CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Tocilizumab (Actemra)

(Hoffman-La Roche Limited)

Indication: For the treatment of giant cell arteritis (GCA) in adult patients.

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Abbreviations

AE	adverse event
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
EQ5D	EuroQoL 5-Dimensions 3-Levels questionnaire
GCA	giant cell arteritis
HTA	health technology assessment
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-years
TCZ	tocilizumab

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Tocilizumab (Actemra)
Study Question	To estimate the incremental cost-effectiveness, over a 20-year time horizon, of weekly tocilizumab + prednisone compared with prednisone alone for adult patients with giant cell arteritis from a Ministry of Health perspective
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults with giant cell arteritis
Treatment	Tocilizumab doses of 162 mg administered via subcutaneous injection weekly plus 26-week prednisone tapering as defined in the GiACTA trial
Outcome	Quality-adjusted life-years (QALY)
Comparators	Prednisone 52-week tapering as defined in the GiACTA trial
Perspective	Canadian Ministry of Health
Time Horizon	Lifetime (20 years)
Results for Base Case	$85,496 per QALY (probabilistic analysis)
Key Limitations	CDR identified the following limitations: • The relative efficacy of tocilizumab + prednisone compared with prednisone alone observed in the 52-week GiACTA trial were assumed to persist indefinitely, even after tocilizumab is no longer administered • Differences in prednisone-related adverse events were estimated using observational data correlating prednisone dose with outcomes • The manufacturer assumed all fractures (including vertebral) were treated as an in-patient, which might overestimate the prednisone-related adverse event costs. • Significant uncertainty exists in many of the clinically important outcomes modelled in the submission
CDR Estimates	• In a plausible CDR base case that assumes the same relative efficacy in flares after the treatment period (after 2 years) and adjusted cost for fracture (accounting for fractures treated in the outpatient setting), the incremental cost-utility ratio (ICUR) for tocilizumab + prednisone was $187,389 per QALY when compared with prednisone alone. The following scenario analyses on the CDR base case that had an impact on the ICUR included: • Removing the disutility of taking prednisone (−0.03) increased the ICUR to $187,689 per QALY • Considering ± 25% of prednisone-related adverse events resulted in an ICUR ranging from $151,364 to $210,847 per QALY

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; ICUR = incremental cost-utility analysis; QALY = quality-adjusted life-year

Drug	Tocilizumab (Actemra)
Indication	Treatment of giant cell arteritis (GCA) in adult patients
Reimbursement Request	As per indication
Dosage Form(s)	Tocilizumab doses of 162 mg administered via subcutaneous injection weekly plus 26-week prednisone tapering
NOC Date	October 27, 2017
Manufacturer	Hoffmann-La Roche Limited

Executive Summary

Background

Tocilizumab (Actemra, TCZ) is an IL-6 receptor agonist indicated for the treatment of giant cell arteritis (GCA) in adult patients.[1] The recommended dose is 162 mg administered via subcutaneous injection weekly for two years plus 26 weeks of prednisone tapering. It is supplied as a solution for injection in a 0.9 mL syringe. The submitted price of TCZ is $358.90 per syringe injection.[2]

The manufacturer submitted a cost-utility analysis comparing TCZ plus prednisone with prednisone alone in adult patients with GCA over a lifetime time horizon of 20 years from the perspective of the Canadian health care payer.[3] A semi-Markov model was developed based on the GiACTA trial data[4] and extrapolated to a second year (on TCZ treatment) and beyond. The model considered flare after treatment, as well as GCA- or prednisone-related adverse events (AEs). The treatment effects and safety of TCZ plus prednisone and prednisone alone were taken from the GiACTA trial. Other inputs such as costs and utility values were obtained from published literature.

In its base case, the manufacturer reported that an incremental cost of $32,612 and incremental quality-adjusted life-years (QALYs) of 0.42, resulting in an incremental cost-utility ratio (ICUR) of $85,496 per QALY when comparing TCZ plus prednisone with prednisone alone (probabilistic analysis).

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified several key limitations with the submitted analysis. First, clinical benefit was assumed to last for the patients' lifetime (20 years) after the treatment period of TCZ (two years), which according to the CDR clinical expert consulted is likely to overestimate the benefit of TCZ. Furthermore, prednisone-related AEs (e.g., fractures, diabetes mellitus) were estimated from observational data. In addition, the manufacturer assumed that all fractures (including vertebral) were treated as an in-patient, which may overestimate the prednisone-related AE costs. Further, there were also uncertainties surrounding the assumption of the disutility associated with being on prednisone, as well as utility estimates from the GiACTA trial data.

The limitation that had a significant impact on results was the assumption of clinical benefits after the treatment period. CDR attempted to address these issues in a plausible CDR base case that assumes the same relative efficacy in flares after the treatment period of two years combining two separate analyses. This new base case also corrected the cost of fractures to account for outpatient treatment of vertebral fractures. The ICUR for TCZ plus prednisone was $187,389 per QALY when compared with prednisone alone.

In further sensitivity and scenario analysis on the CDR base case, removing the prednisone disutility (from simply taking the medication) resulted in an ICUR of $187,689 per QALY. Varying the prednisone-related AEs by ± 25% resulted in ICURs of $151,364 to $210,847.

