CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Certolizumab Pegol (Cimzia)

(UCB Canada Inc.)

Indication: For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.

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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.

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Abbreviations

AE	adverse event
BSC	best supportive care
CDR	CADTH Common Drug Review
ICUR	incremental cost-utility ratio
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PASI	Psoriasis Area Severity Index
QALY	quality-adjusted life-year
SC	subcutaneous
SEB	subsequent entry biologic

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Certolizumab pegol (Cimzia) solution for subcutaneous injection
Study Question	Is certolizumab pegol a cost-effective alternative to existing biologic therapies currently approved and reimbursed by Canadian public drug plans for the treatment of moderate-to-severe psoriasis?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults (age 18 years or older) with moderate-to-severe plaque psoriasis who are candidates for systemic therapy
Treatment	Certolizumab pegol 400 mg: 400 mg by SC injection every 2 weeks (q.2.w.) is the recommended dose OR Certolizumab pegol 200 mg: 400 mg SC initially (week 0) and at weeks 2 and 4 followed by 200 mg q.2.w. may be considered
Outcome	QALYs
Comparators	• BSC consisting of treatment with cyclosporine, methotrexate, acitretin, and/or phototherapy • Adalimumab • Etanercept • Infliximab (branded) • Secukinumab • Ixekizumab • Ustekinumab • Brodalumab • Guselkumab
Perspective	Canadian publicly funded health care payer
Time Horizon	Lifetime (until more than 99% of the modelled cohort is predicted to have died)
Results for Base Case	Based on a sequential probabilistic analysis: • Certolizumab pegol 400 mg was dominated by ixekizumab, whereas certolizumab pegol 200 mg was extendedly dominated by brodalumab and BSC. • BSC had the lowest cost and fewest QALYs, followed by brodalumab, then ixekizumab. • At a willingness-to-pay threshold of $50,000 per QALY gained, certolizumab pegol 200 mg and 400 mg had a 0% probability of being cost-effective.
Key Limitations	• The comparative treatment effects of certolizumab pegol with other biologics are uncertain, given the limitations of the clinical trial studies and the manufacturer-submitted NMA, as identified by CADTH clinical reviewers. • The manufacturer assumed that the efficacy of treatment, measured in terms of PASI response (PASI 75), observed during the clinical trial (48 weeks) will continue until the end of the model time horizon. No evidence has been provided to support this assumption. • The manufacturer assumed that patients who discontinue their primary treatment during the maintenance period would be switched to BSC. However, in clinical practice, patients who discontinue initial treatment would likely receive a higher dose of the same drug or be switched to another active treatment instead of BSC. • In clinical practice BSC is only used prior to patients being eligible for treatment with a biologic; therefore, BSC is not an appropriate comparator. Further, BSC costs were estimated using a UK study; however, Canadian values were available and would be more appropriate. • The use of a lifetime model horizon is likely too long, given the uncertainty in the long-term maintenance of PASI response and the inappropriate assumption that patients who discontinue treatment receive BSC for the remainder of the time horizon.

Key Limitations (cont'd)	• The manufacturer assumed differential time points for the initial assessment of treatment response for comparators, as per product monographs or clinical trials. This assumption is not reflective of clinical practice and favoured certolizumab pegol, which has a longer time for initial assessment of treatment response and therefore a longer initial therapy duration. • The cost of infliximab was based on branded drug prices; an infliximab biosimilar was not included in the analysis.
CDR Estimate(s)	• In the CADTH base case, BSC was excluded as a comparator, a 10-year time horizon and a consistent time point for the initial assessment of treatment response were applied, pharmacotherapy and phototherapy costs for BSC were excluded, and a Canadian source for BSC costs was used. Finally, the cost of infliximab was based on the SEB price. CADTH noted that the uncertainty related to the lack of long-term effectiveness evidence and the assumption of no active treatment following discontinuation could not be addressed in the reanalysis. • In the CADTH base case, etanercept was associated with the lowest cost and fewest QALYs, followed by brodalumab, infliximab, and then guselkumab. • The ICUR for brodalumab compared with etanercept was $13,320 per QALY, while the ICUR for infliximab compared with brodalumab was $155,758 per QALY, and the ICUR for guselkumab compared with infliximab was $407,169. • Certolizumab pegol was dominated or ruled out by extended dominance. At a willingness-to-pay threshold of $50,000 per QALY gained, certolizumab pegol 200 mg and 400 mg had a 0% probability of being cost-effective. • A price reduction of 91% would be required for the recommended dose of certolizumab pegol 400 mg to be on the cost-effectiveness frontier and to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY. • Results should be interpreted with caution, as effectiveness estimates based on the NMA may not be reliable, given the limitations identified by the CADTH clinical reviewers (See CADTH Clinical Report for further details). Even though certolizumab pegol appears to have a higher predicted probability of response than non-biological drugs, some biologic drugs provide higher efficacy in terms of response at a lower total cost (e.g., ixekizumab and guselkumab have a higher efficacy than the recommended dose of certolizumab pegol 400 mg, at a lower total cost). Additionally, based on small differences in costs and benefits across biologics, a lack of information on true comparator costs may have an impact on the cost-effectiveness results.

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; PASI = Psoriasis Area Severity Index; q.2.w. = every 2 weeks; QALY = quality-adjusted life-year; SC = subcutaneous; SEB = subsequent entry biologic.

Drug	Certolizumab Pegol (Cimzia)
Indication	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy
Reimbursement request	As per indication
Dosage form	400 mg by subcutaneous injection (SC) every 2 weeks (q.2.w/) OR 400 mg SC initially (week 0) and at weeks 2 and 4 followed by 200 mg q.2.w.
NOC date	August 16, 2018
Manufacturer	UCB Canada Inc.

Executive Summary

Background

Certolizumab pegol is a recombinant, humanized antibody Fab' fragment with specificity for human tumour necrosis factor alpha that is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.[1] Certolizumab pegol is available as a solution for subcutaneous injection in a single-use, pre-filled syringe or single-use pre-filled autoinjector containing 200 mg/mL of certolizumab pegol. The recommended dose is 400 mg administered via subcutaneous injection every two weeks. A dose of 400 mg at week 0 and week 4 followed by 200 mg every two weeks thereafter may be considered.[1] At the manufacturer's submitted price of $664.51 per pre-filled syringe or autoinjector,[2] and at the recommended dose of 400 mg every two weeks, the annual cost of certolizumab pegol is $34,555, whereas, at a 200 mg dose, the annual cost during the first year is $19,271 and $17,277 thereafter.

The manufacturer submitted a cost-utility analysis based on a Markov state–transition model comparing certolizumab pegol with best supportive care (BSC) and the following biologic therapies reimbursed in Canada for moderate-to-severe plaque psoriasis: adalimumab, brodalumab, etanercept, guselkumab, infliximab (branded), ixekizumab, secukinumab, and ustekinumab.[2] BSC consisted of treatment with cyclosporine, methotrexate, acitretin, and/or phototherapy. The analysis was conducted from a Canadian publicly funded health care payer perspective using two-week cycles over a lifetime horizon (defined as the period over which more than 99% of the modelled cohort is predicted to have died). An annual discount rate of 1.5% was applied to both costs and benefits. The model had two time periods: the initial period, from treatment initiation to the initial assessment of treatment response (i.e., 10 to 16 weeks), and the maintenance period.

Treatment response was defined as achieving a Psoriasis Area Severity Index (PASI) response score of 75 (PASI 75) or greater. Following the initiation period, patients achieving PASI 75 continue treatment and those who do not are switched to BSC. Patients who respond to treatment in the initiation phase continue treatment in the maintenance phase until discontinuation due to loss of response or death. Patients continuing treatment were assumed to maintain the same level of PASI response and remain in the same health state until discontinuation. Upon discontinuation, patients were assumed to receive BSC. Patients entering BSC were distributed across the PASI health states based on the methotrexate

response from the network meta-analysis (NMA). Once patients reached the BSC state, they remained in this state until death or the end of the model. Mortality rates were based on all-cause Canadian mortality data, adjusted by age and gender.

