Common Drug Review
Pharmacoeconomic Review Report

November 2016

Drug	ustekinumab (Stelara) Injection
Indication	The treatment of adult patients with active psoriatic arthritis alone or in combination with methotrexate.
Listing request	For use alone, or in combination with methotrexate, for the treatment of moderate to severe psoriatic arthritis following failure or intolerance to methotrexate or other DMARDs, or anti-TNF alpha therapies.
Manufacturer	Janssen Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in rheumatology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

TABLE OF CONTENTS

ABBREVIATIONS

CDR	CADTH Common Drug Review
DMARD	disease-modifying antirheumatic drug
HAQ	Health Assessment Questionnaire
ICUR	incremental cost-utility ratio
MTC	mixed treatment comparison
NICE	National Institute for Health and Care Excellence
PASI	Psoriasis Area Severity Index
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
QALY	quality-adjusted life-year
SMC	Scottish Medicines Consortium
TNF	tumour necrosis factor

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Ustekinumab (Stelara)
Study Question	To estimate the cost utility of ustekinumab for the treatment of psoriatic arthritis in patients who have failed treatment with, or are intolerant to, conventional therapies, and who are anti-TNF alpha naive or anti-TNF alpha experienced.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with active psoriatic arthritis for whom their response to previous conventional therapy has been inadequate due to lack of efficacy or intolerance
Treatment	Ustekinumab dosed as per the product monograph
Outcome(s)	Life-years, quality-adjusted life-years
Comparators	Placebo, golimumab, infliximab, adalimumab, and etanercept
Perspective	Public payer
Time Horizon	Lifetime (52 years, with a 100-year life expectancy)
Manufacturer's Results (Base Case)	TNF alpha naive (ICUR versus placebo): • Golimumab = $26,264 • Ustekinumab = $40,958 • Adalimumab = $37,946 • Etanercept = $37,604 • Infliximab = $61,945 TNF alpha experienced (ICUR versus placebo): • Ustekinumab = $46,962
Key Limitations and CDR Estimates	• The manufacturer reports in its indirect comparison that other biologic treatments are associated with greater clinical benefits in terms of PsARC, ACR 20, and PASI 75 response. Drug treatment costs for the majority of the biologics are less than that of ustekinumab. Consequently, based on the manufacturer's analysis, there are biologic treatments that are more cost-effective than ustekinumab in patients who are anti-TNF alpha naive. In addition, CDR noted: • Assumptions that quality of life would rebound to a baseline and even worse values suggested that there would no residual effect of treatment after discontinuation. CDR explored a conservative scenario in which quality of life would follow a natural disease progression after treatment discontinuation. • CDR reanalyses tested several identified limitations, resulting in an ICUR of $73,082 for ustekinumab compared with placebo for a conservative scenario in patients with no prior exposure to anti-TNF alpha treatment and $82,611 for patients with prior anti-TNF alpha experience.

ACR = American College of Rheumatology; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; PASI = Psoriasis Area Severity Index; PsARC = Psoriatic Arthritis Response Criteria; TNF = tumour necrosis factor.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Ustekinumab (Stelara) is for the treatment of psoriatic arthritis in patients who have failed treatment with, or are intolerant to, conventional therapies, and who are anti-tumour necrosis factor (TNF) alpha naive or anti-TNF alpha experienced. Ustekinumab is a subcutaneous injection administered at 45 mg or 90 mg, given on weeks 0 and 4 and then every 12 weeks. The manufacturer submitted a price of $4,593.14 per pre-filled syringe for both doses.

Ustekinumab was reviewed by CADTH Common Drug Review (CDR) in 2009 for psoriasis.[1] The Canadian Expert Drug Advisory Committee recommended that ustekinumab be listed with criteria in that indication.

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis based on a short-term decision tree of 12-week cycles, followed by a long-term Markov model in which the distribution of patients across the health states at the beginning of the Markov phase was determined by the distribution of patients at the end of the decision tree. Ustekinumab, golimumab, infliximab, adalimumab, and etanercept were compared with placebo. The manufacturer's analysis presented the efficacy of placebo to represent the efficacy of conventional management, including disease-modifying antirheumatic drugs. The initial response to treatment was estimated using Psoriatic Arthritis Response Criteria (PsARC). Patients who achieve a PsARC response continue treatment, while those who do not discontinue treatment. Within the Markov model, patients could stay in their current health state or transition to conventional management (equivalent to placebo) based on their Psoriasis Area Severity Index (PASI) 75 response and Health Assessment Questionnaire scores. Clinical data used within the model included the proportion of patients who had a PsARC response, and the proportions of patients who had a PASI 50, PASI 75, and PASI 90 response. For the anti-TNF alpha naive population, where possible and appropriate, the relative treatment effects for each comparator for PsARC and PASI response rates were estimated using mixed treatment comparison (MTC) techniques. In the anti-TNF alpha experienced population, efficacy values were taken directly from the PSUMMIT2 study for the subgroup of patients who had received prior anti-TNF alpha therapy.

Results of Manufacturer's Analysis

- In the anti-TNF alpha naive population, ustekinumab was:
  - associated with an incremental cost-utility ratio (ICUR) of $40,958 versus placebo
  - less effective and less costly than adalimumab, etanercept, and infliximab
  - less effective and more costly than golimumab.
- In the anti-TNF alpha experienced population, the ICUR for ustekinumab versus placebo was $46,962 per quality-adjusted life-year gained.

Interpretations and Key Limitations

The manufacturer reports in its indirect comparison that other biologic treatments are associated with greater clinical benefits in terms of PsARC, American College of Rheumatology (ACR) 20 score, and PASI 75 response. Drug treatment costs for a number of the biologics are less than that of ustekinumab. Consequently, based on the manufacturer's analysis, there are biologic treatments that are more cost-effective than ustekinumab in patients who are anti-TNF alpha naive.

CDR identified several limitations with the model:

- **Uncertain assumption relative to disease progression:** The model assumed that quality of life (Health Assessment Questionnaire score) would rebound to a baseline score once the patient had withdrawn from treatment. There is limited information to inform how patients will progress once off treatment. CDR explored a conservative scenario in which quality of life would revert to the score the patient would have progressed to following his or her natural disease progression had he or she not received treatment.
- **Uncertain long-term efficacy and safety profile:** The submitted model projected the analysis to a 52-year time horizon. However, the available evidence of efficacy is limited to 24 weeks in PSUMMIT1 and PSUMMIT2 trials. Both trials had longer safety follow-up periods (180 and 60 weeks in PSUMMIT1 and PSUMMIT2, respectively), during which they reported several cases of malignancies, which raise concerns about long-term safety of ustekinumab.

Results of CADTH Common Drug Review Analysis

Given the issues identified with manufacturer's model, CDR conducted a reanalysis based on the following:

- Using efficacy data as reported in the manufacturer's MTC resulted in minimal change in the ICUR for ustekinumab compared with placebo.
- Assuming that quality of life would worsen in a manner that follows the natural disease progression after treatment discontinuation, the ICUR of ustekinumab increased from $40,958 to $73,051 when compared with placebo in patients with no prior exposure to anti-TNF alpha treatment. This reanalysis did not impact the results for patients with prior experience to anti-TNF alpha treatment.