Based on the CDR revised base case, a priced reduction of ~68% for TCZ would be required to reduce the ICUR to $50,000 per QALY.

Conclusions

The key limitations of this submission were the assumption of relative efficacy from a short-term (52-week) trial and extrapolating the short-term effects to a lifetime time horizon. The ICUR was sensitive to the relative benefits after treatment period, as well as utility decrements for being on prednisone. In the CDR plausible base case, the ICUR was $187,000 per QALY if no additional benefit on GCA and disease flares occurred after discontinuation of TCZ following the two-year treatment period, and the cost of fractures was adjusted. Results were also sensitive to assumptions around the disutility of taking prednisone and rates of AEs on prednisone, which could result in ICURs over $245,000 per QALY.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis (CUA) comparing tocilizumab (TCZ) plus prednisone with prednisone alone in patients with giant cell arteritis (GCA). The time horizon was a patient lifetime (20 years) with a weekly cycle length, and the perspective was the Canadian public payer.[3] The patient cohort entered the model in remission and initiated treatment on either TCZ with 26 weeks prednisone tapering or 52 weeks prednisone tapering alone. The following five health states were included in the model: in remission plus on steroid; in remission plus off steroid; in flare/relapse (one week); in remission plus on maintenance steroids (escape prednisone); and death. For patients receiving TCZ plus prednisone, after the 26-week prednisone taper, patients not in flare were assumed to be treated with TCZ only for an additional 1.5 years (two years in total). Transition probabilities to the first flare or re-flare were derived from the GiACTA trial[4] and extrapolated based on parametric models. The model considered background mortality for all the patients based on annual death probability from Canadian life tables. Indirect mortality due to GCA is incorporated via the occurrence of major stroke during a flare (assumed 50% mortality for major strokes).

The model incorporated consequences of GCA (vision loss and stroke) and prednisone-related adverse events (AEs) (fractures and diabetes mellitus). Rates for GCA or prednisone-related AEs were derived from literature[5] and Manufacturer's Real-World Evidence Report of the [redacted] respectively [redacted] AE-related TCZ were not included in the model.

Health-state utilities for remission (0.7713) and flare (0.642) were estimated using EuroQoL 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) data from the GiACTA trial[4] that was transformed to utility and then adjusted within a mixed model. Utility decrements for GCA- or prednisone-related AEs were obtained from a National Institute for Health Research health technology assessment (HTA) report on a GCA diagnosis cost-effectiveness analysis.[5] For GCA-related AEs (vision loss −0.37272, minor stroke −0.17882, or major stroke −0.49122); the utility decrement was rescaled to the baseline utility for remission. Similar rescaling was performed for the prednisone-related AEs (diabetes mellitus −0.09264, fractures −0.2025 and −0.1128, weighted by the annual risk of different types of fractures). An annual utility decrement of −0.03 was also applied to patients while they were taking prednisone tapers, to account for frequent visits to the doctor and other side effects.

Drug costs of TCZ and prednisone were obtained from provincial formularies. A costing algorithm was used to calculate the minimum cost for each prednisone dose required by patients based on the mode prices from the formularies, and the cost of prednisone varied over time because of the taper regimens ($4.59 per week for the first year, $0.28 to $0.75 per week after one year). Patients were assumed to remain on weekly TCZ until the end of the second year (24 months). The total cost for a flare was the sum of the cost of a visit to the rheumatologist and the cost of additional prednisone. The flare dose was derived from

the increased prednisone doses from the flare patients in the GiACTA trial. Costs of AEs were obtained from Canadian costing studies or tariff cost per event from the Ontario case-costing website.[7,8]

Manufacturer's Base Case

In the base case (probabilistic), the manufacturer reported that TCZ plus prednisone compared with prednisone alone is associated with an additional 0.42 quality-adjusted life-years (QALYs). Treatment with TCZ plus prednisone resulted in higher total health care costs of $32,612 versus prednisone alone, largely driven by drug costs. The incremental cost-utility ratio (ICUR) for TCZ plus prednisone versus prednisone alone is $85,496 per QALY (Table 2).

Table 2: Results of the Manufacturer's Base Case (Probabilistic)

	TCZ + Prednisone	Prednisone Alone	Difference (TCZ + Prednisone – Prednisone Alone)
QALYs			
On Remission	9.90	9.15	0.75
On Flare	0.30	0.78	−0.48
Disutility from GCA-related AE	−0.00003	−0.0007	0.00004
Disutility from prednisone-related AE	−0.20	−0.35	0.15
Total QALYs	**10.00**	**9.57**	**0.43**
Cost ($)			
Drug costs	37,012	455	36,557
Flare cost	548	1,438	−890
GCA-related AE costs	80	211	−131
Prednisone-related AE costs	2,461	5,385	−2,924
Total costs ($)	**40,101**	**7,488**	**32,613**
ICUR ($/QALY)			**85,496**

AE = adverse event; GCA = giant cell arteritis; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TCZ = tocilizumab.
Source: Manufacturer's Pharmacoeconomic Report.[3]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using one-way deterministic sensitivity analyses, which varied model parameters by using alternative values. A series of one-way sensitivity analyses were conducted by the manufacturer, including: time horizon (base case 20 years versus 10 to 30 years); discount rates (1.5% versus 0% and 3.5%); adverse events (included versus excluded); duration of flare disutility (four versus one week); prednisone dose received by TCZ patients (GiACTA versus [redacted]); and duration of TCZ (24 months versus 12 to 72 months); cumulative dose of prednisone (± 30%); reducing the probability of subsequent flare (10% to 50%); and a different method of deriving TCZ efficiency.