The absolute probabilities of PASI 75 response were based on the manufacturer's unpublished NMA.[3] Discontinuation rates during the initial period were also based on the NMA, whereas discontinuation rates during the maintenance period were assumed to be the same for all biologics (20%) based on real-world data[4] and the previous cost-utility analyses submitted to the National Institute for Health and Care Excellence.[5-10] Adverse events were not included in the model, based on clinical advice that serious adverse events are rare and are unlikely to affect results. Health state utilities corresponding to PASI response scores were based on EuroQol 5-Dimensions questionnaire data from the CIMPASI-1 and CIMPASI-2 phase III clinical trials.[11-13] The cost of BSC was estimated from an observational UK cohort study[14] and consisted of emergency visits, in-patient hospital admissions, concomitant medicines, and phototherapy costs.

In the manufacturer's probabilistic base case, BSC had the lowest costs and fewest quality-adjusted life-years (QALYs), followed by brodalumab and ixekizumab. The incremental cost-utility ratio (ICUR) for brodalumab compared with BSC was $148,083, while the ICUR for ixekizumab compared with brodalumab was $1,998,523 per QALY. In the base case, certolizumab pegol 200 mg was dominated by ixekizumab, and certolizumab pegol 400 mg was extendedly dominated by brodalumab and BSC. At a willingness-to-pay threshold of $50,000 per QALY gained, certolizumab pegol had a 0% probability of being cost-effective.

Summary of Identified Limitations and Key Results

CADTH identified several limitations with the model submitted by the manufacturer. The key limitation was the reliance on indirect treatment comparison estimates of the comparative clinical efficacy of certolizumab pegol. The placebo-adjusted binomial model produced inconsistent results, which may be related to concerns about model fit, convergence, and available precision. Therefore, it was not possible to reach conclusions regarding the comparability of certolizumab pegol with other biological drugs (see CADTH Clinical Report for further details). Furthermore, the place in therapy is uncertain, as some drugs provide better efficacy than certolizumab pegol at a lower cost (e.g., for PASI 75, brodalumab is favoured over certolizumab pegol 400 mg at a lower average annual cost [Table 4]).

Additionally, the economic model assumed that patients who discontinue their primary treatment switch to BSC. In clinical practice, patients who discontinue or do not respond to initial treatment would likely receive a higher dose of the same drug or switch to another active treatment. CADTH was unable to address this limitation because of the structural limitations of the model and a lack of evidence on treatment-experienced patients. Another important limitation is the assumption that the clinical efficacy of treatments at the end of the observed follow-up period continues beyond the trial; no consideration was given to waning of treatment effects. Unfortunately, this limitation could not be addressed through reanalysis of the model due to a lack of long-term data (as patients in the clinical trials were only followed for up to 48 weeks) and the inflexibility of the model structure.

In clinical practice, BSC is only used prior to patients being eligible for treatment with a biologic; therefore, the manufacturer should not have considered BSC as a relevant comparator. Furthermore, Canadian costs for BSC are available and more appropriate than the inputs based on UK clinical practice that were used by the manufacturer to inform the costs of BSC. In addition, the cost of infliximab was based on the branded drug price when

the lowest cost for infliximab (i.e., a subsequent entry biologic [SEB]) should have been used.

Additional limitations included the use of a lifetime horizon, given the uncertainty in the long-term effects of treatment, and the use of different time points for the initial assessment of treatment response in different comparators, which is not supported by clinical practice.

CADTH addressed some of these limitations by excluding BSC as a comparator; using the SEB price for infliximab; using a consistent time point for the initial assessment of treatment response for all biologics; using a 10-year time horizon; using a Canadian source for BSC costs; and excluding treatment costs associated with BSC. Based on the CADTH sequential reanalysis of certolizumab pegol 200 mg and 400 mg, adalimumab, ustekinumab 45 mg and 90 mg, ixekizumab, and etanercept 50 mg were dominated, while secukinumab was extendedly dominated.

Conclusions

Based on the CADTH reanalyses, etanercept is the optimal therapy for moderate-to-severe psoriasis if the decision-maker's willingness-to-pay threshold is less than $13,320 per QALY gained; brodalumab is the optimal therapy if the willingness-to-pay threshold is at least $13,320 but less than $155,758 per QALY gained; infliximab (SEB) is the optimal therapy if the willingness-to-pay threshold is at least $155,758 but less than $407,169 per QALY gained; and guselkumab is the optimal therapy at a willingness-to-pay threshold of at least $407,169. A reduction in the submitted price of at least 91% would be required for certolizumab pegol 400 mg to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

It should be noted that there is significant uncertainty around the clinical effectiveness of certolizumab pegol; additionally, the economic model did not allow CADTH to assess the impact of assumptions relating to the waning of treatment effect and the use of treatment sequences in clinical practice. This implies that the results of the economic analysis warrant careful interpretation.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted a cost-utility analysis comparing both certolizumab pegol 200 mg and 400 mg with best supportive care (BSC) and the following biologic therapies reimbursed in Canada for moderate-to-severe plaque psoriasis: adalimumab 40 mg, brodalumab 210 mg, etanercept 25 mg and 50 mg, guselkumab 100 mg, infliximab (branded) 100 mg, ixekizumab 80 mg, secukinumab 300 mg, and ustekinumab 45 and 90 mg.[2] The perspective was that of a Canadian publicly funded health care payer and a lifetime horizon was used (lifetime was assumed to be equivalent to the period of time when 99% of patients would have died). An annual discount rate of 1.5% was applied to both costs and benefits. The target population for the cost-utility analysis was adult patients with moderate-to-severe psoriasis (Psoriasis Area Severity Index [PASI] of 10 to 12, and a category of moderate to severe on the Physician's Global Assessment of psoriasis severity) who are candidates for systemic therapy and are eligible for biologic therapy. The model baseline characteristics were based on the manufacturer's network meta-analysis (NMA).

The economic analysis was conducted using a Markov model where costs and benefits were assessed using two-week cycles. The model was developed in Microsoft Excel and was an adaptation of the York model originally developed to evaluate the cost-effectiveness of etanercept and infliximab for the treatment of psoriatic arthritis.[15] The model had two time periods: the initial period, which was from treatment initiation up to the initial assessment of treatment response (i.e., 10 to 16 weeks), and the maintenance period, the period following primary response. The model included the following health states defined by the following PASI response categories: PASI < 50, PASI 50 to 74, PASI 75 to 89, and PASI 90 to 100. At the point of assessment (i.e., end of the initial period), patients were placed in one of these response categories based on response to treatment (Table 10). Patients who achieved a PASI response score of < 75 (i.e., failed to reach the primary outcome in the clinical trials, PASI 75) were switched to BSC, which consisted of treatment with cyclosporine, methotrexate, acitretin, and/or phototherapy. Patients would either remain in this state or die (due to all-cause mortality). Those with a PASI score of ≥ 75 could either continue in their existing health state, discontinue therapy, or die. Upon discontinuation, patients were assumed to receive BSC. Patients entering BSC were distributed across PASI health states based on the methotrexate response from the NMA. The manufacturer assumed that patients who respond to treatment will maintain their PASI and remain in the same health state (either PASI 75 or PASI 90) until treatment discontinuation or death.

Treatment effectiveness in the economic model was based on a manufacturer-sponsored NMA that assessed treatment response rates in terms of PASI 50, PASI 75, and PASI 90.[3]

Patients could discontinue treatment during the initial period due to lack of efficacy or adverse events (AEs), whereas in the maintenance period, patients could only discontinue treatment due to a lack of efficacy. The model did not account for AEs associated with treatments during the maintenance period; the manufacturer argued that its clinical expert suggested that serious treatment-related AEs are rare and that, as a result, they would not affect the results. Discontinuation rates during the initial phase were based on the NMA. The weekly discontinuation rate during the initial period for certolizumab pegol 200 mg and 400 mg was 0.6% and 0.4%, respectively, while the rate for all other biologics ranged

between 0.4% and 1.1%. The probability of treatment discontinuation during the maintenance period was assumed to be the same (20%) for all biologic therapies, based on real-world data evidence[4] and the constant discontinuation rates used for drugs in previous submissions to the National Institute for Health and Care Excellence for treatment of psoriasis.[5-10]

Health state utilities corresponding to PASI response scores were based on EuroQol 5-Dimensions questionnaire data from the phase III UCB clinical trials (double-blind randomized studies comparing certolizumab pegol with placebo or etanercept in patients with moderate-to-severe psoriasis).[11-13] Mortality rates were based on all-cause Canadian mortality data, adjusted by age and gender. Administration and monitoring costs were obtained from the Ontario Schedule of Benefits. Unit costs of drugs were obtained from the Ontario Drug Benefit Formulary.[16]

Manufacturer's Base Case

In the base case, the manufacturer reported that certolizumab pegol 200 mg dominated ustekinumab (i.e., certolizumab pegol
200 mg was associated with lower total costs and higher quality-adjusted life-years [QALYs]); brodalumab dominated secukinumab and guselkumab; and ixekizumab dominated etanercept 50 mg, infliximab, and certolizumab pegol 400 mg. Whereas etanercept 25 mg, adalimumab, and certolizumab pegol 200 mg were extendedly dominated.

