years: $[redacted]**
Biologic agents					
Adalimumab (Humira)	40 mg/ 0.8 mL	Pre-filled syringe or pen	740.3600	40 mg every other week	$19,249
Etanercept (Enbrel)	50 mg/mL	Pre-filled syringe or pen	395.3900	50 mg per week	$20,560
Infliximab (Remicade)	100 mg	Vial for infusion	987.5600	5 mg/kg for 3 doses (0, 2, 6 weeks) then 5 mg/kg every 8 weeks.	First year: $39,502[e] Subsequent years: $32,096
SEB-infliximab (Inflectra)			650.0000[d]		First year: $26,000 Subsequent years: $21,125
Golimumab (Simponi)	50 mg	Solution for subcutaneous injection	1,520.2100	50 mg per month	18,246
Ustekinumab (Stelara)	45 mg/ 0.5 mL 90 mg/ 1 mL	Pre-filled syringe	4,593.1400 (for both strengths)	< 100 kg patients — 45 mg at weeks 0 and 4, followed by 45 mg every 12 weeks thereafter (same for > 100 kg, except 90 mg)	First and second years: 22,966[f] Subsequent years: 20,669
Certolizumab (Cimzia)	200 mg	Solution for subcutaneous injection	664.5100	Loading dose of 400 mg initially and at weeks 2 and 4. Maintenance dose of 200 mg every 2 weeks (400 mg every 4 weeks may be considered)	First year: 20,600 Subsequent years: 17,277

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Disease-modifying anti-rheumatic drugs					
Methotrexate (generics)	2.5 mg 10 mg/mL 25 mg/mL	Tablet Injection Injection	0.6325 12.5000/2 mL 8.9200/2 mL	7.5 to 25 mg per week until adequate response is achieved. Dosage adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded	Oral: 1.900 – 6.325 per week until response. Then up to 7.590 per week. Oral yearly cost for 30 mg per week: 395.
Methotrexate (generics)	10 mg	Tablet	2.7000[G]	Idem	Oral yearly cost for 30 mg per week: 421
Leflunomide (generics)	10 mg 20 mg	Tablet	2.6433 2.6433	Loading dose of 100 mg per day for 3 days Maintenance therapy of 20 mg per day	First year: 997 Subsequent years: 965
Sulfasalazine (generics)	500 mg	Tablet	0.1804	Titration: Week 1: 500 mg/day week 2: 1,000 mg/day week 3: 1,500 mg/day Maintenance dose: 2,000 mg/day[g]	First year: 255 Subsequent years: 263

SEB = subsequent entry infliximab.

Note: All prices are from the Ontario Drug Benefit Formulary/ Exceptional Access Program (accessed July 2015) unless otherwise indicated, and do not include dispensing fees. If no response has been seen after two months' treatment, dose may be increased to 3 g per day. Some patients may do well with 1.5 g/day.

[a] Manufacturer's submitted confidential price. Note that 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 mg and 20 mg pills.

[c] $25,304 and $20,560 annually if 50 mg vials are used in place of 25 mg vials.

[d] Source: CADTH Drug Expert Committee final recommendation for Inflectra.

Alternatively, 90 mg may be used in patients with a body weight greater than 100 kg.

[e] Based on mean weight of 85.46 kg from PALACE-1, -2, and -3 trials. Assumes wastage of partially used vials, 8 treatments in first year and 6.5 on average in subsequent years (based on weight of 85.36 kg).

[f] 5 treatments first year, 4.5 average subsequent year; prices for 45 mg and 90 mg are the same.

[g] Saskatchewan formulary.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO BSC?

Apremilast vs. BSC	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	$40,572 per QALY					

BSC = best supportive care; CE = cost-effectiveness; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO ADALIMUMAB?

Apremilast vs. Adalimumab	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	$78,992 per QALY (adalimumab vs. apremilast)					

CE = cost-effectiveness; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO ETANERCEPT?

Apremilast vs. Etanercept	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	$60,639 per QALY (etanercept vs. apremilast)					

CE = cost-effectiveness; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

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

Apremilast vs. 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	$115,773 per QALY (infliximab vs. apremilast)					

CE = cost-effectiveness; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO SEB-INFLIXIMAB?

Apremilast vs. SEB-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	$62,174 per QALY (SEB-infliximab vs. apremilast)					

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

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO GOLIMUMAB?

Apremilast vs. Golimumab	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	$50,630 per QALY (golimumab vs. apremilast)					

CE = cost-effectiveness; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

TABLE 11: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO USTEKINUMAB?

Apremilast vs. Ustekinumab	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	$104,862 per QALY (ustekinumab vs. apremilast)					

CE = cost-effectiveness; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS APREMILAST RELATIVE TO CERTOLIZUMAB?

Apremilast vs. Certolizumab	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	$53,824 per QALY (certolizumab vs. apremilast)					

CE = cost-effectiveness; NA = not available; QALY = quality-adjusted life-year; vs. = versus.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 13: 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"*			
Was the material included (content) sufficient?		X	
Comments *Reviewer to provide comments if checking "poor"*			
Was the submission well organized and was information easy to locate?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 14: AUTHORS' INFORMATION

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

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

Assessments of apremilast for treatment of patients with active psoriatic arthritis (PsA) are available from three health technology assessment (HTA) agencies: the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), and the Pharmaceutical Benefits Advisory Committee (PBAC). The table below summarizes the health economic evidence submitted to NICE by the manufacturer and the appraisal by the NICE assessment group. Next, the health economic evidence, appraisal, and conclusions of SMC are discussed. Finally, the conclusions of PBAC are stated.

