Common Drug Review

Pharmacoeconomic Review Report

October 2015

Drug	secukinumab (Cosentyx)
Indication	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Listing request	To be listed in a similar manner to currently prescribed biologics administered by subcutaneous injection indicated for treatment of moderate to severe plaque psoriasis in adult patients, including the following: • Initial response should be assessed after 16 weeks and further doses provided only for responders.
Dosage form(s)	150 mg/1.0 mL subcutaneous injection
NOC date	February 27, 2015
Manufacturer	Novartis Pharmaceuticals Canada Inc.

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

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ABBREVIATIONS

CDR	CADTH Common Drug Review
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol Five-Dimension Health-Related Quality of Life Questionnaire
HODaR	Health Outcomes Data Repository
ICUR	incremental cost-utility ratio
MTC	mixed treatment comparison
PASI	Psoriasis Area and Severity Index
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
SC	subcutaneous
SEB	subsequent entry biologic
SoC	standard of care

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Secukinumab (Cosentyx)
Study Question	To assess the value of secukinumab 300 mg for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy, defined as having chronic plaque psoriasis considered inadequately controlled by at least one of the following therapies: topical treatment, phototherapy, or previous systemic therapy, including biologic therapy, based on the study population of ERASURE and FIXTURE
Treatment	Secukinumab 300 mg
Outcome(s)	QALY
Comparators	• SoC, consisting of oral systemic treatments (methotrexate, cyclosporine), phototherapy, and topical medications • Secukinumab 150 mg • Etanercept 50 mg • Adalimumab 40 mg • Ustekinumab 45 mg • Ustekinumab 90 mg • Infliximab (Remicade[a]) 5 mg/kg
Perspective	Publicly funded health care system
Time Horizon	10 years
Results for Base Case	• Based on the reduced price submitted during the embargo period, secukinumab 300 mg is associated with an ICUR of $78,007 per QALY compared with SoC. When comparing infliximab with secukinumab 300 mg, infliximab is associated with a sequential ICUR of $1.22 million per QALY. • All other biologics (including secukinumab 150 mg) were ruled out either by dominance[b] or extended dominance.[c]
Key Limitations	CDR noted several limitations of the manufacturer's submission: • Comparative efficacy of secukinumab 300 mg with other biologics based on a maintenance dose of 13 doses per year, while the model accounts only for the cost of 12 doses • Lack of consideration of SEB price for infliximab in the base-case analysis • Uncertainty in effectiveness of secukinumab 300 mg compared with other biologics based on submitted mixed treatment comparison • Uncertainty regarding methods used to derive utility values • Lack of subgroup analysis for treatment-naive and treatment-experienced patients.

CDR Estimates	• The CDR base case accounted for revised annual costs of secukinumab 300 mg and inclusion of SEB infliximab as a comparator, resulting in an ICUR of $82,534 for secukinumab 300 mg compared with SoC. • The use of alternative PASI-to-utility mapping algorithms in CDR's base case resulted in ICURs for secukinumab 300 mg compared with SoC ranging from $101,723 to $122,365 per QALY. • With the reduced price submitted by the manufacturer, secukinumab 300 mg dominated ustekinumab (i.e., was less costly and more effective). However, this is based on the list price of ustekinumab and may not reflect existing product listing agreements. With a 10% reduction in the list price of ustekinumab, secukinumab 300 mg was no longer dominant and was associated with an ICUR of $133,751 per QALY compared with ustekinumab.

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

[a] The brand name (Remicade) is provided here because the manufacturer used the existing brand in comparisons; there is also an SEB infliximab (Inflectra).

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

[c] An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

EXECUTIVE SUMMARY

Background

Secukinumab (Cosentyx) is an interleukin-17A inhibitor indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[1] The recommended dose is 300 mg (administered as two subcutaneous [SC] injections of 150 mg each) at weeks 0, 1, 2, and 3, then monthly starting at week 4.

The manufacturer submitted a confidential reduced price during the CADTH Common Drug Review (CDR) embargo period of [redacted] per 300 mg dose kit (two pre-filled syringes of 150 mg), [2] for an annual patient cost of [redacted] in year 1 (assuming five doses are administered in the first month and one dose in each of the following months) and [redacted] to [redacted] in subsequent years, depending on the interval between doses (28 days as per clinical trials, up to 31 days). This represents a vv% price reduction from the originally submitted price of $1,645 per 300 mg dose kit.[2]

The manufacturer is requesting that secukinumab be listed in a manner similar to other SC biologics that are indicated for the treatment of moderate to severe plaque psoriasis in adult patients, including the following: initial response should be assessed after 16 weeks, and further doses provided only for responders.

The manufacturer submitted a cost-utility analysis based on a Markov model evaluating the cost-effectiveness of secukinumab 300 mg in patients with moderate to severe plaque psoriasis who are eligible for phototherapy or systemic therapy.[3] Comparators were other biologics (etanercept 50 mg, adalimumab 40 mg, ustekinumab 45 mg and 90 mg, infliximab 5 mg/kg, and secukinumab 150 mg) as well as standard of care (SoC), defined as a combination of oral systemic drugs (methotrexate, cyclosporine), phototherapy, and topical emollients. The model made use of four-week cycles in the first year, with patients assessed for treatment response (defined as a 75% reduction in Psoriasis Area and Severity Index score [PASI 75]) at weeks 12 and 52. Annual cycles were used from years 2 to 10 and treatment response was assessed annually after the first year. Responders were assumed to continue treatment; once they had withdrawn from treatment, they would lose response and receive SoC. Non-responders and those who withdrew from treatment received SoC. Treatment efficacy values were obtained from a manufacturer-funded mixed treatment comparison (MTC). The association of PASI scores to utilities was based on a two-step mapping, from PASI response to Dermatology Life Quality Index (DLQI) scores and then to EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) utilities. The analysis was undertaken from the Canadian public payer perspective, with a time horizon of 10 years.

The manufacturer reported that secukinumab 300 mg is the most cost-effective biologic drug compared with SoC (incremental cost-utility ratio [ICUR] $78,007 per quality-adjusted life-year [QALY] with the revised price), followed by infliximab with an ICUR of more than $1.22 million per QALY when compared with secukinumab 300 mg. All other biologics (including secukinumab 150 mg) were ruled out, as they were less effective and more costly than secukinumab 300 mg, infliximab, SoC, or some combination of the three.

Summary of Identified Limitations and Key Results

CDR noted several limitations with the submitted economic analysis. A key limitation of the submitted economic model is that, while efficacy data were based on the ERASURE and FIXTURE trials in which maintenance doses were administered every four weeks (13 doses per year), treatment costs in the economic analysis were based on 12 doses per year.[4] The assumption of a dosing interval of 28 days, as per clinical trials for secukinumab 300 mg, increased the ICUR for secukinumab 300 mg compared to SoC to $82,534 per QALY.

In addition, the subsequent entry biologic (SEB) infliximab was not included as part of the manufacturer's base-case analysis. When the price of SEB infliximab is used, the sequential ICUR of infliximab compared with secukinumab 300 mg is reduced from $1.22 million per QALY to $152,694 per QALY.

Other identified limitations of the manufacturer's economic analysis include uncertainty regarding the comparative efficacy of secukinumab 300 mg versus other biologics arising from issues identified with the manufacturer-submitted MTC (see Cosentyx CDR Clinical Review report); uncertainty regarding methods to derive utility values; and lack of subgroup analysis for treatment-naive and treatment-experienced patients.