BSC had the lowest costs and fewest QALYs followed by brodalumab, and then ixekizumab. The incremental cost-utility ratios (ICURs) were estimated in the same order: the ICUR for brodalumab compared with BSC was $148,083, while the ICUR for ixekizumab compared with brodalumab was $1,998,523 (Table 2). The manufacturer reported that certolizumab pegol 200 mg was associated with a total cost of $71,392 and 21.592 QALYs, whereas certolizumab pegol 400 mg was associated with a total cost of $131,650 and 21.642 QALYs over the lifetime analysis horizon. Certolizumab pegol 200 mg and 400 mg were either dominated or extendedly dominated in the base case. At a willingness-to-pay threshold of $50,000 per QALY gained, certolizumab pegol 200 mg and 400 mg had a 0% probability of being cost-effective.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus BSC ($)[a]	Sequential ICUR
Non-Dominated Options				
BSC	20,114	21.290	–	–
Brodalumab 210 mg	72,952	21.647	148,083	$148,083 versus BSC
Ixekizumab 80 mg	91,593	21.656	195,222	$1,998,523 versus brodalumab
Dominated Options				
Etanercept 25 mg	52,980	21.402	292,969	Subject to extended dominance by adalimumab and BSC
Adalimumab 40 mg	68,539	21.511	219,145	Subject to extended dominance by certolizumab pegol and BSC
Certolizumab pegol 200 mg	71,392	21.592	169,721	Subject to extended dominance by brodalumab and BSC

	Total Costs ($)	Total QALYs	Incremental Cost per QALY Gained Versus BSC ($)[a]	Sequential ICUR
Ustekinumab 45 mg	72,273	21.524	222,771	Dominated by certolizumab pegol 200 mg
Ustekinumab 90 mg	72,384	21.531	216,939	Dominated by certolizumab pegol 200 mg
Secukinumab 300 mg	85,021	21.636	187,657	Dominated by brodalumab
Guselkumab 100 mg	86,525	21.642	188,857	Dominated by brodalumab
Etanercept 50 mg	92,659	21.423	544,488	Dominated by ixekizumab
Infliximab 100 mg	127,124	21.640	305,329	Dominated by ixekizumab
Certolizumab pegol 400 mg	131,650	21.642	316,696	Dominated by ixekizumab

BSC = best supportive care; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Calculated by CADTH from costs reported in the manufacturer's submission and QALYs.

Source: Adapted from manufacturer's pharmacoeconomic submission.[17]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted a range of scenario analyses. Under each scenario, results in terms of costs and QALYs were estimated using probabilistic analysis.

The following scenarios were considered:

- set time horizon to 10 and 20 years
- set discount rates for both costs and benefits to 0% and 3%
- define treatment response as achievement of PASI 50
- set discontinuation rate to 10% for newer biologics and 20% for older biologics (anti–tumour necrosis factor [TNF] drugs)
- use infliximab subsequent entry biologic (SEB) as comparator instead of branded product
- increase cost of in-patient admission to $1,000 per day
- assume cost of certolizumab pegol 400 mg is the same as certolizumab pegol 200 mg
- increase BSC cost by increasing the cost of methotrexate to $500
- assume standard of care consists of 75% methotrexate, 50% phototherapy, 35% acitretin, and 15% cyclosporine
- incorporate treatment-specific utility gains
- conduct subgroup analyses of patients who are biologic-naive.

The results of the manufacturer's scenario analysis led to findings that were similar to the base-case analysis. The cost-effective options included BSC, brodalumab, and ixekizumab in all scenarios except when PASI 50 was used as the definition of treatment response, when BSC costs were increased, and when looking at the biologic-naive subpopulation. Using PASI 50 for treatment response resulted in BSC and brodalumab being the only cost-effective options, as ixekizumab was dominated, whereas increasing BSC costs resulted in brodalumab and ixekizumab being the only cost-effective options, as BSC was no longer the lowest-cost option and was dominated. In the biologic-naive population, the cost-effective options included brodalumab and ixekizumab, and the sequential ICUR for ixekizumab compared with brodalumab was $2,212,461 (Table 11). The ICURs for brodalumab and

ixekizumab ranged from $145,567 to $274,333 and from $1,481,957 to $2,603,982, respectively.

Limitations of Manufacturer's Submission

- **Uncertainty in treatment effectiveness and safety:** Certolizumab pegol has been compared head to head with placebo and etanercept; however, there is a lack of head-to-head randomized studies comparing certolizumab pegol with other biologics. Relative treatment efficacy was informed by an unpublished NMA conducted by the manufacturer; however, these estimates may not be reliable, given the limitations identified by the CADTH clinical reviewers. In particular, clinical reviewers noted there were significant concerns about model fit, convergence, and the available precision; therefore, it is not possible to reach an overall conclusion about the effectiveness of certolizumab pegol relative to other biological drugs (See CADTH Clinical Report for further details). Furthermore, the indirect comparison with methotrexate, which was used to represent BSC, was not reported by the manufacturer and, therefore, CADTH clinical reviewers were unable to appraise it. The place in therapy of certolizumab pegol is uncertain, as the currently available biologics, especially the newer drugs (anti-interleukin [IL]-17 and anti-IL-23), provide good efficacy and a durable response; in particular, some drugs provide better efficacy than certolizumab pegol at a lower cost (e.g., for PASI 75, ixekizumab is favoured over certolizumab 400 mg, at a lower average annual cost [Table 4]).

  Additionally, evidence on the long-term effectiveness of certolizumab pegol was not available. As a result, the manufacturer assumed that the difference in PASI scores between certolizumab pegol and BSC at the end of the observed follow-up period continues for patients remaining on treatment for the rest of the lifetime horizon, i.e., the model did not assess the potential waning of treatment effect of certolizumab pegol or any other biologic.

  Also, the manufacturer used a PASI response score of 75 (PASI 75) to measure treatment response during the trial period. However, the clinical expert consulted by CADTH advised that a PASI 75 response is not consistent with how treatment success is measured in clinical practice, as PASI 90 is now the preferred response score to measure treatment success. The use of a PASI 90 response may lead to different conclusions about both absolute and relative efficacy and, as a result, to different conclusions about the cost-effectiveness of certolizumab pegol. However, given the structure of the model, it was not feasible to explore the cost-effectiveness of certolizumab pegol using PASI 90 as a measure of response or using alternate assumptions about long-term treatment effect.
- **Treatment pathway does not reflect clinical practice.** The natural history of the condition was not captured in the model, as the manufacturer only modelled PASI response to treatment but did not model disease progression over time. Additionally, the manufacturer's model assumed that patients who discontinue their primary treatment switch to BSC. However, as per the clinical expert consulted by CADTH, in clinical practice, patients who discontinue or do not respond to initial treatment would likely receive a higher dose of the same drug or be switched to another active treatment. Furthermore, in clinical practice, BSC is used only prior to patients being eligible for treatment with a biologic, as noted by the manufacturer. The clinical expert consulted by CADTH also noted it is unlikely for BSC to be used as the last line of therapy. Therefore, the treatment pathway in the economic model that includes BSC as a comparator does not reflect clinical practice.

While the manufacturer's sensitivity analysis explored the use of active treatment sequences (instead of BSC), this analysis had limited value, as it only evaluated a few treatment options (up to four lines of biologics were included in the model) and assumed that the probability of response of each successive biologic treatment is independent of its position in the treatment sequence; this assumption has been considered inappropriate in previous submissions to CADTH for psoriasis.[18,19] CADTH was unable to address this limitation because of the structural limitations of the model and because of a lack of evidence on the efficacy of treatment for treatment-experienced patients.

