CADTH

CADTH Common Drug Review

Pharmacoeconomic Review Report

Tildrakizumab (Ilumya)

(Sun Pharma Global FZE)

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

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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.

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

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Abbreviations

BSC	best supportive care
CEF	cost-effectiveness efficiency frontier
ICUR	incremental cost-utility ratio
PASI	Psoriasis Area and Severity Index
QALY	quality-adjusted life-year
SC	subcutaneous
SEB	subsequent entry biologic
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Tildrakizumab (Ilumya) solution for injection
Study question	Is tildrakizumab cost-effective compared with existing biologic therapies for the treatment of moderate-to-severe psoriasis in Canada?
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 or phototherapy
Treatment	Tildrakizumab as first-line therapy (100 mg administered subcutaneously at weeks 0, 4, and every 12 weeks thereafter), followed by second-line treatment with other biologics, and by BSC as third-line treatment
Outcome	QALYs
Comparators	First-line adalimumab, etanercept SEB, infliximab SEB, secukinumab, ixekizumab, ustekinumab, brodalumab, guselkumab, and risankizumab, followed by second- and third-line treatment with other biologics and BSC, respectively
Perspective	Canadian publicly funded health care payer
Time horizon	10 years
Results for base case	• Etanercept SEB, brodalumab, and risankizumab were the optimal treatment options (on the cost-effectiveness efficiency frontier), while other treatments were either dominated or extendedly dominated • Tildrakizumab was dominated by brodalumab • Etanercept SEB had the lowest cost and fewest QALYs, followed by brodalumab and risankizumab
Key limitations	• The sponsor assumed that treatment efficacy, observed during the induction period in the clinical trial, will continue until the end of the model time horizon, without supporting evidence. • The sponsor assumed that patients who discontinue their second-line treatment during the maintenance period would be switched to BSC, which comprises topical therapies. However, in clinical practice, patients who discontinue treatment would likely receive a higher dose of the same drug or switch to an active third-line treatment. • 50% of patients on second-line treatment were assumed to receive biologic treatment and the rest received a combination of methotrexate, cyclosporine, acitretin, and phototherapy; however, in clinical practice, all patients are likely to receive a second-line biologic. • The sponsor used different discontinuation rates for each treatment, which favours tildrakizumab. However, data for only 2 biologics (adalimumab and etanercept) were provided to support this assumption and no further evidence was provided for the remaining biologics, including tildrakizumab. Furthermore, the data provided were based on US claims data, which may have been subject to coverage changes and might not reflect clinical practice. • The sponsor used differential time points for the initial assessment of treatment response for different comparators. This is not reflective of clinical practice and favoured tildrakizumab, which has a longer induction period and time for initial assessment of treatment response.

CADTH estimate(s)	• In the CADTH base case, the following revisions were made: all patients received second-line biologic therapy after discontinuing first-line treatment, a 20% discontinuation rate was considered for all treatments, a 16-week induction period (i.e., time to initial assessment of treatment response) was applied to all comparators, a Canadian source for BSC costs was used, along with the cost of branded etanercept and up-to-date prices for all biologics.
	• The CADTH results aligned with those of the sponsor:
	  ○ Etanercept was associated with the lowest cost and fewest QALYs, followed by infliximab SEB, brodalumab, and then risankizumab.
	  ○ Tildrakizumab was dominated by brodalumab and infliximab (both of which are associated with a greater number of QALYs and lower total costs). At a WTP threshold of $50,000 per QALY gained, tildrakizumab had a 0% probability of being cost-effective.
	• At a price reduction of 20%, tildrakizumab would be on the cost-effectiveness efficiency frontier and cost-effective at a WTP threshold of $50,000 per QALY.
	• Results should be interpreted with caution, given the uncertainty in the long-term clinical effectiveness of tildrakizumab. Additionally, based on small differences in costs and benefits across biologics, a lack of information on true comparator costs may impact the cost-effectiveness results.

BSC = best supportive care; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; WTP = willingness to pay.

Drug	Tildrakizumab (Ilumya)
Indication	For the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Reimbursement request	As per indication
Dosage form	100 mg/mL pre-filled syringe for subcutaneous injection
NOC date	May 19, 2021
Sponsor	Sun Pharma Global FZE

Executive Summary

Background

Tildrakizumab is a humanized immunoglobulin G1 kappa monoclonal antibody indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1] Tildrakizumab is available as a solution for subcutaneous injection in a single-dose, pre-filled syringe containing 100 mg/mL of product. The recommended dose is 100 mg administered via subcutaneous injection at weeks, 0, 4, and every 12 weeks thereafter.[1] At the sponsor's submitted price of $4,935 per pre-filled syringe,[2] the annual cost of tildrakizumab is $24,675 in the first year and $21,385 thereafter.

The sponsor submitted a cost-utility analysis based on a Markov model comparing tildrakizumab with the following biologic therapies reimbursed in Canada for moderate-to-severe plaque psoriasis: adalimumab, brodalumab, etanercept subsequent entry biologic (SEB), guselkumab, infliximab SEB, ixekizumab, secukinumab, ustekinumab, and risankizumab.[2] The analysis was conducted from a Canadian publicly funded health care payer perspective using 2-week cycles over a 10-year time horizon. The model had 2 time periods: the induction period (from treatment initiation to the initial assessment of treatment response, i.e., 10 to 16 weeks), and the maintenance period. Four states were defined by the following Psoriasis Area and Severity Index (PASI) response categories: a PASI of less than 50, 50 to 74, 75 to 89, and 90 to 100. Treatment response was defined as achieving a PASI response score of 75 (PASI 75) or greater. Following the induction period, patients who achieved a PASI 75 response continued treatment in the maintenance phase until discontinuation due to loss of response or death; those who did not respond or who discontinued therapy were switched to another active therapy, as determined by the physician (second-line treatment), which included biologics (50% of patients), systemic immunosuppressants, and phototherapy. Patients who did not achieve a PASI 75 response after receiving second-line treatment and a 12-week induction period were switched to best supportive care (BSC), which comprised topical therapies. Patients continuing first- or second-line treatment were assumed to maintain the same level of PASI response and remain in the same health state until discontinuation. Once patients reached the BSC state, they remained in that state until death or the end of the model time horizon.

The probabilities of PASI 75 response were based on the tildrakizumab reSURFACE clinical trials[3] and on a network meta-analysis (NMA) published by the Institute for Clinical and Economic Reviews (ICER).[4] Discontinuation rates for both the first year of therapy and for the following years were also based on the report published by ICER.[4] Utility values were stratified according to the PASI response categories.

In the sponsor's probabilistic base case, tildrakizumab was dominated by brodalumab (i.e., tildrakizumab was more costly and associated with fewer quality-adjusted life-years [QALYs]). At a willingness-to-pay (WTP) threshold of $50,000 per QALY, tildrakizumab had a 0% probability of being cost-effective. Etanercept SEB had the lowest costs and fewest QALYs followed by brodalumab and risankizumab.

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the model submitted by the sponsor. CADTH clinical reviewers noted that even though the trials reported efficacy outcomes up to week 52 or week 64, conclusions on the comparative efficacy of tildrakizumab could only be drawn from the induction period due to the design of the studies and, as such, there is significant uncertainty around the long-term clinical effectiveness of tildrakizumab. Additionally, any efficacy outcomes reported after week 12 were reported descriptively based on observed case data, which could potentially inflate the effects of tildrakizumab (see CADTH Clinical Review Report for further details). The sponsor assumed that the clinical efficacy of treatment at the end of the induction period continues beyond the induction period; no consideration was given to the waning of treatment effects. Furthermore, the clinical expert consulted by CADTH advised that 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 result in different conclusions about the cost-effectiveness, as indirect evidence suggests that tildrakizumab may be less effective in inducing PASI 75 and PASI 90 responses compared with IL-17 inhibitors, IL-23 inhibitors, and infliximab. Unfortunately, this limitation could not be addressed through reanalysis of the model due to a lack of long-term data and the lack of flexibility with the model structure. Discontinuation rates, which were sourced from the ICER report, were based on US claims data on patients receiving adalimumab and etanercept; no evidence was provided for the remaining biologics, including tildrakizumab. Furthermore, claims data may be subject to coverage changes (as noted by ICER) and, therefore, might not fully reflect clinical practice. This is an important assumption, as the use of different discontinuation rates, along with the assumption that patients who discontinue second-line treatment switch to BSC (instead of another active treatment), favours tildrakizumab, which has the lowest discontinuation rate in the model. Additionally, the model included the use of different time points for the initial assessment of treatment response in different comparators, which is not consistent with clinical practice; an assessment time point of 16 weeks for all treatments was more reflective of clinical practice, according to the clinical expert consulted by CADTH.