TABLE 15: NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE FINDINGS

	NICE (August 2015)[21]
Treatment	Apremilast (Otezla) for the treatment of patients with active PsA.
Similarities with CDR submission	• Markov model with a 28-day cycle length, a 40-year time horizon, and developed from a health care system perspective. • For each treatment, 2 possible health states: trial period (response) and continued use (maintenance). • Response to treatment (with apremilast or TNF alpha inhibitors) evaluated at end of each treatment-specific trial period according to PsARC criteria (at 16 weeks for apremilast and 12 weeks for the TNF alpha inhibitors). • Transition probabilities for both response and maintenance determined by the PsARC response criteria, calculated from an NMA. • Responders continued treatment until experienced lack of efficacy or AEs, and switched treatment. • Patient with BSC were assumed to experience natural progression of their disease, with increase (worsening) of HAQ-DI score.
Differences with CDR submission	• The model compared treatment sequences of TNF alpha inhibitors and BSC including and excluding apremilast. Non-responders moved to next treatment option in the pathway. • The submitted CEAs to CADTH compared apremilast to TNF alpha inhibitors and to BSC, the latter being informed by placebo arm in clinical trials.
Manufacturer's results	• The manufacturer's base case ICUR for apremilast treatment sequence (apremilast followed by adalimumab, etanercept and BSC) vs. comparator treatment sequence (adalimumab followed by etanercept and BSC) was £14,683 (£1 = $2.03: http://www.google.ca/finance?q=GBPCAD, accessed September 29, 2015) per QALY gained. • Revised base case submitted by the manufacturer during the consultation period of the assessment report, correcting some limitations noted by NICE, resulted in an ICUR of £19,510 per QALY.
Issues noted by the review group	• Original model compared treatment sequences, including and excluding apremilast, rather than evaluating apremilast versus single comparators or allowing the assessment of apremilast to displace a treatment within a sequence. The assessment group highlighted that comparing treatment sequences creates significant uncertainty. • A main concern was the key model assumption that apremilast halts HAQ-DI progression for PsARC responders (i.e., stops disease progression) while people remain on treatment, which has not been demonstrated. This maintenance of effect was not applied to subsequent TNF alpha inhibitor therapies. The maintenance of effect assumption has been applied to subsequent TNF alpha inhibitors in the revised base-case analysis submitted by the manufacturer during the consultation period.

	NICE (August 2015)[21]
	• For apremilast, there was an underestimation of the cost related to patient management and other disease-related costs. This was corrected in the revised base case submitted by the manufacturer. • EQ-5D data were collected during apremilast trials; however, the utility scores used in the original model were calculated using the correlation coefficient between the PsARC scores and PASI scores making use of a previously published regression equation (Rodgers et al., 2011). This was corrected in the revised base-case analysis submitted by the manufacturer. • Different treatment trial periods were used in the model for apremilast (16 weeks) and the TNF alpha inhibitors (12 weeks), and these additional 4 weeks of treatment would be likely to increase the number of people who respond to treatment. • No inclusion of the placebo response in BSC.
Results of reanalyses by the review group (if any)	• The assessment group concluded that the manufacturer original base case as well as the revised one included several uncertainties. • Based on the results from the scenarios tested by the assessment group and the clinical evidence, it was concluded that apremilast, if used at all, should not be used before a TNF alpha inhibitor. • The option of displacing treatments within the treatment sequence by apremilast was submitted by the manufacturer during the consultation period of the assessment report. The reviewers' preferred base case, accounts for apremilast displacing a TNF alpha inhibitor. This apremilast sequence is compared with a treatment sequence that includes the same number of active comparators before BSC. This analysis found the apremilast option being less costly but less effective in all scenarios. The results in terms of £ saved per QALY lost were between £10k and £30k. The assessment group interpreted this to mean that the savings are not sufficient to compensate for the clinical effectiveness that would be lost.
Recommendation	"Apremilast alone or in combination with DMARD therapy is not recommended within its marketing authorisation for treating adults with active psoriatic arthritis that have not responded to prior DMARD therapy, or such therapy is not tolerated."

AE = adverse event; BSC = best supportive care; CDR = CADTH Common Drug Review; CEA = cost-effectiveness analysis; DMARD = disease-modifying anti-rheumatic drug; EQ-5D = EuroQol 5-Dimensions Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; QALY = quality-adjusted life-year; TNF = tumour necrosis factor; vs. = versus.

Scottish Medicine Consortium

The same original model submitted to NICE was submitted to the SMC (May 2015).[22] The base-case result presented was similar to that presented to NICE with an ICUR of £14,691 per QALY for the apremilast sequence versus the comparator sequence (incremental cost of £10,879; incremental QALY of 0.74). The main driver of the difference in cost came from the inclusion of apremilast as an additional treatment in the apremilast sequence. The additional QALY gain was from patients being on an active treatment for a longer period of time and thus spending less time in best supportive care in the apremilast sequence.