- **Time horizon:** Given the assumption that patients who discontinue treatment receive BSC, patients in the model will spend a significant amount of time experiencing the clinical effects of BSC. This assumption was clinically inappropriate and does not reflect current clinical practice. Therefore, a time horizon of 10 years was considered more appropriate by CADTH, as a shorter time horizon will reduce the impact the BSC health state would have on model costs and outcomes.
- **Differential timing of initial assessment of treatment response:** The manufacturer assumed different time points for the initial assessment of treatment response for different comparators. For first-line treatments, the time to assessment was assumed to be either 10 weeks (infliximab), 12 weeks (etanercept, brodalumab, ixekizumab, guselkumab, secukinumab, and ustekinumab) or 16 weeks (certolizumab and adalimumab). At the assessment time, the cohort was allocated a distribution of PASI scores based on the manufacturer's submitted NMA, and patients were then subject to treatment discontinuation. Thus, the differential timing would likely impact the results of the analysis, as it impacts the duration and benefit of the treatment. The CADTH Common Drug Review (CDR) reanalysis adopted a consistent time point for the initial assessment of treatment response (16 weeks) for each biologic.
- **Cost of BSC:** The costs of BSC were based on resource use estimates from the UK (Fonia et al. [2010]);[14] however, a more recent Canadian study by Levy et al. (2012) is available.[20] CADTH used the Canadian source for BSC costs (the Levy et al. [2012] study). [20] However, patients in the Levy et al. (2012)[20] study received a mix of phototherapy and pharmacotherapy, including 13% of patients who received a biologic therapy. As biologic therapy has significantly higher costs than methotrexate (average annual drug cost of biologics and methotrexate ranges from $16,023 to $39,080 and $140 to $813, respectively), CADTH excluded pharmacotherapy (topical, systemic, and biologic therapy) and phototherapy costs from the BSC arm in order to be consistent with the BSC efficacy based on the methotrexate response assumption.
- **Exclusion of SEB price for infliximab:** An SEB for infliximab (Inflectra) was approved by Health Canada and reviewed by CDR.[3] The manufacturer's base case did not use the SEB cost for infliximab; however, the manufacturer explored the use of the SEB price for infliximab in a scenario analysis. The lowest cost for infliximab (i.e., an SEB) was used in the CADTH base case, as per CADTH costing guidelines.

CADTH Common Drug Review Reanalyses

The CADTH reanalysis could not address the following limitations: lack of evidence on long-term effectiveness of certolizumab beyond the clinical trial period; structural limitations of the model that do not correctly reflect current clinical practice, such as switching to BSC upon discontinuation of first-line therapy (instead of switching to a different biologic); and the use of PASI 75 as treatment response (instead of PASI 90). CADTH's reanalysis included the following changes to the manufacturer's base case (see results in Table 3 and Table 12):

1. Excluded BSC as comparator (although it remains as a subsequent treatment after first-line therapy)
2. Used Levy et al. (2012) as a source for BSC costs, excluding pharmacotherapy and phototherapy costs from BSC
3. Used SEB price for infliximab
4. Applied consistent time point (16 weeks) for initial assessment of treatment response for all biologics
5. Applied a 10-year time horizon
6. **CADTH base case (1 + 2 + 3 + 4 + 5).**

Scenario analyses using the CADTH base case:

6a. CADTH base case plus subgroup of patients who are biologic-naive.

Based on the CADTH sequential reanalysis of certolizumab 200 mg and 400 mg, adalimumab, ustekinumab 45 mg and 90 mg, secukinumab, ixekizumab, and etanercept 50 mg were either dominated or extendedly dominated. The following four treatments were on the cost-effectiveness efficiency frontier: etanercept 25 mg, brodalumab, infliximab, and guselkumab. Based on CADTH reanalyses: etanercept 25 mg would be cost-effective if a decision-maker is willing to pay less than $13,320 per QALY; brodalumab would be cost-effective if a decision-maker is willing to pay at least $13,320 but less than $155,758 per QALY; infliximab would be optimal if a decision-maker is willing to pay at least $155,758 but less than $407,169 per QALY; and guselkumab would be cost-effective if a decision-maker is willing to pay at least $407,169 per QALY (Table 3). At a willingness-to-pay threshold of $50,000 per QALY gained, certolizumab pegol had a 0% probability of being cost-effective.

Table 3: CADTH Base Case

	Total Costs ($)	Total QALYs	Sequential ICUR
Non-Dominated Options			
Etanercept 25 mg	120,020	7.1403	–
Brodalumab 210 mg	122,652	7.3379	$13,320
Infliximab 100 mg	123,166	7.3412	$155,758 versus brodalumab
Guselkumab 100 mg	136,684	7.3744	$407,169 versus infliximab
Dominated Options			
Certolizumab pegol 200 mg	124,822	7.3056	Dominated by infliximab
Adalimumab 40 mg	127,330	7.2373	Dominated by certolizumab pegol 200 mg
Ustekinumab 45 mg	130,688	7.2729	Dominated by certolizumab pegol 200 mg
Ustekinumab 90 mg	131,419	7.2898	Dominated by certolizumab pegol 200 mg
Secukinumab 300 mg	134,811	7.3417	Subject to extended dominance through guselkumab and infliximab

	Total Costs ($)	Total QALYs	Sequential ICUR
Ixekizumab 80 mg	140,005	7.3603	Dominated by guselkumab
Etanercept 50 mg	153,827	7.1558	Dominated by ixekizumab
Certolizumab pegol 400 mg	176,748	7.3476	Dominated by ixekizumab

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

An additional scenario analysis on the biologic-naive population produced a sequential ICUR of $81,644 for brodalumab compared with etanercept 25 mg, and an ICUR of $1,998,523 for ixekizumab compared with brodalumab. The full results of the sequential analysis can be found in Table 12.

CADTH also conducted a price-reduction scenario analysis based on the CADTH base case. A price reduction of 91% was required for certolizumab pegol 400 mg to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

Patient Input

Patient input was received from two patient groups: The Psoriasis Society of Canada and a joint submission from the Canadian Association of Psoriasis Patients and the Canadian Psoriasis Network. Patients reported the significant impact of psoriasis on their quality of life when they are not being treated or when treatment is not working; patients experience feelings of embarrassment, loss of sleep, problems with intimacy, feelings of depression, and discrimination in the workplace. Quality of life was included in the economic model by using utility values for health states defined by PASI scores.

Patients described having used several treatments with different levels of response. Many respondents stated that their treatments eventually stopped working, were too inconvenient, or had too many side effects. No consideration, however, was given to the waning of treatment effects in the manufacturer's submission. Patients mentioned the importance of access to new medications. The economic analysis did not evaluate active treatment sequences after initial treatment failure.

Caregivers of patients with psoriasis often experience emotional challenges, increased costs associated with travel to appointments and medications, lack of support, and difficulties with intimacy. This was not reflected in the manufacturer's submission, as a societal perspective was not explored.

Issues for Consideration

- According to the clinical expert consulted as part of this CDR review, there is uncertainty regarding the place in therapy for certolizumab pegol in clinical practice. There are a number of comparators available in Canada, including three original TNF inhibitors and at least two biosimilar TNF inhibitors. According to the clinical expert, the currently available biologics, especially the newer drugs (anti-IL-17 and anti-IL-23), provide good efficacy and durable response. However, certolizumab pegol is the only anti-TNF with formal pharmacokinetic studies on placental and breast-milk transfer, providing more reassuring data to clinicians and pregnant and nursing women that certolizumab pegol is safe in pregnancy and lactation.

- In 2017, two biosimilars of etanercept became available in Canada,[21,22] but these are currently not approved for the treatment of psoriasis. Additionally, a novel anti-IL-23 (risankizumab) has received Health Canada approval for the treatment of moderate-to-severe plaque psoriasis. The potential introduction of these comparators could impact the findings of the economic analysis.

Conclusions

Based on CADTH reanalyses, etanercept was the optimal therapy for moderate-to-severe psoriasis if the decision-maker's willingness to pay is less than $13,320 per QALY gained; brodalumab was the optimal therapy if the willingness-to-pay threshold is at least $13,320 but less than $155,758 per QALY gained; infliximab was the optimal therapy if the willingness-to-pay threshold is at least $155,758 but less than $407,169 per QALY gained; and guselkumab was the optimal therapy at a willingness-to-pay threshold of at least $407,169. At the recommended maintenance dose of certolizumab pegol 400 mg every 2 weeks, a reduction in the submitted price of at least 91% would be required for certolizumab pegol to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

It should be noted that there is significant uncertainty around the clinical effectiveness and, therefore, the place in therapy of certolizumab pegol. Additionally, the economic model did not allow CADTH to assess the impact of assumptions related to the waning of treatment effect and the use of treatment sequences in clinical practice. These significant limitations imply that the results of economic analysis warrant careful interpretation.