The sponsor assumed that 50% of the patients on second-line treatment received biologics and the remaining 50% received a combination of methotrexate, cyclosporine, acitretin, and phototherapy. Additionally, the model assumed that patients who discontinue second-line treatment switch to BSC. In clinical practice, patients who discontinue or do not respond to treatment would likely receive a higher dose of the same drug or switch to another active treatment. In clinical practice, BSC is only used prior to patients being eligible for treatment with a biologic. CADTH addressed this limitation by assuming that 100% of the patients on second-line treatment received biologic therapy; however, CADTH was unable to address the limitation of patients receiving BSC upon discontinuation of second-line treatment because of the structural limitations of the model and a lack of evidence on treatment-experienced patients.

A costing study that estimated the direct costs of plaque psoriasis in a Canadian population was available and was a more appropriate source of BSC costs than the average costs of cortical steroids used by the sponsor, as the study also includes the cost of health care provider visits, pharmacotherapy, laboratory tests and procedures, hospitalizations, and non-conventional treatment and management. Additionally, the cost of etanercept was based on the SEB drug price. However, etanercept biosimilars are not approved for the treatment of psoriasis in Canada; therefore, the branded cost should have been used. Finally, outdated prices were used for several of the biologic treatments.

CADTH addressed some of these limitations by: assuming 100% of the patients on second-line treatment received biologic therapy; using a 20% discontinuation rate for all biologics; using the branded price for etanercept and up-to-date costs for the rest of the biologics; using a consistent time point (16 weeks) for the initial assessment of treatment response for all biologics; and, using a Canadian source for BSC costs.

Based on the CADTH reanalysis, tildrakizumab, adalimumab, guselkumab, secukinumab, ixekizumab, and ustekinumab were either dominated or extendedly dominated. Etanercept, infliximab SEB, brodalumab, and risankizumab were the optimal treatments (on the cost-effectiveness efficiency frontier [CEF]). Etanercept was associated with the lowest cost and fewest QALYs, followed by infliximab SEB, brodalumab, and then risankizumab.

Conclusions

Based on CADTH's reanalysis, tildrakizumab is not cost-effective at a WTP threshold of $50,000 per QALY; CADTH's findings on the cost-effectiveness of tildrakizumab are aligned with the sponsor's results. Some biologic drugs provide better efficacy in terms of response at a lower total cost (e.g., adalimumab, brodalumab, and infliximab have better efficacy than tildrakizumab at a lower total cost). At least a 20% reduction in the submitted price would be required for tildrakizumab to be cost-effective at a WTP threshold of $50,000 per QALY. It should be noted there is significant uncertainty around the clinical effectiveness of tildrakizumab; 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 alternative treatment sequences in clinical practice. This adds to the uncertainty of the cost-effectiveness of tildrakizumab.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a cost-utility analysis comparing tildrakizumab with the following biologic therapies reimbursed in Canada for moderate-to-severe plaque psoriasis: adalimumab, brodalumab, etanercept SEB, guselkumab, infliximab SEB, ixekizumab, risankizumab, secukinumab, and ustekinumab. The model was from the perspective of a Canadian publicly funded health care payer over a 10-year time horizon. An annual discount rate of 1.5% was applied to both costs and benefits. The target population was adult patients with moderate-to-severe psoriasis (a PASI of 8 and patches on 3% to 10% of body surface area according to the Canadian Dermatology Association guidelines). The model baseline characteristics were based on the reSURFACE clinical trials.[3]

The economic analysis was conducted using a Markov model where costs and benefits were assessed using 2-week cycles. The model was developed in Microsoft Excel and was an adaptation of the Markov York model originally developed to evaluate the cost-effectiveness of etanercept and infliximab for the treatment of psoriatic arthritis.[5] The model had 2 time periods: the induction period (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 states defined by the PASI response categories: a PASI of less than 50, 50 to 74, 75 to 89, and 90 to 100. At the point of initial assessment (i.e., end of the induction period), patients were in 1 of the aforementioned response categories based on the probability of response to treatment (Table 10 in Appendix 4). Patients who achieved a PASI response score of less than PASI 75 (i.e., the primary outcome in the clinical trials) were switched to second-line treatment, which was assumed to consist of a mix of systemic therapies, including biologics, systemic immunosuppressants, and phototherapy. The sponsor assumed that 50% of the patients receiving second-line treatment were treated with biologics (assumed to represent a mix of all biologic treatments), while the remaining 50% were treated with a combination of methotrexate, cyclosporine, acitretin, and phototherapy, based on expert clinical advice. Patients on second-line treatment who did not achieve a PASI 75 response score after a 12-week induction period were switched to BSC, which comprises topical therapies. Those with a PASI score of 75 or greater could either continue in their existing health state, discontinue therapy, or die (due to all-cause mortality). Upon discontinuation, patients were assumed to receive the next-line therapy (either second-line treatment or third-line BSC). Patients moving to BSC were distributed across PASI health states based on placebo response from the tildrakizumab reSURFACE clinical trials. Patients would either remain in this state or die (due to all-cause mortality). The sponsor assumed that patients who respond to treatment will maintain their PASI score and remain in the same health state (either PASI 75 or PASI 90) until treatment discontinuation or death.

Treatment effectiveness for tildrakizumab was based on the reSURFACE phase III trials,[3] whereas comparative efficacy was based on an NMA published by ICER, which assessed treatment response rates in terms of PASI 50, PASI 75, and PASI 90 for the rest of the biologic therapies.[4] Second-line treatment was assumed to be 10% less effective than the average of first-line treatments. The sponsor implemented this assumption by increasing by 5% the probability of achieving a PASI response of less than 50 or a PASI response of 50 to 74, while decreasing by 5% the probability of achieving a PASI 75 or PASI 90 response.

Patients could discontinue treatment due to lack of efficacy. The model did not account for adverse events associated with treatments. Discontinuation rates during and after the first year of treatment were based on the 2018 ICER report.[4] The probabilities of treatment discontinuation during the first year of therapy were based on a study that reported on US claims data from 2007 to 2012,[6] while treatment discontinuation after the first year of therapy was based on results from the Biological Treatment in Danish Dermatology (DERMBIO) registry of patients receiving ustekinumab and secukinumab for the treatment of psoriasis[7] (Table 11).

Health state utilities corresponding to PASI response scores were estimated using an additive approach in which an incremental value associated with each response category was added to a baseline utility value. The baseline utility was based on a systematic review of health utilities across conditions such as asthma, cancer, chronic disease, diabetes, and skin disease (including psoriasis).[8] The systematic review identified 3 clinical trials that included Canadian patients and compared adalimumab with placebo for the treatment of moderate-to-severe plaque psoriasis. The sponsor estimated the baseline utility as the average of the baseline utilities of patients within the placebo arm of the 3 trials identified in the review. The incremental value associated with each PASI response was sourced from a cost-utility analysis based on the ustekinumab phase III clinical trial.[9] The incremental values were added to the baseline utility in order to estimate a utility value for each PASI response health state.[9]

Mortality rates were based on all-cause Canadian mortality data.[10] The cost of BSC was calculated as the average of the following topical therapies: fluticasone propionate, amcinonide, and mometasone furoate lotions, whereas the cost of second-line treatment was calculated as the weighted average of the lowest-cost biologic, the cost of phototherapy, and the average cost of immunosuppressants. Administration costs were assumed to be covered by the sponsor's patient support programs, whereas monitoring costs were obtained from the Ontario Schedule of Benefits. Unit costs of drugs were obtained from the Ontario Drug Benefit Formulary.[11]

Sponsor's Base Case

In the base case, the sponsor reported that tildrakizumab was dominated by brodalumab (i.e., brodalumab was associated with lower total costs and higher QALYs). The sequential incremental cost-utility ratios (ICURs) were incorrectly calculated by the sponsor. This error was addressed by CADTH; the correct results are reported in Table 2. Adalimumab, tildrakizumab, secukinumab, and ustekinumab were dominated, whereas infliximab SEB, guselkumab, and ixekizumab were extendedly dominated.

