Common Drug Review
Pharmacoeconomic Review Report

August 2015

Drug	tocilizumab (Actemra) (162 mg/0.9 mL solution for subcutaneous injection)
Indication	Adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to one or more DMARDs and/or TNF antagonists
Listing request	Tocilizumab (Actemra SC) alone or in combination with methotrexate (MTX) for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to one or more DMARDs and/or TNF antagonists
Manufacturer	Hoffmann-La Roche Ltd.

This review report was prepared by 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.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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.

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ABBREVIATIONS

ACR	American College of Rheumatology
bDMARD	biologic disease-modifying antirheumatic drug
CDR	CADTH Common Drug Review
DMARD	disease-modifying antirheumatic drug
IL	interleukin
IV	intravenous
MTX	methotrexate
NMA	network meta-analysis
ODB	Ontario Drug Benefit
PFS	pre-filled syringe
RA	rheumatoid arthritis
SC	subcutaneous
TCZ	tocilizumab
TNF	tumour necrosis factor

SUMMARY

Background

Tocilizumab (Actemra) for subcutaneous (SC) injection is a recombinant humanized anti-human interleukin (IL)-6 receptor monoclonal antibody indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis (RA) who have inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists or both.[1] It is available in 162 mg/0.9 mL solution for injection in a single-use pre-filled syringe (PFS) for SC injection. Patients weighing less than 100 kg should start at 162 mg SC once every two weeks, followed by an increase to once every week based on the clinical response. Patients at or above a 100 kg weight should be given 162 mg every week. It is recommended that tocilizumab (TCZ) be given in combination with methotrexate (MTX) or other DMARDs, or as a monotherapy in cases when the patient has an intolerance to MTX or treatment with MTX is not appropriate.[1] The manufacturer submitted a price of $355 per PFS, which corresponds to an annual cost of $9,230 if administered once every two weeks and $18,460 if administered weekly.

The intravenous formulation of TCZ was previously reviewed for RA by the CADTH Common Drug Review (CDR) in 2010 and received a listing recommendation with clinical criteria.[2]

1. SUMMARY OF THE ECONOMIC ANALYSIS SUBMITTED BY THE MANUFACTURER

The manufacturer submitted a cost-minimization analysis for a one-year timeframe, comparing TCZ-SC with TCZ administered intravenously (IV) (80 mg, 200 mg, and 400 mg vials) and other biologic DMARDs (bDMARDs). These included abatacept SC (125 mg/mL PFS); abatacept IV (250 mg/15 mL vial); adalimumab (40 mg/0.8 mL autoinjector pen or PFS); certolizumab pegol (200 mg/mL PFS); etanercept (25 mg vial, 50 mg/mL autoinjector or PFS); golimumab (50 mg/0.5 mL autoinjector or PFS); infliximab (100 mg vial); and rituximab (100 mg/10 mL, 500 mg/50 mL vial).[3] The manufacturer's assumption of similar efficacy for TCZ-SC and TCZ-IV was based on the SUMMACTA trial,[4,5] which concluded that TCZ-SC 162 mg weekly was non-inferior to TCZ-IV 8 mg/kg every four weeks, determined by American College of Rheumatology (ACR) 20 response at week 24. In the absence of head-to-head trials comparing TCZ-SC with other bDMARDs, the assumption of similar efficacy was based on the network meta-analysis (NMA) submitted at the time of the CDR review for TCZ-IV.[6,7] The NMA included 16 trials, which compared TCZ-IV 8 mg/kg every four weeks (no trial with TCZ-SC), abatacept, adalimumab, etanercept, and infliximab.[7]

The manufacturer estimated annual and daily drug costs (based on a 75 kg patient weight and several assumptions concerning utilization of various doses) in addition to a range of costs (based on 50 kg to 100 kg patient weight).[3] For TCZ-IV, the manufacturer assumed that [redacted]% of patients would receive 4 mg/kg every four weeks and [redacted]% would receive 8 mg/kg every four weeks, based on utilization data from the manufacturer's patient assistance program. For TCZ-SC, however, the manufacturer assumed that [redacted]% of patients would receive an injection once every two weeks and [redacted]% would receive weekly dosing, based on market research conducted by the manufacturer. For treatments with a loading dose, the manufacturer included the first and subsequent years in determining the range of costs by averaging the costs over a three-year period.