When the CDR analyses were combined, the ICUR for ustekinumab increased to $73,082 compared with placebo for patients with no prior exposure to anti-TNF alpha treatment. For patients with prior experience to anti-TNF alpha treatment, the ICUR for ustekinumab was $82,611 compared with placebo when these considerations are taken into account.

Conclusions

CDR identified concerns with respect to assumptions used to estimate the quality of life and utility values. Based on the manufacturer's indirect comparison, other biologics appear to have greater clinical efficacy compared with ustekinumab, and ustekinumab treatment costs are greater than other biologics (with the exception of infliximab) for patients with no prior exposure to anti-TNF alpha treatment. For patients with prior exposure to anti-TNF alpha treatment, CDR estimated that the ICUR for ustekinumab could be $82,611 compared with placebo, under more conservative scenarios.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

"The aim of this study is to carry out a cost-utility analysis of [ustekinumab] for the treatment of psoriatic arthritis in patients who have failed treatment with, or are intolerant to, conventional therapies, that are anti-TNF alpha naive and anti-TNF alpha experienced."
(Manufacturer's submission,[2] page 3.)

1.2 Treatment

Ustekinumab (45 mg or 90 mg), given on weeks 0 and 4, and then every 12 weeks as a subcutaneous injection. The recommended dose of ustekinumab is 45 mg, although 90 mg may be used in patients with a body weight greater than 100 kg.[3]

1.3 Comparators

The manufacturer stated that ustekinumab was compared with conventional management (i.e., non-biologic disease-modifying antirheumatic drugs) in anti-tumour necrosis factor (TNF) alpha experienced patients, as there are no randomized controlled trials evaluating any other biologic other than ustekinumab in anti-TNF alpha experienced patients. In all submitted analyses, placebo was the basis of the efficacy estimates (from PSUMMIT trials) for conventional management, which was not accounted for in the cost of treatments for any of the treatment groups; therefore, conventional management was more accurately relabelled as "placebo" in this report.

For patients with no previous exposure to anti-TNF alpha medications (anti-TNF alpha naive patients), ustekinumab was compared with golimumab, infliximab, adalimumab, etanercept, and placebo. The Canadian Expert Drug Advisory Committee reviewed golimumab and adalimumab and recommended these treatments receive formulary listing with criteria,[4,5] while infliximab and etanercept have not been reviewed at this time. Golimumab, adalimumab, and etanercept are currently funded as a restricted benefit across all the provinces of Canada; infliximab is funded for psoriatic arthritis (PsA) as a restricted benefit in British Columbia, Alberta, Saskatchewan, Manitoba, and Yukon.

1.4 Type of Economic Evaluation

The manufacturer undertook a cost-utility analysis. This is appropriate given the potential impact this disorder may have on quality of life, according to CADTH Guidelines for Economic Evaluations of Health Technologies.[6]

The analysis takes a public payer perspective, including only direct health care costs. This is also appropriate according to CADTH guidelines.[6]

1.5 Population

Ustekinumab is indicated for the treatment of adult patients with active PsA; it can be used alone or in combination with methotrexate.[3] The manufacturer requested reimbursement of ustekinumab for the treatment of moderate to severe PsA following failure or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs), or to other anti-TNF alpha therapies. The patient groups included in the economic model were adult patients with active PsA for whom their response to previous conventional therapy has been inadequate due to lack of efficacy or to intolerance.

There are two distinct subgroups of these patients:

- Anti-TNF alpha naive: Patients who have never been exposed to an anti-TNF alpha therapy.
- Anti-TNF alpha experienced: Patients who have been exposed to previous anti-TNF alpha therapy.

2. METHODS

Please see Table 8 for a summary of the key limitations associated with the methodology used by the manufacturer.

2.1 Model Structure

The submitted model was adapted from a previous model developed for England's National Institute for Health and Care Excellence (NICE), guidance on the use of golimumab, etanercept, infliximab, and adalimumab.[7] The same model structure was previously submitted to CDR for the assessment of golimumab for the treatment of PsA.

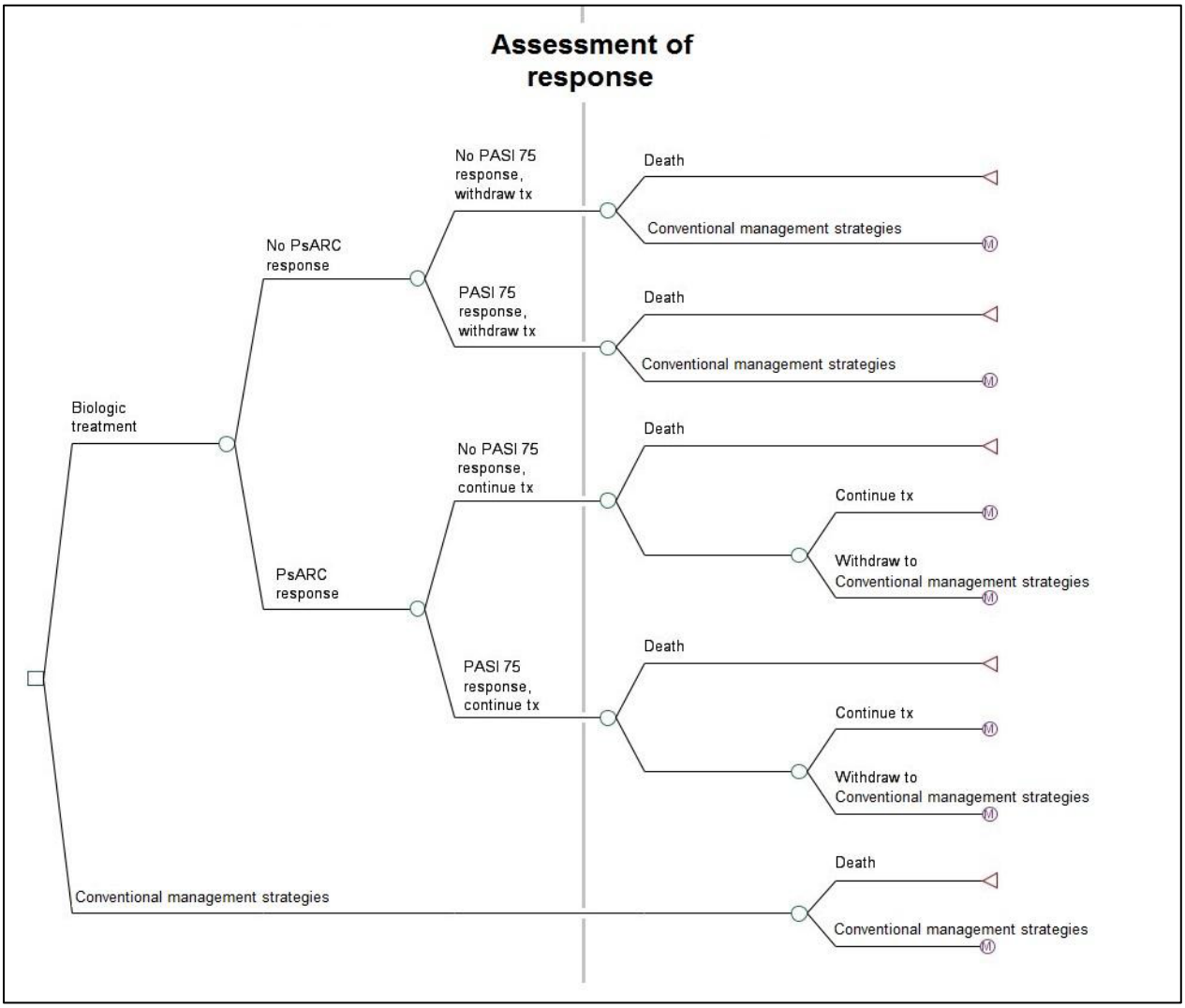
The economic model was constructed in two parts: a short-term decision tree (Figure 1), followed by a long-term Markov model in which the distribution of patients across the health states at the beginning of the Markov phase was determined by the distribution of patients at the end of the decision tree.