Etanercept SEB had the lowest costs and fewest QALYs followed by brodalumab and then risankizumab, all of which are on the CEF. The ICURs were estimated in the same order: the ICUR for brodalumab compared with etanercept SEB was $86,703, while the ICUR for risankizumab compared with brodalumab was $839,868 (Table 2). The sponsor reported that tildrakizumab was associated with a total cost of $116,234 and 7.589 QALYs over the 10-year time horizon. At a WTP threshold of $50,000 per QALY gained, tildrakizumab had a 0% probability of being cost-effective.

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

Treatment	Total costs ($)	Total QALYs	Sequential ICUR[a]
Non-dominated options			
Etanercept SEB	56,571	7.231	—
Brodalumab	108,766	7.833	$86,703 versus etanercept SEB
Risankizumab	140,681	7.871	$839,868 versus brodalumab
Dominated options			
Infliximab SEB	81,865	7.457	Subject to extended dominance through brodalumab and etanercept SEB
Adalimumab	87,900	7.424	Dominated by infliximab SEB
Tildrakizumab	116,234	7.589	Dominated by brodalumab
Guselkumab	129,628	7.841	Subject to extended dominance through ixekizumab and brodalumab
Ixekizumab	133,520	7.859	Subject to extended dominance through risankizumab and brodalumab
Secukinumab	133,709	7.793	Dominated by brodalumab, guselkumab, ixekizumab
Ustekinumab	158,877	7.637	Dominated by brodalumab, guselkumab, ixekizumab, risankizumab, secukinumab

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.

[a] Calculated by CADTH based on the costs and QALYs reported in the sponsor's submission.

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

Summary of the Sponsor's Sensitivity Analyses

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

The following scenarios were considered:

- Time horizon set to 1, 5, and 20 years and, additionally, with an induction phase only (16 weeks).
- Discount rates for both costs and benefits set to 0% and 5%.
- Proportion of patients in second-line treatment being treated with biologics set to 25% and 75%.
- Subgroup analysis of treatment-experienced patients.

The sequential ICURs were incorrectly calculated by the sponsor; CADTH calculated sequential ICURs for each scenario from the sponsor's reported costs and QALYs. Etanercept SEB had the lowest costs and fewest QALYs in all scenarios except when the time horizon was set to the induction phase only (16 weeks).

The results of the sponsor's scenario analysis led to findings that were similar to the base-case analysis. The CEF included etanercept SEB, brodalumab, and risankizumab in all scenarios except when the time horizon was set to the induction phase only, which resulted in brodalumab being the lowest-cost option and infliximab SEB being the only biologic on the CEF. In the treatment-experienced population, the sequential ICUR for brodalumab compared with etanercept was $84,205, and the ICUR for risankizumab compared with brodalumab was $801,306 (Table 13 of Appendix 4). In the treatment-experienced population, the ICURs for brodalumab and risankizumab ranged between $42,878 to $91,526 and between $752,159 to $1,823,250, respectively.

Limitations of Sponsor's Submission

- **Uncertainty with respect to treatment effectiveness and safety.** Tildrakizumab has been compared head to head with placebo and etanercept; however, there are no head-to-head randomized studies comparing tildrakizumab with other biologics. Relative treatment efficacy was informed by the reSURFACE clinical trials[3] and by a published NMA from ICER;[4] however, these estimates may not be reliable, given the limitations identified by the CADTH clinical reviewers. In particular, the clinical reviewers noted that even though the trials reported efficacy outcomes up to week 52 and week 64, conclusions about the comparative efficacy of tildrakizumab could only be drawn from the induction period (12 weeks) due to the design of the studies and, as such, there is significant uncertainty around the long-term clinical effectiveness of tildrakizumab. Furthermore, efficacy outcomes reported after week 12 were reported descriptively based on observed case data, which could potentially inflate the effects of tildrakizumab. Additionally, the NMA report did not include an assessment of inconsistency or statistical heterogeneity (see CADTH Clinical Review Report for further details). The place in therapy of tildrakizumab is uncertain, as currently available biologics, especially the newer drugs (IL-17 and IL-23 inhibitors), provide good efficacy and durable response. Furthermore, according to the clinical expert, IL-17 inhibitors are anticipated to be favoured over IL-23 inhibitors such as tildrakizumab due to the limited data regarding the efficacy of IL-23 inhibitors in psoriatic arthritis.

  Evidence on the long-term comparative effectiveness of tildrakizumab was not available. As a result, the sponsor assumed that the difference in PASI scores between tildrakizumab and the rest of the biologics, and BSC at the end of the induction period, continues for patients remaining on treatment for the rest of the lifetime horizon, i.e., the model did not assess potential waning of the treatment effect of tildrakizumab or any other biologic. This was considered inappropriate by the clinical expert consulted by CADTH, as a reduction in the effectiveness of biologic treatments is expected over time.

  Additionally, the sponsor 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 the PASI 90 response may lead to different conclusions about both absolute and relative efficacy and result in different conclusions about the cost-effectiveness of tildrakizumab. As indicated in the CADTH Clinical Review Report, indirect evidence suggests that tildrakizumab may be less effective in inducing PASI 75 and PASI 90 responses compared with IL-17 inhibitors (ixekizumab, brodalumab, secukinumab), other IL-23 inhibitors (guselkumab, risankizumab), and infliximab, but may be more effective than etanercept (Table 10). However, given the structure of the model, it was not feasible to explore the cost-effectiveness of tildrakizumab using PASI 90 as a measure of response or using alternate assumptions about long-term treatment effects.

- **Treatment pathway does not reflect clinical practice.** The natural history of the condition was not captured in the model, as the sponsor only modelled PASI response to treatment but did not model disease progression over time. Additionally, the sponsor's model assumed that patients who discontinue their second-line treatment switch to BSC. However, as per the clinical expert consulted by CADTH, in clinical practice, patients who discontinue or do not respond to treatment would likely receive a higher dose of the same drug or switch to another biologic treatment. Furthermore, in clinical practice, BSC is only used prior to patients being eligible for treatment with a biologic. The clinical expert consulted by CADTH also noted it is unlikely for BSC to be used as the last line of therapy. This assumption has been considered inappropriate in previous submissions to CADTH for psoriasis.[12] Therefore, the treatment pathway in the economic model does not reflect clinical practice.

The sponsor included the second-line treatment health state; however, this inclusion did not fully address the treatment pathway limitation, as only 50% of the patients on second-line treatment were assumed to receive biologic therapy and the remaining patients received a combination of methotrexate, cyclosporine, acitretin, and phototherapy. CADTH addressed this limitation by assuming that 100% of the patients on second-line treatment would receive biologic therapy; however, CADTH was unable to address the limitation related to BSC as a third-line treatment because of the structural inflexibility of the model.