The unit drug prices were obtained from the Ontario Drug Benefit (ODB) formulary, and excluded markup and dispensing fees.[3] The manufacturer considered drug costs only, omitting any costs associated with drug administration, monitoring, or adverse events, as they assumed these were equivalent among all biologics. The manufacturer also conducted sensitivity analyses in which the Association québécoise des pharmaciens propriétaires unit prices were used, and other parameters, such as the proportion of patients receiving TCZ weekly versus once every two weeks, were varied.

2. KEY LIMITATIONS

- **The proportion of patients who will receive TCZ-SC weekly versus once every two weeks is unknown:** As acknowledged by the manufacturer, the proportion of patients who will receive TCZ-SC weekly or every other week is unknown.[3] Further, no clinical trial directly compared the efficacy of weekly versus every-two-weeks dosing. The manufacturer assumed that more patients would receive TCZ-SC every other week ([redacted]%) than TCZ-IV 4 mg/kg every four weeks ([redacted]%). However, there are no data to support this assumption, and it may underestimate the average cost of TCZ-SC.
- **Assumption of similar efficacy for TCZ-SC and TCZ-IV and other bDMARDs:** There is no head-to-head trial that compared the low doses of TCZ-IV (4 mg/kg every four weeks) and SC (every-two-weeks dosing). The MUSASHI trial compared every-two-weeks dosing of TCZ-SC with TCZ-IV 8 mg/kg every four weeks,[8,9] but the trial assessed monotherapy only and was conducted in a Japanese population with patients with a mean body weight of 54 kg, limiting the generalizability of the results to the North American population. With regard to the assumption of similar efficacy between TCZ-SC and other bDMARDs, although two NMAs support similar efficacy between TCZ-IV 8 mg/kg every four weeks and most biologics,[7,10] it is important to note that none of the NMAs included the SC formulation of TCZ. As noted in the CDR clinical report, in the absence of any evidence that compares TCZ-SC with other biologics, whether TCZ-SC is similar to other bDMARDs remains uncertain.
- **Exclusion of relevant comparator:** Anakinra was not considered in the manufacturer's base-case analysis. Despite low utilization, it is still listed under drug plans across Canada and represents a valid option in the treatment of RA. Omitting anakinra may have resulted in the manufacturer overestimating the cost savings associated with TCZ-SC compared with other bDMARDs in its base-case analysis.

3. ISSUES FOR CONSIDERATION

- Many drug plans provide initial coverage of TCZ-IV for 16 weeks and require an assessment of clinical response for further coverage. In addition, some drug plans allow the dose to be increased to 8 mg/kg every four weeks only after the 16-week trial period at 4 mg/kg. If no minimum trial period were required before increasing the dose of TCZ-SC from once every two weeks to weekly, this would result in incremental costs compared with TCZ-IV.
- The clinical expert noted that patients of higher weight (> 100 kg) might not respond to the highest available dose of TCZ, even up to a maximum of 800 mg, owing to low efficacy in this subgroup of patients; thus, physicians might increase the frequency of dosing. Further, the clinical expert indicated that, in certain cases, physicians would administer the higher dose of TCZ-IV (8 mg/kg) first followed by the lower dose (4 mg/kg), depending on clinical response.
- The clinical expert noted that, in many remote regions, physicians may be more likely to prescribe the SC formulation of TCZ, as the IV infusion might not be available.

4. RESULTS/CONCLUSIONS

The average cost of TCZ-SC will depend on the proportion of patients receiving treatment weekly versus every two weeks and on the proportion of patients in each weight category.