The short-term decision tree consists of four 12-week cycles. The model included the option to assess initial response to each treatment at either 12 or 24 weeks. The initial response to treatment was estimated using Psoriatic Arthritis Response Criteria (PsARC). In addition to this, the health states captured patients' Psoriasis Area Severity Index (PASI) 75 response to further assess the impact of treatment on the dermatological aspect of the disease.

The base-case analysis assessed initial response for patients receiving ustekinumab at 24 weeks; patients receiving all other treatments were assessed at week 12. This assumption is tested in the sensitivity analysis. The manufacturer's justification was that ustekinumab would be administered less frequently than other anti-TNF alpha drugs and, in practice, patients receiving ustekinumab would be assessed for response to treatment after three injections (week 16) but before a fourth injection (week 28). For this reason, week 24 was thought to be an appropriate time point for initial response to ustekinumab. The consulted clinical expert validated the model assumption. Of note, clinical guidelines recommend that patients be assessed for initial response to treatment after 12 weeks; responders should continue to receive treatment, and non-responders should be withdrawn from treatment.[8] However, the inclusion of four 12-week cycles enables the flexibility to assess initial response to treatment at either week 12 or week 24 for all compared treatments.

In the base case, patients who achieved a PsARC response remained on treatment, and those who did not respond withdrew from treatment (or, as the manufacturer states, continued on conventional management — as described by the clinical effects of placebo, with no associated treatment costs). Following assessment of initial response to treatment, patients entered the Markov model immediately after being categorized by their response at week 12 or week 24.

FIGURE 1: SHORT-TERM DECISION TREE



PASI = Psoriasis Area Severity Index; PsARC = Psoriatic Arthritis Response Criteria; tx = treatment.

During the Markov phase, all patients who remained on active treatment were at risk of withdrawal to conventional therapy (equivalent to placebo). Based on Health Assessment Questionnaire (HAQ) and PASI scores from the clinical trials, patients could stay in their current health state or transition to conventional management (equivalent to placebo). All patients were at risk of death based on the British Office for National Statistics life tables, which were adjusted to include additional mortality associated with PsA using multipliers. The model did not attempt to use Canadian sources for life expectancy; however, the impact of this might be limited, because these estimates were applied equally to all comparators, and the model did not claim any gain in survival.

2.2 Clinical Inputs

2.2.1 Efficacy

Clinical data used within the model included the proportion of patients who had a PsARC response, and the proportions of patients who had a PASI 50, PASI 75, or PASI 90 response. For the anti-TNF alpha naive population, where possible and appropriate, the relative treatment effects for each comparator for PsARC and PASI response rates were estimated using mixed treatment comparison (MTC) techniques. The details on the MTC were provided in the CDR clinical report.

In the anti-TNF alpha experienced population, efficacy values were taken directly from the PSUMMIT2 study for the subgroup of patients who had received prior anti-TNF alpha therapy. In all analyses, the efficacy of placebo was used to represent the efficacy of conventional management.

Where insufficient data were available to perform an MTC for relevant outcomes, or where insufficient data were available for a comparator of interest to include within the network of evidence for anti-TNF alpha naive patients, data from Yang et al. or Rodgers et al. were used as a proxy.[9,10] Outcomes for which an MTC could be performed for this submission were PsARC, PASI 75, and PASI 90; however, for PASI 90 no outcomes were available in the published literature for etanercept. However, CDR reviewers identified some discrepancies between the MTC results and the values used in the model (summarized in Appendix 2). The manufacturer explained that the reason for discrepancies in efficacy results was due to the weight-based analysis employed in the economic model.

2.2.2 Harms

Harms were not included in the submitted model; subsequently, costs and disutilities associated with adverse events were not assessed.

2.2.3 Mortality

Patients were at risk of all-cause mortality at every time point in the model, although it was assumed that there were no different rates of mortality among therapies. Mortality rates were based on the British Office of National Statistics life tables from 2011. As mentioned earlier, these data were not adapted to the Canadian population, but the impact of this might be limited because these estimates were applied equally to all comparators, and the model did not claim any gain in survival. Based on literature data, a standardized mortality rate of 1.59 in women and 1.65 in men was used to reflect the higher risk of mortality in patients with PsA.

2.2.4 Quality of life

The model used the change in HAQ score experienced by PsARC responders and non-responders as a measure of quality of life. The model assumed that PsARC responders would experience an initial reduction in HAQ score (improvement), and PsARC non-responders would experience a smaller reduction in HAQ score, based on an MTC performed by Yang et al. for anti-TNF alpha treatments.[10] Yang's MTC compared HAQ scores after 12 to 16 weeks' treatment with conventional management (usual care including use of nonsteroidal anti-inflammatory drugs [NSAIDs] or DMARDs), infliximab, etanercept, adalimumab, or golimumab.

The manufacturer's model used the HAQ scores reported in Yang's MTC for the biologic comparators and used HAQ scores pooled from PSUMMIT1 and PSUMMIT2 for ustekinumab. The manufacturer did not conduct a formal indirect comparison between ustekinumab and the other biologic treatment; the manufacturer's justification was based on similar placebo HAQ results in both pooled analyses (–0.27 in Yang et al. versus –0.26 from the pooled PSUMMIT1 and PSUMMIT2 studies). However, comparability of

results for the common comparator group does not guarantee the comparability of the evaluated population, interventions, or outcomes. For example, Yang's MTC reported HAQ scores at 12 weeks, while the manufacturer's MTC evaluated the outcome at 12 to 16 weeks and at 24 weeks. For the interventions included in Yang's MTC, the model assumed that HAQ scores at 24 weeks would be equal to those reported at 12 weeks. This assumption might have biased the cost-effectiveness ratio in favour of ustekinumab, because the HAQ scores in PSUMMIT1 and PSUMMIT2 studies decreased (showing improvement) from –0.40 to –0.49 for PsARC responders and from –0.05 to –0.10 for PsARC non-responders. However, the model did not attribute any amelioration at 24 weeks for the other biologics. Therefore, it would be justifiable to evaluate the cost-effectiveness ratios at 12 weeks rather than at 24 weeks in order to avoid this source of bias.