Conclusions

The manufacturer's submission was limited by the lack of direct comparative randomized controlled trials for secukinumab 300 mg and other biologics. The manufacturer's MTC attempted to address this; however, a number of limitations identified with the analysis limit the conclusions that can be drawn.

Based on the reduced price for secukinumab submitted during the embargo period, when assuming the same dosage interval for maintenance for secukinumab 300 mg as in the clinical trials (28 days, 13 doses per year) and including SEB infliximab as a comparator in the analysis, CDR found that secukinumab 300 mg was associated with an ICUR of $82,534 compared with SoC. With the reduced price, secukinumab 300 mg dominates (i.e., costs less and is more effective) ustekinumab. When comparing SEB infliximab with secukinumab, SEB infliximab was associated with a sequential ICUR of $152,694 per QALY. When accounting for uncertainty in utility values, the ICUR for secukinumab 300 mg could vary from $82,534 to $122,365 per QALY compared with SoC.

The results of the analyses were sensitive to changes in the price of comparators. Assuming a 10% lower price of ustekinumab than the current list price resulted in secukinumab 300 mg having a sequential ICUR of $133,751 per QALY compared with ustekinumab.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis comparing secukinumab 300 mg with standard of care ([SoC] defined as oral systemic therapy, phototherapy, and topical treatment) and other biologic treatments approved for the treatment of plaque psoriasis (adalimumab, ustekinumab 45 mg, ustekinumab 90 mg, etanercept, and infliximab [Remicade]) among patients with moderate to severe plaque psoriasis. The model population was assumed to have characteristics similar to patients included in ERASURE and FIXTURE, with a mean age of 45 years and weight of 86.6 kg.[4] The base-case time horizon was 10 years, using a publicly funded health care system perspective.[3]

The first 52 weeks of the Markov model consists of four health states based on Psoriasis Area and Severity Index (PASI) response (defined as the percentage reduction in score; PASI < 50, PASI 50 to 74, PASI 75 to 89, and PASI 90 to 100), with four-week cycles. Patients are treated during the first 12 weeks with the initial therapy. Transition probabilities between PASI response health states are based on a manufacturer-funded mixed treatment comparison (MTC). The probability of PASI < 50, PASI 50 to 74, PASI 75 to 89, and PASI 90 to 100 at weeks 4, 8, and 12 were calculated for all treatments relative to SoC. At week 13, those who responded (PASI ≥ 75) continued with their initial therapy, while non-responders switched to SoC. Among responders, withdrawal to SoC was assumed to be 9.7% until week 52 as per the results from the ERASURE trial.[4] Responders are assumed to receive 16 doses of secukinumab 300 mg during year 1 (six doses between weeks 0 and 12, three doses between weeks 12 and 24, and seven doses between weeks 24 and 52) and 12 doses in subsequent years.

In years 2 to 10, the model is composed of three health states (response to treatment, defined as achieving PASI ≥ 75 and continuing active therapy; non-response, defined as PASI < 75 and being switched to SoC; and death), with annual cycles. A constant annual dropout rate of 20% for years 2 to 10 was applied for all biologics. Individuals who initially respond to, then drop out of, biologic treatment transition to SoC.

The utilities associated with treatment were based on the proportion of patients in different PASI response categories (i.e., 75 to 90, 90 to 100), and change in utility from baseline was associated with different PASI responses. The utility gain associated with PASI response was taken from Pan et al.'s study,[5] which provides utilities based on Canadian data. Pan et al. initially mapped PASI response to Dermatology Life Quality Index (DLQI) scores based on ustekinumab trials in which both sets of values were collected. DLQI scores were then mapped to EuroQol 5-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) utilities using the Health Outcomes Data Repository (HODaR) database. Utilities for PASI ≥ 75 and PASI < 75 in years 2 to 10 were based on averaging PASI 75 to 89/PASI 90 to 100 and PASI < 50/PASI 50 to 74 utilities, respectively, weighted by proportion in each category at week 12.

Costs considered were drug acquisition costs and costs of monitoring and follow-up. Dosages were assumed from the product monographs. The cost of secukinumab was obtained from the manufacturer's submitted price, while the costs of all other medications were from the Ontario Drug Benefit formulary (2014).[6] Schedules of monitoring and follow-up were based on clinical expert input and consisted of doctor's visits and laboratory testing. Drug administration costs were not considered,

as the costs of injection were assumed to be covered by the manufacturer of the respective biologics. The costs of physician visits were obtained from the Ontario Health Insurance Plan schedule of benefits (2012),[7] while the costs of laboratory tests were taken from the 1999 Schedule of Benefits for Laboratory Services for Ontario.[8]

2. MANUFACTURER'S BASE CASE (BASED ON REDUCED PRICE)

The manufacturer reported in its base case that secukinumab 300 mg is associated with a total cost of $63,994 and a quality-adjusted life-year (QALY) gain of 1.146. When compared with SoC, secukinumab 300 mg was $52,655 more costly and associated with a gain of 0.675 QALYs, for an incremental cost-utility ratio (ICUR) of $78,007 per QALY (Table 17). The manufacturer reported ICURs of other treatments compared with SoC:

- $88,829 for ustekinumab 90 mg
- $141,791 for ustekinumab 45 mg
- $93,009 for adalimumab
- $113,997 for etanercept
- $133,190 for infliximab-Remicade
- $81,816 for secukinumab 150 mg.

When comparing comparators sequentially, the most cost-effective options were SoC, secukinumab 300 mg, and infliximab-Remicade. The sequential ICUR for secukinumab 300 mg compared with SoC was $78,007 per QALY, and for infliximab compared with secukinumab 300 mg, it was $1,224,643 per QALY (Table 17).

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer was not requested to provide sensitivity analysis using the reduced price, and only CADTH Common Drug Review (CDR) reanalyses will be presented in this revised report.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

The manufacturer assumed a maintenance annual cost of secukinumab 300 mg based on 12 doses per year, while efficacy data are based on 13 doses per year: While efficacy data from the manufacturer's MTC were based on the ERASURE and FIXTURE trials, in which maintenance doses were administered every four weeks (13 doses per year), costs in the manufacturer's economic model are based on 12 doses per year, assuming one dose every 30 or 31 days.[4] Incorporating the efficacy of 13 annual doses at the cost of 12 doses may bias results in favour of secukinumab 300 mg. CADTH Common Drug Review (CDR) reanalysis incorporating 13 annual administrations of secukinumab 300 mg in year 2 and beyond resulted in an ICUR of $82,534 compared with SoC. Further, in the resubmission,[2] the manufacturer reiterated that 15 doses (as opposed to 16) are to be administered in the first year — its calculations are presented in Table 4. This concurs neither with the product monograph[1] nor with the manufacturer's use of 16 doses in the first year in the economic model. CDR's calculation of first-year doses can be found in Appendix 2: NUMBER OF DOSES of Doses.