- If administered once every two weeks (assuming a patient weight of 75 kg), for the first year of treatment, TCZ-SC ($9,230) is less costly than TCZ-IV (savings of $1,253 versus 4 mg/kg and $8,242 versus 8 mg/kg every four weeks) and less costly than all other bDMARDs (savings ranging from $8,137 to $14,471), with the exception of one course of rituximab ($168 more costly). However, for patients who weigh less than 75 kg, TCZ-SC becomes more costly than TCZ-IV 4 mg/kg every four weeks ($3,406 more costly).
- If administered weekly (assuming a patient weight of 75 kg), for the first year of treatment, TCZ-SC ($18,460) is more costly than TCZ-IV (incremental cost of $7,977 versus TCZ-IV 4 mg/kg and $988 versus TCZ-IV 8 mg/kg every four weeks), anakinra, golimumab SC, subsequent entry infliximab, and rituximab (incremental cost ranging from $217 to $9,398), but less costly than abatacept (SC and IV), adalimumab, etanercept, and infliximab (Remicade) (cost savings ranging from $203 to $5,241).

Based on the same ratio of patients receiving low-dose to high-dose TCZ-IV and SC ([redacted]% low dose/[redacted]% high dose), an average patient weight of 75 kg, and an average annual cost based on a three-year timeframe to account for loading doses required with some bDMARDs, TCZ-SC was more expensive than TCZ-IV (incremental cost ranging from $827 to $1,538 annually, depending on whether a 16-week trial period before increasing the dose of TCZ-IV was included) and rituximab (incremental cost ranging from $3,426 to $4,993 annually), but less costly than other bDMARDs. For patients weighing more than 100 kg, TCZ-SC was a cost-saving alternative in comparison with TCZ-IV (savings ranging from $2,073 to $3,089 annually).

4.1 Cost-Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. 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; therefore, costs may not represent the actual costs to public drug plans.

TABLE 1: COST-COMPARISON TABLE FOR BIOLOGIC DISEASE-MODIFYING DRUGS FOR RHEUMATOID ARTHRITIS

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Annual Drug Cost ($)
Tocilizumab SC (Actemra)	**162 mg/ 0.9 mL**	**Pre-filled syringe**	**355.0000**[a]	**Patients < 100 kg: 162 mg SC once every other week, increasing to every week based on clinical response** **Patients ≥ 100 kg: 162 mg SC every week**	Every two weeks: 9,230 Weekly: 18,460
Tocilizumab IV (Actemra)	80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	Vial	179.2000 448.0000 896.0000	4 mg/kg every 4 weeks followed by an increase to 8 mg/kg based on clinical response	4 mg/kg: 10,483[b] 8 mg/kg: 17,472[b]
Abatacept SC (Orencia)	125 mg/mL	Pre-filled syringe	358.9000	125 mg weekly[c]	18,663[c]
Abatacept IV (Orencia)	250 mg/15 mL	Vial	480.4100	Patients < 60 kg: 500 mg Patients 60 kg to 100 kg: 750 mg Patients > 100 kg: 1,000 mg Initial dose at weeks 0, 2, and 4, then every 4 weeks	Year 1: 20,177[d] Thereafter: 18,736
Adalimumab SC (Humira)	40 mg/0.8 mL	Pre-filled syringe or pen	740.3600	40 mg every other week	19,249
Anakinra (Kineret)	100 mg	Pre-filled syringe	47.5814	100 mg daily	17,367
Certolizumab pegol (Cimzia)	200 mg/mL	Pre-filled syringe	664.5100	Year 1: 400 mg at weeks 0, 2, and 4, then 200 mg every 2 weeks	Year 1: 19,271 Thereafter: 17,277
Etanercept (Enbrel)	25 mg	Vial	194.2450	50 mg weekly or two 25 mg doses on same day every week or every 3 or 4 days	20,201
	50 mg/mL	Pre-filled syringe or autoinjector	388.6050		20,207
Golimumab SC (Simponi)	50 mg/0.5 mL	Pre-filled syringe or autoinjector	1,520.2100	50 mg monthly	18,243
Golimumab IV (Simponi)	50 mg/4 mL	Vial	897.1500[e]	2 mg/kg at weeks 0 and 4, then every 8 weeks thereafter	Year 1: 18,840[bf] Thereafter: 17,494[bf]
Infliximab (Remicade)	100 mg	Vial	987.5600	3 mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter Depending on clinical response, dose can be increased to 10 mg/kg or up to every four weeks or both	Year 1: 23,701[bg] Thereafter: 19,257[bg] 10 mg/kg every 4 weeks: 102,706 annually[b]
Infliximab (Inflectra)	100 mg	Vial	650.0000[h]		Year 1: 15,600[bg] Thereafter: 12,675[bg] 10 mg/kg every 4 weeks: 67,600 annually[b]