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. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 4: CADTH Common Drug Review Cost-Comparison Table for the Treatment of Plaque Psoriasis

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Certolizumab pegol	200 mg 400 mg	Pre-filled syringe or autoinjector	664.5100[a]	400 mg initial dose at weeks 0, 2, and 4 followed by 400 mg or 200 mg every two weeks	First year: 19,271 to 34,555 Subsequent years: 17,277 to 34,555
Other Biologics					
Risankizumab	75 mg/ 0.83 mL	Pre-filled syringe	2,467.5000[b]	150 mg at week 0 and 4 followed by 150 mg every 12 weeks thereafter	First year: 24,675 Subsequent years: 21,385
Adalimumab (Humira)	40 mg/0.8 mL	Syringe or pen	769.9700	80 mg initial dose, then 40 mg every other week starting one week after initial dose	First year: 21,559 Subsequent years: 20,019
Brodalumab (Siliq)	210 mg/ 1.5 mL	Pre-filled syringe	645.0000	210 mg SC at weeks 0, 1, and 2 followed by every 2 weeks thereafter	First year: 17,415 Subsequent years: 16,770
Etanercept (Enbrel)	50 mg/mL 25 mg/vial	Syringe or pen Vial	405.9850 202.9300	50 mg twice weekly for 12 weeks, then 50 mg weekly	First year: 25,975 to 25,983 Subsequent years: 21,105 to 21,111
Guselkumab (Tremfya)	100 mg/mL	Pre-filled syringe	3,059.7400[c]	100 mg SC at weeks 0 and 4 followed by every 8 weeks thereafter	First year: 21,418 Subsequent years: 19,888
Infliximab (Remicade)	100 mg/vial	Vial	977.0000[d]	5 mg/kg/dose for 3 doses (0, 2, and 6 weeks), then 5 mg/kg every 8 weeks	First year: 39,080[e] Subsequent years: 31,753[e]
Infliximab (Inflectra, SEB)			525.0000		First year: 21,000[e] Subsequent years: 17,063[e]
Infliximab (Renflexis, SEB)			493.0000		First year: 19,720[e] Subsequent years: 16,023[e]
Ixekizumab (Taltz)	80 mg/1 mL	Pre-filled syringe	1,582.2400	160 mg initial dose, 80 mg at 2, 4, 6, 8, 10, and 12 weeks followed by 80 mg every four weeks	First year: 26,898 Subsequent years: 21,559
Secukinumab (Cosentyx)	150 mg/mL	Pre-filled syringe or pen	831.1100	300 mg SC injection at weeks 0, 1, 2, and 3, then monthly injections starting at week 4	First year: 24,933 Subsequent years: 19,947

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/1 mL	Pre-filled syringe	4,593.1400	< 100 kg patients: 45 mg at weeks 0 and 4 followed by 45 mg every 12 weeks thereafter (same for > 100 kg at 90 mg)	First year: 22,966 Subsequent years: 19,904
Conventional Systemic Treatments					
Methotrexate	2.5 mg 10 mg 20 mg/2 mL 50 mg/2 mL	Tablet Tablet Vial Vial	0.6325 2.7000[d] 12.5000 8.9200	10 mg to 25 mg orally **or** IM weekly	140 to 325 232 to 813
Cyclosporine (generics)	10 mg 25 mg 50 mg 100 mg	Capsule	0.6520 0.9952 1.9400 3.8815	2.5 mg to 5 mg/kg daily in 2 divided doses	3,269 to 10,709[e]
Acitretin (generics)	10 mg 25 mg	Capsule	1.2965 2.2770	25 mg to 50 mg daily	831 to 2,366
Phosphodiesterase Type 4 Inhibitor					
Apremilast (Otezla)	30 mg	Tablet	18.9041[f]	30 mg twice daily	13,800

IM = intramuscular; SC = subcutaneous; SEB = subsequent entry biologic.

Note: All prices are from the Ontario Drug Benefit Formulary[16] (accessed May 2019) unless otherwise indicated, and do not include dispensing fees. Two biosimilars of etanercept are currently available in Canada[21,22] but are not currently approved for the treatment of psoriasis.

[a] Manufacturer's submitted price.[2]

[b] Manufacturer's submitted price.[23]

[c] IQVIA[24] (May 2019).

[d] Saskatchewan Formulary[25] (May 2019).

[e] Assumes patient weight of 90 kg and wastage of excess medication in vials, if applicable.

[f] Quebec formulary[26] (May 2019).

Appendix 2: Additional Information

Table 5: 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”			

Table 6: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

☐ Unclear

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

CDR = CADTH Common Drug Review.

Appendix 3: Summary of Other HTA Reviews of Drug

The cost-effectiveness of certolizumab pegol was assessed by the Scottish Medicines Consortium and the National Institute for Health and Care Excellence in April 2019.

Table 7: Other HTA Findings

	SMC (April 2019)[27]	NICE (April 2019)[28]
Treatment	CZP pre-filled pen or syringe (200 mg)	
Price	£357.50 per 200 mg pre-filled pen or syringe (C$625.66)[a]	
Similarities with CDR submission	• Lifetime horizon • Model structure (Markov) • Utility values derived from the clinical trials • Treatment allocation based on PASI 75 response • Treatment-related AEs were not included in the model	
Differences with CDR submission	• CZP vs. SoC, candidates for systemic non-biologic treatment, and vs. ADA, UST, SEC, and IXE in a CMA for inadequate responders to standard non-biologic systemic treatment. CDR-submitted CUA included BSC, ADA, ETAN, INF, SEC, IXE, UST, BROD, and GUS for both subgroups. • Maintenance dose CZP = 200 mg (after a 400 mg dose at weeks 0, 2, and 4), CDR-submitted CUA included two maintenance doses: 200 mg and 400 mg. • PASI response based on pooled CZP studies for systemic non-biologic treatment subgroup. All efficacy inputs in CDR submission based on NMA. • CMA most appropriate for patients who are inadequate responders to non-biologic systemic treatment.	• CZP vs. SoC for candidates for systemic non-biologic treatment, vs. ADA, ETAN, UST, SEC, IXE, BROD, and GUS for whom systemic non-biologic treatment is inadequately effective, not tolerated, or contraindicated. The CDR-submitted CUA included BSC, ADA, ETAN, INF, SEC, IXE, UST, BROD, and GUS for both subgroups. • The submission included an escalation scenario in which CZP 200 mg was escalated to 400 mg, vs. adalimumab 40 mg, which was escalated to 80 mg. • PASI response rates were based on pooled CZP studies for systemic non-biologic therapy subgroup. All efficacy inputs in the CDR submission were based on manufacturer-conducted NMA.
Results	• Annual drug cost of CZP in first year = £9,295 to £18,590 (C$16,266 to C$32,533) and £10,010 to £18,590 (C$17,518 to C$32,533) subsequently. • ICER of £20,019 (C$35,033)/QALY vs. SoC for patients who are candidates for non-biologic systemic therapy. • Incremental cost of £1,065 (C$1,864) vs. ADA, −£374 (−C$655) vs. UST 90 mg and 45 mg, −£30,454 (−C$53,295) vs. SEC, and −£31,202 (−C$54,604) vs. IXE for inadequate responders to standard non-biologic systemic treatment subgroup. • Results do not consider PAS for SEC, IXE, or CZP, although considered by SMC.	• In systemic non-biologic inadequate responders, treatment sequences starting with CZP are cost-effective vs. all other biologic comparators. • Vs. ADA escalation strategy, CZP was more efficacious but more costly: ICER = £37,054 (C$64,845) per QALY. • In the candidates for systemic non-biologic population, CZP is a cost-effective treatment option vs. the SoC treatment sequence (ICER for CZP 200 mg vs. SoC: £3,650 [C$6,388] per QALY).
Issues noted by the review group	• Uncertainty in clinical efficacy for SoC patients. Despite the limitations of the manufacturer's NMA, the SMC noted it was reasonable to suggest comparable efficacy with CZP and other biologic medicines.	• Manufacturer did not present sufficient evidence to support CZP as an alternative to systemic non-biological treatment. • Manufacturer's base case did not use biosimilar costs.