The base-case deterministic result is $82,445 per QALY when comparing TCZ plus prednisone with prednisone alone. The results were robust except for the following parameters:

- Time horizon of 10 years: cost per QALY gained for TCZ plus prednisone is $137,555

- AEs removed from model (specific nature of AE not specified in the submission): cost per QALY gained for TCZ plus prednisone is $250,830
- Reduce duration of flare disutility to one week: cost per QALY gained for TCZ plus prednisone is $180,084
- Cumulative prednisone dose based on [redacted] data: cost per QALY gained for TCZ plus prednisone is $106,993
- Duration of TCZ: cost per QALY gained for TCZ plus prednisone is $125,969 (36 months) to $248,554 (72 months)
- Lifetime cumulative prednisone dose reduced by 30%: cost per QALY gained for TCZ plus prednisone is $110,787
- Reducing the probability of subsequent flare: cost per QALY gained for TCZ plus prednisone is $121,346 (10%) to $192,603 (50%).

According to the cost acceptability curve from the probabilistic sensitivity analyses, 10% and 76% of the ICURs would fall below $50,000 and $100,000 per QALY thresholds, respectively.

Limitations of Manufacturer's Submission

A. **Assumption of clinical benefit of TCZ after treatment period.** The relative efficacy of TCZ observed in the GiACTA trial was assumed to persist indefinitely, and was extrapolated to last for the patient's lifetime (20 years in the model). There is uncertainty in extrapolation of benefit in the second year. Further, there is no evidence (or theoretical justification) to assume that incremental benefit exists after two years (after which tocilizumab is stopped). According to the CADTH Common Drug Review (CDR) clinical expert, regardless of how patients are treated in the first one to two years, they are likely to have the same clinical course of GCA, including frequencies of flare, once they complete treatment. Further, relative efficacy will be influenced by prednisone dosing — this was protocolized in the trial and may differ from real-world practice, which may influence real-world incremental efficacy — and this adds to the uncertainty of relative efficacy. Finally, clinically relevant events that occur with GCA disease activity (stroke, vision loss) were estimated from observational data.

B. **Prednisone-related AEs.** The frequency of prednisone-related AEs is based on the association of cumulative prednisone dose, and fractures, and diabetes from an observational data set. While this is a reasonable approach, the absence of measurement of these outcomes in a trial adds uncertainty. Further, as above, prednisone doses are defined by the trial protocol in the study and may differ in the real-world setting, adding further uncertainty in the actual probability of these AEs.

C. **Overestimates of fracture costs.** The model assumed all fractures, including vertebral fractures, which constitute 31.4% of all fractures in the model, were treated as in-patient; vertebral fractures are commonly treated as an outpatient.

D. **Prednisone disutility.** A utility decrement of 0.03 was applied to patients while they were taking prednisone tapers. Given that disutility from prednisone-related AEs (fractures and diabetes) and flares has already been taken account in the model, the disutility from prednisone alone might overestimate the benefits of TCZ. There was also no between-group comparisons for

EQ-5D-3L and the values between the treatment groups from the GiACTA trial were similar (see CDR Clinical Report for details).

E. **Uncertainty regarding baseline and flare utility.** Baseline utility (in remission) and utility in flare were estimated from the GiACTA trial, from which EQ-5D-3L data were converted to utility using a mapping algorithm (which differs from population algorithms). The manufacturer provided additional information, stating that a mixed model was developed to convert the utility data to the utility estimates for each health state. The validity of this approach (compared with simply using EQ-5D-3L–derived utility directly, or using population algorithm coefficients) was not provided. Further, EQ-5D-3L data were captured at regular intervals during the trial, not specifically during a flare/non-flare period. As such, there is uncertain utility for these states (both the value of the utility score as well as the duration of the state and disutility).

F. **Assumed stroke mortality rate.** A 50% mortality rate was assumed for major stroke. However, a multi-centre cohort study in Canada suggested that the mortality rate for patients aged 70 to 79 (note: mean age from GiACTA was 69 years) with ischemic stroke was only 13.4%.[9]

CADTH Common Drug Review Reanalyses

CDR considered the following analyses to address the limitations identified above: The following considerations and reanalyses apply to the comparison of TCZ plus prednisone to prednisone alone.