Assumption concerning the price of the subsequent entry biologic infliximab: A subsequent entry biologic (SEB) infliximab (Inflectra) was recently approved by Health Canada and reviewed by CADTH.[9] While the manufacturer included it as a comparator in a sensitivity analysis, the manufacturer assumed its price as being a 30% reduction from branded infliximab-Remicade (which costs $987.56 per vial), while the price per the Canadian Drug Expert Committee (CDEC) recommendation is a 34% reduction.[9] Using a 34% price reduction for SEB infliximab ($650 per vial for Inflectra) results in a sequential ICUR of $242,286 compared with secukinumab 300 mg. When SEB infliximab and 13 annual doses of secukinumab 300 mg are considered simultaneously, the sequential ICUR of SEB infliximab compared with secukinumab 300 mg is $152,694.

Uncertainty in comparative effectiveness of secukinumab against other biologics: Comparative effectiveness was assessed by a manufacturer-funded MTC. As noted in the Cosentyx CDR Clinical Review report, issues with the MTC include heterogeneity in the patient populations (including treatment experience and disease severity), a large number of treatment-naive patients in the phase 3 clinical trials of secukinumab, a lack of definition of treatment failure, and a low number of studies per treatment comparison — all of which introduce uncertainty into estimates of comparative effectiveness. The credible intervals [redacted] when comparing secukinumab 300 mg and ustekinumab 90 mg. Furthermore, [redacted] (see Issues for Consideration).

Uncertainty regarding utility values: The manufacturer used utility values from Pan et al., in which reduction in the PASI score is initially mapped to a DLQI score according to values from ustekinumab trials.[5] DLQI scores are then mapped to EQ-5D utilities according to a linear regression analysis developed on the basis of patients in the HODaR database for whom DLQI scores and EQ-5D utilities were available. The use of an indirect method, the existence of multiple mappings, and doubts concerning the correlation between PASI and DLQI and between DLQI and EQ-5D[10-12] introduce uncertainty regarding the manufacturer's calculated QALYs. Use of available utility mappings from recent publications[13-15] led to ICURs for secukinumab 300 mg ranging from $78,007 to $115,652 per QALY compared with SoC for the manufacturer's base case, and ranging between $101,723 and $122,365 per QALY for CDR's base case.

Lack of subgroup analyses: The manufacturer did not provide information for subgroups based on experience with previous treatment (i.e., treatment-naive, treatment-experienced, and biologic-experienced) in its economic evaluation. As noted in the Cosentyx CDR Clinical Review report, there were large numbers of treatment-naive patients in the trials that informed estimates of treatment efficacy, and these would be expected to make treatment appear more efficacious than it would be in the requested listing population. [redacted]

5. CADTH COMMON DRUG REVIEW ANALYSES (BASED ON REDUCED PRICE)

To account for the limitations identified above, the following analyses were undertaken and informed the CDR revised base case (

Table 2).

Note: During the CDR review of secukinumab, the Ontario Exceptional Access Program price for etanercept was increased from $195.3125 to $197.6350 per 25 mg vial and from $390.7425 to $395.3900 per 50 mg/mL syringe. The cost comparison table (Appendix 1) was updated; however, because this change did not affect the overall conclusions (etanercept remains dominated), the original price of etanercept was kept in the CDR analyses.

Annual Cost of Secukinumab 300 mg

Per the dosing schedules in the ERASURE and FIXTURE trials used in efficacy estimates, secukinumab 300 mg was modelled as being administered once every 28 days instead of once every 30 to 31 days, for a total of 13 yearly administrations instead of 12 (Table 18).[4]

Inclusion of Subsequent Entry Biologic Infliximab

The price of SEB infliximab, as per CDEC's recommendation on Inflectra,[9] is 34% below that of branded infliximab ($650 per vial as opposed to $987.56). CDR included SEB infliximab in its base case (Table 20**)**.

TABLE 2: CADTH COMMON DRUG REVIEW BASE CASE

	ICUR ($/QALY) for SEC 300 mg vs. SoC	Results of Sequential Analysis
Manufacturer's base case	$78,007	Sequential ICUR of $78,007 compared with SoC
CDR base case • **Recalculation of number of dose administrations in subsequent years (13 instead of 12).** • **Inclusion of SEB INF.**	$82,534	**Sequential ICUR of $82,534 compared with SoC**

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

As shown in Table 20, when considering sequential ICURs and based on public list prices of other biologics, secukinumab 300 mg was the most cost-effective drug, followed by SEB infliximab. All other biologics were either dominated or extendedly dominated.

6. CADTH COMMON DRUG REVIEW SCENARIO ANALYSES

CDR considered the effects of uncertainty in the efficacy of secukinumab 300 mg and uncertainty in utility estimates. These are tested on both the manufacturer's base case and CDR's base case.

Alternative Utility Mappings

Given the sensitivity of the results to the choice of utility values, a search for mapping studies was conducted to identify other sources of information. Three studies were identified that used a similar approach.[13-15] Considering these alternative mapping algorithms in addition to the manufacturer's base case resulted in incremental costs per QALY for secukinumab 300 mg of $78,007 to $115,652 when compared with SoC. Applying these alternative mapping algorithms to CDR's base case resulted in ICURs of $101,723 to $122,365 per QALY. In both instances, results of the sequential analysis did not change (Table 22).

7. PATIENT INPUT

Input was received from the Arthritis Consumer Experts and Canadian Skin Patient Alliance, in affiliation with the Canadian Association of Psoriasis Patients. In these inputs, patients noted that plaque psoriasis symptoms have a significant impact on their quality of life in addition to their ability to engage in the activities of daily living. This was accounted for in the model by inclusion of PASI score and the associated quality-of-life impact.

Patients noted that current treatments include methotrexate, cyclosporine, etanercept, adalimumab, infliximab, ustekinumab, topical therapies, and phototherapy. Among issues noted were treatment toxicity (such as liver and kidney damage due to oral systemic therapies), fear of liver and kidney damage, high costs, an insufficient number of options, time commitments, and difficulties in access due to the need to repeatedly file paperwork. Loss of treatment effectiveness was noted as a concern. Patients want additional options to treat their psoriasis and are eager to try new medications in the hope of better controlling their condition. Adverse events were not considered in the manufacturer's model; nor were assumptions regarding the impact of decreasing treatment effectiveness over time.

Anticipated advantages of secukinumab include better management of symptoms and the provision of an additional therapeutic option. Among patients who had tried secukinumab, there was a noted improvement in psoriasis symptoms and it was found to be easier to use than other therapies, although one patient noted that cost was prohibitive. Of side effects reported in the phase 3 trials, none were severe enough to warrant discontinuation.

8. ISSUES FOR CONSIDERATION

Comparative efficacy and costs of ustekinumab 45 mg and ustekinumab 90 mg in patients < 100 kg: Considering that the economic model is based on a patient weight of 86.6 kg, while ustekinumab 90 mg is typically used only in patients weighing more than 100 kg,[16] it could be considered as a proxy for ustekinumab 45 mg efficacy in this analysis. [redacted][17] Furthermore, as reported in Lebwohl et al.,[17] the efficacy of ustekinumab 90 mg is similar to that of ustekinumab 45 mg in patients weighing < 100 kg, and they both have the same price.

9. PRICE REDUCTION ANALYSIS

The results (e.g., whether secukinumab 300 mg is dominant over ustekinumab) are sensitive to the price of ustekinumab. CDR explored the effects of price reduction of ustekinumab (Table 25). Assuming the manufacturer's MTC findings for ustekinumab 90 mg can be applied to ustekinumab 45 mg (see the Issues for Consideration section), CDR found that a 10% reduction in the price of ustekinumab would result in it being the most cost-effective biologic (followed by secukinumab with a sequential ICUR of $133,751). Reductions of 15% or greater result in secukinumab 300 mg being ruled out through extended dominance by ustekinumab and SEB infliximab (Table 25).