The manufacturer conducted a sensitivity analysis in which all treatments were assessed for initial response and continuation of treatment at week 24. The relative treatment effects in terms of PsARC responses were used in conjunction with the assumption that treatment halts disease progression, while patients receiving placebo were subject to the natural history of the disease. The manufacturer used this analysis to model the changes in HAQ score over time.

2.2.5 Utilities

The model employed HAQ and PASI scores to generate quality-adjusted life-year (QALY) estimates. In the base case, the Bojke equation, which has been used in a number of previous economic evaluations,[11] was used to estimate utilities based on HAQ and PASI.

Using Bojke's equation might ensure consistency with previous reviews of other biologic treatments; however, it might not be able to capture variations across different trials. Therefore patient-level data would be more appropriate whenever available. PSUMMIT1 and PSUMMIT2 trials reported patient-level Short Form (36) Health Survey data, and the submitted economic model mapped this data to EuroQol 5-Dimensions Questionnaire utility values, using a published algorithm by Rowen at al.,[12] which were used as a sensitivity analysis. CDR reviewers favoured this analysis for two reasons: the first was to avoid the potential bias produced by the assumptions used to estimate HAQ results, and the second was to ensure the use of the most up-to-date and relevant utility estimates for the population studied in PSUMMIT1 and PSUMMIT2 trials.

2.2.6 Withdrawal from active treatment

The model assumed that the rate of withdrawal from biologic treatments after the assessment of initial response reflects the risk of withdrawal due to adverse events and loss of efficacy. This assumes patients withdraw from biologic therapy to placebo without receiving a second biologic, which might not be reflective of true clinical practice. There were, however, no appropriate data supporting the use of a second anti-TNF alpha drug to support switching within the model.

The model used an annual risk of withdrawal from active treatment equal to 16.5% for all treatment. This rate was in line with previous economic evaluations of treatments for PsA.[7]

2.2.7 Disease progression

The model assumed that patients who remain on treatment did not experience any progression of their condition and patients who moved onto placebo experienced natural progression of their disease. This assumption was applied to PASI and HAQ scores.

The model assumed that patients who achieved a PASI 75 response would experience an initial reduction (improvement) in their PASI score, and this was maintained while the patients were on biologic treatment. Patients not achieving a PASI 75 response were assumed to experience a smaller reduction in PASI score, which was also maintained while on treatment. These scores would then rebound back to baseline values and remain constant while the patients were on placebo.

The model assumed two HAQ score rebound scenarios for patients who stopped the biologic treatment; in the base-case scenario, patients rebounded back to their baseline HAQ score. In the sensitivity analysis, patients rebounded to an HAQ score lower than their baseline HAQ score; a score of 1 was chosen arbitrarily without evidence to support an assumption. Both scenarios assumed that HAQ scores would worsen after treatment discontinuation. This might be an acceptable assumption; however, the proposed magnitude of this worsening might not be realistic. The two scenarios suggested that patients' quality of life would rebound to a baseline state or even worse; however, a third more conservative scenario suggested that quality of life would follow a natural disease progression after treatment discontinuation.

2.2.8 Costs

The model attributed costs based on health states to represent other costs associated with the disease. The model applied two equations for these costs; one was used to estimate the mean annual direct costs according to HAQ level, and the other equation was used to estimate costs and resource use related to PASI score. The two equations were used to evaluate the cost-effectiveness of the previously reviewed PsA biologic treatments.

2.2.9 Drug costs

The number of units per injection (or infusion) and the number of injections (or infusions) per year for each product were determined based on the recommended doses according to the product monographs. The unit pricing was taken from the Ontario Drug Benefit price list (2013). The model assumed no cost associated with placebo, as all treatment groups include use of conventional therapy (defined as treatment with DMARDs and NSAIDs), and therefore no differential cost exists. The manufacturer did not provide evidence that the use of conventional management would be equal, whether used alone or with various other biologic therapies.

2.2.10 Administration costs

Administration costs were not included in the analysis. For all anti-TNF alpha treatments that are administered by subcutaneous injection, it was assumed that these would be administered by the patient and therefore result in no cost to the health care system. For infliximab, which is administered as an intravenous infusion through manufacturer-sponsored infusion clinics, no administration cost was assumed.

2.2.11 Time horizon

The manufacturer presented the results of the economic evaluation using a lifetime time horizon, which was supported by the CADTH Economic Evaluation guidelines[6] and the chronic nature of PsA. The model assumed a time horizon of 52 years, and the sensitivity analysis evaluated the impact of a time horizon that ranged from 10 to 52 years.

2.2.12 Discounting

In accordance with the Canadian guidelines for the economic evaluation of health technologies, costs and effects were discounted at 5% per annum.[6]

3. RESULTS

3.1 Manufacturer's Base Case

3.1.1 Anti-TNF alpha naive patients

The base-case results of the model are presented in Table 2 for anti-TNF alpha naive patients. For the base-case deterministic results, the incremental cost-utility ratios (ICURs) generated range from $27,000 to $63,000 when comparing biologic therapies with placebo.

The ICUR for ustekinumab is $40,958, which is slightly higher than the ICUR for etanercept ($37,604) and adalimumab ($37,946) therapies, and lower than infliximab ($61,945). Golimumab is the most cost-effective biologic with the lowest reported ICUR at $26,264.

TABLE 2: MANUFACTURER'S BASE-CASE RESULTS FOR ANTI-TNF ALPHA NAIVE PATIENTS

	Total Costs ($)	Total QALYs	Versus Placebo		
			Incremental Costs ($)	Incremental QALYs	ICUR ($)
Placebo	51,269	5.14	-	-	-
Golimumab	106,084	7.23	54,815	2.09	26,264
Ustekinumab	112,268	6.63	60,999	1.49	40,958
Adalimumab	114,184	6.80	62,914	1.66	37,946
Etanercept	132,854	7.31	81,585	2.17	37,604
Infliximab	196,391	7.48	145,122	2.34	61,945

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.
Source: Adapted from Manufacturer's pharmacoeconomic submission, page 18.

3.1.2 Anti-TNF alpha experienced patients

The base-case results of the model are presented in Table 3 for anti-TNF alpha experienced patients. For the base-case deterministic results, the ICUR was $46,692 when comparing ustekinumab with placebo.

TABLE 3: MANUFACTURER'S BASE-CASE RESULTS FOR ANTI-TNF ALPHA EXPERIENCED PATIENTS VERSUS PLACEBO

	Total Costs ($)	Incremental Costs ($)	Total QALYs	Incremental QALYs	ICUR
Placebo	66,328		2.70		
Ustekinumab	127,231	60,904	3.99	1.30	46,962

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.
Source: Manufacturer's pharmacoeconomic submission, page 26.

3.2 Summary of the Manufacturer's Sensitivity Analyses

3.2.1 One-way sensitivity analyses

a) Anti-TNF alpha naive patients

Based on deterministic sensitivity analyses, the manufacturer reported that the most influential parameter was the HAQ score change per 28 days associated with natural history of PsA. This is due to the fact that the changes in HAQ score have a large impact on health-related quality of life (HRQoL) and QALYs gained. Therefore, if the natural progression in HAQ score is minimal, then the HRQoL and QALYs gained from therapy will also be minimal.