Uncertainty in the treatment discontinuation rate. Treatment discontinuation rates in year 1 in the economic model were based on US claims data on patients receiving adalimumab, etanercept, and a very small number receiving ustekinumab.[6] Discontinuation rates reported in the study used by the sponsor may also be due to coverage changes in the US (e.g., plans no longer supporting a particular psoriasis drug, or patients moving to different plans), as noted in the 2018 ICER report.[4] There is a lack of evidence for the remaining biologics; therefore, the sponsor assumed a discontinuation rate for infliximab between those of etanercept and adalimumab, and assumed secukinumab, ixekizumab, and brodalumab, risankizumab, guselkumab, and tildrakizumab had the same discontinuation rate as ustekinumab. This is an important assumption, because patients who discontinue second-line treatment are assumed to receive BSC (instead of an active treatment), which is associated with a very low response rate. Since tildrakizumab has the lowest discontinuation rates in the model (16% during the first year and 5% after the first year), this approach favours tildrakizumab. CADTH also noted that previous submissions to CADTH for treatments for psoriasis have used constant discontinuation rates across all treatments (typically 20%).[13-19] The discontinuation rate used for tildrakizumab in the economic model (i.e., 16%) is also lower than the rates reported in the literature for other biologics (range between 19% and 31%). Additionally, the sponsor assumed discontinuation rates would decrease after the first year. Treatment discontinuation after the first year of therapy was based on results from the Danish DERMBIO registry of patients receiving ustekinumab and secukinumab for the treatment of psoriasis. Only evidence for ustekinumab was provided to support the assumption that discontinuation rates would decrease over time; however, ustekinumab discontinuation rates for the first year and the following years are based on different study designs and might not be comparable. No further evidence was provided to support this assumption, and no evidence was provided for the remaining biologics. In line with previous CADTH reviews, CADTH took the conservative approach of using an overall discontinuation rate of 20% for all treatments during and after the first year. However, since the assumption of differential discontinuation rates was considered plausible by the clinical expert, CADTH explored this assumption as a scenario analysis.

- **Differential timing of initial assessment of treatment response.** The sponsor 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 (tildrakizumab, etanercept, brodalumab, ixekizumab, guselkumab, secukinumab, and ustekinumab) or 16 weeks (adalimumab). At the time of assessment, the cohort was allocated a distribution of PASI scores based on the ICER NMA and the reSURFACE clinical trials; 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. Furthermore, the sponsor used a 12-week induction period for tildrakizumab; however, response was evaluated at 28 weeks in the tildrakizumab clinical trials.

  The CADTH reanalysis adopted a consistent time point for the initial assessment of treatment response (16 weeks) for each biologic as per clinical expert advice, and explored a 28-week induction period for tildrakizumab and retained a 16-week period for the rest of the biologics as a scenario analysis.

- **Cost of BSC.** The cost of BSC used in the economic model is based on the average costs of cortical steroids. However, a Canadian costing study by Levy et al. is available.

CADTH considered the Levy study to be a more appropriate source of BSC costs, as it estimated the direct costs of plaque psoriasis in a Canadian population taking into account health care provider visits, frequency of prescription and over-the-counter pharmacotherapy, laboratory tests and procedures, hospitalizations, and frequency of non-conventional treatment and management. Patients in the Levy et al.[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 topical therapy (average annual drug cost of biologics ranges between $16,023 and $39,080), 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 placebo response assumption.

- **Cost of biologics.** Two biosimilars of etanercept became available in Canada,[21,22] but these are currently not approved for the treatment of psoriasis; the indication of these products is for ankylosing spondylitis and rheumatoid arthritis. The sponsor's base case used the SEB cost for etanercept; however, the branded cost should have been used. Furthermore, the sponsor used outdated prices for several of the biologic treatments (infliximab SEB, ixekizumab, and secukinumab). The branded cost of etanercept as well as the correct price of the biologics (Table 12) were used in the CADTH base case.

CADTH Common Drug Review Reanalyses

The CADTH reanalysis could not address the following limitations: the lack of evidence on the long-term effectiveness of tildrakizumab beyond the clinical trial period, and the structural limitations of the model, which do not correctly reflect current clinical practice such as switching to BSC upon discontinuation of second-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 sponsor's base case (see results in Table 3 and Table 14 in Appendix 4):

1. Assumed that 100% of the patients on second-line treatment receive biologic therapy (which represents a mix of all biologic treatments in terms of their efficacy; second-line treatment is assumed to be 10% less effective than the average of first-line treatments).
2. Used a 20% discontinuation rate for all biologics in all years.
3. Applied a consistent time point (16 weeks) for the initial assessment of treatment response for all biologics.
4. Used Levy et al. as a source for BSC costs, excluding pharmacotherapy and phototherapy costs from BSC.
5. Used the branded price for etanercept.
6. Used the correct prices of infliximab SEB, ixekizumab and secukinumab as per Table 4.
7. **CADTH base case (1 + 2 + 3 + 4 + 5 + 6).**

The following scenario analyses were conducted based on the CADTH base case:

7a. The subgroup of patients who are treatment experienced.

7b. A 28-week induction period for tildrakizumab; 16-week induction period for the rest of the biologics.

7c. The different discontinuation rates as per the sponsor's base-case analysis.

7d. An exploration of the alternative utilities from the ICER report, as per the sponsor's scenario analysis.

7e. A 20% discontinuation rate during the first year and a 5% discontinuation rate thereafter.

Based on the CADTH sequential reanalysis, adalimumab, tildrakizumab, guselkumab, secukinumab, ixekizumab, and ustekinumab were either dominated or extendedly dominated. Tildrakizumab was dominated by infliximab SEB, i.e., infliximab SEB was associated with lower total costs and higher QALYs. The following 4 treatments were on the CEF: etanercept, infliximab SEB, brodalumab, and risankizumab. Etanercept would be cost-effective if a decision-maker is willing to pay less than $5,459 per QALY, infliximab SEB would be cost-effective if a decision-maker was willing to pay at least $5,459 but less than $43,560 per QALY, brodalumab would be cost-effective if a decision-maker was willing to pay at least $43,560 but less than $879,094 per QALY, and risankizumab would be cost-effective if a decision-maker was willing to pay at least $879,094 per QALY (Table 3). At a WTP threshold of $50,000 per QALY gained, tildrakizumab had a 0% probability of being cost-effective. CADTH conducted a price-reduction analysis based on the CADTH base case. A price reduction of 20% was required for tildrakizumab to be cost-effective at a WTP threshold of $50,000 per QALY (Table 16).

Table 3: CADTH Base Case

Treatment	Total costs ($)	Total QALYs	Sequential ICUR
Non-dominated options			
Etanercept	94,206	7.246	—
Infliximab SEB	95,364	7.458	5,459
Brodalumab	97,677	7.511	43,560
Risankizumab	119,700	7.536	879,094
Dominated options			
Adalimumab	100,884	7.396	Dominated by infliximab SEB and brodalumab
Tildrakizumab	105,189	7.361	Dominated infliximab SEB and brodalumab
Guselkumab	111,642	7.517	Subject to extended dominance through ixekizumab and brodalumab
Secukinumab	116,214	7.486	Dominated by brodalumab and guselkumab
Ixekizumab	118,532	7.528	Subject to extended dominance through risankizumab and brodalumab
Ustekinumab	132,041	7.388	Dominated infliximab SEB, brodalumab, adalimumab, guselkumab, secukinumab, and risankizumab

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.

A scenario analysis assuming a 28-week induction period for tildrakizumab resulted in ICURs of $86,745 for brodalumab compared with etanercept and $824,478 for risankizumab compared with brodalumab. Whereas using the ICER report utilities resulted in ICURs of $7,252 for infliximab compared with etanercept, $46,370 for brodalumab compared with infliximab, and $919,597 for risankizumab compared with brodalumab.

An additional scenario analysis on the treatment-experienced population produced ICURs of $7,252 for infliximab compared with etanercept, $46,370 for brodalumab compared with infliximab, and $919,597 for risankizumab compared with brodalumab. Full results of the sequential analysis can be found in Table 14 of Appendix 4. Tildrakizumab was consistently dominated by brodalumab across all scenarios.

Patient Input

Patient input was received from 2 patient groups: the Canadian Organization for Rare Disorders, and a joint submission from the Canadian Association of Psoriasis Patients, the Canadian Psoriasis Network, and the Canadian Skin Patient Alliance.