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Annual Drug Cost ($)
Rituximab (Rituxan)	100 mg/10 mL 500 mg/50 mL	Vial	453.1000 2,265.5000	A course consists of 1,000 mg infusions at weeks 0 and 2. 1,000 mg at weeks 0 and 2; reassess for retreatment at week 26, no sooner than 16 weeks after previous	18,124 assumes 2 courses Per course: 9,062

IV = intravenous; SC = subcutaneous.
[a] Manufacturer-submitted price.
[b] Costs include wastage of unused medication in vial.
[c] Abatacept-naive patients require a single weight-based loading dose of 500 mg, 750 mg, or 1,000 mg IV abatacept, with weekly SC injections to start within one day thereafter, not included in cost.
[d] Assumes 14 doses in year 1 (one dose every four weeks with an additional dose at week 2).
[e] McKesson Canada wholesale price; includes markup (October 2014).
[f] Assumes 7 doses in first year and 6.5 per year thereafter.
[g] Assumes 8 doses in first year and 6.5 doses per year thereafter.
[h] Canadian Drug Expert Committee final recommendation for infliximab (Inflectra – Hospira Healthcare Corporation); December 19, 2014. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_SE0384_Inflectra_Dec-23-14.pdf.
Source: Ontario Drug Benefit Formulary Exceptional Access Program (October 2014), unless otherwise indicated. Patient weight assumed to be 75 kg. Annual period assumes 52 weeks, 26 × 2 weeks, or 13 × 4 weeks per year.

APPENDIX 1: REVIEWER WORKSHEETS

TABLE 2: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug product	**Actemra SC (tocilizumab)**
Treatment	TCZ-SC should be given in combination with MTX or other DMARDs; TCZ-SC may also be given as a monotherapy in cases when the patient has an intolerance to MTX or MTX is inappropriate
Comparators	• TCZ-IV • Abatacept IV • Abatacept SC • Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Infliximab • Rituximab
Study question	To estimate the incremental cost of TCZ-SC for the treatment of RA to support a request for reimbursement based on use according to the expected indication
Type of economic evaluation	Cost-minimization analysis
Target population	Adult patients with moderately to severely active RA who have inadequate response to one or more DMARDs and/or tumour necrosis factor antagonists
Perspective	Ministry of Health
Outcome considered	• ACR20 response
Key data sources	
Cost	• Cost of TCZ-SC was obtained from the manufacturer. • Costs of all comparators were sourced from the Ontario Drug Benefit formulary. • Administration costs, monitoring costs, and costs associated with adverse events were not included. • All costs excluded markup and dispensing fees.
Clinical efficacy	• SUMMACTA[4,5]: 2-year double-blind, randomized, parallel-group study that compared the efficacy and safety of TCZ-SC (162 mg weekly + IV placebo every 4 weeks) with TCZ-IV (8 mg/kg every 4 weeks + SC placebo every week) in combination with traditional DMARDs in patients with moderate to severe RA. The proportion of patients with an ACR20 response at 24 weeks (primary objective) was 69.4% in the TCZ-SC group and 73.4% in the TCZ-IV group. Thus, TCZ-SC was determined to be non-inferior to TCZ-IV. • TCZ-IV (reviewed by CDR in 2010)[6] was previously compared with other biologics (abatacept, adalimumab, etanercept, and infliximab) in several studies that were included in the manufacturer-conducted NMA. The NMA suggested similar clinical efficacy among these biologics.
Harms	• Not considered
Time horizon	1 year
Results for base case	• The estimated annual range of costs with TCZ-SC was calculated to be $9,230 to $18,460 as compared with $5,824 to $23,296 for TCZ-IV. The costs were determined based on a minimum patient weight of 50 kg and a maximum weight of 100 kg, in addition to various dosing assumptions.