	SMC (April 2019)[27]	NICE (April 2019)[28]
	• SMC clinical experts consider place in therapy for CZP to be patients who have previously tried non-biologic treatment. • CMA uncertain due to possible dose escalation for CZP.	• Number of sequences evaluated by the manufacturer were restrictive. • Utility regression model limited to patients with DLQI ≥ 10.
Results of reanalyses by the review group	None reported.	• ICER for CZP escalation strategy vs. switching to UST = £22,618 (C$39,582) per QALY. • CZP not cost-effective in sequences where CZP is followed by UST, INF, and BSC in candidates for non-biologics. • Using INB of each treatment vs. CZP, CZP ranks second at a threshold of £20,000, and first at a threshold of £30,000.
Recommendation	SMC recommended CZP for restricted use for adult patients with moderate-to-severe plaque psoriasis who need systemic treatment. This acceptance is limited to use in patients who have not responded to or are unable to take standard systemic treatment, including ciclosporin, methotrexate, and phototherapy.	CZP recommended for adults with plaque psoriasis only if: • disease is severe and has not responded to other systemic treatment, or options are contraindicated or not tolerated • the lowest maintenance dose of CZP was used (200 mg every 2 weeks) after loading dose • manufacturer provides CZP according to PAS arrangement. Stop CZP at 16 weeks if not responded to adequately. If patients and their clinicians consider CZP to be one of a range of suitable treatments, the least expensive should be chosen.

ADA = adalimumab; BROD = brodalumab; BSC = best supportive care; C$ = Canadian dollars; CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; CUA = cost-utility analysis; CZP = certolizumab pegol; GUS = guselkumab; ICER = incremental cost-effectiveness ratio; INF = infliximab; INB = incremental net benefit; IXE = ixekizumab; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PAS = patient access scheme; PASI = Psoriasis Activity and Severity Index; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SEC = secukinumab; SoC = standard of care; SMC = Scottish Medicines Consortium; UST = ustekinumab; vs. = versus.

[a] Currency converted based on Bank of Canada rates (www.bankofcanada.ca/rates/exchange/currency-converter/) for the month of April 1, 2019. C$1 = £0.5714.[29]

Appendix 4: Reviewer Worksheets

Table 8: Data Sources

Data Input	Description of Data Source	Comment
Baseline Cohort Characteristics	Pharmacoeconomic model reflected the average patient in the pooled NMA: mean starting age of 44.9 years, 69% male.	Appropriate.
Efficacy, Safety, and Withdrawal		
Efficacy • PASI response rates	Effects of treatment on the distribution of patients across the PASI response categories were derived from the manufacturer's NMA.	Uncertain. The CADTH Clinical Review noted it is not possible to reach conclusions regarding the comparability of certolizumab pegol with other biological drugs from the analysis due to concerns about model fit, convergence, and the available precision. Additionally, the indirect comparison with methotrexate, which was representative of BSC, was not reported (see CADTH Clinical Review Report for further details). Additionally, CADTH noted a discrepancy between the PASI response distribution values included in the manufacturer's pharmacoeconomic submission and the values included in the manufacturer's NMA report. The manufacturer's submitted model seems to use the correct values reported in the NMA; however, there are still small discrepancies between the values used in the model and the values reported in the NMA. Since the discrepancies are very small (only certain values differ by < 1%) and may be due to rounding error, CADTH did not consider this to be a limitation of the model.
Adverse Events	As per the manufacturer's clinical expert's suggestion, no AEs were included in the maintenance phase, as they were assumed to be rare.	Acceptable. The exclusion of AEs in the maintenance phase will lead to longer use of certain biologics than seen in clinical practice; this assumption will likely bias results in favour of treatments with higher rates of AEs. However, due to lack of long-term safety data for the newer biologics, and as per clinical expert advice, this approach was considered acceptable.
Discontinuation	Patients may discontinue treatment in the initial period due to AEs or lack of efficacy, whereas in the maintenance period, patients may only discontinue treatment due to lack of efficacy. For discontinuation rates during the maintenance period, data from a UK registry (the British Association of Dermatologists Biologic and Immunomodulators Register [BADBIR][30]) was used; the manufacturer	Appropriate. Using equal discontinuation rates during the maintenance period was considered appropriate, as it is consistent with previous submissions to NICE and CDR.[18, 5-10]

Data Input	Description of Data Source	Comment
	assumed that all drugs have the same discontinuation rate (i.e., 20%).	
Natural History		
Mortality	Transition to death was informed by age and gender-specific all-cause mortality rates for the Canadian general population.	Appropriate.
Utilities		
Health State Utilities	Data were derived from responses to the EQ-5D utility instrument completed as part of the phase III trials.[11-13]	Appropriate. Even though the full methodology was not reported by the manufacturer, the chosen method for the increments associated with a PASI 75 response appeared appropriate.
Resource Use and Costs		
Costs	Cost of certolizumab pegol provided by the manufacturer.[2] Unit costs of relevant comparators were obtained from the Ontario Benefit Formulary.[16] Dosages were assumed to be the recommended doses from product monographs. BSC costs were based on a UK study by Fonia et al. (2010).[14]	Appropriate. Dosing regimens and drug costs were appropriate. Inappropriate. BSC costs were based on UK sources; however, Canadian sources were available[20] and should have been used instead.

AE = adverse event; BSC = best supportive care; CDR = CADTH Common Drug Review; EQ-5D = EuroQol 5-Dimensions questionnaire; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PASI = Psoriasis Area Severity Index.

Table 9: Manufacturer's Key Assumptions

Assumption	Comment
Baseline characteristics of cohort match pooled NMA characteristics.	Appropriate.
PASI definition of response.	Acceptable. The clinical expert consulted by CDR advised that a PASI 75 response is not consistent with how treatment success is measured in Canadian clinical practice, as PASI 90 is the current standard outcome. However, since comparative evidence for PASI 90 is not available for all biologic therapies used in Canada, PASI 75 is the outcome upon which comparative efficacy could be assessed.
Data on short-term clinical effectiveness indicative of long-term benefits.	Inappropriate. If clinical effectiveness reduces over time, then the cost-effectiveness of treatments in this clinical area will change significantly. This can potentially introduce significant bias in the analysis.
Movement from active treatment to BSC.	Inappropriate. It is not common for a biologic failure population to move to BSC. Additionally, the use of multiple lines of biologics is established practice, as per the clinical expert.

BSC = best supportive care; CDR = CADTH Common Drug Review; NMA = network meta-analysis; PASI = Psoriasis Area Severity Index.

Table 10: Distribution of Patients by Psoriasis Area Severity Index Response Score at the End of the Primary Response Period (Network Meta-Analysis Results)

	PASI 50 (%)	PASI 75 (%)	PASI 90 (%)
BSC	55	31	11
Certolizumab pegol 200 mg	87	70	42
Certolizumab pegol 400 mg	91	77	50
Etanercept 50 mg	66	41	17
Etanercept 25 mg	58	34	13
Infliximab	91	77	50
Secukinumab	92	78	52
Guselkumab	94	83	59
Adalimumab	80	59	31
Brodalumab	92	79	53
Ustekinumab 90 mg	87	70	42
Ustekinumab 45 mg	84	64	36
Ixekizumab	94	83	60

BSC = best supportive care; PASI = Psoriasis Area Severity Index.

Source: Adapted from manufacturer's pharmacoeconomic submission.[2]

CADTH noted a discrepancy between the Psoriasis Area Severity Index response distribution values included in the manufacturer's pharmacoeconomic submission and the values included in the manufacturer's network meta-analysis (NMA) report. The manufacturer's submitted model seems to use the correct values reported in the NMA; however, there are still small discrepancies between the values used in the model and the values reported in the NMA. Since the discrepancies are very small (only certain values differ by < 1%) and may be due to rounding error, CADTH did not consider this to be a limitation of the model.

Manufacturer's Base Case

Table 11: Summary of Results of the Manufacturer's Exploratory Analysis in the Biologic-Naive Subgroup

	Total Costs ($)	Total QALYs	Sequential ICUR
Non-Dominated Options			
Brodalumab 210 mg	736,405	21.68	–
Ixekizumab 80 mg	753,718	21.69	$2,212,461 versus brodalumab
Dominated Options			
Certolizumab pegol 200 mg	743,347	21.63	Dominated by brodalumab
Guselkumab 100 mg	749,734	21.68	Dominated by brodalumab
Secukinumab 300 mg	749,964	21.67	Dominated by brodalumab
Adalimumab 40 mg	754,224	21.55	Dominated by ixekizumab and brodalumab
Ustekinumab 90 mg	754,286	21.57	Dominated by ixekizumab and brodalumab
Ustekinumab 45 mg	754,861	21.56	Dominated by ixekizumab and brodalumab
Etanercept 25 mg	758,585	21.44	Dominated by ixekizumab and brodalumab
BSC	761,953	21.33	Dominated by ixekizumab and brodalumab

	Total Costs ($)	Total QALYs	Sequential ICUR
Infliximab 100 mg	791,263	21.68	Dominated by ixekizumab and brodalumab
Etanercept 50 mg	794,264	21.46	Dominated by ixekizumab and brodalumab
Certolizumab pegol 400 mg	795,265	21.68	Dominated by ixekizumab and brodalumab

BSC = best supportive care; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Calculated by CADTH from costs reported in manufacturer's submission and QALYs.