1. **No difference in incremental efficacy after two years**. Given the challenges in exploring this in the manufacturer's model, three approaches were explored:

    a) Manufacturer-suggested approach, where the slope of time to first flare and subsequent flare rate for TCZ were set to the same as prednisone after two years. However, there were still sustained benefits (e.g., a lower absolute rate of flares) after stopping treatment (after two years), resulting in more TCZ patients in the remission state by the end of the model duration (20 years).

    b) CDR approach using manufacturer model, which was similar to the previous approach but the absolute time to flare and flare rates (for subjects that had already experienced a flare) were set to the same as the prednisone group after two years. This resulted in fewer benefits in TCZ-treated patients, but TCZ-treated patients still experienced incremental benefits (more remissions) after two years.

    c) Manual calculations were performed assuming the same proportion of TCZ and prednisone patients in the remission state after two years, with no incremental benefits by treatment group with TCZ treatment. The benefits from remission and flare of GCA with TCZ were only allowed for the first two years (based on the two-year model), and assumed to be similar after this time. The long-term benefits of prednisone-related AEs and differences in GCA-related AEs for TCZ were unchanged in all models. Details on the calculation are presented in Appendix 4.

2. **Fracture costs**. The weighted average cost of $10,971 used in the model assumed all fractures were treated in the in-patient setting. In a sensitivity analysis outpatient cost of vertebral fractures was used (weighted average cost of $7,666) to address limitation C above.

3. **Prednisone disutility**. To assess the speculative disutility of prednisone taper administration (limitation D), the utility decrement of 0.03 was removed (changed to −0.000001 for the probabilistic model to run).

4. **Baseline and flare utility from literature**. To address uncertainty in baseline and flare utility (limitation E), baseline utility (0.716) from the National Institute for Health Research HTA report was used.[5] As flare was not modelled in the HTA report, the flare utility was assumed to be the same as baseline in the sensitivity analysis.

5. **Mortality rate for major stroke**. The mortality rate for major stroke was changed from 50% to 13.4% in the model.

6. **One-year treatment of TCZ**. One-year treatment cost of TCZ was used. A scenario in which benefits with TCZ were allowed for the first year was also presented.

7. **Prednisone-related AEs.** A range of ± 25% of the prednisone-related AEs (i.e., fractures and diabetes) was tested in the sensitivity analysis. The intercepts in the predicted equations were changed to the following: fractures −2.446 and −2.924; diabetes: −3.686 and −4.196 (the model did not allow directly changing the risk).

8. **CDR base case**. A plausible CDR base case assumed no benefits after the treatment period. Given that model-based approaches still led to incremental benefits accrued to the TCZ group after two years, the manual CDR calculation (1c) was determined to best represent the scenario of no continued benefit after two years. In addition, the weighted fracture cost of $7,666 was used. Scenario analyses were also performed to assess the impact of uncertainty in other parameters on this CDR base case. A scenario analysis that considered an alternate plausible reference case, and included a sensitivity analysis on the uncertainty in the risk of prednisone-related AEs, led to ICURs of between $151K and $245K per QALY gained.

    a) Additional sensitivity analysis using 1a and 1b are provided in Appendix 4 (Table 12). Briefly, the range of 1a is $108,735 to $173,350 per QALY (reference case $121,547/QALY); the range for 1b is $125,259 to $180,680 per QALY (reference case $138,041/QALY).

Note: CDR attempted to replicate the manufacturer's sensitivity analysis using the cumulative prednisone dose based on [redacted] in the CDR base case. However, no detailed information on the analysis was provided in the submission, and it could not be assessed in the CDR reanalyses.

Table 3: CDR Reanalysis Plausible Base Case (Based on Probabilistic Models)

	Description	TCZ + Prednisone Compared With Prednisone Alone		
		Incremental Cost	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	$32,613	0.43	$85,496
	Manufacturer base case (2-year time horizon)	$36,477	0.05	$795,162
1	**No benefits after treatment period**			
1a	Manufacturer's adjusted rates	$33,343	0.32	$129,505
1b	CDR approach using model	$33,839	0.28	$138,041
1c	CDR calculation	$33,658	0.19	$177,148
2	**Fracture costs**			
	Weighted average cost of $7,666	$32,841	0.41	$90,941
3	**Prednisone disutility**			
	Assume 0 prednisone disutility	$32,608	0.41	$92,531
4	**Baseline and flare utility**			
4a	Baseline utility of 0.716	$32,662	0.35	$104,752
4b	Baseline and flare utility of 0.716	$32,708	0.30	$120,485
5	**Mortality rate for major stroke**			
	13.4%	$32,589	0.41	$88,696
6	**One-year treatment of TCZ**			
6a	Base case with 1-year cost	$14,581	0.43	$38,526
7	**Prednisone-related AEs**			
7a	Increased risk by 25%	$33,198	0.40	$93,208
7b	Decreased risk by 25%	$32,073	0.44	$81,317
8	**Plausible base case (1c, 2)**	**$33,730**	**0.18**	**$187,389**
8a	Scenario analysis of CDR base case with 0 prednisone disutility	$33,784	0.18	$187,689
8b	Scenario analysis of CDR base case with baseline and flare utility of 0.716	$33,815	0.17	$198,910
8c	Scenario analysis of CDR base case with stroke mortality of 13.4%	$33,760	0.19	$177,685
8d	Scenario analysis of CDR base case with 25% more prednisone-related AEs	$33,300	0.22	$151,364
8e	Scenario analysis of CDR base case with 25% fewer prednisone-related AEs	$34,314	0.17	$210,847
8f	Scenario analysis of CDR base case with 1 week in flare	$33,836	0.17	$199,034
8g	8a + 8c	$33,795	0.18	$187,748
8h	8a + 8c + 8d	$34,326	0.14	$245,188
8i	8a + 8c + 8e	$33,231	0.20	$166,154

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TCZ = tocilizumab.