The manufacturer conducted scenario analyses to evaluate the impact of alternative assumptions on the base-case analysis. The results from these sensitivity analyses showed that the ICUR compared with placebo for ustekinumab ranged from $38,429 (HAQ rebounds to lower score than baseline from withdrawal active treatment) to $73,051 (HAQ rebounds to natural history on withdrawal from active treatment). For all analyses, golimumab was found to be the most cost-effective treatment. The relative position of ICURs remained similar for comparators with all sensitivity analyses.

b) Anti-TNF alpha experienced patients

The results from alternative-assumptions analyses showed that the ICUR compared with placebo for ustekinumab ranged from $44,085 (PsARC and PASI responders continue treatment) to $82,611 (HAQ rebounds to natural history on withdrawal from active treatment).

3.2.2 Probabilistic sensitivity analysis

For both the anti-TNF alpha naive and experienced patients, the probability of ustekinumab being cost-effective compared with placebo at a willingness to pay per QALY gained of $50,000 was 74%. For a willingness to pay of $25,000 there was a 0% probability of ustekinumab being cost-effective.

3.3 CADTH Common Drug Review Analyses

CDR analyses were conducted in order to evaluate uncertainties about the efficacy values used in the model and the assumptions about quality of life worsening after treatment discontinuation.

3.3.1 Anti-TNF alpha naive patients

- Using efficacy data reported in the manufacturer's MTC resulted in minimal change in the ICUR for ustekinumab compared with placebo (Table 4).
- CDR also assumed that the patients' quality of life would revert to the score following their natural disease progression had they not received treatment.
- When the two analyses were combined to form the "conservative scenario," the analysis indicated that the ICUR for ustekinumab increased to $73,082 compared with placebo. When the other biologics were compared with placebo, in patients with no prior exposure to anti-TNF alpha treatment, their ICURs increased to $48,340; $70,679; $65,186; $104,064 for golimumab, adalimumab, etanercept, and infliximab, respectively (Table 4).

Table 5 summarizes ICURs of ustekinumab compared with placebo resulting from different price-reduction scenarios. For example, a 50% price reduction would reduce the ICUR from $73,051 to $34,967.

TABLE 4: CADTH COMMON DRUG REVIEW REANALYSIS INCREMENTAL COST-UTILITY RATIOS FOR USTEKINUMAB VERSUS COMPARATORS, ANTI-TNF ALPHA NAIVE PATIENTS

	Total Costs ($)	Incremental Cost Versus Placebo($)	Total QALYs	Incremental QALYs Versus Placebo	Incremental Cost Per QALY Versus Placebo ($)
Manufacturer's Base-Case Analysis					
Placebo	51,269		5.14		
Ustekinumab	112,268	60,999	6.63	1.49	40,958
Golimumab	106,084	54,815	7.23	2.09	26,227
Adalimumab	114,184	62,915	6.80	1.66	37,901
Etanercept	132,854	81,585	7.31	2.17	37,597
Infliximab	196,391	145,122	7.48	2.34	62,018
Using Corrected Efficacy Values From the MTC[a]					
Placebo	51,269		5.14		
Ustekinumab	112,700	61,431	6.64	1.5	40,964
Golimumab	106,354	55,085	7.24	2.1	26,231
Adalimumab	115,009	63,740	6.82	1.68	37,940
Etanercept	131,649	80,380	7.28	2.14	37,561
Infliximab	196,626	145,357	7.49	2.35	61,854
Assuming HAQ Worsening that Follows the Natural Disease Progression After Treatment Discontinuation					
Placebo	51,269		5.14		
Ustekinumab	112,631	61,362	5.98	0.84	73,051
Golimumab	106,608	55,339	6.28	1.14	48,543
Adalimumab	114,611	63,342	6.03	0.89	71,171
Etanercept	133,359	82,090	6.40	1.26	65,151
Infliximab	196,915	145,646	6.54	1.4	104,033
Based on "Conservative Scenario"[b]					
Placebo	51,269		5.14		
Ustekinumab	113,065	61,796	5.99	0.85	73,082
Golimumab	106,881	55,612	6.29	1.15	48,340
Adalimumab	115,441	64,172	6.05	0.91	70,679
Etanercept	132,147	80,878	6.38	1.24	65,186
Infliximab	197,151	145,882	6.54	1.40	104,064

CDR = CADTH Common Drug Review; HAQ = Health Assessment Questionnaire; MTC = mixed treatment comparison; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.

[a] See Appendix 2 for a summary of the data.

[b] Conservative scenario combining the four CDR reanalyses.

TABLE 5: CADTH COMMON DRUG REVIEW ANALYSIS OF INCREMENTAL COST-UTILITY RATIOS BASED ON VARIOUS PRICE REDUCTION SCENARIOS: ANTI-TNF ALPHA NAIVE PATIENTS

Scenario	ICUR Based on Manufacturer's Analysis (Versus Placebo)	Revised ICUR Based on CDR "Conservative Scenario" (Versus Placebo)
No price reduction	$40,958	$73,051
10% price reduction	$36,662	$65,434
20% price reduction	$32,367	$57,817
30% price reduction	$28,071	$50,201
40% price reduction	$23,775	$42,584
50% price reduction	$19,479	$34,967
60% price reduction	$15,183	$27,351
70% price reduction	$10,887	$19,734
80% price reduction	$6,591	$12,118
90% price reduction	$2,295	$4,501
100% price reduction	Dominant	Dominant

CDR = Common Drug Review; ICUR = incremental cost-utility ratio; TNF = tumour necrosis factor.

3.3.2 Anti-TNF alpha experienced patients

For anti-TNF alpha experienced patients, CDR analyses yielded similar results as those reported for the manufacturer's analyses. CDR analyses showed that the ICUR compared with placebo for ustekinumab ranged from $46,962 (using corrected efficacy values from the MTC) to $82,611 (HAQ rebounds to natural history on withdrawal from active treatment). When the two CDR analyses were combined to form the "conservative scenario," the analysis indicated the ICUR for ustekinumab increased to $82,611 compared with placebo.

TABLE 6: CADTH COMMON DRUG REVIEW REANALYSIS INCREMENTAL COST-UTILITY RATIOS FOR USTEKINUMAB VERSUS COMPARATORS, ANTI-TNF ALPHA EXPERIENCED PATIENTS

	Total Costs ($)	Incremental Cost of Ustekinumab ($)	Total QALYs	Incremental QALYs of Ustekinumab	Incremental Cost Per QALY of Ustekinumab Versus Comparators ($)
Manufacturer's Base-Case Analysis					
Ustekinumab	127,231		3.99		
Placebo	66,328	60,904	2.70	1.3	46,962
Using Corrected Efficacy Values From the MTC[a]					
Ustekinumab	127,231		3.99		
Placebo	66,328	60,904	2.70	1.3	46,962
Assuming HAQ Worsening that Follows the Natural Disease Progression After Treatment Discontinuation					
Ustekinumab	127,542		3.44		
Placebo	66,328	61,215	2.70	0.74	82,611
Based on "Conservative Scenario"[b]					
Ustekinumab	127,542		3.44		
Placebo	66,328	61,215	2.70	0.74	82,611

CDR = Common Drug Review; HAQ = Health Assessment Questionnaire; MTC = mixed treatment comparison; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.
[a] See Appendix 2 for a summary of the data.
[b] Conservative scenario combining the four CDR reanalyses.