10. CONCLUSIONS

The manufacturer's submission was limited by the lack of direct comparative randomized controlled trials for secukinumab 300 mg and other biologics. The manufacturer's MTC attempted to address this; however, a number of limitations were identified with the analysis that limit the conclusions that can be drawn.

Based on the reduced price for secukinumab submitted during the embargo period, when assuming the same dosage interval for maintenance for secukinumab 300 mg as in the clinical trials (28 days, 13 doses per year) and including SEB infliximab as a comparator in the analysis, CDR found that secukinumab 300 mg was associated with an ICUR of $82,534 compared with SoC. With the reduced price, secukinumab 300 mg dominates (i.e., costs less and is more effective) ustekinumab; however, the results are sensitive to the price of ustekinumab. When comparing SEB infliximab with secukinumab, SEB infliximab was associated with a sequential ICUR of $152,694 per QALY. When accounting for uncertainty in utility values, the ICUR for secukinumab 300 mg could vary from $82,534 to $122,365 per QALY compared with SoC.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, rather than actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Product Listing Agreements are not reflected in the table and therefore costs may not represent the actual costs to public drug plans.

TABLE 3: COST COMPARISON TABLE FOR TREATMENTS USED FOR TREATMENT OF PLAQUE PSORIASIS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Yearly Cost
Secukinumab (Cosentyx)	**150 mg/mL**	**Pre-filled glass syringe**	[redacted][a] **per 300 mg dose (2 × 150 mg syringes per package)**	**300 mg SC injection at weeks 0, 1, 2, and 3, then monthly injections starting week 4**	**First year:** [redacted][b] **Subsequent years:** [redacted] **to** [redacted][c]
Biologics					
Adalimumab (Humira)	40 mg/0.8 mL	Pre-filled syringe or pen	740.3600	80 mg initial dose, 40 mg every 2 weeks starting 1 week after initial dose	First year: $20,730 Subsequent years: $19,249
Etanercept (Enbrel)	50 mg/mL 25 mg	Pre-filled syringe or pen Vial	395.3900 197.6350	50 mg twice weekly for 12 weeks, then 25 mg twice weekly	First year: $25,297[d] Subsequent years: $20,554
Infliximab (Remicade)	100 mg	Vial for infusion	987.5600	5 mg/kg for 3 doses (0, 2, 6 weeks) then 5 mg/kg every 8 weeks	First year: $39,502[f] Subsequent years: $32,096[f]
Infliximab (Inflectra)			650.0000[e]		First year: $26,000[f] Subsequent years: $21,125[f]
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/mL	Pre-filled syringe	4,593.1400	45 mg at weeks 0 and 4, followed by 45 mg every 12 weeks thereafter	First year: $22,966[g] Subsequent years: $20,669[g]
Systemic treatments and phototherapy					
Methotrexate	2.5 mg 10 mg 25 mg/mL	Tablet Injection	0.6325 2.7000[h] 8.9200/injection	10 mg to 25 mg by mouth **or** IM Weekly	$132 to $329 $464
Cyclosporine (Neoral)	10 mg 25 mg 50 mg 100 mg	Capsule	0.6238 0.9952 1.9400 3.8815	2.5 mg/kg daily (rounded to 200 mg daily)	$1,304 to $1,578[i]

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Yearly Cost
Acitretin (Soriatane)	25 mg	Capsule	$4.1400	25 mg to 50 mg daily	$1,507 to $3,014
Apremilast (Otezla)[j]	10 mg[k] 20 mg[k] 30 mg	Tablet	$20.14[l]	30 mg twice daily	$14,702

IM = intramuscular; NA = not available; SC = subcutaneous.
[a] Manufacturer's revised price during embargo period.[2] Original submitted price was $1,645 per 300 mg dose.
[b] Based on 16 administrations in first year (5 doses in month 1 at weeks 0, 1, 2, 3, and 4; 11 doses from month 2 to month 12).
[c] Range between 12 and 13 doses per year, depending on frequency of dosing. Dosing every 4 weeks, as in the clinical trials, would result in 13 doses per year.
[d] $25,304 and $20,560 annually if 50 mg vials are used in place of 25 mg vials.
[e] Source: Canadian Drug Expert Committee Recommendation for Inflectra.[9]
[f] Based on mean weight of 86.6 kg from ERASURE and FIXTURE trials.[4] Assumes wastage of partially used vials. Eight treatments in the first year,
and 6.5 average in subsequent years.
[g] Five treatments in the first year, 4.5 average in subsequent years. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. In patients weighing > 100 kg, both 45 mg and 90 mg dosages were shown to be efficacious. However, 90 mg was efficacious in a higher percentage of these patients than the 45 mg dose.[16] Price for 45 mg and 90 mg is the same.
[h] Source: Saskatchewan formulary (July 2015).[18]
[i] Lower value assumes 200 mg per day; upper end assumes dosage for average body weight from ERASURE and FIXTURE trials (rounded up to 225 mg per day).[4] In all cases, 2.5 mg/kg per day on average, administered in intermittent periods of 6 months.[19]
[j] Apremilast (Otezla) is currently being reviewed by the CADTH Common Drug Review for moderate to severe plaque psoriasis.
[k] Note that the 10 mg and 20 mg dose tablets are available only through the 27-count starter pack.
[l] Apremilast cost is estimated using data for private plans in Ontario from IMS PharmaStat, using cost/unit and units/day to determine a cost/day and removing current ODB dispensing fees and mark-up rates.
Source: Ontario Drug Benefit (July 2015)[6] except where noted.

APPENDIX 2: NUMBER OF DOSES OF SECUKINUMAB IN THE FIRST YEAR OF TREATMENT

In the resubmission,[2] the manufacturer states that 15 doses are to be administered in year 1, and provides a table (Table 4) to support this contention. As per the product monograph,[1] during the first year, doses are provided at weeks 0, 1, 2, and 3, and then monthly starting week 4. Notably, the interval between dose 5 and dose 6 in the manufacturer's table was 33 days, corresponding neither to a monthly dosing schedule (as per product monograph) nor dosing every four weeks (as per clinical trials). Further, in the manufacturer's pharmacoeconomic model, 16 doses were used in the first year.

Based on CADTH Common Drug Review (CDR) calculation, when secukinumab is administered at weeks 0, 1, 2, and 3, and monthly starting week 4, 16 doses are administered in the first year (Table 5), and this number is used in CDR's analysis.