In the new CDR base-case analysis, assuming no additional benefits after treatment period and outpatient cost for vertebral fractures, the ICUR is $187,389 per QALY. Given inherent uncertainty, an additional sensitivity analysis was performed, indicating that the results vary between an ICUR of $151,364 to $245,188 per QALY. A series of price-reduction analyses were undertaken based on the CDR base case (Table 4). These indicate that a price reduction of 68% may be required to lead to an ICUR < $50,000/QALY.

Table 4: CDR Reanalysis Price Reduction Scenarios Based on the CDR Base Case

ICURs of TCZ + Prednisone Versus Prednisone Alone		
Price	**Base-case analysis submitted by manufacturer ICUR ($/QALY)**	**Reanalysis by CDR (based on plausible base case) ICUR ($/QALY)**
Submitted	85,495	187,389
10% reduction	76,246	166,920
20% reduction	65,205	146,450
30% reduction	59,061	126,061
40% reduction	46,912	105,582
50% reduction	37,665	85,103
60% reduction	24,829	64,624
70% reduction	18,972	44,145

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quantity-adjusted life-year; TCZ = tocilizumab.

Note: Price reductions for scenarios that used alternate approaches to minimizing benefit after two years (1a and 1b above) are presented in Appendix 4 (Table 13). Briefly, a price reduction of ~20% to 30% results in an ICUR of < $100,000/QALY; slightly greater than 50% to 60% reductions result in an ICUR of ~$50,000/QALY.

Issues for Consideration

- There is a spectrum of disease from polymyalgia rheumatica to GCA, but the distinction is not always clear. According to the CDR clinical expert, there is a possibility that TCZ might be used off-label for the treatment of polymyalgia rheumatica. Further, as it is difficult to definitively diagnose GCA in many situations, the availability of TCZ might shift clinical diagnoses so that a larger group of patients are clinically diagnosed with GCA — and may be treated with TCZ — than is the case in current practice,
- As the prednisone dosing and tapering regime is frequently individualized, the prednisone costs and efficacy of disease treatment may be different from those in the model.

Patient Input

Patient input was received from one patient with GCA, who perceived TCZ to as an option to avoid risks associated with long-term prednisone therapy. These potential benefits were considered in the economic model (e.g., diabetes and fractures).

Conclusions

The key limitations of this submission were the assumption of relative efficacy from a short-term (52-week) trial and extrapolating the short-term effects to a lifetime time horizon. In addition to this limitation, there exists significant uncertainty in key areas, including health-related quality of life attributable to GCA management as well as differences in prednisone-related AEs.

The CDR reanalysis to address the identified limitations with the manufacturer's economic analysis showed that results were sensitive to the assumption of ongoing relative benefit after the treatment period. In the CDR plausible base case, the ICUR was $187,000 per QALY (ranging from $122,000 to $187,000) if no additional benefits on flares were assumed after the two-year treatment period and using an adjusted cost for fractures (accounting for fractures treated as an outpatient). Results were also sensitive to assumptions around the disutility of taking prednisone and rates of AEs on prednisone, which could result in ICURs over $245,000 per QALY.

Appendix 1: Cost Comparison

The comparators presented in Table 5 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 5: CDR Cost Comparison Table for Giant Cell Arteritis

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Annual Drug Cost ($)
Tocilizumab (Actemra)	**162 mg/ 0.9 mL**	**Pre-filled syringe**	**358.9050**	**162 mg SC once a week in combination with a tapering course of glucocorticoids. May be used alone after glucocorticoid taper.**	**51.27**	**18,663**
Glucocorticoid						
Prednisone (generic[a])	50 mg 5 mg 1 mg	tab	0.1735 0.0220 0.1066[a]	40 mg to 60 mg per day until ESR is normal and patient asymptomatic. Decrease by 10 mg every 2 weeks to 20 mg, then by 2.5 mg every 2 to 4 weeks to 10 mg, then by 1 mg every 1 to 2 months provided no relapse.[b]	0.02 to 0.45	Approximately 70 to 100 depending on timing of taper

CDR = CADTH Common Drug Review; ESR = erythrocyte sedimentation rate; SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed November 2017)[10] unless otherwise indicated and do not include dispensing fees.

[a] 1 mg prednisone is branded (Winpred).

[b] Source: Rheumatology Guidelines.[11]

Appendix 2: Summary of Key Outcomes

The following summaries have been provided based on the CDR base case.

Table 6: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is TCZ + Prednisone Relative to Prednisone Alone?