Table 7 summarizes ICURs of ustekinumab compared with placebo resulting from different price-reduction scenarios. For example, a 50% price reduction would reduce the ICUR from $82,611 to $39,069.

TABLE 7: CADTH COMMON DRUG REVIEW ANALYSIS OF INCREMENTAL COST-UTILITY RATIOS BASED ON VARIOUS PRICE-REDUCTION SCENARIOS

Scenario	ICUR Based on Manufacturer's Analysis (Versus Placebo)	Revised ICUR Based on CDR "Conservative Scenario" (Versus Placebo)
No price reduction	$46,962	$82,611
10% price reduction	$41,986	$73,903
20% price reduction	$37,010	$65,194
30% price reduction	$32,035	$56,486
40% price reduction	$27,059	$47,777
50% price reduction	$22,083	$39,069
60% price reduction	$17,107	$30,360
70% price reduction	$17,131	$21,651
80% price reduction	$7,155	$12,943
90% price reduction	$2,180	$4,234
100% price reduction	Dominant	Dominant

CDR = Common Drug Review; ICUR = incremental cost-utility ratio.

4. DISCUSSION

The CDR pharmacoeconomic review included the structure, assumptions, data, and results presented in the manufacturer's economic submission. The key limitations associated with the manufacturer's submission are summarized in Table 8.

NICE (England) and Scottish Medicines Consortium (SMC) reviewed ustekinumab and raised concerns similar to those identified by CDR. Namely, both agencies were concerned by uncertainty around the comparative clinical effectiveness of ustekinumab with other biologic treatments used for PsA. The manufacturer submitted an MTC that compared ustekinumab with infliximab, etanercept, adalimumab, and golimumab; however, the CDR clinical review reported that, for almost all outcomes presented, ustekinumab 45 mg and 90 mg versus placebo had lower odds ratios than all other comparators. The authors of the MTC speculate that the reason for the lower response rates in ustekinumab, relative to other drugs, is related to the high placebo response rate in the ustekinumab trials, relative to the placebo response rate in the other trials. However, this explanation might not be accurate, because the placebo rates for the mean difference of change in the HAQ-DI outcome were approximately at the median level of placebo response rate across all the trials, yet ustekinumab still had low HAQ-DI results relative to the other drugs.

The NICE review raised concerns about appropriateness of the HAQ-DI assumptions. The economic evaluation submitted by the manufacturer used HAQ scores for PsARC responders and non-responders as a measure of quality of life. However, the submitted model used different sources for HAQ scores between treatments. HAQ scores for ustekinumab were obtained from pooling PSUMMIT1 and PSUMMIT2 results, while HAQ scores for the comparators were obtained from a published MTC by Yang et al.[10] Yang et al.'s MTC reported HAQ scores at 12 weeks, while the manufacturer's MTC evaluated the outcome at 12 to 16 weeks and at 24 weeks; the model assumed equal HAQ scores for comparators at 12 and 24 weeks. This assumption might have biased the cost-effectiveness ratio in favour of ustekinumab because the HAQ scores in PSUMMIT1 and PSUMMIT2 studies decreased (showing improvement) from –0.40 to –0.49 for PsARC responders and from –0.05 to –0.10 for PsARC non-responders. Of note, the NICE technology appraisal guidance for ustekinumab concluded that there is considerable uncertainty as to how the HAQ-DI assumptions would apply to ustekinumab, but the guidance considered that model assumptions were sufficient to make a decision.[13] However, the guidance did not comment on the fact that the model used different sources for HAQ scores.

CDR identified other limitations associated with the manufacturer's submission; however, the impact of these limitations could not be evaluated. Of these, two limitations are of particular importance. The first was related to the assumptions about modelling the effect of conventional management on skin symptoms. The model gave more weight to joint lesions, and thus it might have underestimated the clinical benefits of true conventional management, which would include NSAIDs and DMARDs.[13] The second limitation was related to the use of ustekinumab in patients with prior use of anti-TNF alpha drugs. The evidence supporting the claims of ustekinumab in this population was uncertain because it was obtained from a small group of patients who were included in the PSUMMIT2 trial after its initiation. Furthermore, the model did not include information about the number of previous attempts of anti-TNF alpha treatment. This might have an impact on the quality of life of these patients, utility of therapy, and the associated costs.

TABLE 8: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter / Assumption	Issue	Impact
Inaccurate efficacy data	Efficacy results used in the model differed from the results reported in the MTC	Minimal impact on ICUR
Uncertain assumption relative to disease progression	The model assumed that HAQ scores would rebound to either a baseline value or a lower value after treatment discontinuation. Assuming that quality of life would decline in a manner that follows natural disease progression might have been more appropriate	Underestimates the ICUR for ustekinumab versus placebo

ICUR = incremental cost-utility ratio; HAQ = Health Assessment Questionnaire; MTC = mixed treatment comparison.

4.1 Patient Input

Five patient groups submitted feedback: the Canadian Skin Patients Alliance and the Canadian Association of Psoriasis Patients, the Canadian Psoriasis Network, the Arthritis Society, and Arthritis Consumer Experts. No conflicts of interest were declared in the submissions.

Patient groups reported:

- Physical implications (e.g., pain, swelling, and stiffness), emotional implications (e.g., helplessness, frustration, fear, anxiety, and loss of independence), and disfiguring psoriatic plaques, which can be both physically painful and effect emotional well-being.
- Caregivers have a large role in managing the disease, as they are often required to assist with administering needles and to assist patients in carrying out simple tasks and daily activities.
- Caregivers' emotional well-being is often affected.
- Current medications used to treat PsA may be reasonably effective for some patients, but are associated with a range of adverse events, from stomach trouble, tiredness, and high blood pressure, to severe events such as liver toxicity and kidney dysfunction.
- There remain other barriers to treatment, such as the high price for biologic DMARDs, restrictions to access, and loss of efficacy in current treatment; inconvenience of infusion therapies and requirements for refrigeration represent significant barriers to treatment.

The manufacturer's economic analyses implicitly cover many of these concerns, as outcome measures such as the PASI, HAQ, and PsARC provide a quantitative measurement of concerns such as swollen joints, skin conditions, and other physical aspects reported.

5. CONCLUSIONS

CDR identified concerns with respect to assumptions used to estimate the quality of life and utility values. Based on the manufacturer's indirect comparison, other biologic treatments appear to have greater clinical efficacy compared with ustekinumab, and ustekinumab treatment costs are greater than other biologics (with the exception of infliximab) for patients with no prior exposure to anti-TNF alpha treatment. For patients with prior exposure to anti-TNF alpha treatment, CDR estimated that the ICUR for ustekinumab could be $82,611 compared with placebo, under more conservative scenarios.