TABLE 4: MANUFACTURER'S CALCULATION OF NUMBER OF SECUKINUMAB 300 MG DOSES IN FIRST YEAR

Week 0	Week 1	Week 2	Week 3	Week 4
June 1 Dose 1	June 8 Dose 2	June 15 Dose 3	June 22 Dose 4	June 29 Dose 5
Monthly				
August 1 Dose 6 No. of days since previous dose: 33	September 1 Dose 7 No. of days since previous dose: 31	October 1 Dose 8 No. of days since previous dose: 30	November 1 Dose 9 No. of days since previous dose:31	December 1 Dose 10 No. of days since previous dose: 30
January 1 Dose 11 No. of days since previous dose: 31	February 1 Dose 12 No. of days since previous dose: 31	Mar 1 Dose 13 No. of days since previous dose:28	Apr 1 Dose 14 No. of days since previous dose: 31	May 1 Dose 15 No. of days since previous dose: 30

Source: Adapted from the manufacturer's resubmission.[2]

TABLE 5: CADTH COMMON DRUG REVIEW CALCULATIONS OF NUMBER OF SECUKINUMAB 300 MG DOSES IN FIRST YEAR

Week 0	Week 1	Week 2	Week 3	Week 4
June 1 Dose 1	June 8 Dose 2	June 15 Dose 3	June 22 Dose 4	June 29 Dose 5
Monthly				
July 29 Dose 6 No. of days since previous dose: 30	August 29 Dose 7 No. of days since previous dose: 31	September 29 Dose 8 No. of days since previous dose: 31	October 29 Dose 9 No. of days since previous dose: 30	November 29 Dose 10 No. of days since previous dose: 31
December 29 Dose 11 No. of days since previous dose: 30	January 29 Dose 12 No. of days since previous dose: 31	February 28 Dose 13 No. of days since previous dose: 30	March 29 Dose 14 No. of days since previous dose: 29	April 29 Dose 15 No. of days since previous dose: 31
May 29 Dose 16 No. of days since previous dose: 30				

APPENDIX 3: SUMMARY OF KEY OUTCOMES

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SECUKINUMAB 300 MG RELATIVE TO STANDARD OF CARE?

Secukinumab 300 mg vs. Standard of Care	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio	$78,007 per QALY					

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

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SECUKINUMAB 300 MG RELATIVE TO ETANERCEPT 50 MG?

Secukinumab 300 mg vs. Etanercept 50 mg	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio	$37,594 per QALY					

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

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SECUKINUMAB 300 MG RELATIVE TO ADALIMUMAB 40 MG?

Secukinumab 300 mg vs. Adalimumab 40 mg	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio	$52,748 per QALY					

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

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SECUKINUMAB 300 MG RELATIVE TO USTEKINUMAB 45 MG?

Secukinumab 300 mg vs. Ustekinumab 45 mg	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)			X			
Drug treatment costs alone			X			
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio	Secukinumab 300 mg dominates (less costly, more effective)					

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

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SECUKINUMAB 300 MG RELATIVE TO USTEKINUMAB 90 MG?

Secukinumab 300 mg vs. Ustekinumab 90 mg	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)			X			
Drug treatment costs alone			X			
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio	Secukinumab 300 mg dominates (less costly, more effective)					

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

TABLE 11: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SECUKINUMAB 300 MG RELATIVE TO SECUKINUMAB 150 MG?

Secukinumab 300 mg vs. Secukinumab 150 mg	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)			X			
Drug treatment costs alone			X			
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio	$45,741 per QALY					

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

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS SECUKINUMAB 300 MG RELATIVE TO INFLIXIMAB (REMICADE) 5 MG/KG?

Secukinumab 300 mg vs. Infliximab 5 mg/kg	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)	X					
Drug treatment costs alone	X					
Clinical outcomes				X		
Quality of life				X		
Incremental CE ratio **(of INF vs. SEC 300 mg)**	$1,224,643 per QALY					

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

APPENDIX 4: ADDITIONAL INFORMATION

TABLE 13: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments *Reviewer to provide comments if checking "no"*	Derivation of PASI distributions from MTC results required clarification from manufacturer. Furthermore, there was a discrepancy between information presented in Tables 9 and 14 of the manufacturer's pharmacoeconomic evaluation report and the submitted pharmacoeconomic model. The manufacturer states 15 doses of secukinumab 300 mg are to be used in year 1, while the economic model used 16 doses in year 1.		
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

MTC = mixed treatment comparison; PASI = Psoriasis Area and Severity Index; SEC = secukinumab.

TABLE 14: AUTHOR INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review
☐ Adaptation of Global model/Canadian model done by the manufacturer
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

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

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis using a Markov state-transition model to assess the cost-effectiveness of secukinumab 300 when compared with other biologic treatments (adalimumab, ustekinumab 45 mg, ustekinumab 90 mg, etanercept, and infliximab) and standard of care ([SoC] defined as oral systemic therapy, phototherapy, and topical treatment) among patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.[3] In the first 52 weeks, a Markov model with four states based on Psoriasis Area and Severity Index (PASI) response (PASI < 50, PASI 50 to 74, PASI 75 to 89, PASI 90 to 100) and four-week cycles is used (Figure 1).

In years 2 to 10, the three-state model (response to treatment defined as achieving PASI ≥ 75, non-response and withdrawal to SoC defined as PASI < 75, and death) is used, based on annual Markov cycles (Figure 2). Response is assessed after an induction period of 12 weeks. Those who responded (where response is defined as achieving PASI ≥ 75) continued with initial therapy, while non-responders switched to SoC. Treatment response is assessed at weeks 12 and 52, and annually thereafter. Responders remain on treatment until loss of treatment effectiveness (defined as failure to achieve PASI 75) or death. Non-responders and those who withdraw from treatment move to SoC and remain there until death. A 10-year time horizon and a public health care payer perspective were used.

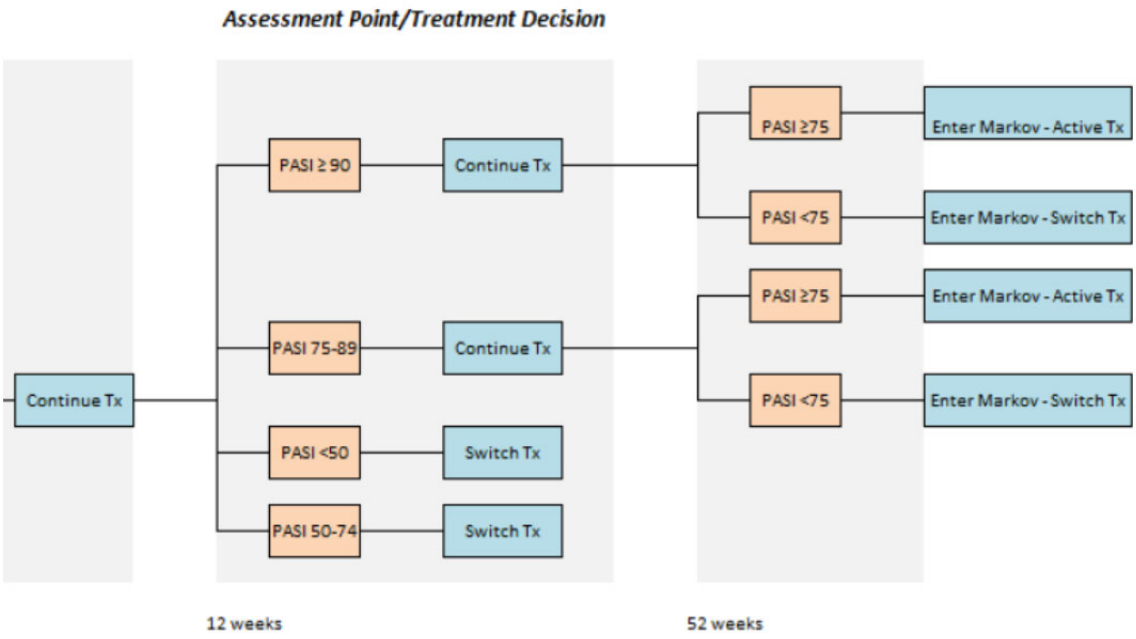
Treatment effectiveness was assessed in terms of the proportion of patients achieving a particular PASI score response at weeks 4, 8, and 12 and was assessed by a manufacturer-commissioned mixed treatment comparison (MTC). The probability of PASI < 50, PASI 50 to 74, PASI 75 to 89, and PASI 90 to 100 were calculated for all treatments relative to SoC. In total, 33 studies were assessed, including the pivotal phase 3 double-blind randomized controlled trials for secukinumab, described in detail in the Cosentyx CADTH Common Drug Review (CDR) clinical report. All treatments were assumed to have an induction period of 12 weeks, which may not be appropriate for adalimumab or ustekinumab (16 weeks in the product monograph). Among responders at week 12, withdrawal to SoC was assumed to be 9.7% until week 52, according to the results from the ERASURE trial. Thereafter, annual withdrawal probabilities were assumed to be 20%. This value was justified by noting that it is the most common probability encountered in recent pharmacoeconomic evaluations of psoriasis drugs.