Alternative scenarios tested by the SMC involved changing treatment sequences, which led to ICURs lower than £20k per QALY gained. Testing non-maintenance of effect for apremilast led to an ICUR of £38k per QALY gained. Reducing the time horizon to 10 years resulted in an ICUR of £33k per QALY gained.

The SMC did not highlight the major limitations identified by NICE (the SMC assessment being concluded before the NICE one), such as the fact that apremilast was added to the treatment sequence instead of displacing another treatment. The SMC considered the economic case to be sound.

The SMC recommendation is as follows: "Apremilast (Otezla) is accepted for restricted use within NHS Scotland. SMC restriction: for use in adult patients with active PsA who have had an inadequate response with at least two prior DMARD therapies or who are intolerant to such therapies."[22]
Finally, PBAC[23] assessed apremilast and rejected the submission. This was based on the comparison of apremilast versus cyclosporine submitted by the manufacturer. The cost-effectiveness compared with cyclosporine treatment had not been adequately established at the price proposed in the submission. The difference in efficacy for apremilast versus cyclosporine was not statistically significant, and the point estimate for PASI50 from the indirect comparison tended toward inferiority.

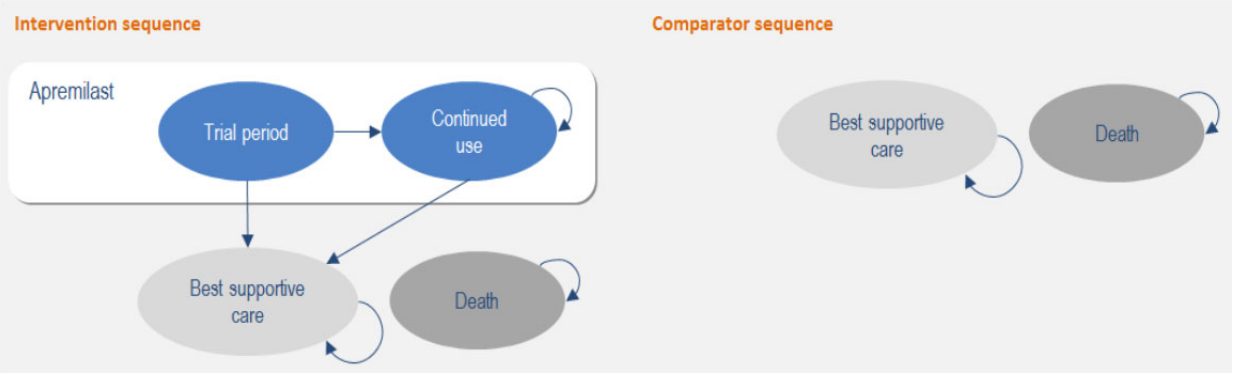
APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis using a Markov model comparing apremilast against best supportive care (BSC) and biologics indicated for the treatment of psoriatic arthritis (PsA) (etanercept, infliximab, subsequent entry biologic [SEB] infliximab, ustekinumab, adalimumab, golimumab subcutaneous [SC], and certolizumab pegol) among patients with active PsA who have previously failed on a conventional disease-modifying anti-rheumatic drug (DMARD).[4] BSC was defined as use of DMARDs ([redacted]% methotrexate [MTX], [redacted]% leflunomide, and [redacted]% sulfasalazine) based on the distribution observed at baseline among DMARD-users in the placebo arm of the PALACE trials.[5-7] The model population was assumed to have characteristics similar to patients in PALACE trials, with a mean age of 50.3 years and weight of 85.46 kg. A time horizon of 40 years was assessed, using model cycles 28 days in length and a publicly funded health care system perspective.