APPENDIX 1: COST COMPARISON TABLE FOR BIOLOGICS USED FOR THE TREATMENT OF PSORIATIC ARTHRITIS

The comparator treatments presented in Table 9 have been deemed the appropriate comparators by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified.

TABLE 9: COST COMPARISON FOR BIOLOGICS USED FOR THE TREATMENT OF PSORIATIC ARTHRITIS

Drug / Comparator	Strength	Dosage Form	Price ($)	Average Use	Average Daily Drug Cost ($)[a]	Average Annual Cost ($)
Ustekinumab (Stelara)	**45 mg/0.5 mL 90 mg/1.0 mL**	**Vial**	**4593.1400[b]**	**45 mg or 90 mg SC at weeks 0 and 4 and then every 12 weeks thereafter**	**Year 1: 62.92 Thereafter: 54.53**	**Year 1: 22,966 Thereafter: 19,903**
Biologic Response Modifiers						
Adalimumab (Humira)	40 mg/0.8 mL	Syringe or pen	740.3600	40 mg SC every other week	52.74	19,249
Etanercept (Enbrel)	50 mg/mL 25 mg/vial	Syringe or pen vial	388.6050 194.2450	50 mg once weekly OR 25 mg twice weekly	55.35 to 55.36	20,201 to 20,207
Golimumab (Simponi)	50 mg/0.5 mL	Syringe or pen	1520.2100	50 mg SC once a month	49.98	18,243
Certolizumab pegol (Cimzia)	200 mg/mL	Pre-filled syringe	664.5100	Loading dose: 400 mg at weeks 0, 2, and 4 Maintenance dose: 200 mg every 2 weeks (400 mg every 4 weeks may be considered)	47.47 to 94.93	Year 1: 19,318 Thereafter: 17,325
Infliximab (Remicade)	100 mg/vial	Vial	976.0000[c]	5 mg/kg IV at weeks 0, 2, and 6 then every 8 weeks thereafter	Year 1: 85.57[b,d] Thereafter: 69.52 [b,d]	Year 1: 31,232 [b,d] Thereafter: 25,376 [b,d]

Drug / Comparator	Strength	Dosage Form	Price ($)	Average Use	Average Daily Drug Cost ($)[a]	Average Annual Cost ($)
Ustekinumab (Stelara)	**45 mg/0.5 mL 90 mg/1.0 mL**	**Vial**	**4593.1400[b]**	**45 mg or 90 mg SC at weeks 0 and 4 and then every 12 weeks thereafter**	**Year 1: 62.92 Thereafter: 54.53**	**Year 1: 22,966 Thereafter: 19,903**
Other Drugs						
Auranofin (Ridaura)	3 mg	Capsule	6.0141	3 mg once to twice daily	6.01 to 12.03	2,195 to 4,390
Methotrexate (generics)	2.5 mg 10 mg 20 mg/2 mL 50 mg/2 mL	Tablet Tablet Injection Injection	0.6325 2.4541[c] 12.5000 8.9200	10 mg to 25 mg weekly	0.36 to 0.90	132 to 330
Sodium aurothiomalate (generic)	10 mg/mL 25 mg/mL 50 mg/mL	Injection Injection Injection	6.3100 7.6567 11.8900	25 mg to 50 mg IM every 2 to 4 weeks	0.27 to 0.85	100 to 309

IM = intramuscularly; IV = intravenously; SC = subcutaneously.
All prices are from Ontario Drug Benefit Formulary (April 2014) unless otherwise indicated. Administration costs are not included.
[a] Manufacturer's submitted price.
[b] Weight-based dosing assumes a 70 kg patient.
[c] Saskatchewan Drug Benefit (April 2014).
[d] Includes wastage of excess vials.

APPENDIX 2: DISCREPANCIES BETWEEN THE MTC RESULTS AND THE DATA USED IN THE MODEL

TABLE 10: COMPARISON BETWEEN THE PROBABILITIES OF RESPONSE REPORTED IN THE SUBMITTED MIXED TREATMENT COMPARISON AND THE PROBABILITIES USED IN THE MODEL

	PsARC (12 weeks)		PsARC (24 weeks)		ACR 20 (12 weeks)		ACR 20 (24 weeks)		PASI 75 (12 weeks)		PASI 75 (24 weeks)	
	MTC[a]	Used[b]	MTC[a]	Used[b]	MTC[a]	Used[b]	MTC[a]	Used[b]	MTC[a]	Used[b]	MTC[a]	Used[b]
Adalimumab 40 mg	62.2%	61.3%	68.5%	68.6%	52.3%	49.7%	64.8%	63.8%	48.8%	47.0%	78%	78%
Placebo	28.0%	27.7%	29.8%	29.6%	14.4%	14.3%	19.5%	18.7%	4.3%	NU	4.0%	NU
Etanercept 25 mg	74.2%	75.3%	77.2%	76.8%	61.4%	63.3%	53.8%	52.3%	26.4%	25.0%	26%	24%
Golimumab 100 mg	78.7%	78.2%	85.3%	85.4%	59.0%	59.2%	73.0%	71.8%	71.1%	69%	85%	84%
Golimumab 50 mg	79.8%	79.3%	70.5%	70.4%	64.0%	64.2%	65.0%	63.8%	54.2%	51.0%	78%	77%
Infliximab 5 mg	79.1%	79.0%	67.8%	67.6%	68.7%	69.2%	59.8%	58.9%	72.0%	71.0%	84%	82%
Ustekinumab 45 mg	47.3%	52.0%	47.3%	47.4%	31.3%	35.5%	39.5%	37.3%	28.9%	30.7%	32%	33%
Ustekinumab 90 mg	48.9%	42.3%	52.8%	50.7%	28.7%	25.6%	44.0%	38.6%	31.6%	41.8%	36%	27%

ACR = American College of Rheumatology; PASI = Psoriasis Area Severity Index; PsARC = Psoriatic Arthritis Response Criteria; MTC = mixed treatment comparison.
[a] Source: Manufacturer's mixed treatment comparison table 14-19.[14]
[b] Source: Manufacturer's pharmacoeconomic model and review.[2]

APPENDIX 3: SUMMARY OF KEY OUTCOMES

When considering only costs, outcomes, and quality of life, how attractive is ustekinumab acetate relative to placebo?

TABLE 11: ANTI-TNF ALPHA NAIVE PATIENTS

Ustekinumab Versus Placebo	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$132,713					

CE = cost-effectiveness; NA = not applicable; TNF = tumour necrosis factor.

The above is based on CDR reanalysis.

When considering only costs, outcomes, and quality of life, how attractive is ustekinumab acetate relative to placebo?

TABLE 12: ANTI-TNF ALPHA EXPERIENCED PATIENTS

Ustekinumab Versus Placebo	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$137,298					

CE = cost-effectiveness; NA = not applicable; TNF = tumour necrosis factor.