Patients reported that psoriasis resulted in itchiness and pain in the inflamed skin; additionally, the skin may crack and bleed. Patients also reported the significant impact of psoriasis on their quality of life when the condition is not being effectively treated. Patients experienced feelings of embarrassment, loss of sleep, problems with intimacy, lack of self-confidence, and feelings of depression. 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. Based on the survey and interview responses, many patients reported the treatments as ineffective in addressing their key concerns; additionally, respondents stated that treatment worked only for a period of time. However, no consideration was given to the waning of treatment effects in the sponsor's submission, and the economic analysis did not evaluate active treatment sequences after initial treatment failure. Three patients had experience with tildrakizumab and were unanimous in their opinion that the drug was highly effective and that, although the long-term impact is still unknown, in the shorter term, tolerability was good.

Family members and caregivers of patients with psoriasis often experience challenges. However, this was not reflected in the sponsor's submission as a societal perspective was not explored.

Issues for Consideration

- According to the clinical expert consulted as part of this CADTH review, there is uncertainty regarding the place in therapy for tildrakizumab in clinical practice. There are a number of comparators available in Canada; if approved, tildrakizumab will be the third IL-23 blocker for the treatment of plaque psoriasis in Canada. Even though there is some dosing advantage over guselkumab, there are no advantages over risankizumab.
- In 2017, 2 biosimilars of etanercept became available in Canada. [21,22] These are currently not approved for the treatment of psoriasis. Additionally, a novel human tumour necrosis factor alpha (certolizumab pegol) 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's reanalysis, tildrakizumab is not cost-effective at a WTP of $50,000 per QALY; CADTH's findings are aligned with the sponsor's results. In the CADTH base case: etanercept was the optimal therapy for moderate-to-severe psoriasis if the decision-maker's WTP threshold is less than $5,459 per QALY; infliximab SEB was the optimal therapy if the WTP threshold is at least $5,459 but less than $43,560 per QALY; brodalumab was the optimal therapy if the WTP threshold is at least $43,560 but less than $879,094 per QALY; and, risankizumab was the optimal therapy at a WTP threshold of at least $879,094.

It should be noted that some biologic drugs provide better efficacy in terms of response at a lower total cost (e.g., adalimumab, brodalumab, and infliximab have better efficacy than tildrakizumab, at a lower total cost). At least a 20% reduction in the submitted price would be

required for tildrakizumab to be cost-effective at a WTP threshold of $50,000 per QALY. It should be noted, however, that there is significant uncertainty around the clinical effectiveness of tildrakizumab. 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 alternative treatment sequences in clinical practice. This adds to the uncertainty of the cost-effectiveness of tildrakizumab.

Appendix 1: Cost Comparison

The comparators presented in the following table 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 sponsor 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 Cost Comparison Table for the Treatment of Plaque Psoriasis

Treatment	Strength	Dosage form	Price ($)	Recommended dose	Average annual drug cost ($)
Tildrakizumab	100 mg	Pre-filled syringe	4,935.0000[a]	100 mg at weeks 0 and 4, followed by 100 mg every 12 weeks thereafter	First year: 24,675 Subsequent years: 21,385
Biologics					
Certolizumab pegol	200 mg 400 mg	Pre-filled syringe or auto-injector	664.5100[b]	400 mg initial dose at weeks 0, 2, and 4, followed by 400 mg or 200 mg every 2 weeks	First year: 19,271 to 34,555 Subsequent years: 17,277 to 34,555
Risankizumab	75 mg/0.83 mL	Pre-filled syringe	2,467.5000[c]	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, 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[d]	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[e]	5 mg/kg/dose, for 3 doses (0, 2, 6 weeks) then 5 mg/kg every 8 weeks	First year: 39,080[e] Subsequent years: 31,753[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 4 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
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

Treatment	Strength	Dosage form	Price ($)	Recommended dose	Average annual drug cost ($)
Conventional systemic treatments					
Methotrexate	2.5 mg 10 mg 20 mg/2 mL 50 mg/2 mL	Tab Tab Vial Vial	0.6325 2.7000[e] 12.5000 8.9200	10 mg to 25 mg by mouth or IM weekly	140 to 325 232 to 813
Cyclosporine (generics)	10 mg 25 mg 50 mg 100 mg	Cap	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[f]
Acitretin (generics)	10 mg 25 mg	Cap	1.2965 2.2770	25 mg to 50 mg daily	831 to 2,366
Phosphodiesterase type 4 inhibitor					
Apremilast (Otezla)	30 mg	Tab	18.904[g]	30 mg twice daily	13,800

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

Note: All prices are from the Ontario Drug Benefit Formulary (accessed August 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] Sponsor's submitted price.[23]

[b] Sponsor's submitted price.

[c] Sponsor's submitted price.[12]

[d] IQVIA (August 2019).

[e] Saskatchewan formulary (August 2019).

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

[g] Quebec formulary (August 2019).

Appendix 2: Additional Information

Table 5: Submission Quality

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

Table 6: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CADTH

☐ Adaptation of Global model/Canadian model done by the sponsor
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the sponsor
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the sponsor
☐ 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		

Appendix 3: Summary of Other HTA Reviews of Drug

The cost-effectiveness of tildrakizumab was assessed by the Scottish Medicines Consortium and the National Institute for Health and Care Excellence in July and April 2019, respectively.

Table 7: Other HTA Findings

Description	SMC (July 2019)[24]	NICE (April 2019)[25]
Treatment	Tildrakizumab (TIL) solution for injection in pre-filled syringe (100 mg)	
Price	Not reported	Redacted
Similarities with CADTH submission	• Model structure (Markov) • Tx allocation based on PASI 75 response • Tx-related AEs not included • 14-w cycle length	• Model structure (Markov) • Tx allocation based on PASI 75 response • Tx-related AEs not included
Differences with CADTH submission	• RIS and INF not included as comparators • 5-y TH (CADTH submission 10-y TH base case; 5-y as scenario analysis) • Second-line treatment not included in SMC submission • Tx discontinuation from UK BADBIR observational study and assumed consistent across all tx • Utility estimates derived using EQ-5D-3L data from reSURFACE 1 clinical study and pooled across study arms according to PASI status • SMC submission seems to have included a sponsor-conducted Bayesian NMAs, CADTH submission existing NMA was used[4] • CMA vs adalimumab and ustekinumab. CUA vs others	• Lifetime TH • RIS and INF not included as comparators • Second-line treatment not used • Base case includes tx sequences • Tx discontinuation from UK BADBIR observational study and assumed consistent for all tx • Utility estimates using EQ-5D-3L data from reSURFACE 1 clinical study • Common 14-w induction length for each tx • NICE submission seems to have included a sponsor-conducted Bayesian NMAs, in CADTH submission existing NMA used[4] • Discount rate of 3.5%
Results	• ICERs were provided for each cost-utility analysis as a pairwise comparison. Secukinumab and guselkumab were dominated by TIL, whereas brodalumab and ixekizumab were less effective but less costly • CMA results not reported — commercial in confidence	• There were 2 non-dominated sequences. The least effective and lowest cost was TIL-ustekinumab-secukinumab sequence. The ICER was £152,838 (CA$94,653)[a] per QALY vs non-TIL sequence.
Issues noted by the review group	• Costs of BSC are based on outdated data • Uncertainty in relative effectiveness of TIL • Assumptions that patients only receive one line of tx before BSC, and PASI 90 to 99 and 100 could be combined are simplifying • Utilities for BSC state assumed to be equivalent to patients' baseline utility in reSURFACE 1, despite majority being biologic-naive and therefore potentially unrepresentative	• Tx sequences included restricted number of tx and position of TIL. • Company's base case evaluated TIL with 14-w induction in base case. The indication for TIL states that a 28-w induction is appropriate. • Company calculated cost of induction for TIL and all comparators using a common 14-w stopping rule. • BSC costs from Fonia (2010) more appropriate. • European value set for EQ-5D-3L rather than the UK value set. • Company base case does not include health care costs for patients who fail to respond to biologics and switch to another tx or BSC. • INF not included.