[redacted]	• The manufacturer also estimated the average annual and daily costs; TCZ-SC was estimated to result in a cost savings of $96.00 annually and $0.27 daily when compared with TCZ-IV. The average costs were based on an average patient weight of 75 kg and various dosing assumptions. • The average annual and daily cost of TCZ-SC was also calculated to be less than that of all other comparators considered in the manufacturer's base-case analysis, excluding rituximab.

ACR = American College of Rheumatology; CDR = CADTH Common Drug Review; DMARD = disease-modifying antirheumatic drug; IV = intravenous; MTX = methotrexate; NMA = network meta-analysis; RA = rheumatoid arthritis; SC =subcutaneous; TCZ = tocilizumab.

Manufacturer's Results

In the manufacturer's base-case analysis, the range of annual treatment costs with TCZ-SC was calculated to be $9,230 to $18,460, as compared with $5,824 to $23,296 for TCZ-IV (Table 3). The lower end of the range was based on a patient weight of 50 kg and assumed 100% of patients were on every-two-weeks dosing of TCZ-SC, the lower dose of TCZ-IV (4 mg/kg), and a loading dose of 3 mg/kg with a maintenance dose of 10 mg/kg for infliximab. The higher end of the range was based on a maximum patient weight of 100 kg and assumed 100% of patients were on weekly dosing of TCZ-SC, the higher dose of TCZ-IV (8 mg/kg), and a dose of 10 mg/kg for infliximab.

The average annual cost per patient with TCZ-SC was estimated at $16,153, compared with $16,249 for TCZ-IV ($96 savings annually), while the average daily cost per patient was calculated to be $44.25 for TCZ-SC, as compared with $44.52 for TCZ-IV ($0.27 saving daily). Furthermore, TCZ-SC was determined to be less costly than all other biologic treatment options, excluding rituximab. These costs were based on a patient weight of 75 kg and assumed [redacted]% of patients would be on a weekly dosing schedule of TCZ-SC, [redacted]% of patients would be on the 8 mg/kg dose of TCZ-IV, and patients on infliximab would start at a loading dose of 3 mg/kg and maintain at a dose of 5 mg/kg in subsequent years.

For treatments with a loading dose, the manufacturer included the first and subsequent years in determining the range of costs; this was done by averaging the costs over a three-year period.

TABLE 3: MANUFACTURER'S BASE-CASE ANALYSIS RESULTS

Drug	Range of Annual Treatment Costs	Average Annual Cost per Patient	Range of Daily Treatment Costs	Average Daily Cost per Patient
TCZ-SC	$9,230 to $18,460	$16,153	$25.29 to $50.58	$44.25
TCZ-IV	$5,824 to $23,296	$16,249	$15.96 to $63.82	$44.52
Abatacept IV	$12,491 to $20,177	$19,216	$34.22 to $55.28	$52.65
Abatacept SC	$18,297 to $19,386	$18,660	$50.13 to $54.08	$51.12
Adalimumab	$19,249 to $19,249	$19,249	$52.74 to $52.74	$52.74
Certolizumab pegol	$17,277 to $19,271	$17,942	$47.33 to $52.80	$49.16
Etanercept	$20,207 to $20,207	$20,207	$55.36 to $55.36	$55.36
Golimumab	$17,885 to $17,885	$17,885	$49.00 to $49.00	$49.00
Infliximab	$12,587 to $62,933	$26,141	$34.48 to $172.42	$71.62
Rituximab	$9,062 to $18,124	$12,083	$24.83 to $49.65	$33.10