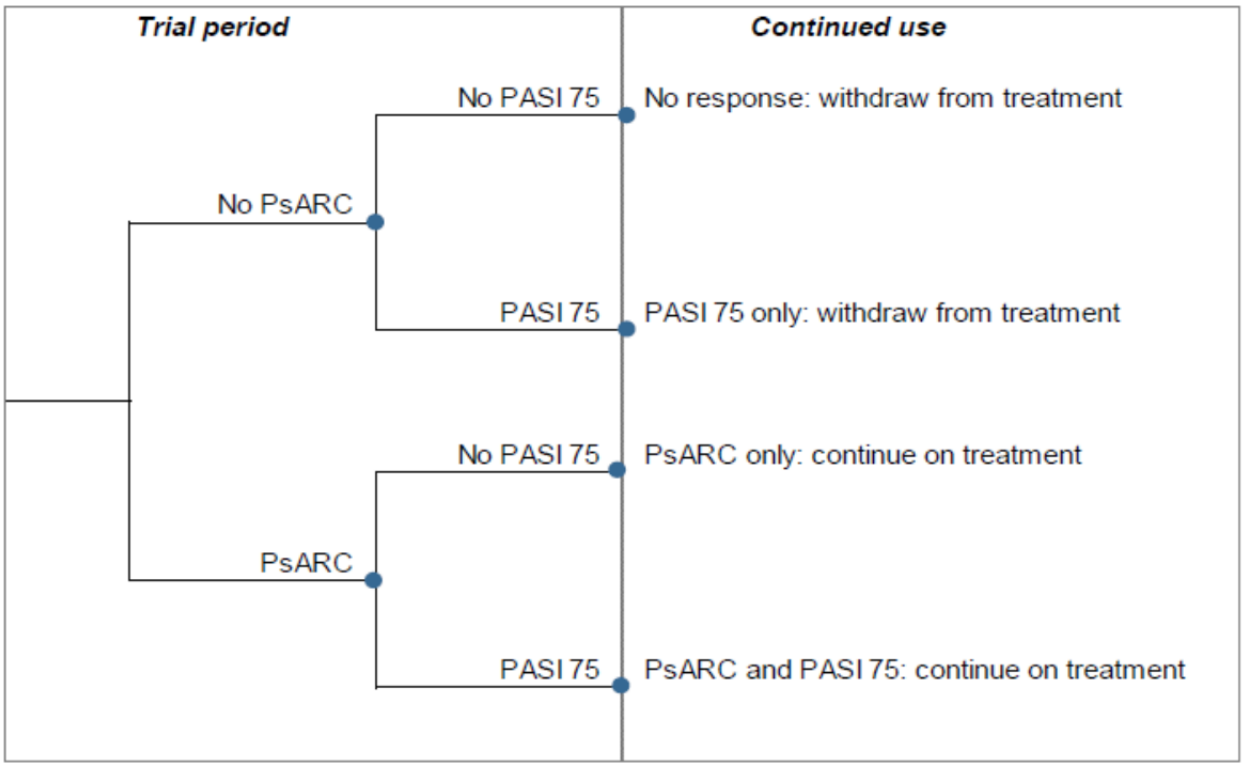
Among patients receiving one of the active interventions, treatment response was assessed after a variable treatment trial period (12 weeks for ustekinumab, certolizumab, etanercept, and adalimumab; 14 weeks for infliximab, SEB-infliximab, and golimumab; and 16 weeks for BSC and apremilast) based on Psoriatic Arthritis Response Criteria (PsARC) response (defined as showing improvement in at least two of the following four measures: patient-self assessment, physician assessment, joint pain/tenderness score, and a joint swelling score, one of which is the joint pain/tenderness score or joint swelling score, with no worsening in any of these four measures). After the treatment trial period, patients either entered the "continued use" or BSC state. Responders entered and remained in the continued use state until withdrawal due to loss of treatment efficacy or onset of adverse events (AEs). Non-responders and patients who withdrew from the continued treatment state moved to the BSC state. Patients in the BSC could either achieve PsARC response (according to the rate of response in the placebo arms of the PALACE trials) or fail to respond, in which case they experienced disease progression, as reflected by an increment of their Health Assessment Questionnaire–Disability Index (HAQ-DI) score. A constant HAQ-DI score increment of 0.006 per cycle was assigned to BSC non-responders, based on the figure used by Rodgers et al.[9] Incremental cost-utility ratios (ICURs) for all treatments were calculated relative to BSC. Figure 1 shows the model structure for patients receiving active treatment (using apremilast as an example) and for the comparator BSC sequence.

FIGURE 1: MODEL STRUCTURE FOR PATIENTS RECEIVING ACTIVE TREATMENT VERSUS BEST SUPPORTIVE CARE



Source: Manufacturer's pharmacoeconomic submission.[4]

FIGURE 2: TREATMENT RESPONSE CRITERIA



PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria.
Source: Manufacturer's pharmacoeconomic submission.[4]

Clinical effectiveness data for apremilast were derived from three placebo-controlled randomized clinical trials (PALACE-1, -2, and -3).[5-7] Efficacy inputs to the economic model were obtained from the manufacturer's network meta-analysis (NMA). Treatment- and response-specific changes in HAQ-DI and Psoriasis Area and Severity Index (PASI) scores were associated with the continued use and BSC states based on the NMA (e.g., the schematic of PsARC response/non-response and subsequent HAQ-DI and PASI responses in Figure 2). The utilities associated with treatment were based on changes in HAQ-DI and PASI scores, which were mapped to EuroQol 5-Dimensions Questionnaire (EQ-5D) utilities based on a linear regression used by Rodgers et al.[9] Responders experienced a decrease in HAQ-DI and PASI score. While patients remained in the continued use state, it was assumed that there was no progression in HAQ-DI score, reflecting arrest of disease progression. Non-responders to active treatment experienced an increase HAQ-DI score equal to the initial decrement, while non-responders to BSC experienced an increase in HAQ-DI score.

Costs considered were for drug acquisition and monitoring and follow-up. Dosages were assumed to be the recommended doses from product monographs. The cost of apremilast was taken from the manufacturer's confidential submitted price, while the costs of all other medications were from the Ontario Drug Benefit (ODB) formulary (2014).[12] Schedules of monitoring and follow-up were based on clinical expert input and consisted of doctors' visits and laboratory testing. Drug administration costs were not considered, as they were not relevant for apremilast or BSC. For biologics, the infusion costs were assumed to be covered by the manufacturers. The costs of physician visits were obtained from the Ontario Health Insurance Plan (OHIP) schedule of benefits (2014),[13] while the costs of laboratory tests were obtained from the 1999 Schedule of Benefits for Laboratory Services.[14]