The utilities associated with treatment were based on the proportion of patients in different PASI response categories (i.e., 75 to 90, 90 to 100) and change in utility from baseline associated with different PASI responses. The utility gain associated with PASI response was taken from Pan et al.'s study,[5] which provides utilities based on Canadian data. Pan et al. initially mapped PASI response to Dermatology Life Quality Index (DLQI) scores based on ustekinumab trials in which both sets of values were collected. DLQI scores were then mapped to EuroQol 5-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) utilities using the Health Outcomes Data Repository database. Utilities for PASI ≥ 75 and PASI < 75 in years 2 to 10 were based on averaging PASI 75 to 89/PASI 90 to 100 and PASI < 50/PASI 50 to 74 utilities, respectively, weighted by proportion in each category at week 12.

Costs considered were drug acquisition costs and costs of monitoring and follow-up. Dosages were assumed from the product monographs. The cost of secukinumab was obtained from the manufacturer's submitted price, while the costs of all other medications were taken from the Ontario Drug Benefit formulary (2014).[6] Schedules of monitoring and follow-up were based on clinical expert input and consisted of doctor's visits and laboratory testing. Drug administration costs were not

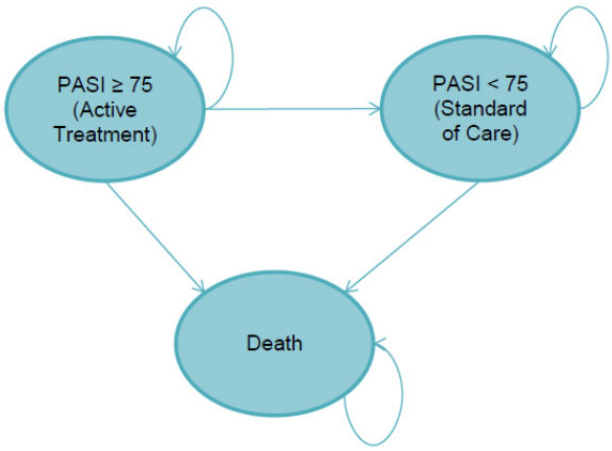
considered, as the costs of injection were assumed to be covered by the manufacturer. The costs of physician visits were obtained from the Ontario Health Insurance Plan schedule of benefits (2012),[7] while the costs of laboratory tests were obtained from the 1999 Schedule of Benefits for Laboratory Services for Ontario.[8]

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE FOR FIRST YEAR



PASI = Psoriasis Area and Severity Index; Tx = therapy.
Source: Manufacturer's pharmacoeconomic submission.[3]

FIGURE 2: MANUFACTURER'S MODEL STRUCTURE FOR YEARS 2 TO 10



PASI = Psoriasis Area and Severity Index.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 15: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Efficacy inputs to the economic model were from a manufacturer-commissioned MTC. Results from a Bayesian ordinal fixed effects analysis were used to derive distributions of PASI scores for each comparator at weeks 4, 8, and 12.	As noted in CDR's clinical report, there are concerns regarding the high degree of patient heterogeneity in terms of psoriasis severity and treatment experience.
Baseline cohort characteristics	Baseline patient age is 45 years, based on the pooled results of the phase 3 trials for secukinumab. Average weight (as required for weight-based dosing for INF and cyclosporine in SoC) is 86.6 kg, based on values from an earlier infliximab trial.	Baseline patient characteristics deemed appropriate by clinical expert
Dropout rates	Dropout rates for the first year were based on dropout rates from the ERASURE trial of secukinumab among those who responded to treatment at week 12 and did not maintain their response up to week 52.[4] All other drugs were assumed to have the same dropout rate. For years 2 to 10, an annual dropout rate of 20% was used for all biologics. This was justified by noting its use in other recent economic evaluations of biologic drugs in psoriasis.	Deemed appropriate by clinical expert.
Utilities	The utility gain associated with PASI response was taken from Pan et al.'s study.[5] Four PASI response categories are considered in the first year, while in years 2 to 10, only PASI ≥ 75 and PASI < 75 are considered. Because Pan et al. did not differentiate between these two coarser categories, the manufacturer used a weighted average of utilities based on the proportion in PASI 75 to 89 and PASI 90 to 100 at week 12 to derive a treatment-specific utility for PASI ≥ 75 in years 2 to 10.	Results are sensitive to utility gains associated with PASI scores. Alternative PASI values were considered in the CDR reanalysis. Use of PASI distributions at week 12 may be inappropriate, as it is not clear that the ratio of patients with PASI 90 to 100 response to those with PASI 75 to 89 response is constant over 10 years.
Mortality	All-cause mortality was included in the model using annual rates based on Statistics Canada data.	Appropriate
Resource use	Drug acquisition costs and costs of monitoring and follow-up, largely based on expert opinion.	
Adverse events	Adverse events were not considered.	The manufacturer's MTC did not consider safety outcomes. This has precedents in other studies. Given the higher rates of side effects seen in infliximab compared with other biologics,[20] this may be a conservative assumption.

Data Input	Description of Data Source	Comment
Costs		
Drug	• Secukinumab – manufacturer's submitted reduced price • Comparators – from the Ontario Drug Benefit Formulary (2014) • Assumption of 30% reduction in price of SEB INF	The price of SEB INF (Inflectra) from CDEC's recommendation was used in CDR's analysis.
Administration	• Costs of injections were not considered separately; instead, they were included in administration fees of drugs themselves. • Biologic-related resource use was based on Pan et al.[5] and verified by clinical expert. • Components of SoC, schedule of follow-ups, and laboratory tests were based on expert opinion. • Costs of administration from Ontario Schedule of Benefits (2013). • Costs of laboratory tests from Ontario 1999 Schedule of Benefits.	Clinical expert deemed schedule of follow-ups, complement of laboratory tests and definition of SoC to be acceptable, although it was noted that these may differ between jurisdictions.

CDEC = Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; INF = infliximab; MTC = mixed treatment comparison; PASI = Psoriasis Area and Severity Index; SEB = subsequent entry biologic; SoC = standard of care.