IV = intravenous; SC = subcutaneous; TCZ= tocilizumab.
Source: Manufacturer's pharmacoeconomic submission.[3]

In addition, the manufacturer also conducted various sensitivity analyses, in which it considered exclusion of drug wastage, no IV load dose with abatacept SC, and Association québécoise des pharmaciens propriétaires unit prices instead of the ODB formulary unit prices.

CADTH Common Drug Review Results

CDR conducted a reanalysis based on several key parameters. These included: 1) updating ODB prices for abatacept SC, infliximab, and golimumab; 2) varying assumptions concerning dosing and utilization of TCZ-SC and TCZ-IV for different patient weights; 3) averaging the costs over a three-year period to account for loading doses; and 4) including anakinra as a comparator.

In the reanalysis, there were two scenarios considered for the dosing of TCZ-IV. In the first scenario, at any given point in time, CDR assumed the same ratio between patients receiving TCZ-SC once every two weeks to weekly and TCZ-IV 4 mg/kg and 8 mg/kg ([redacted]%/[redacted]%). Subsequently, the second scenario considered a delay in the administration of the higher dose of TCZ-IV to reflect clinical practice and the standard reimbursement criteria for selected public drug plans in Canada. In this scenario, for the first 16 weeks of treatment, all patients would receive the lower dose of TCZ-IV (4 mg/kg). Following 16 weeks, [redacted]% would stay on the lower dose, while [redacted]% would switch to the higher dose (8 mg/kg). All of the analyses were stratified by patient weights of 50 kg, 75 kg, and 100 kg (Table 4).

TABLE 4: CDR REANALYSIS SCENARIOS, BASED ON A VARIATION OF PATIENT WEIGHTS AND DOSING REGIMENS

Drug	Patient Weight of 50 kg		Patient Weight of 75 kg		Patient Weight of 100 kg[a]	
	Annual Treatment Cost	Incremental Cost (Savings) With TCZ-SC	Annual Treatment Cost	Incremental Cost (Savings) With TCZ-SC	Annual Treatment Cost	Incremental Cost (Savings) With TCZ-SC
TCZ-SC	$17,076	Reference	$17,076	Reference	$18,460	Reference
TCZ-IV						
Scenario 1[b]	$10,774	$6,302	$16,249	$827	$21,549	($3,089)
Scenario 2[c]	$10,267	$6,809	$15,538	$1,538	$20,533	($2,073)
Abatacept IV	$12,811	$4,265	$19,216	($2,140)	$19,216	($756)
Abatacept SC	$19,141	($2,065)	$19,381	($2,305)	$19,381	($921)
Adalimumab SC	$19,249	($2,173)	$19,249	($2,173)	$19,249	($789)
Anakinra	$17,367	($291)	$17,367	($291)	$17,367	$1,093
Certolizumab pegol	$17,942	($866)	$17,942	($866)	$17,942	$518
Etanercept	$20,207	($3,131)	$20,207	($3,131)	$20,207	($1,747)
Golimumab SC	$18,243	($1,167)	$18,243	($1,167)	$18,243	$217
Infliximab[d]	$13,826	$3,250	$20,739	($3,663)	$20,739	($2,279)
Rituximab	$12,083	$4,993	$12,083	$4,993	$12,083	$6,377