Costs and disutilities associated with AEs were not considered. The manufacturer stated that the effects of AEs on outcomes were partially accounted for by the all-cause withdrawal from active treatment to BSC. Further, it noted the lack of long-term data on AEs associated with apremilast and biologics. Among responders, withdrawal to BSC was assumed to be 16.5% annually, based on the figure derived in Rodgers et al.'s meta-analysis of withdrawal rates.[9] Patients could die at any time, according to age-specific Canadian mortality tables corrected for a PsA standardized mortality ratio of 1.36, as per Ali et al.[11]

TABLE 16: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Efficacy inputs to the economic model came from a manufacturer-sponsored NMA. Results from a Bayesian fixed effects analysis were used to derive PsARC response rates as well as treatment- and response-specific changes in HAQ-DI score and PASI score.	As noted in CDR's Clinical Report, there are concerns regarding the lack of transparency in analytic methodology. Variability in DMARD use in the placebo arms of included studies meant that the efficacy of apremilast relative to DMARDs may be uncertain when used for the cost-utility analysis. Note the primary outcome in the trials was ACR20 while estimates of PsARC were assumed in the model. Sensitivity analyses reveal that definition of response did not impact ICURs.
Disease progression — HAQ-DI score while on treatment	The model assumed that patients who responded to treatment did not experience any disease progression, as reflected by a constant HAQ-DI score.	Unclear whether appropriate or not.
Baseline cohort characteristics	Baseline patient age is 50.3 years and baseline weight (as required for weight-based dosing of infliximab) is 86.6 kg, based on pooled results from the PALACE-1 to -3 trials.[5-7]	Baseline patient characteristics deemed appropriate by clinical expert. Given that the manufacturer's model made use of several assumptions due to Rodgers et al.,[9] it may have been appropriate to consider a 70 kg body weight, as considered by Rodgers et al.
Dropout rates	The same annual withdrawal rate (16.5% annually) was assumed for all biologics, apremilast, and withdrawal from BSC response to non-response, based on the figure used in Rodgers et al.[9]	Deemed appropriate by clinical expert.
Utilities — derivation from PASI and HAQ-DI	Based on treatment- and response-specific HAQ-DI and PASI scores using the linear regression mapping of Rodgers et al.[9]	Unclear how appropriate this is. Note that the PALACE trials did not demonstrate consistent differences between apremilast and placebo in directly measured EQ-5D utilities. Any mapped utilities should be interpreted cautiously. The use of alternative

Data Input	Description of Data Source	Comment
		mappings was either inconsequential (Abbott) or changed ICURs considerably (Schering-Plough) without changing sequential results.
Utility — HAQ-DI rebound model	Assumed that upon discontinuation of treatment, there was an increase in HAQ-DI score (reflecting worsening of disease) equal to the initial treatment response.	As noted by Rodgers et al.,[9] there is a paucity of data to inform this point. While CDR used the conservative assumption of rebound to natural history for all comparators, it should be noted that radiologic evidence of slowed progression of joint damage is not available for apremilast, whereas it is available for golimumab.[24]
AEs	Costs and disutilities associated with AEs were not considered in the model.	Justified by noting that all-cause withdrawal from treatment accounted partially for AEs, as well as noting the paucity of extant data on AEs. Confirmed as acceptable by clinical expert.
Mortality	Age-specific all-cause mortality from Canadian mortality tables with a PsA specific SMR of 1.36 as per Ali et al.[11] This estimate was based on Canadian data.	Appropriate. Alternative SMR estimates made no impact on ICURs in sensitivity analyses. Note that SMRs stratified by gender are available (e.g., Wong et al. 1997),[25] and it is not expected that this would affect results.
Costs		
• Drug	• Apremilast — manufacturer's submitted price. • Comparators — from the Ontario Drug Benefit Formulary (2014).	Appropriate.
• Administration	• Costs of injections were not considered separately; instead, they were included in the administration fees of the drugs themselves. • Costs of administration from Ontario Schedule of Benefits (2014). • Costs of laboratory tests from Ontario 1999 Schedule of Benefits.	Appropriate.
• Follow-up/laboratory testing	• Costs of administration from Ontario Schedule of Benefits (2014). • Costs of laboratory tests from Ontario 1999 Schedule of Benefits.	Deemed appropriate by clinical expert. While failure to account for concurrent MTX use among apremilast patients meant that the schedule of follow-ups was also underestimated for apremilast (given the more intense follow-ups associated with MTX), this did not affect resulting ICURs.

ACR = American College of Rheumatology; AE = adverse event; BSC = best supportive care; CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; DMARD = disease-modifying anti-rheumatic drug; EQ-5D = EuroQol 5-Dimensions Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; ICUR = incremental cost-utility ratio; MTX = methotrexate; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SEB = subsequent entry biologic; SMR = standardized mortality ratio.