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT DECISIONS

At least two European health technology assessment bodies have published recommendations regarding ustekinumab for psoriatic arthritis: England's National Institute for Health and Care Excellence (NICE) and Scotland's Scottish Medicines Consortium (SMC). NICE provided guidance that ustekinumab is not recommended for treating psoriatic arthritis within its approved marketing authorization, while SMC recommended ustekinumab be used in patients with active psoriatic arthritis who have failed on, or are unsuitable for, treatment with an anti-TNF drug. Summaries of these recommendations are provided here.

TABLE 13: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	NICE	SMC
Drug	Ustekinumab (Stelara)	
Price	Average annual acquisition costs: 45 mg: year 1 = £10,735, subsequent years = £9,304 90 mg: year 1 = £21,470, subsequent years = £18,608	Average annual acquisition costs: Year 1 = £10,735 to £21,470 Subsequent years = £8,588 to £21,470
Treatment	Initial dose of 45 mg, followed by a dose 4 weeks later and further doses every 12 weeks thereafter. A dose of 90 mg may be used in people with a body weight over 100 kg.	Initial dose of 45 mg, followed by a 45 mg dose 4 weeks later and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with body weight above 100 kg.
Comparator	TNF alpha inhibitors (in people who were TNF alpha inhibitor naive) and conventional management without TNF alpha inhibitors (in people who were TNF alpha inhibitor exposed)	Anti -TNF drugs licensed for this indication: adalimumab, etanercept, golimumab, and infliximab
Population modelled	Adults with active psoriatic arthritis for whom the response to previous DMARD therapy has been inadequate	Adult patients with active psoriatic arthritis who have an inadequate response to previous non-biologic DMARD therapy (alone or in combination with methotrexate)
Time horizon	Lifetime (52 years)	Lifetime (length not specified)
Discount rate	3.5% per annum on both costs and outcomes	Not reported
Type of model	Initial decision tree model followed by long-term Markov model	Simplified Markov model
Key outcomes	QALYs	QALYs
Results	TNF alpha naive population: Adalimumab dominated ustekinumab • In the TNF alpha naive population, all SAs found ustekinumab to be dominated by adalimumab. TNF alpha exposed population: ustekinumab had an ICUR of £29,132 per QALY gained compared with conventional management. • NICE reanalyses found that, in the TNF alpha exposed population, ustekinumab was associated with ICURs of between £28,670 and £69,139 per QALY gained compared with	TNF alpha naive population: • Ustekinumab dominated by adalimumab • Ustekinumab had an ICUR of £21,550 per QALY gained versus conventional management. TNF alpha experienced population: • Ustekinumab had an ICUR of £27,751 per QALY gained versus conventional management.

	NICE	SMC
	conventional management.	Results were sensitive to estimated natural history decline in HAQ assumed. Adopting a single 24-week time period for assessing response resulted in increased ICURs for ustekinumab versus conventional management in both populations.
Sources of uncertainty	Assumptions around HAQ-DI are not necessarily appropriate for ustekinumab. Comparative clinical effectiveness is uncertain. Clinical benefits of conventional management appear to be underestimated. Withdrawal rates used may not be appropriate.	Lack of direct comparisons in the indication of interest. Limitations with the comparative clinical data.
CDR assessment	Similar model structure submitted to CDR	The model structure submitted to CDR appears to have been similar to those submitted to other health technology assessment agencies.

CDR = CADTH Common Drug Review; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year; SA = sensitivity analysis; SMC = Scottish Medicines Consortium; TNF = tumour necrosis factor.

APPENDIX 5: ADDITIONAL INFORMATION

TABLE 14: 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"*	None		
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		

TABLE 15: AUTHOR INFORMATION

Authors	Affiliations
Chrissy Almond Janssen Inc.	Not reported Janssen Inc.

	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	

REFERENCES

1. CEDAC final recommendation and reasons for recommendation: Ustekinumab (Stelara™ - Janssen-Ortho Inc.) Indication: chronic moderate to severe plaque psoriasis [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2009 May 20. [cited 2014 May 8]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Stelara_June-17-2009.pdf
2. Pharmacoeconomic evaluation. In: CDR submission: Stelara® (ustekinumab) solution for injection 45mg/0.5mL, 90mg/1.0mL. Company: Janssen Inc. [**CONFIDENTIAL** manufacturer's submission]. Toronto: Janssen Inc; 2013 Oct 28.
3. Stelara (ustekinumab) injection sterile solution 45mg/0.5mL [product monograph]. Toronto: Janssen-Ortho Inc.; 2008 Dec 12.
4. CEDAC final recommendation and reasons for recommendation: Adalimumab resubmission (Humira® - Abbott Laboratories Ltd.) [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2006 Nov 29. [cited 2014 May 8]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Humira_Resubmission_Nov29-06.pdf
5. CEDAC final recommendation: Golimumab (Simponi - Schering Plough Inc.) Indication: psoriatic arthritis [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2010 Feb 17. [cited 2014 May 8]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Simponi-PsA_March-17-2010_e.pdf
6. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 3rd ed. Ottawa: The Agency; 2006 Mar. [cited 2014 Apr 17]. Available from: http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf
7. National Institute for Clinical Excellence. Golimumab for the treatment of psoriatic arthritis [Internet]. London: The Institute; 2011 Apr. [cited 2014 May 8]. (NICE technology appraisal guidance 220). Available from: http://www.nice.org.uk/nicemedia/live/13441/54169/54169.pdf
8. Kyle S, Chandler D, Griffiths CE, Helliwell P, Lewis J, McInnes I, et al. Guideline for anti-TNF-a therapy in psoriatic arthritis. Rheumatology (Oxford, England) [Internet]. 2005 Mar [cited 2014 May 8];44(3):390-7. Available from: http://rheumatology.oxfordjournals.org/content/44/3/390.full.pdf+html
9. Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T, et al. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess [Internet]. 2011 Feb [cited 2014 May 8];15(10):i-329. Available from: http://www.hta.ac.uk/fullmono/mon1510.pdf
10. Yang H, Craig D, Epstein D, Bojke L, Light K, Bruce IN, et al. Golimumab for the treatment of psoriatic arthritis: a NICE single technology appraisal. PharmacoEconomics. 2012 Apr;30(4):257-70.
11. Bojke L, Epstein D, Craig D, Rodgers M, Woolacott N, Yang H, et al. Modelling the cost-effectiveness of biologic treatments for psoriatic arthritis. Rheumatology (Oxford) [Internet]. 2011 Sep [cited 2014 May 8];50 Suppl 4:iv39-iv47. Available from: http://rheumatology.oxfordjournals.org/content/50/suppl_4/iv39.full.pdf+html
12. Rowen D, Brazier J, Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? [Internet]. Health Qual Life Outcomes. 2009 [cited 2014 May 8];7:27. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683169

13. National Institute for Clinical Excellence. Ustekinumab for treating active psoriatic arthritis [Internet]. London: The Institute; 2014 May. [cited 2014 May 30]. (NICE technology appraisal guidance TA313). Available from: http://publications.nice.org.uk/ustekinumab-for-treating-active-psoriatic-arthritis-ta313

14. Janssen Inc. response to April 17, 2014 CDR request for additional information: systematic review & mixed treatment comparison (MTC) **[CONFIDENTIAL** additional manufacturer's information]. Toronto: Janssen Inc.; 2014 May 1.