CDR = CADTH Common Drug Review; IV = intravenous; SC = subcutaneous; TCZ = tocilizumab.
Note: in the reanalysis, the updated unit prices in the ODB were applied, in addition to a [redacted]/[redacted]% split among patients receiving every-two-weeks and weekly dosing of TCZ-SC, respectively.
[a] At 100 kg, all patients on TCZ-SC were given weekly administration, as per the product monograph.[1]
[b] Assuming [redacted]/[redacted]% split among patients using the lower dose (4 mg/kg) and higher dose (8 mg/kg) of TCZ-IV.
[c] Assuming all patients were on the lower dose of TCZ-IV (4 mg/kg) for the first 16 weeks of treatment; following this, [redacted]% stayed on the lower dose and [redacted]% switched to the higher dose (8 mg/kg).
[d] Assumed all patients would be treated at a dose of 3 mg/kg (maintenance).

Therefore, when the same ratio between patients receiving TCZ-SC once every two weeks to weekly and TCZ-IV 4 mg/kg and 8 mg/kg ([redacted]%/[redacted]%) was assumed, for a patient weight of 50 kg or 75 kg, the annual treatment cost of TCZ-SC ($17,076) was $6,302 and $827 more costly, respectively, than TCZ-IV. However, for a patient weight of 100 kg, the annual treatment cost ($18,460) was $3,089 less costly than TCZ-IV.

TABLE 5: KEY LIMITATIONS

Identified Limitation	Description	Implication
Assumed similar efficacy between TCZ-SC and TCZ-IV and other bDMARDs	TCZ-SC weekly was assumed to be clinically equivalent to TCZ-IV 8 mg/kg, based on the results of the SUMMACTA.[4,5] In addition, TCZ-SC weekly was assumed to be similar to most other bDMARDs based on 2 NMAs[10,11] that compared TCZ-IV 8 mg/kg with abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, and rituximab. These NMAs were critically appraised by the CDR clinical review team (see CDR clinical review report, Appendix 7). There is limited evidence supporting the clinical equivalence of the TCZ-SC every other week to TCZ-IV 4 mg/kg. There was one study conducted in a Japanese population (MUSASHI);[8,9] however, it only considered the 8 mg/kg dose of TCZ-IV in monotherapy and the average patient weight was 54 kg, which is not reflective of a Canadian population. There is lack of direct or indirect evidence comparing TCZ-SC with other bDMARDs.	It is uncertain whether efficacy of TCZ administered every 2 weeks and TCZ 4 mg/kg every 4 weeks, as well as that of other bDMARDs, is similar.
Proportion of patients on the different doses of TCZ-SC, TCZ-IV, and infliximab	The manufacturer considered a [redacted]%/[redacted]% ratio of patients receiving TCZ-IV 4 mg/kg versus 8 mg/kg. This was based on data received from the manufacturer's patient assistance program.[3] Alternatively, the manufacturer assumed [redacted]% of patients would be on the weekly dosing of TCZ-SC, while [redacted]% would be on the every-two-weeks dosing when calculating the average annual and daily drug costs, (based on a patient weight of 75 kg). There are no data to support this assumption.	This may underestimate the total treatment costs associated with TCZ-SC.
Sixteen week trial period with TCZ-IV	In the case of TCZ-IV, the manufacturer did not account for a 16 week delay in the administration of the higher dose (8 mg/kg); this would reflect clinical practice and standard reimbursement criteria for select drug plans in Canada.	This would reflect listing criteria of TCZ-IV in some jurisdictions. This may overestimate the cost of TCZ-IV.
Missing comparator from the base-case analysis	The manufacturer's base-case analysis did not include anakinra. Despite low utilization, it is listed by participating drug plans across Canada and represents a valid treatment option.	The manufacturer's reported cost savings may be overestimated (anakinra may be less costly). Further, inclusion of all comparators provides more complete analysis.

bDMARD = biologic disease-modifying antirheumatic drug; CDR = CADTH Common Drug Review; IV = intravenous; NMA = network meta-analysis; SC = subcutaneous; TCZ = tocilizumab.

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