TABLE 17: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
HAQ-DI score rebounds by same amount as initial response, as opposed to rebounding to natural history (i.e., to HAQ-DI score as it would be in the absence of any treatment)	Unclear whether appropriate based on paucity of data. Possibly defensible for some biologics on the basis of radiologic evidence[24] and control of multiple assessed disease areas,[20] likely not for apremilast where there was neither radiologic evidence nor clear differences from placebo for dactylitis and enthesitis. Addressed in limitations and CDR's base case.
No progression of HAQ-DI score during response to treatment	Unclear whether appropriate based on paucity of data. Failure of apremilast to control all disease areas during treatment indicates that disease progression may not be arrested and that apremilast may not slow HAQ-DI progression.
Constant per cycle HAQ-DI increase (0.006) upon failure of BSC	Based on the meta-analysis of Rodgers et al.[9] Results are highly sensitive to this assumption. As noted by NICE[21] in another inflammatory arthritis (rheumatoid arthritis), the rate of disease progression often slows over time, indicating that a time-dependent HAQ-DI increase may be appropriate. If disease progression slows over time, it is expected that the QALY gain of apremilast over BSC would be reduced and the ICUR would increase.
Equal withdrawal from treatment for all comparators	Likely appropriate as per clinical expert.
PsARC definition of response matches response as it would be assessed in the clinic	Likely appropriate as per clinical expert: results are the same under ACR20 criteria (which was the primary outcome in the trials). However, while ACR20 is accepted as the MCID for response to treatment, there are indications that ACR50 and ACR70 may be more clinically relevant measures (see CDR Clinical Report). Apremilast did not demonstrate significant differences from placebo in ACR70 at 16 weeks, but did demonstrate nominal significance at 24 weeks in PALACE-1. Nominal significance was demonstrated in ACR50 at 16 weeks in PALACE-1 but not PALACE-2 or -3.
Clinical trial populations match indication listing request population	As noted in the CDR Clinical Report, there are concerns regarding the presence of entirely DMARD-naive patients as well as unclear definition of treatment failure.
Different lengths of treatment trial periods for different comparators	The use of a longer treatment trial period for apremilast compared to biologics may serve to bias results in favour of apremilast, as more time is allowed for detection of response than for other comparators.
Composition of BSC	Appropriate, as per clinical expert.
Baseline characteristics of cohort match clinical trial characteristics	Appropriate, as per clinical expert.
Movement from active treatment to BSC	Likely inappropriate. First, it is unclear that a DMARD failure population would move to DMARDs. Second, the use of multiple lines of biologics is established practice as per the clinical expert. Addressed by CDR in scenario analysis using a shortened horizon.

ACR = American College of Rheumatology; AE = adverse event; BSC = best supportive care; CDR = CADTH Common Drug Review; DMARD = disease-modifying anti-rheumatic drug; EQ-5D = EuroQol 5-Dimensions Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; ICUR = incremental cost-utility ratio; MCID = minimal clinically important difference; MTX = methotrexate; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; QALY = quality-adjusted life-year.

Manufacturer's Results Base Case

The manufacturer reported in its base case that apremilast is associated with a total cost of $52,895 and 5.28 QALYs over 40 years. When compared with BSC, apremilast was $36,035 more costly and was associated with a gain of 0.89 QALYs, leading to an ICUR of $40,572 per QALY. Sequential analysis revealed that the efficiency frontier consisted of BSC, apremilast, golimumab, and SEB-infliximab with sequential ICURs of $40,572 (apremilast), $50,630 (golimumab), and $150,378 (SEB-infliximab). All other comparators were extendedly dominated by apremilast and golimumab, apart from infliximab (Remicade), which was dominated by SEB-infliximab, and adalimumab, which was dominated by certolizumab pegol (Table 2).

CADTH Common Drug Review Reanalysis

The following scenarios were explored by CDR to assess limitations identified. All analyses include the updated list price of etanercept as per Table 4.

HAQ-DI Rebound Model

CDR explored a conservative scenario under which quality of life (HAQ-DI score) would rebound to natural history levels (i.e., what the patient's HAQ-DI score would have been in the absence of treatment) instead of rebounding to baseline HAQ-DI. Under this scenario, apremilast is extendedly dominated by BSC and golimumab, irrespective of horizon (Table 18, Table 19).

TABLE 18: CADTH COMMON DRUG REVIEW REANALYSIS — HAQ-DI REBOUND TO NATURAL HISTORY: 40-YEAR HORIZON

Intervention	Total Costs ($)	Total QALYs	Compared With BSC			Sequential ICUR ($)
			Incremental Costs ($)	Incremental QALYs	ICUR ($)	
BSC	16,860	4.07	Reference	Reference	Reference	Reference
Golimumab	94,753	5.26	77,893	1.19	65,459	65,459
SEB-Infliximab	111,025	5.38	94,165	1.31	72,378	146,508
Dominated and extendedly dominated options						
Apremilast	**52,895**	**4.62**	**36,035**	**0.55**	**66,201**	**Extendedly dominated by BSC and GOL**
Ustekinumab	77,997	4.85	61,137	0.78	79,091	Extendedly dominated by BSC GOL
Adalimumab	82,138	4.91	65,278	0.84	78,024	Dominated
Certolizumab Pegol	78,557	5.02	61,697	0.95	65,610	Extendedly dominated by BSC and GOL
Etanercept	98,044	5.21	81,184	1.14	71,841	Dominated
Infliximab (Remicade)	161,137	5.38	144,277	1.31	110,895	Dominated

BSC = best supportive care; GOL = golimumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.
Notes: 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. A dominant strategy is less costly and more effective than a dominated strategy.