Source: Adapted from manufacturer's pharmacoeconomic submission.[2]

CADTH Reanalysis

Table 12: CADTH Reanalysis and Exploratory Analyses Results

	Scenario	Treatments	Total Costs ($)	Total QALYs	Sequential ICUR ($ per QALY)
	Base case submitted by manufacturer	BSC	20,114	21.290	–
		Etanercept 25 mg	52,980	21.402	Ext. dominated
		Adalimumab 40 mg	68,539	21.511	Ext. dominated
		Certolizumab pegol 200 mg	71,392	21.592	Ext. dominated
		Ustekinumab 45 mg	72,273	21.524	Dominated
		Ustekinumab 90 mg	72,384	21.531	Dominated
		Brodalumab 210 mg	72,952	21.647	$148,083
		Secukinumab 300 mg	85,021	21.636	Dominated
		Guselkumab 100 mg	86,525	21.642	Dominated
		Ixekizumab 80 mg	91,593	21.656	$1,998,523
		Etanercept 50 mg	92,659	21.423	Dominated
		Infliximab 100 mg	127,124	21.640	Dominated
		Certolizumab pegol 400 mg	131,650	21.642	Dominated
1.	**Excluding BSC as comparator**	Etanercept 25 mg	52,980	21.40	–
		Adalimumab 40 mg	68,539	21.51	Ext. dominated
		Certolizumab pegol 200 mg	71,392	21.59	Ext. dominated
		Ustekinumab 45 mg	72,273	21.52	Dominated
		Ustekinumab 90 mg	72,384	21.53	Dominated
		Brodalumab 210 mg	72,952	21.65	$81,518
		Secukinumab 300 mg	85,021	21.64	Dominated
		Guselkumab 100 mg	86,525	21.64	Dominated
		Ixekizumab 80 mg	91,593	21.656	$2,071,222
		Etanercept 50 mg	92,659	21.423	Dominated
		Infliximab 100 mg	127,124	21.64	Dominated
		Certolizumab pegol 400 mg	131,650	21.642	Dominated
2.	**BSC annual costs from Levy et al. (2012)**	BSC	318,149	21.2915	–
		Etanercept 25 mg	336,196	21.4024	Ext. dominated
		Siliq 210 mg	339,353	21.6478	$59,513
		Certolizumab pegol 200 mg	341,144	21.5937	Dominated
		Adalimumab 40 mg	343,917	21.5124	Dominated
		Ustekinumab 90 mg	346,132	21.5322	Dominated

Scenario		Treatments	Total Costs ($)	Total QALYs	Sequential ICUR ($ per QALY)
		Ustekinumab 45 mg	346,274	21.5254	Dominated
		Secukinumab 300 mg	351,962	21.6365	Dominated
		Guselkumab 100 mg	352,818	21.6433	Dominated
		Ixekizumab 80 mg	357,469	21.6583	$1,726,877
		Etanercept 50 mg	374,399	21.4246	Dominated
		Remicade 100 mg	393,775	21.6417	Dominated
		Certolizumab pegol 400 mg	398,155	21.6437	Dominated
3.	**Use of SEB cost for infliximab**	BSC	20,131	21.2915	–
		Etanercept 25 mg	62,916	21.4379	Ext. dominated
		Adalimumab 40 mg	69,960	21.5172	Ext. dominated
		Certolizumab pegol 200 mg	71,438	21.5937	Ext. dominated
		Brodalumab 210 mg	73,149	21.6485	$148,487
		Ustekinumab 45 mg	73,218	21.5288	Dominated
		Ustekinumab 90 mg	73,256	21.5354	Dominated
		Biosimilar Infliximab 100 mg	74,005	21.6462	Dominated
		Secukinumab 300 mg	85,364	21.6379	Dominated
		Guselkumab 100 mg	86,913	21.6445	Dominated
		Ixekizumab 80 mg	92,192	21.6600	$1,655,873
		Etanercept 50 mg b.i.w.	93,645	21.4280	Dominated
		Certolizumab pegol 400 mg	131,780	21.6437	Dominated
4.	**Consistent time point for assessment (16 weeks)**	BSC	20,131	21.2915	
		Etanercept 25 mg	52,492	21.3966	Ext. dominated
		Adalimumab 40 mg	68,606	21.5124	Ext. dominated
		Certolizumab pegol 200 mg	71,438	21.5937	Ext. dominated
		Brodalumab 210 mg	71,553	21.6318	$151,091
		Ustekinumab 45 mg	75,157	21.5549	Dominated
		Ustekinumab 90 mg	77,184	21.5747	Dominated
		Secukinumab 300 mg	84,971	21.6365	Ext. dominated
		Guselkumab 100 mg	89,618	21.6753	$415,481
		Etanercept 50 mg	90,726	21.4150	Dominated
		Ixekizumab 80 mg	91,701	21.6583	Dominated
		Infliximab 100 mg	126,326	21.6359	Dominated
		Certolizumab pegol 400 mg	131,780	21.6437	Dominated

Scenario		Treatments	Total Costs ($)	Total QALYs	Sequential ICUR ($ per QALY)
5.	**10-year time horizon**	BSC	6,273	7.0525	
		Etanercept 25 mg b.i.w. or 50 mg q.w.	36,342	7.1464	Ext. dominated
		Adalimumab 40 mg	50,831	7.2373	Ext. dominated
		Certolizumab pegol 200 mg	53,400	7.3056	Ext. dominated
		Ustekinumab 45 mg	54,086	7.2437	Dominated
		Ustekinumab 90 mg	54,121	7.2497	Dominated
		Brodalumab 210 mg	54,639	7.3531	$160,899
		Secukinumab 300 mg	65,847	7.3417	Dominated
		Guselkumab 100 mg	66,992	7.3421	Dominated
		Ixekizumab 80 mg	72,150	7.3603	$2,406,827
		Etanercept 50 mg b.i.w.	72,850	7.1650	Dominated
		Remicade 100 mg	104,516	7.3469	Dominated
		Certolizumab pegol 400 mg	108,342	7.3476	Dominated
6	**CADTH base case**	Etanercept 25 mg	120,020	7.1403	
		Brodalumab 210 mg	122,652	7.3379	$13,320
		Infliximab 100 mg	123,166	7.3412	$155,758
		Certolizumab pegol 200 mg	124,822	7.3056	Dominated
		Adalimumab 40 mg	127,330	7.2373	Dominated
		Ustekinumab 45 mg	130,688	7.2729	Dominated
		Ustekinumab 90 mg	131,419	7.2898	Dominated
		Secukinumab 300 mg	134,811	7.3417	Ext. dominated
		Guselkumab 100 mg	136,684	7.3744	$407,169
		Ixekizumab 80 mg	140,005	7.3603	Dominated
		Etanercept 50 mg	153,827	7.1558	Dominated
		Certolizumab pegol 400 mg	176,748	7.3476	Dominated
6a.	**CADTH base case + patients who are biologically naive**	Etanercept 25 mg	52,980	21.4021	
		Adalimumab 40 mg	68,539	21.5109	Ext. dominated
		Certolizumab pegol 200 mg	71,392	21.5920	Ext. dominated
		Ustekinumab 45 mg	72,273	21.5240	Dominated
		Ustekinumab 90 mg	72,384	21.5308	Dominated
		Brodalumab 210 mg	72,952	21.6467	$81,644
		Secukinumab 300 mg	85,021	21.6358	Dominated
		Guselkumab 100 mg	86,525	21.6415	Dominated
		Ixekizumab 80 mg	91,593	21.6560	$1,998,523
		Etanercept 50 mg	92,659	21.4231	Dominated
		Infliximab 100 mg	127,124	21.6404	Dominated
		Certolizumab pegol 400 mg	131,650	21.6421	Dominated

b.i.w. = twice weekly; BSC = best supportive care; ext. = extendedly; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; q.w. = once weekly; SEB = subsequent entry biologic.