Description	SMC (July 2019)[24]	NICE (April 2019)[25]
Results of reanalyses by the review group	None reported.	• λ = £20,000 per QALY: adalimumab, etanercept, TIL 100 mg (14 w), TIL 100 mg (28 w) cost effect vs BSC. • λ = £30,000 per QALY: adalimumab, etanercept, ustekinumab, TIL 100 mg (14 w), TIL 100 mg (28 w) cost effect vs BSC.
Recommendation	TIL recommended for patients who failed to respond to conventional systemic tx (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contraindication to these tx.	TIL recommended for treating plaque psoriasis in adults, only if disease is severe and not responded to other systemic tx, or these options are contraindicated or not tolerated Consider stopping TIL from 12 to 28 w if not at least a 50% reduction in PASI score from when treatment started. Stop TIL at 28w inadequate response.

AE = adverse event; BSC = best supportive care; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; INF = infliximab; λ = willingness-to-pay threshold; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life-year; RIS = risankizumab; SMC = Scottish Medical Consortium; TH = time horizon; TIL = tildrakizumab; tx = treatment; vs = versus; w = week.

[a] Currency converted based on Bank of Canada rates (https://www.bankofcanada.ca/rates/exchange/currency-converter/) for the month of August 2019 (CA$1 = £0.6193).

Appendix 4: Reviewer Worksheets

Table 8: Data Sources

Data input	Description of data source	Comment[a]
Baseline cohort characteristics	Baseline characteristics reflected patients in the reSURFACE clinical trials.[3]	Appropriate.
Efficacy, safety, and withdrawals		
Efficacy PASI response rates	Treatment effectiveness for tildrakizumab was based on the reSURFACE phase III trials, whereas comparative efficacy was based on a network meta-analysis (NMA) published by the Institute for Clinical and Economic Review (ICER).[4]	The CADTH Clinical Review noted that even though the trials reported efficacy outcomes up to week 52 and week 64, conclusions about the comparative efficacy of tildrakizumab could only be drawn from the induction period (12 weeks) due to the design of the studies and as such long-term results should be interpreted with caution (see CADTH Clinical Review Report for further details).
Adverse events	No adverse events were included in the model.	Acceptable. The exclusion of adverse events will lead to longer use of certain biologics than seen in clinical practice, this assumption will likely bias results in favour of other treatments. However, due to the lack of long-term safety data for the newer biologics, and as per clinical expert advice, this approach was considered acceptable.
Discontinuation	Discontinuation rates were treatment specific and were based on the 2016 ICER report. Rates during the first year were informed by US claims data[6] whereas after the first year of therapy they were estimated using the Danish DERMBIO registry of patients receiving ustekinumab and secukinumab for the treatment of psoriasis.[7]	Inappropriate. Discontinuation rates were informed by US claims data; however, discontinuation may be due to lack of efficacy or to coverage changes in the US (such as plans no longer supporting a particular drug, or patients moving to different plans). Furthermore, the study only included patients on adalimumab and etanercept and a small number on ustekinumab. The discontinuation rate used for tildrakizumab in the economic model is lower than the discontinuation rate of 20% used in previous submissions to CADTH for treatments for psoriasis; this discontinuation rate is also lower than the rates reported in the literature for other biologics. Finally, using different discontinuation rates for different biologics is inconsistent with previous submissions to CADTH. Additionally, the sponsor assumed that discontinuation rates would decrease after the first year. Only evidence for ustekinumab was provided to support this assumption, however discontinuation rates for ustekinumab were based on different studies (i.e., US claims data and the Danish DERMBIO registry) and

Data input	Description of data source	Comment[a]
		therefore might not be comparable. No further evidence was provided.
Natural history		
Mortality	The probability of death was informed by all-cause mortality rates for the Canadian general population.	Appropriate
Utilities		
Health state utilities	Health state utilities corresponding to PASI response scores were estimated using an additive approach in which an incremental value (associated with each PASI response score) was added to a baseline utility value. The baseline utility was based on a systematic review (of health utilities across conditions including asthma, cancer, chronic disease, diabetes and skin disease including psoriasis) which identified 3 clinical trials that included Canadian psoriasis patients [8], whereas the incremental value was sourced from a cost-utility analysis based on the ustekinumab phase III clinical trial.[9]	Unclear. The baseline utility was based on 3 adalimumab clinical trials including Canadian patients. However, there are a number of concerns with this approach. First, the exact proportion of Canadian patients was not reported, it is therefore uncertain if the population from the clinical trials is reflective of the Canadian population. Furthermore, this approach excluded studies without Canadian patients that might have been relevant. Second, 2 of the studies seem to be based on the same clinical trial. However, since baseline characteristics of the adalimumab clinical trials are similar to the baseline characteristics of the tildrakizumab clinical trials, and due to the lack of other estimates, CADTH adopted the sponsor's approach in the base case.
Resource use and costs		
Costs	Cost of tildrakizumab provided by the sponsor.[23] Unit costs of relevant comparators were obtained from the Ontario Drug Benefit Formulary.[11] Dosages were assumed to be the recommended doses from product monographs. Best supportive care (BSC) costs were based on the average cost of cortical steroids	Dosing regimens and drug costs were appropriate. The source is appropriate, however the sponsor used outdated prices for infliximab subsequent entry biologic (SEB), ixekizumab, and secukinumab. Furthermore, the sponsor's base case used the SEB cost for etanercept, however the branded cost should have used as etanercept SEB is not approved for the treatment of psoriasis. Details on drug costs can be found in Table 12. Appropriate. A Canadian costing study by Levy et al. (2012)[20] is available and was considered to be a more appropriate source of BSC costs by CADTH as it estimated the direct costs of plaque psoriasis in a Canadian population taking into account health care provider visits, frequency of prescription and over-the-counter pharmacotherapy, laboratory tests and procedures, hospitalizations, and frequency of non-conventional treatment and management.

Table 9: Sponsor's Key Assumptions

Assumption	Comment
Baseline characteristics of cohort match the characteristics of the reSURFACE clinical trials.	Appropriate.
PASI definition of response.	Acceptable. The clinical expert consulted by CADTH advised that PASI 75 response is not consistent with how treatment success is measured in Canadian clinical practice with PASI 90 being the current standard outcome. However, since comparative evidence for PASI 90 is not available for all biologic therapies used in Canada, and since PASI 75 is the required measure for reimbursement, PASI 75 is the outcome upon which comparative efficacy should be assessed.
Data on short-term clinical effectiveness indicative of long-term benefits.	If clinical effectiveness reduces over time, then the cost-effectiveness of treatments in this clinical area will change significantly. Furthermore, the model did not assess the potential waning of treatment effects of tildrakizumab or any other biologic. This was considered inappropriate by the clinical expert consulted by CADTH as a reduction in the effectiveness of biologic treatments is expected over time. This can potentially introduce significant bias in the analysis.
Data from the reSURFACE clinical trials and from a published NMA is indicative of comparative clinical effectiveness.	The clinical reviewers noted that even though the trials reported efficacy outcomes up to week 52 or week 64, conclusions on the comparative efficacy of tildrakizumab could only be drawn from the induction period (12 weeks) due to the design of the studies, and as such there is significant uncertainty around the long-term clinical effectiveness of tildrakizumab. Additionally, the NMA report did not include an assessment of inconsistency or statistical heterogeneity (CADTH Clinical Review).
50% of the patients on second-line treatment were assumed to be receiving biologic therapy and the remaining patients received a combination of methotrexate, cyclosporine, acitretin, and phototherapy.	Inappropriate. In clinical practice patients who discontinue or do not respond to first-line biologic treatment would likely receive a higher dose of the same drug or switch to another biologic treatment, patients will not receive standard of care.
Second-line treatment was assumed to be 10% less effective than the average of first-line treatments.	Unclear. No evidence was provided to support this assumption. Furthermore, ICER noted that data on the effectiveness of second-line targeted treatments "has not been collected in a well-controlled setting that eliminates the influence of unobserved confounding factors."[4] However, the clinical expert consulted by CADTH noted that assuming a decrease in effectiveness for second-line targeted treatments is appropriate.
Movement from active treatment to BSC at third line.	Inappropriate. Firstly, it is not common that a biologic failure population would move to BSC. Secondly, the use of multiple lines of biologics is an established practice as per the clinical expert consulted by CADTH.