TABLE 16: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Set of assumptions regarding PASI-to-utility mappings: • Correlation of PASI and DLQI scores and a linear relationship between DLQI scores and EQ-5D utilities	These may be inappropriate but there is a lack of better sources. • PASI/DLQI correlation: studies differ on how well they correlate.[10,11,21] • Regarding linearity of the DLQI and EQ-5D, in different disease areas, non-linear mappings have been employed to derive utilities from disease-specific measures.[22] Furthermore, correlation between DLQI and EQ-5D has been found to be poor.[12]
20% annual withdrawal rate after year 1	INF is known to have a higher withdrawal rate than other biologics.[20] By assigning equal withdrawal probabilities to all comparators, the manufacturer is making a conservative assumption.
PASI scores after year 1 are based on a weighted average of values using distribution of PASI scores at week 12	It is uncertain how appropriate this assumption is. Given that biologic fatigue results in a general decline in treatment effectiveness over time,[23] relative proportions of PASI 90 and PASI 75 may differ.
12-week induction period for all drugs	Likely inappropriate. The ADA product monograph states that a response assessment period of 16 weeks is required.[24] May have underestimated effectiveness of ADA, as response may not have become apparent.
Cohort is 45 years old and weighs 86.6 kg.	Appropriate, as confirmed by clinical expert for this review
Adverse events are not considered.	Reasonable, as there is limited evidence, and no severe adverse events were noted in the CDR clinical review
Schedule of follow-up and monitoring	The CDR clinical expert noted that different follow-up and monitoring schedules are possible, although this did not affect the results.

Assumption	Comment
No mortality attributable to psoriasis or drugs; considered only Canadian background mortality rates	Appropriate.

ADA = adalimumab; CDR = CADTH Common Drug Review; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimension Health-Related Quality of Life Questionnaire; INF = infliximab; PASI = Psoriasis Area and Severity Index.

Manufacturer's Results (Based on Reduced Price)

Base Case

The manufacturer's base case found secukinumab 300 mg to have an incremental cost-utility ratio (ICUR) of $78,007 per QALY when compared with SoC (Table 17).

TABLE 17: MANUFACTURER'S BASE CASE

Intervention	Total Costs ($)	Total QALY Gain	Incremental Costs ($)	Incremental QALYs	ICUR Compared With SoC ($)	Sequential ICUR ($)
SoC	11,339	0.471	Reference	Reference	Reference	Reference
ETA	52,036	0.828	40,697	0.357	113,997	Dominated by ADA
UST 45 mg	64,369	0.845	53,030	0.374	141,791	Dominated by ADA
ADA	50,775	0.896	39,436	0.424	93,009	Extendedly dominated by SoC and SEC 300 mg
SEC 150 mg	60,734	1.075	49,395	0.604	81,816	Extendedly dominated by SoC and SEC 300 mg
UST 90 mg	67,834	1.107	56,495	0.636	88,829	Dominated by SEC 300 mg
SEC 300 mg	63,994	**1.146**	**52,655**	**0.675**	**78,007**	**78,007**
INF (Remicade) 5 mg/kg	105,771	1.180	94,432	0.709	133,190	$1,224,643

ADA = adalimumab; ETA = etanercept; ICUR = incremental cost-utility ratio; INF = infliximab; QALY = quality-adjusted life-year; SEC = secukinumab; SoC = standard of care; UST = ustekinumab.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.
Source: Adapted from manufacturer's pharmacoeconomic submission.[3]

CADTH Common Drug Review Reanalysis (Based on Reduced Price)

The following scenarios were explored by CDR to assess limitations identified. All CDR analyses assume that the MTC results [redacted], as described in the Issues for Consideration section.

Recalculation of Secukinumab 300 mg Annual Costs, Years 2 to 10

The costs of 13 administrations of secukinumab 300 mg were incurred in years 2 to 10 instead of 12; the same is true of secukinumab 150 mg.

TABLE 18: RECALCULATION OF SECUKINUMAB (150 MG AND 300 MG) ANNUAL COSTS

Intervention	Total Costs ($)	Total QALY Gain	Incremental Costs ($)	Incremental QALYs	ICUR Compared With SoC ($)	Sequential ICUR ($)
SoC	11,339	0.471	Reference	Reference	Reference	Reference
ETA	52,036	0.828	40,697	0.357	113,998	Dominated by ADA
ADA	50,775	0.896	39,436	0.424	93,009	Extendedly dominated by SoC and SEC 300 mg
SEC 150 mg	63,568	1.075	52,229	0.604	86,510	Extendedly dominated by SoC and SEC 300 mg
UST	67,834	1.107	56,495	0.636	88,829	Dominated by SEC 300 mg
SEC 300 mg	67,051	**1.146**	**55,712**	**0.675**	82,534	**82,534**
INF (Remicade) 5 mg/kg	105,771	1.180	94,432	0.709	133,190	1,135,050

ADA = adalimumab; ETA = etanercept; ICUR = incremental cost-utility ratio; INF = infliximab; QALY = quality-adjusted life-year; SEC = secukinumab; SoC = standard of care; UST = ustekinumab.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

Inclusion of Subsequent Entry Biologic Infliximab Cost

SEB infliximab has a cost 34% below that of branded infliximab ($650 per vial as opposed to $987.56).[9] Inclusion of SEB infliximab resulted in its sequential ICUR falling to $242,286 compared with secukinumab 300 mg (Table 19).

TABLE 19: MANUFACTURER'S BASE CASE WITH SUBSEQUENT ENTRY BIOLOGIC INFLIXIMAB

Intervention	Total Costs ($)	Total QALY Gain	Incremental Costs ($)	Incremental QALYs	ICUR Compared With SoC ($)	Sequential ICUR ($)
SoC	11,339	0.471	Reference	Reference	Reference	Reference
ETA	52,036	0.828	40,697	0.357	113,997	Dominated by ADA
ADA	50,775	0.896	39,436	0.424	93,009	Extendedly dominated by SoC and SEB INF
SEC 150 mg	60,734	1.075	49,395	0.604	81,816	Extendedly dominated by SoC and SEC 300 mg
UST	67,834	1.107	56,495	0.636	88,829	Dominated by SEC 300 mg
SEC 300 mg	63,994	**1.146**	**52,655**	**0.675**	**78,007**	**78,007**
SEB INF (Inflectra) 5 mg/kg	72,260	1.180	60,920	0.709	85,924	242,286

ADA = adalimumab; ETA = etanercept; ICUR = incremental cost-utility ratio; INF = infliximab; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SEC = secukinumab; SoC = standard of care; UST = ustekinumab.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

Applying the cost of SEB infliximab to the CDR base case with revised annual dose calculations resulted in a sequential ICUR of $152,694 (Table 20).

TABLE 20: CADTH COMMON DRUG REVIEW BASE CASE — SUBSEQUENT ENTRY BIOLOGIC INFLIXIMAB

Intervention	Total Costs ($)	Total QALY Gain	Incremental Costs ($)	Incremental QALYs	ICUR Compared With SoC ($)	Sequential ICUR ($/QALY)
SoC	11,339	0.471	Reference	Ref	Reference	Reference
ETA	52,036	0.828	40,697	0.357	113,998	Dominated by ADA
ADA	50,775	0.896	39,436	0.424	93,009	Extendedly dominated by SoC and SEB INF
SEC 150 mg	63,568	1.075	52,229	0.604	86,510	Extendedly dominated by SoC and SEC 300 mg
UST	67,834	1.107	56,495	0.636	88,829	Dominated by SEC 300 mg
SEC 300 mg	67,051	**1.146**	**55,712**	**0.675**	82,534	**82,534**
SEB INF (Inflectra) 5 mg/kg	72,260	1.180	60,920	0.709	85,924	152,694

ADA = adalimumab; ETA = etanercept; ICUR = incremental cost-utility ratio; INF = infliximab; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SEC = secukinumab; SoC = standard of care; UST = ustekinumab.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

CDR's base case, excluding infliximab, was used to assess the manufacturer's request for secukinumab 300 mg to be listed in a manner similar to other subcutaneous biologics (Table 21).