Note: Since results are based on probabilistic analysis, the estimates may vary slightly between scenario analyses.

Detailed costs can be found in Table 13; these costs are based on deterministic results, as the manufacturer did not provide a detailed cost breakdown of the total probabilistic costs.

Table 13: Detailed Cost Results – CADTH Base Case

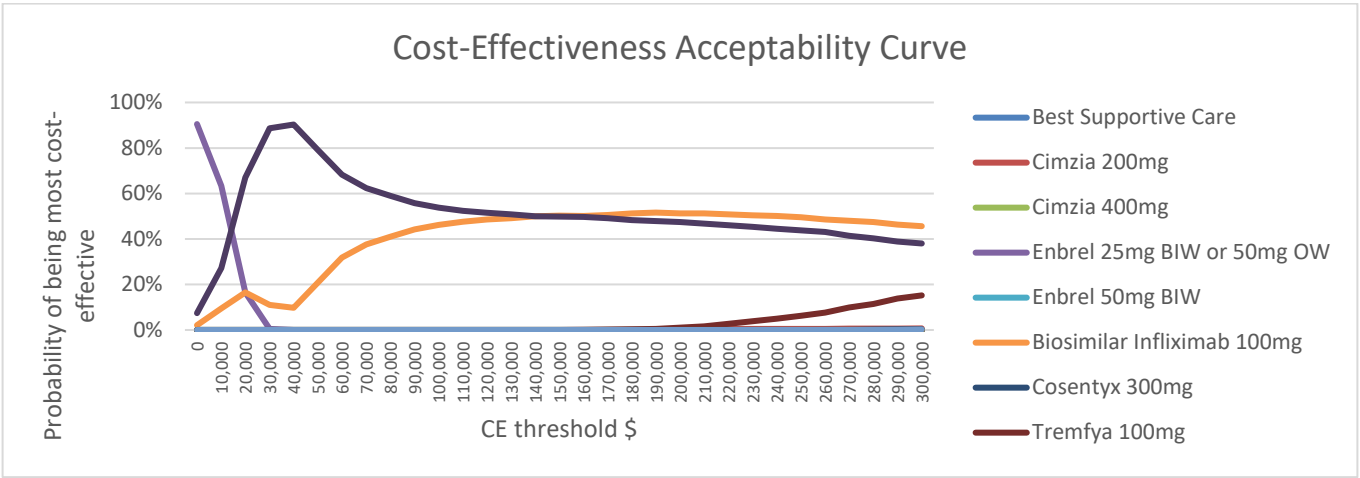
Treatment	Costs				
	Drug Acquisition ($)	Drug Administration and Monitoring ($)	Disease Management Costs ($)	TRAE/AE Costs	Total ($)
Etanercept 25 mg	30,401	1,562	88,017	0	119,980
Brodalumab 210 mg	48,854	1,277	72,546	0	122,677
Certolizumab pegol 200 mg	48,583	1,320	74,869	0	124,772
Adalimumab 40 mg	45,865	1,416	80,070	0	127,351
Ustekinumab 45 mg	51,978	1,365	77,309	0	130,652
Ustekinumab 90 mg	53,940	1,343	76,129	0	131,412
Secukinumab 300 mg	61,368	1,270	72,188	0	134,826
Guselkumab 100 mg	65,754	1,226	69,746	0	136,727
Ixekizumab 80 mg	67,675	1,250	71,065	0	139,990
Etanercept 50 mg	65,351	1,539	86,774	0	153,663
Certolizumab pegol 400 mg	103,902	1,260	71,613	0	176,775

AE = adverse event; TREA = treatment-related adverse event.

Note: detailed costs are based on deterministic results as the manufacturer did not provide a breakdown of probabilistic costs.

At a willingness-to-pay threshold of $50,000 per quality-adjusted life year (QALY) gained, certolizumab pegol 200 mg and 400 mg had a 0% probability of being cost-effective, whereas brodalumab (Siliq) had the highest probability (79%) of being cost-effective. At a willingness-to-pay threshold of $100,000 per QALY gained, certolizumab pegol 200 mg and 400 mg had a 0% probability of being cost-effective, whereas brodalumab had the highest probability (54%) of being cost-effective and infliximab had a 46% of being cost-effective (see Figure 1).

Figure 1: CADTH Base Case Cost-Effectiveness Acceptability Curve



BIW = twice weekly; CE = cost-effectiveness; OW = once weekly.

In the CADTH base case, at the recommended maintenance dose of certolizumab pegol 400 mg every two weeks, a reduction in the submitted price of at least 91% would be required for certolizumab pegol to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY. If a maintenance dose of 200 mg every two weeks is considered, a reduction in the submitted price of at least 5% would be required for certolizumab pegol to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY. Certolizumab pegol 200 mg is associated with smaller costs and therefore a significantly smaller price reduction is necessary for certolizumab pegol to be cost-effective. At a 10% reduction, certolizumab pegol 200 mg will be the lowest-cost option and therefore cost-effective at a willingness-to-pay threshold of $50,000 per QALY; however, if the payer is willing to pay approximately $83,400 per QALY, brodalumab will be the cost-effective option. Based on small differences in costs and benefits across biologics, a lack of information on the true comparator costs may have an impact on the cost-effectiveness results.

Table 14: Price Reduction for Certolizumab Pegol Based on CADTH Base Case

Price of Certolizumab Pegol		
	Base-case analysis submitted by manufacturer	**Based on the CADTH base case**
No Reduction	If λ < $148,000 BSC is optimal If $2 million > λ ≥ $148,000 brodalumab is optimal If λ ≥ $2 million ixekizumab is optimal	If λ < $13,300 etanercept is optimal If $155,800 > λ ≥ $13,300 brodalumab is optimal If $407,200 > λ ≥ $155,800 infliximab is optimal If λ ≥ $407,200 guselkumab is optimal
10% Reduction	If λ < $149,700 BSC is optimal If $1.8 million > λ ≥ $149,700 brodalumab is optimal If λ ≥ $1.8 million ixekizumab is optimal	If λ < $83,400 certolizumab pegol 200 mg is optimal If $155,800 > λ ≥ $83,400 brodalumab is optimal If $407,200 > λ ≥ $155,800 infliximab is optimal If λ ≥ $407,200 guselkumab is optimal
30% Reduction	If λ < $118,800 BSC is optimal If $309,500 > λ ≥ $118,800 certolizumab pegol 200 mg is optimal If $2.2 million > λ ≥ $309,500 brodalumab is optimal If λ ≥ $2.2 million ixekizumab is optimal	If λ < $363,800 certolizumab pegol 200 mg is optimal If $363,800 > λ ≥ $407,200 infliximab is optimal If λ ≥ $407,200 guselkumab is optimal
50% Reduction	If λ < $82,100 BSC is optimal If $501,300 > λ ≥ $82,100 certolizumab pegol 200 mg is optimal If $2.3 million > λ ≥ $501,300 brodalumab is optimal If λ ≥ $2.3 million ixekizumab is optimal	If λ < $525,800 certolizumab pegol 200 mg is optimal If λ ≥ $525,800 guselkumab is optimal
80% Reduction	If λ < $29,600 BSC is optimal If $232,300 > λ ≥ $29,600 certolizumab pegol 200 mg is optimal If $3.5 million > λ ≥ $232,300 certolizumab pegol 400 mg is optimal If λ ≥ $3.5 million, ixekizumab is optimal	If λ < $181,400 certolizumab pegol 200 mg is optimal If $1.6 million > λ ≥ $181,400 certolizumab pegol 400 mg is optimal If λ ≥ $1.6 million guselkumab is optimal
90% Reduction	If λ < $11,800 BSC is optimal	If λ < $54,600 certolizumab pegol 200 mg is optimal

Price of Certolizumab Pegol		
	Base-case analysis submitted by manufacturer	**Based on the CADTH base case**
	If $113,800 > λ ≥ $11,800 certolizumab pegol 200 mg is optimal If $4.3 million > λ ≥ $113,800 certolizumab pegol 400 mg is optimal If λ ≥ $4.3 million, ixekizumab is optimal	If $2 million > λ ≥ $54,600 certolizumab pegol 400 mg is optimal If λ ≥ $2 million guselkumab is optimal

BSC: best supportive care; λ: willingness-to-pay threshold.

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