Table 10: Distribution of Patients by PASI Response Score at End of the Primary Response Period (NMA Results)

Treatment	PASI < 50	PASI 50 to 74	PASI 75 to 89	PASI 90+
BSC	85%	10%	4%	1%
Second-line treatment	18%	19%	16%	48%
Tildrakizumab	15%	19%	27%	39%
Adalimumab	13%	17%	23%	47%
Brodalumab	4%	9%	18%	69%
Etanercept	27%	22%	23%	28%
Guselkumab	4%	8%	17%	71%
Infliximab	8%	13%	21%	58%
Ixekizumab	3%	8%	16%	73%
Secukinumab	6%	11%	20%	63%
Ustekinumab	13%	17%	24%	47%

BSC = best supportive care; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 11: Discontinuation Rates

	Discontinuation rate	
Treatment	First year of treatment	After first year of treatment
Second-line treatment	20%	15%
Tildrakizumab	16%	5%
Adalimumab	27%	15%
Brodalumab	16%	5%
Etanercept	35%	15%
Guselkumab	16%	5%
Infliximab	30%	15%
Ixekizumab	16%	5%
Risankizumab	16%	5%
Secukinumab	16%	5%
Ustekinumab	16%	5%

Note: The second-line treatment discontinuation rate during the first year of treatment was calculated as the average of the discontinuation rates of other targeted treatments (20%). After the first year of treatment, the second-line treatment discontinuation rate was estimated from the DERMBIO study analysis of patients who had previously received a targeted treatment (15%).

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

Table 12: Drug Costs

Treatment	Strength per unit	Pack size	Sponsor-submitted price[a]	Price revised by CADTH[b]
Tildrakizumab	100 mg	1	4,935	4,935
Adalimumab	40 mg	2	1,540	1,540
Brodalumab	210 mg	2	1,290	1,290
Etanercept	50 mg	1	255	406[c]
Guselkumab	100 mg	1	3,060	3,060
Infliximab	100 mg	1	525	493
Ixekizumab	80 mg	1	1,519	1,582
Risankizumab	75 mg	1	2,468	2,468
Secukinumab	150 mg	1	823	831
Ustekinumab	45 mg	1	4,593	4,593

[a] As per the sponsor's pharmacoeconomic submission.[2]

[b] As per the CADTH cost comparison (Table 4).

[c] Branded price of etanercept.

Sponsor's Base Case

Table 13: Summary of Results of the Sponsor's Exploratory Analysis in the Treatment-Experienced Subgroup

Treatment	Total costs ($)	Total QALYs	Sequential ICUR [a]
Non-dominated options			
Etanercept SEB	49,749	7.095	—
Brodalumab	98,167	7.670	$84,205 vs etanercept SEB
Risankizumab	127,014	7.706	$801,306 vs brodalumab
Dominated options			
Adalimumab	75,480	7.266	Dominated
Tildrakizumab	**108,732**	**7.484**	**Dominated**
Secukinumab	120,601	7.636	Dominated
Ustekinumab	141,947	7.494	Dominated
Infliximab SEB	69,822	7.276	Ext. dominated
Guselkumab	116,685	7.679	Ext. dominated
Ixekizumab	120,806	7.694	Ext. dominated

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

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

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

CADTH Reanalysis

CADTH's reanalysis (1 to 7) and scenario analyses (7a to 7e) are reported in the following table. Based on CADTH reanalysis, tildrakizumab was dominated by infliximab SEB. Tildrakizumab was consistently dominated across all scenario analyses.

Table 14: CADTH Reanalysis and Exploratory Analyses Results

Scenario		Treatment	Total costs ($)	Total QALYs	Sequential ICUR ($ per QALY)
Base case submitted by sponsor		Etanercept SEB	56,571	7.231	—
		Infliximab SEB	81,865	7.457	Ext. dominated
		Adalimumab	87,900	7.424	Dominated
		Brodalumab	108,766	7.833	$86,703
		Tildrakizumab	**116,234**	**7.589**	**Dominated**
		Guselkumab	129,628	7.841	Ext. dominated
		Ixekizumab	133,520	7.859	Ext. dominated
		Secukinumab	133,709	7.793	Dominated
		Risankizumab	140,681	7.871	$839,868
		Ustekinumab	158,877	7.637	Dominated
1	**100% of patients on second-line treatment receive biologic therapy**	Etanercept SEB	$70,525	7.222	—
		Infliximab SEB	$93,959	7.446	Ext. dominated
		Adalimumab	$99,869	7.413	Dominated
		Brodalumab	$116,010	7.821	$75,935
		Tildrakizumab	**$125,697**	**7.576**	**Dominated**
		Guselkumab	$136,861	7.830	Ext. dominated
		Ixekizumab	$140,766	7.846	Ext. dominated
		Secukinumab	$141,693	7.781	Dominated
		Risankizumab	$148,013	7.859	$842,184
		Ustekinumab	$167,420	7.624	Dominated
2	**Constant discontinuation rate (20%)**	Etanercept SEB	$55,116	7.199	—
		Infliximab SEB	$79,407	7.418	Ext. dominated
		Brodalumab	$79,414	7.477	$87,403
		Adalimumab	$83,005	7.362	Dominated
		Tildrakizumab	**$85,874**	**7.319**	**Dominated**
		Guselkumab	$93,086	7.483	Ext. dominated
		Secukinumab	$96,853	7.450	Dominated
		Ixekizumab	$97,401	7.494	Ext. dominated
		Risankizumab	$101,492	7.503	$849,154
		Ustekinumab	$112,295	7.348	Dominated
3	**Consistent time point of assessment (16 weeks)**	Etanercept SEB	$58,192	7.240	—
		Infliximab SEB	$84,999	7.476	Ext. dominated
		Adalimumab	$87,986	7.423	Dominated
		Brodalumab	$110,240	7.839	$86,891
		Tildrakizumab	**$117,475**	**7.595**	**Dominated**
		Guselkumab	$131,576	7.849	Ext. dominated
		Ixekizumab	$135,389	7.865	Ext. dominated
		Secukinumab	$135,889	7.799	Dominated
		Risankizumab	$142,966	7.878	$839,128
		Ustekinumab	$161,075	7.643	Dominated

Scenario		Treatment	Total costs ($)	Total QALYs	Sequential ICUR ($ per QALY)
4	**Levy et al. (2012) as source of BSC costs**	Etanercept SEB	$56,699	7.226	—
		Infliximab SEB	$81,813	7.449	Ext. dominated
		Adalimumab	$87,798	7.416	Dominated
		Brodalumab	$108,586	7.822	$87,055
		Tildrakizumab	**$116,050**	**7.581**	**Dominated**
		Guselkumab	$129,444	7.831	Ext. dominated
		Ixekizumab	$133,596	7.849	Ext. dominated
		Secukinumab	$133,777	7.784	Dominated
		Risankizumab	$141,217	7.862	$810,577
		Ustekinumab	$158,543	7.628	Dominated
5	**Branded price for etanercept**	Etanercept	$75,644	7.237	—
		Infliximab SEB	$83,411	7.458	$35,083
		Adalimumab	$89,424	7.426	Dominated
		Brodalumab	$109,566	7.825	$71,328
		Tildrakizumab	**$117,171**	**7.588**	**Dominated**
		Guselkumab	$130,657	7.835	Ext. dominated
		Secukinumab	$134,440	7.786	Dominated
		Ixekizumab	$134,519	7.852	Ext. dominated
		Risankizumab	$141,994	7.864	$826,579
		Ustekinumab	$159,355	7.633	Dominated
6	**Up-to-date prices for biologics**	Etanercept SEB	$56,785	7.218	—
		Infliximab SEB	$78,319	7.441	Ext. dominated
		Adalimumab	$88,040	7.409	Dominated
		Brodalumab	$108,433	7.814	$86,781
		Tildrakizumab	**$115,834**	**7.573**	**Dominated**
		Guselkumab	$129,586	7.823	Ext. dominated
		Secukinumab	$134,974	7.776	Dominated
		Ixekizumab	$138,647	7.840	Ext. dominated
		Risankizumab	$141,021	7.854	$813,300
		Ustekinumab	$158,959	7.620	Dominated
7	**CADTH base case**	Etanercept	$94,206	7.246	-
		Infliximab SEB	$95,364	7.458	$5,459
		Brodalumab	$97,677	7.511	$43,560
		Adalimumab	$100,884	7.396	Dominated
		Tildrakizumab	**$105,189**	**7.361**	**Dominated**
		Guselkumab	$111,642	7.517	Ext. dominated
		Secukinumab	$116,214	7.486	Dominated
		Ixekizumab	$118,532	7.528	Ext. dominated
		Risankizumab	$119,700	7.536	$879,094
		Ustekinumab	$132,041	7.388	Dominated