TABLE 21: CADTH COMMON DRUG REVIEW BASE CASE — SUBCUTANEOUS BIOLOGICS ALONE

Intervention	Total Costs ($)	Total QALY Gain	Incremental Costs ($)	Incremental QALYs	ICUR Compared With SoC ($)	Sequential ICUR ($/QALY)
SoC	11,339	0.471	Reference	Ref	Reference	Reference
ETA	52,036	0.828	40,697	0.357	113,998	Dominated by ADA
ADA	50,775	0.896	39,436	0.424	93,009	Extendedly dominated by SoC and UST
SEC 150 mg	63,568	1.075	52,229	0.604	86,510	Extendedly dominated by SoC and SEC 300 mg
UST	67,834	1.107	56,495	0.636	88,829	Dominated by SEC 300 mg
SEC 300 mg	67,051	**1.146**	**55,712**	**0.675**	82,534	**82,534**

ADA = adalimumab; ETA = etanercept; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEC = secukinumab; SoC = standard of care; UST = ustekinumab.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

PASI-to-Utility Mapping Algorithms

Given the sensitivity of the results to the choice of utility values, a search for mapping studies was conducted to identify other sources of information. Utility mappings available from recent publications were used.[13-15] The reanalysis was conducted with the CDR base case using the corrected number of maintenance doses according to the ERASURE and FIXTURE trials.[4] Results of this reanalysis using both the cost of brand infliximab and SEB infliximab are presented in Table 22.

TABLE 22: ALTERNATIVE PASI-TO-UTILITY MAPPINGS — THE CADTH COMMON DRUG REVIEW BASE CASE

Mapping Algorithm	Utility Gain by PASI Score	ICUR (SEC 300 vs. SoC) ($/QALY)	Sequential Analysis — INF (Remicade)	Sequential Analysis — SEB INF (Inflectra)
Manufacturer's base case (Pan et al. 2011)[5]	PASI 90 to 100: 0.250 PASI 75 to 89: 0.220 PASI 50 to 74: 0.170 PASI < 50: 0.040	$82,534	$82,534 compared with SoC	$82,534 compared with SoC
Anis et al. 2011[14]	PASI 90 to 100: 0.21 PASI 75 to 89: 0.12 PASI 50 to 74: 0.12 PASI < 50: 0.04	$122,365	$122,365 compared with SoC	$122,365 compared with SoC
Woolacott et al. 2007[15]	PASI 90 to 100: 0.21 PASI 75 to 89: 0.19 PASI 50 to 74: 0.17 PASI < 50: 0.05	$101,723	$101,723 compared with SoC	$101,723 compared with SoC
Knight et al. 2012[13]	PASI 90 to 100: 0.232 PASI 75 to 89: 0.232 PASI 50 to 74: .201 PASI < 50: 0.101	$119,965	$119,965 compared with SoC	$119,965 compared with SoC

ICUR = incremental cost-utility ratio; INF = infliximab; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SEC = secukinumab; SoC = standard of care; UST = ustekinumab; vs. = versus.

Low Efficacy of Secukinumab

CDR noted uncertainty regarding estimates of comparative efficacy with other biologics. In addition to issues of patient heterogeneity and low number of studies per comparison, [redacted] with ustekinumab 90 mg were observed at 12 weeks and high-iteration probabilistic sensitivity analyses resulted in a wide range of ICURs for secukinumab 300 mg compared with ustekinumab 90 mg. CDR undertook an exploratory analysis using conservative efficacy values for secukinumab 300 mg for a worst-case scenario. CDR considered the effects of low treatment efficacy with secukinumab 300 mg by using the lower end of the 95% confidence interval for PASI distributions (Table 23 and Table 24). Efficacy values for all other comparators were held constant.

TABLE 23: PSORIASIS AREA AND SEVERITY INDEX DISTRIBUTIONS

	PASI < 50	PASI 50 to 74	PASI 75 to 89	PASI 90 to 99	PASI 100
4-week default values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4-week low efficacy values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8-week default values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8-week low efficacy values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-week default values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-week low efficacy values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PASI = Psoriasis Area and Severity Index.
Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 24: ASSUMPTION OF LOWER BOUND EFFICACY FOR SECUKINUMAB 300 MG — CADTH COMMON DRUG REVIEW BASE CASE

Treatment	Total Costs ($)	Total Gain in QALYs	Incremental Costs ($)	Incremental Gain in QALYs	ICUR Compared With SoC ($)	Sequential ICUR ($/QALY)
SoC	11,339	0.471	Reference	Reference	Reference	—
ETA	52,036	0.828	40,697	0.357	113,997	Dominated by ADA
ADA	50,775	0.896	39,436	0.424	93,009	Extendedly dominated by SoC and SEB INF
SEC 150 mg	63,568	1.075	58,477	0.604	96,816	Dominated by UST
SEC 300 mg	**64,918**	**1.103**	**53,579**	**0.631**	84,852	**84,852**
UST	67,834	1.107	56,495	0.636	88,829	Extendedly dominated by SEC 300 mg and SEB INF
SEB INF	72,260	1.180	60,920	0.709	85,924	94,509

ADA = adalimumab; ETA = etanercept; ICUR = incremental cost-utility ratio; INF = infliximab; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SEC = secukinumab; SoC = standard of care; UST = ustekinumab.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

Price Reduction Analysis

With the manufacturer's reduced price, secukinumab 300 mg dominates ustekinumab (i.e., costs less and produces more QALYs). However, as previously noted, this result presupposes that the list price of ustekinumab corresponds to the price paid by drug plans under product listing agreements.

CDR considered the effects of a reduced cost of ustekinumab (Table 25). In CDR's base case, if the price of ustekinumab is reduced by 10%, secukinumab 300 mg no longer dominates and is associated with an ICUR of $133,751. Further reductions result in secukinumab 300 mg being ruled out by extended dominance.

TABLE 25: CADTH COMMON DRUG REVIEW REANALYSIS — PRICE REDUCTION SCENARIOS

ICURs of SEC 300 mg ($/QALY)		
Price of UST[a]	**Manufacturer's Base Case (ICUR vs. UST)**	**CDR Base Case (ICUR vs. UST)**
List price ($4,593/dose)	SEC 300 mg dominates	SEC 300 mg dominates
10% reduction ($4,134)	$56,002	$133,751
15% reduction ($3,904)	$132,839	SEC 300 mg extendedly dominated by UST and SEB INF[b]
20% reduction ($3,675)	$209,676	SEC 300 mg extendedly dominated by UST and SEB INF[b]
25% reduction ($987)	$286,513	SEC 300 mg extendedly dominated by UST and SEB INF[b]

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; INF = infliximab; SEB = subsequent-entry biologic; SEC = secukinumab; SoC = standard of care; UST = ustekinumab; vs. = versus.

[a] Assuming that the manufacturer's results for UST 90 mg apply to UST 45 mg and serve as a proxy for weight-appropriate dosing of UST, as described in the Issues for Consideration section.

[b] An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

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