TCZ + Prednisone Vs. Prednisone Alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	CDR base case: $187,689 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness ratio; QALY = quality-adjusted life-year. TCZ = tocilizumab

Appendix 3: Additional Information

Table 7: Submission Quality

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

Table 8: Authors information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

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

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

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

☐ Other (please specify)

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

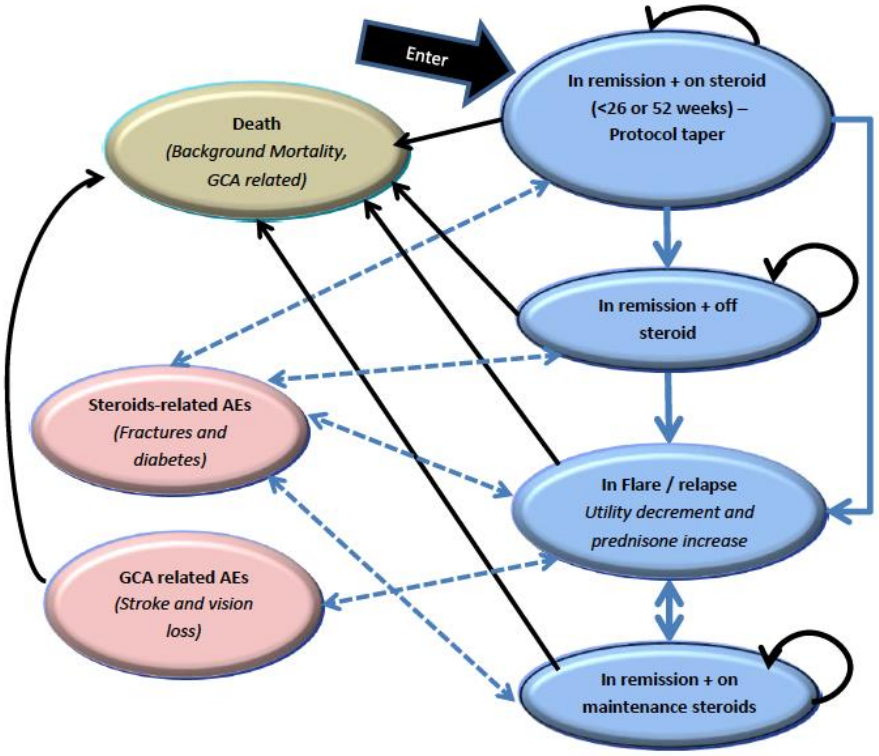
Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

A semi-Markov model was developed based on the GiACTA trial data.

Details of the semi-Markov structure are shown in Figure 1.

Figure 1: Semi-Markov Model Structure



Source: Manufacturer's Pharmacoeconomic Report.[3]

Health-state utilities in the manufacturer's submission were obtained from subjects in the GiACTA trial.[4] Utility decrements from giant cell arteritis or prednisone-related adverse events were adopted based on the utilities used in the National Institute for Health Research health technology assessment report,[5] and rescaled to the health-state utilities. The utility decrement for fractures was calculated as the average utility decrement of different types of fractures.

Table 9 and Table 10 report the relevant data sources and assumptions incorporated by the manufacturer.

Table 9: Data Sources

Data Input	Description of Data Source	Comment
Patient characteristics	Baseline characteristics were informed by the GiACTA trial (phase III, 52-week, randomized, double-blind, placebo-controlled; n = 251).[4]	Appropriate
Efficacy	Efficacy on time to first flare and transition to subsequent flares were taken from the GiACTA trial.[4]	Likely appropriate for year 1, but uncertainty exists regarding extrapolation in year 2. Further, prednisone dosing is protocolized and may differ from real-world administration (which may impact relative efficacy between the 2 treatment groups). It is inappropriate to assume continued benefit of tocilizumab after year 2 (when no further tocilizumab is administered).
Natural history	Model structure was conceptualized after considering the natural history of the disease and the insights from the manufacturer's clinical team regarding the GiACTA data.[4]	Appropriate; disease is not common.
Utilities	Health-state utilities were obtained from the GiACTA trial data.[4] Decrements for GCA or prednisone-related adverse events were obtained from the literature.	While appropriate, the specific details of modelling from EQ-5D data collected from the trial were not provided. All studies used to inform were non-Canadian, as studies on Canadian populations were unavailable; this approach is reasonable.
Resource use	See costs section.	
Dose of prednisone	The prednisone dose for the treatment period was derived from the GiACTA trial.[4] Until the first flare (primary remission), the cumulative dose was 2,632 mg for TCZ and 3,945 mg for prednisone alone. During flare, a predictive equation of the prednisone dose increase was estimated from trial data, based on the last effective dose (1.6472 for TCZ and 1.6493 for prednisone alone). After the flare, patients would switch to the "escape" prednisone tapering regimen, a logistic growth regression was applied derived from the GiACTA trial, and [redacted].[6]	Appropriate. However, prednisone dosing is driven by the protocol. Actual dosing may differ in clinical practice and there is noted variability in treatment.
Adverse events (indicate which specific adverse events were considered in the model)	Adverse events related to TCZ were not included as isolation of these events from AEs caused by prednisone or GCA was not possible, and GiACTA trial showed that the rates of AEs between the treatment groups were very similar.[4] GCA-related AEs included both vision loss and stroke (minor or major), as they were the most costly and debilitating AEs. Rate estimated from the NHS HTA report.[5] Prednisone-related AEs included fractures and diabetes mellitus where considered most relevant	Uncertain, but the GiACTA trial showed the rates of AEs and SAEs between the treatment groups were similar. Appropriate although uncertain; uncommon events not captured in trial and estimated from observational data. Appropriate although uncertain; these events were not obtained from the trial but estimated using observation data linking cumulative dose of prednisone and