Scenario		Treatment	Total costs ($)	Total QALYs	Sequential ICUR ($ per QALY)
7a	**CADTH base case, treatment-experienced patients**	Etanercept	$94,221	7.251	—
		Infliximab SEB	$95,370	7.466	$5,360
		Brodalumab	$97,298	7.518	$36,504
		Adalimumab	$100,859	7.404	Dominated
		Tildrakizumab	**$105,271**	**7.368**	**Dominated**
		Guselkumab	$111,368	7.525	Ext. dominated
		Secukinumab	$116,329	7.494	Dominated
		Ixekizumab	$118,682	7.536	Ext. dominated
		Risankizumab	$119,784	7.543	$899,980
		Ustekinumab	$131,664	7.394	Dominated
7b	**CADTH base case + 28-week induction period for tildrakizumab**	Etanercept	$56,571	7.231	
		Infliximab SEB	$81,865	7.457	Ext. dominated
		Adalimumab	$87,900	7.424	Dominated
		Brodalumab	$108,766	7.833	$86,745
		Tildrakizumab	**$116,234**	**7.589**	**Dominated**
		Guselkumab	$129,628	7.841	Ext. dominated
		Ixekizumab	$133,520	7.859	Ext. dominated
		Secukinumab	$133,709	7.793	Dominated
		Risankizumab	$140,681	7.871	$824,478
		Ustekinumab	$158,877	7.637	Dominated
7c	**CADTH base case + Discontinuation rates from sponsor**	Etanercept	$93,570	7.244	—
		Infliximab SEB	$96,058	7.480	$10,525
		Adalimumab	$103,057	7.428	Dominated
		Brodalumab	$119,276	7.845	$63,623
		Tildrakizumab	**$129,482**	**7.598**	**Dominated**
		Guselkumab	$140,972	7.854	Ext. dominated
		Secukinumab	$146,529	7.804	Dominated
		Ixekizumab	$149,516	7.871	Ext. dominated
		Risankizumab	$151,508	7.884	$826,984
		Ustekinumab	$171,993	7.646	Dominated
7d	**CADTH base case + Utilities from ICER report**	Etanercept	$93,904	7.181	—
		Infliximab SEB	$95,307	7.374	$7,252
		Brodalumab	$97,499	7.422	$46,370
		Adalimumab	$100,930	7.312	Dominated
		Tildrakizumab	**$105,225**	**7.280**	**Dominated**
		Guselkumab	$111,470	7.425	Ext. dominated
		Secukinumab	$116,374	7.400	Dominated
		Ixekizumab	$118,821	7.436	Ext. Dom
		Risankizumab	$119,691	7.446	$919,597
		Ustekinumab	$132,085	7.307	Dominated

Scenario		Treatment	Total costs ($)	Total QALYs	Sequential ICUR ($ per QALY)
7e	CADTH base case + 20% discontinuation rate year 1, 5% in year 2	Etanercept	$109,932	7.400	—
		Infliximab SEB	$111,919	7.718	$6,248
		Brodalumab	$116,887	7.799	$61,333
		Adalimumab	$122,495	7.621	Dominated
		Tildrakizumab	$126,649	7.568	**Dominated**
		Guselkumab	$137,856	7.807	Ext. Dom
		Secukinumab	$143,650	7.761	Dominated
		Ixekizumab	$146,132	7.823	Ext. dominated
		Risankizumab	$148,332	7.836	$849,865
		Ustekinumab	$167,886	7.613	Dominated

BSC = best supportive care; ICUR = incremental cost-utility ratio; ICER = Institute for Clinical and Economic Review; QALY = quality-adjusted life-year; SEB = subsequent entry biologic.

Table 15: Detailed Cost Results — CADTH Base Case

Treatment	Costs				
	First-line costs ($)	Second-line costs ($)	Third line BSC costs ($)	Monitoring costs ($)	Total
Etanercept	49,598	40,678	2,516	1,414	94,206
Infliximab SEB	55,686	36,229	2,076	1,373	95,364
Brodalumab	59,534	35,023	1,956	1,163	97,677
Adalimumab	60,029	37,272	2,178	1,406	100,884
Tildrakizumab	63,833	38,017	2,252	1,087	105,189
Guselkumab	73,772	34,767	1,931	1,172	111,642
Secukinumab	77,208	35,692	2,023	1,291	116,214
Ixekizumab	80,664	34,620	1,917	1,331	118,532
Risankizumab	81,679	34,656	1,920	1,444	119,700
Ustekinumab	91,098	37,430	2,194	1,318	132,041

BSC = best supportive care; SEB = subsequent entry biologic.

Table 16: Price Reduction for Tildrakizumab — Based on CADTH Base Case

Price (tildrakizumab)	Sponsor's base case	CADTH's base case
No reduction	If < 87 K etanercept If $840 K > λ ≥ $87 K brodalumab If λ ≥ $840 K risankizumab	If λ < $5 K etanercept If $5 K > λ ≥ $44 K infliximab If $44 K > λ ≥ $879 K brodalumab If λ ≥ $879 K risankizumab
20% reduction	If λ < $86 K etanercept If $843 K > λ ≥ $86 K brodalumab If λ ≥ $843 K risankizumab	If λ < $30 K tildrakizumab If $30 K > λ ≥ $43 K infliximab If $43 K > λ ≥ $908 K brodalumab If λ ≥ $908 K risankizumab
30% reduction	If λ < $85 K etanercept If $91 K > λ ≥ $85 K tildrakizumab If $860 K > λ ≥ $91 K brodalumab If λ ≥ $843 K risankizumab	If λ < $76 K tildrakizumab If $76 K > λ ≥ $913 K brodalumab If λ ≥ $913 K risankizumab
50% reduction	If λ < $30 K etanercept	If λ < $158 K tildrakizumab

Price (tildrakizumab)	Sponsor's base case	CADTH's base case
	If $170 K > λ ≥ $30 K tildrakizumab If $843 K > λ ≥ $170 K brodalumab If λ ≥ $843 K risankizumab	If $158 K > λ ≥ $879 K brodalumab If λ ≥ $879 K risankizumab
60% reduction	If λ < $3 K etanercept If $211 K > λ ≥ $3 K tildrakizumab If $843 K > λ ≥ $211 K brodalumab If λ ≥ $843 K risankizumab	If λ < $203 K tildrakizumab If $203 K > λ ≥ $887 K brodalumab If λ ≥ $887 K risankizumab
70% reduction	If λ < $247 K tildrakizumab If $247 K > λ ≥ $858 K brodalumab If λ ≥ $858 K risankizumab	If λ < $245 K tildrakizumab If $245 K > λ ≥ $916 K brodalumab If λ ≥ $916 K risankizumab
90% reduction	If λ < $324 K tildrakizumab If $324 K > λ ≥ $855 K brodalumab If λ ≥ $855 K risankizumab	If λ < $329 K tildrakizumab If $329 K > λ ≥ $920 K brodalumab If λ ≥ $920 K risankizumab

BSC = best supportive care; K = thousand; λ = willingness-to-pay threshold.

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