TABLE 19: CADTH COMMON DRUG REVIEW REANALYSIS — HAQ-DI REBOUND TO NATURAL HISTORY: 10-YEAR HORIZON

Intervention	Total Costs ($)	Total QALYs	Compared With BSC			Sequential ICUR ($)
			Incremental Costs ($)	Incremental QALYs	ICUR ($)	
BSC	$8,732	3.28	Reference	Reference	Reference	Reference
Golimumab	$78,438	4.17	69,706	0.89	78,978	78,978
SEB-Infliximab	$93,428	4.27	84,696	0.99	86,244	150,725
Dominated and extendedly dominated options						
Apremilast	**$41,148**	**3.66**	**32,416**	**0.38**	**85,621**	**Extendedly dominated by BSC and GOL**
Ustekinumab	64,110	3.86	55,378	0.58	96,223	Extendedly dominated by BSC and GOL
Adalimumab	67,205	3.89	58,473	0.61	96,289	Dominated
Certolizumab Pegol	64,297	3.98	55,565	0.70	79,574	Extendedly dominated by BSC and GOL
Etanercept	81,349	4.13	72,617	0.85	86,049	Dominated
Infliximab (Remicade)	138,471	4.27	129,739	0.99	132,110	Dominated

BSC = best supportive care; GOL = golimumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.
Notes: 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. A dominant strategy is less costly and more effective than a dominated strategy.

Adjusted Costs

The costs of BSC were set at 65% of the original costs in the model to account for efficacy based on 65% baseline DMARD use in the PALACE trials. The costs of MTX were changed from a 20 mg dose to a 15 mg dose in accordance with the average dose in the PALACE trials (Table 20; Table 21). Markup fees were removed for all drugs. CDR attempted to incorporate concurrent MTX and appropriate monitoring schedules for all comparators, but found the model resistant to changing treatment costs for all comparators; thus, costs of concurrent MTX and appropriate monitoring were excluded from CDR's base case. These costs were found to have a negligible influence on the ICUR of apremilast relative to BSC, changing the ICUR from $63,071 to $64,655 and from $81,572 to $83,633 for a 40- and 10-year horizon, respectively. Further, inclusion of these costs did not appear to change the relative rankings of ICURs.

TABLE 20: CADTH COMMON DRUG REVIEW REANALYSIS — ADJUSTED COSTS: 40-YEAR HORIZON

Intervention	Total Costs ($)	Total QALY Gain	Compared With BSC			Sequential ICUR ($)
			Incremental Costs ($)	Incremental QALYs	ICUR ($)	
BSC	10,206	4.39	Reference	Reference	Reference	Reference
Apremilast	**44,538**	**5.28**	**34,332**	**0.89**	**38,654**	**38,654**
Golimumab	83,918	6.11	73,712	**1.72**	42,983	47,632
SEB-Infliximab	98,974	6.22	88,768	**1.83**	48,690	139,149
Dominated and extendedly dominated options						
Ustekinumab	67,875	5.52	57,669	**1.13**	51,145	Extendedly dominated by apremilast and GOL
Adalimumab	71,919	5.65	61,713	**1.26**	49,042	Dominated
Certolizumab Pegol	68,612	5.76	58,406	**1.37**	42,790	Extendedly dominated by apremilast and GOL
Etanercept	86,849	6.01	76,643	**1.62**	47,411	Dominated
Infliximab (Remicade)	145,374	6.22	135,168	1.83	74,141	Dominated

BSC = best supportive care; GOL = golimumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic

Notes: 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. A dominant strategy is less costly and more effective than a dominated strategy.

TABLE 21: CADTH COMMON DRUG REVIEW REANALYSIS — ADJUSTED COSTS: 10-YEAR HORIZON

Intervention	Total Costs ($)	Total QALY Gain	Compared With BSC			Sequential ICUR ($)
			Incremental Costs ($)	Incremental QALYs	ICUR ($)	
BSC	5,305	3.39	Reference	Reference	Reference	Reference
Golimumab	71,266	4.35	65,961	**0.96**	68,245	68,245
SEB-Infliximab	85,138	4.45	79,833	**1.06**	74,911	139,890
Dominated and extendedly dominated options						
Apremilast	**36,188**	**3.83**	30,883	**0.44**	**69,589**	**Extendedly dominated by BSC and GOL**
Ustekinumab	57,532	4.03	52,227	**0.64**	81,801	Extendedly dominated by apremilast and GOL
Adalimumab	60,584	4.07	55,279	**0.68**	81,532	Dominated
Certolizumab Pegol	57,900	4.16	52,595	**0.77**	68,362	Extendedly dominated by apremilast and GOL
Etanercept	73,859	4.31	68,554	**0.92**	74,342	Dominated
Infliximab (Remicade)	126,843	4.45	121,538	**1.06**	114,046	Dominated

BSC = best supportive care; GOL = golimumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.
Notes: 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. A dominant strategy is less costly and more effective than a dominated strategy.

CADTH Common Drug Review Base Case

CDR's base case combined the above analyses (HAQ-DI rebound to natural history and adjusted costs), finding apremilast to be dominated by BSC and golimumab irrespective of horizon (Table 22; Table 23).