Data Input	Description of Data Source	Comment
	from literature review and [redacted].[6] Algorithms were developed from [redacted].	development of fractures and diabetes.
Mortality	The model considered background mortality for all patients based on Canadian life tables. Mortality due to GCA was indirectly incorporated via the occurrence of death with major stroke (in 50%).	Mortality due to stroke is higher than the Canadian data.[9]
Costs		
Drug (tocilizumab, TCZ)	The cost of TCZ was based on the mode prices reported by the provincial formularies. A cost of $358.905 was used for each 162 mg syringe of TCZ. Patients were assumed to remain on weekly TCZ until the end of the second year.	Appropriate
Drug (prednisone)	A costing algorithm was used to calculate the minimum cost for each prednisone dose required by patients. The costs used for prednisone tablets were based on the mode prices reported by the provincial formularies. The weekly cost of prednisone for the first year was $4.59; after one year, the weekly cost was $0.75 for TCZ + prednisone and $0.28 for prednisone only.	Appropriate
Flare management	The total cost for a flare was the sum of the cost of a visit to the rheumatologist (code A480 from the Ontario Schedule of Benefits) and the cost of additional prednisone for one cycle.	Appropriate
GCA-related AEs	Annual costs of $3,152 for vision loss, $25,655 for non-fatal stroke, and $9,295 for fatal stroke were obtained from a Canadian study.[8]	Appropriate
Prednisone-related AEs	The cost of diabetes was derived from a Canadian costing study in which incident diabetes cases in Ontario were matched with subjects without diabetes to determine the attributable costs.[7] For factures, a tariff cost per event was obtained from the Ontario case costing and a weighted average cost of $10,971 was used in the model assuming all fractures were treated in-patient.	Appropriate. According to the CDR clinical expert, most vertebral fractures (31.4% of fractures) would be treated in an outpatient setting; the approach used likely overestimates costs.

Table 10: Manufacturer's Key Assumptions

Assumption	Comment
Natural history and efficacy	
The patients' characteristics from the GiACTA trial were assumed to be representative of the target population.	Reasonable. However, diagnosis of GCA is often made on clinical grounds and there may be variability in how this is defined.
The extrapolation beyond the study follow-up time was based on parametric models.	Uncertain. Relative efficacy may be influenced by the dosing of prednisone, which was protocolized in the trial (and may affect relative efficacy). Further, year 2 efficacy was extrapolated using parametric models and uncertainty exists. Finally, assuming incremental efficacy of TCZ persists after this medication is stopped (beyond 2 years) is not justified by either data or speculation; the clinical expert indicated that relative efficacy is likely to be similar between the two treatment groups after TCZ administration has ceased.
Adverse events related to TCZ were not included in the model.	Uncertain. However, the GiACTA trial showed similar AEs rates between the treatment groups.
Non-Canadian utilities and decrements were used in the model.	Uncertain. May not represent the Canadian patients' population quality of life, but reasonable approach.
Mortality	
50% of major strokes were assumed to be fatal.	Higher than the Canadian data.[9] Saposnik's values were tested in the CDR reanalyses.

AE = adverse event; CDR = CADTH Common Drug Review; GCA = giant cell arteritis; HTA = heath technology assessment; NIHR = National Institute for Health Research; SAE = serious adverse event; TCZ = tocilizumab.

CADTH Common Drug Review Reanalyses (TCZ Plus Prednisone Versus Prednisone alone)

As the provided model did not transparently allow similar efficacy between the two treatment groups after the treatment period (two years), this was attempted through two separate analyses. The following assumptions were made in the CADTH Common Drug Review (CDR) revised model:

1. Remission and Flare: Assumed the same rates for both tocilizumab (TCZ) and prednisone after two years.

   The adjusted model was based on the two-year and the two-year-plus models. To assume no benefits on flare (same patients in remission) after two years, the numbers (highlighted in red in column d) were derived from column c – prednisone group were added to column b – TCZ group. For example, in the adjusted model, the quality-adjusted life-year (QALY) on remission would be 1.45 (TCZ from column b) + 7.79 (prednisone from column c) = 9.24 (Table 11). That is, the costs and QALY for TCZ from years 0 to 2 would be kept as is, and the costs/QALY for TCZ after two years would be the same as the prednisone arm.

2. Giant cell arteritis (GCA)- and prednisone-related adverse events (AEs): Assumed continued benefits for TCZ after two years, although this might overestimate the benefits of TCZ.

   In the CDR revised model, costs and QALYs for TCZ from GCA-/prednisone-related AE = Manufacturer's base case (column (a) in Table 11).