TABLE 22: CADTH COMMON DRUG REVIEW BASE CASE — 40-YEAR HORIZON

Intervention	Total Costs ($)	Total QALY Gain	Compared With BSC			Sequential ICUR ($)
			Incremental Costs ($)	Incremental QALYs	ICUR ($)	
BSC	10,206	4.07	Reference	Reference	Reference	Reference
Golimumab	83,918	5.26	**73,712**	**1.19**	61,944	61,944
SEB-Infliximab	98,974	5.38	**88,768**	**1.31**	68,229	135,569
Dominated and extendedly dominated options						
Apremilast	**44,538**	**4.62**	**34,332**	**0.55**	**63,071**	**Extendedly dominated by BSC and GOL**
Ustekinumab	67,875	4.85	**57,669**	**0.78**	74,604	Extendedly dominated by apremilast and golimumab
Adalimumab	71,919	4.91	**61,713**	**0.84**	73,763	Dominated
Certolizumab Pegol	68,612	5.02	**58,406**	**0.95**	62,110	Extendedly dominated by apremilast and GOL
Etanercept	86,849	5.21	**76,643**	**1.14**	67,822	Dominated
Infliximab (Remicade)	145,374	5.38	**135,168**	**1.31**	103,894	Dominated

BSC = best supportive care; GOL = golimumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.

TABLE 23: CADTH COMMON DRUG REVIEW BASE CASE — 10-YEAR HORIZON

Intervention	Total Costs ($)	Total QALY Gain	Incremental Costs ($)	Incremental QALYs	ICUR Compared With BSC ($)	Sequential ICUR ($)
BSC	5,305	3.28	Reference	Reference	Reference	Reference
Golimumab	71,266	4.17	65,961	0.89	74,736	74,736
SEB-Infliximab	85,138	4.27	79,833	0.99	81,292	139,474
Dominated and extendedly dominated options						
Apremilast	**36,188**	**3.66**	30,883	**0.38**	**81,572**	**Extendedly dominated by BSC and GOL**
Ustekinumab	57,532	3.86	52,227	0.58	90,749	Extendedly dominated by apremilast and GOL
Adalimumab	60,584	3.89	55,279	0.61	91,030	Dominated
Certolizumab Pegol	57,900	3.98	52,595	0.7	75,320	Extendedly dominated by apremilast and GOL
Etanercept	73,859	4.13	68,554	0.85	81,235	Dominated
Infliximab (Remicade)	126,843	4.27	121,538	0.99	123,760	Dominated

BSC = best supportive care; GOL = golimumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.

Price Analysis of Golimumab

Golimumab is the most cost-effective option after apremilast in the manufacturer's base case. However, the finding that apremilast is more cost-effective (i.e., has a lower ICUR compared with BSC) than golimumab assumes that the list price of golimumab represents the price actually paid by drug plans and may not represent existing Product Listing Agreements.

Where golimumab is > 10% less than the list price, apremilast would be extendedly dominated by BSC and golimumab for the manufacturer's base case (Table 24). Further, golimumab is more effective than apremilast (as per the manufacturer's NMA[8]) and the earlier use of aggressive treatments may lead to improved patient outcomes in terms of joint damage and minimizing disease activity.[10]

TABLE 24: CADTH COMMON DRUG REVIEW REANALYSIS — GOLIMUMAB PRICE REDUCTION SCENARIO

Price of GOL	ICUR of Apremilast vs. BSC	ICUR of Golimumab vs. BSC
List price ($1,520.21/dose)	$40,572	$45,421 (sequential ICUR of $50,630 GOL vs. apremilast)
10% reduction ($1,368.19)	$40,572	$40,743 (sequential ICUR of $40,926 GOL vs. apremilast)
15% reduction ($3,904)	Extendedly dominated by BSC and GOL	$38,403
20% reduction ($3,675)	Extendedly dominated by BSC and GOL	$36,064

BSC = best supportive care; GOL = golimumab; ICUR = incremental cost-utility ratio; vs. = versus.

Price Analysis of Apremilast

In CDR's base case, apremilast was extendedly dominated by BSC and golimumab. Price reduction analyses on the submitted confidential price of apremilast found that, assuming a 40-year horizon, reductions of 5% or more were sufficient to bring apremilast onto the cost-effectiveness frontier (and make apremilast the most cost-effective option), and that reductions of 10% or more were necessary when a 10-year horizon was assumed (refer to Table 25). These analyses assume that the prices paid for all other comparators reflect their respective list prices.

TABLE 25: CDR REANALYSIS — APREMILAST PRICE REDUCTION SCENARIO

Price of Apremilast	10-Year Horizon	40-Year Horizon
	ICUR of Apremilast vs. BSC	ICUR of Apremilast vs. BSC
Submitted price ([redacted]/30 mg tablet)	$81,572 (apremilast extendedly dominated by BSC and GOL)	$63,071 (apremilast extendedly dominated by BSC and GOL)
5% reduction ([redacted]/30 mg tablet)	$77,395 (extendedly dominated by BSC and GOL)	$59,839 (sequential ICUR of $59,839 vs. BSC)
10% reduction ([redacted]/30 mg tablet)	$73,218 (sequential ICUR of $73,218 vs. BSC)	$56,607 (sequential ICUR of $56,607 vs. BSC)

BSC = best supportive care; GOL = golimumab; ICUR = incremental cost-utility ratio; vs. = versus.

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