Table 11: CDR Reanalysis Plausible Base Case (Probabilistic Models)

	Manufacturer's Base Case (a)		2-Year Model (b)		Difference (a)-(b) (c)		Adjusted Model (b)+(c) (d)	
	TCZ	Prednisone	TCZ	Prednisone	TCZ	Prednisone	TCZ	Prednisone
QALYs breakdown								
On remission	9.90	9.14	1.45	1.35	8.45	7.79	9.24	9.14
On flare	0.29	0.78	0.03	0.1	0.26	0.68	0.71	0.78
Disutility from GCA-related AE	0	0	0	0	0	0	0	0
Disutility from prednisone-related AE	−0.2	−0.36	−0.03	−0.04	−0.17	−0.32	−0.2	−0.36
Total QALYs	10.00	9.57	1.45	1.41	8.55	8.16	9.79997	9.57
Cost breakdown ($)								
Tocilizumab cost	36,861	0	36,861	0	0	0	36,861	0
Prednisone cost	154	454	127	154	27	300	427	454
Flare cost	547	1,446	62	181	485	1,265	1,327	1,446
GCA-related costs	79	212	9	26	70	186	79	212
Prednisone AE costs	2,312	5,164	893	1,058	1,418	4,106	2,312	5,164
Total costs	39,951	7,276	37,952	1,419	1,999	5,857	41,006	7,276
Incremental cost	32,675		36,533				33,730	
Incremental QALY	0.43		0.04				0.18	
ICUR ($/QALY)	85,501		803,190				187,389	

AE = adverse event; GCA = giant cell arteritis; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TCZ = tocilizumab.

As noted on page 11 (CDR Reanalysis), the manufacturer proposed a model-based approach to assuming equal efficacy between the two treatment groups after two years (see 1a; CDR base case 2); CDR conducted additional model-based analysis to attempt this (1b; CDR base case 3). However, these two approaches led to incremental benefits still accruing for the TCZ group after two years due to GCA (not due to prednisone-related AE). They are shown here for completeness.

Table 12: Additional CDR Reanalysis Plausible Base Case (Probabilistic Models)

	Description	TCZ + Prednisone Compared With Prednisone Alone		
		Incremental Cost	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	$32,613	0.43	$85,496
8.2	**Plausible base case 2 (1a, 2)**[a]	**$33,561**	**0.32**	**$121,547**
8.2a	Scenario analysis of CDR base case with 0 prednisone disutility	$33,343	0.31	$124,164
8.2b	Scenario analysis of CDR base case with baseline and flare utility of 0.716	$33,540	0.26	$125,453
8.2c	Scenario analysis of CDR base case with stroke mortality of 13.4%	$33,504	0.32	$122,779
8.2d	Scenario analysis of CDR base case with 25% more prednisone-related AEs	$34,068	0.30	$130,864
8.2e	Scenario analysis of CDR base case with 25% fewer prednisone-related AEs	$32,964	0.35	$108,735
8.2f	Scenario analysis of CDR base case with 1 week in flare	$33,510	0.22	$173,350
8.2g	8.2a + 8.2c	$33,514	0.31	$141,957
8.2h	8.2a + 8.2c + 8.2d	$34,074	0.29	$140,516
8.2i	8.2a + 8.2c + 8.2e	$33,005	0.34	$113,001
8.3	**Plausible base case 3 (1b, 2)**[b]	**$33,839**	**0.28**	**$138,041**
8.3a	Scenario analysis of CDR base case with 0 prednisone disutility	$33,875	0.27	$156,797
8.3b	Scenario analysis of CDR base case with baseline and flare utility of 0.716	$33,898	0.25	$180,680
8.3c	Scenario analysis of CDR base case with stroke mortality of 13.4%	$33,784	0.28	$167,188
8.3d	Scenario analysis of CDR base case with 25% more prednisone-related AEs	$34,329	0.26	$168,144
8.3e	Scenario analysis of CDR base case with 25% less prednisone-related AEs	$22,225	0.31	$163,521
8.3f	Scenario analysis of CDR base case with 1 week in flare	$33,857	0.26	$155,764
8.3g	8.3a + 8.3c	$33,519	0.31	$129,542
8.3h	8.3a + 8.3c + 8.3d	$34,074	0.29	$140,516
8.3i	8.3a + 8.3c + 8.3e	$33,341	0.30	$125,259

AE = adverse event; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TCZ = tocilizumab.

[a] Plausible base case 2 uses the manufacturer's approach and a modified weighted average fracture costs.

[b] Plausible base case 3 uses CDR approach with manufacturer's model and a modified weighted average fracture costs.

Table 13: CDR Reanalysis Price Reduction Scenarios Based on the Alternate CDR Base Case

ICURs of TCZ Plus Prednisone Versus Prednisone Alone			
Price	**Base-case analysis submitted by manufacturer ICUR ($/QALY)**	**Reanalysis by CDR (based on plausible base case 2) ICUR ($/QALY)**	**Reanalysis by CDR (based on plausible base case 3) ICUR ($/QALY)**
Submitted	85,495	121,547	138,041
10% reduction	76,246	101,712	130,959
20% reduction	65,205	99,755	127,851
30% reduction	59,061	79,762	100,898
40% reduction	46,912	68,799	83,124
50% reduction	37,665	53,994	69,703
60% reduction	24,829	41,516	51,195
70% reduction	18,972	28,151	41,140

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TCZ = tocilizumab.

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