Common Drug Review
Pharmacoeconomic Review Report

April 2015

Drug	certolizumab pegol (Cimzia) SC
Indication	For use alone, or in combination with methotrexate (MTX), for reducing signs and symptoms and inhibiting the progression of structural damage as assessed by X-ray in adult patients with moderately to severely active psoriatic arthritis who have failed one or more disease-modifying antirheumatic drugs (DMARDs).
Listing request	As per indication
Manufacturer	UCB Canada Inc.

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

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ABBREVIATIONS

ACR	American College of Rheumatology
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
CZP	certolizumab pegol
DMARD	disease-modifying antirheumatic drug
MTC	mixed-treatment comparison
PASI	Psoriasis Area Severity Index
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
SEB	subsequent entry biologic
TNF	tumour necrosis factor

EXECUTIVE SUMMARY

Background

Certolizumab pegol (CZP) (Cimzia) is a tumour necrosis factor alpha (TNF-alpha) inhibitor indicated — alone or in combination with methotrexate (MTX) — for reducing the signs and symptoms and inhibiting the progression of structural damage as assessed by X-ray in adult patients with moderately to severely active psoriatic arthritis (PsA) who have failed one or more disease-modifying antirheumatic drugs (DMARDs).[1] CZP is available as a 200 mg/mL pre-filled syringe. The recommended loading dose of CZP is 400 mg at weeks 0, 2 and 4, followed by a maintenance dose of either 200 mg every two weeks or 400 mg every four weeks.[1] The currently marketed price of CZP is $664.51 per 200 mg/mL pre-filled syringe, which equates to a cost of $19,271 in year 1 and $17,277 in subsequent years.[2] The manufacturer is requesting reimbursement of CZP as per the Health Canada approved indication.[3]

CZP has been reviewed by CADTH Common Drug Review (CDR) for adult patients with moderately to severely active rheumatoid arthritis where the Canadian Drug Expert Committee (CDEC) recommended that CZP not be listed, given the limited quality of the trials and the other therapeutic options available.[4] At the time of this review, CZP was also being reviewed by CDR for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost-minimization analysis over a three-year time frame comparing CZP with the four biologic DMARDs (adalimumab, etanercept, golimumab SC, and infliximab) currently available for reducing signs and symptoms and inhibiting the progression of structural damage as assessed by X-ray in adult patients with moderately to severely active (PsA) who have failed one or more DMARDs.[2] Ustekinumab was not included in the base-case analysis, as it did not receive a positive CDR recommendation and was not listed on a provincial formulary for this indication at the time of the submission. As no head-to-head trials were available comparing CZP to the comparator biologic DMARDs, the assumption of similar efficacy was based on two manufacturer-funded adjusted mixed-treatment comparisons (MTC).[5,6]

The primary outcomes assessed in the MTC included: American College of Rheumatology (ACR) 20% improvement (ACR 20), ACR 50, Psoriatic Arthritis Response Criteria (PsARC), Psoriasis Area Severity Index 75% improvement (PASI 75), Health Assessment Questionnaire – Disability Index (HAQ-DI), Short Form (36) Health Survey (SF-36), as well as pain and fatigue scores. Safety was not assessed in the manufacturer's MTC. [redacted] The manufacturer stated that the adjusted MTC indicated that CZP had similar efficacy to the four relevant comparator biologic DMARD treatments in terms of ACR 20, ACR 50, PASI 75, and PsARC responses at week 24.

The manufacturer's base-case analysis was conducted from the Canadian public payer perspective. Only drug acquisition costs were considered (not including markup). The average weight per patient was assumed to be 80 kg. No direct costs related to infusions were included. The manufacturer also provided an analysis from a societal perspective that included indirect costs associated with lost time attributable to infusions. A compliance rate of 100% was assumed for all treatments, and no dropouts were considered. Unit drug prices were obtained from the Ontario Drug Benefit Expanded Access Program Formulary (August 2014). Five one-way sensitivity analyses were undertaken, based on compliance rate, dropout rates, discount rate, markups, and the inclusion of ustekinumab as a comparator.

Key Limitations

Few limitations were identified with the economic submission:

- **Use of a three-year time horizon:** The manufacturer's three-year time horizon in the base-case analysis is arbitrary. While varied compliance and dropout rates were provided in sensitivity analyses, the manufacturer did not look at the time at which patients drop out or discontinue treatment with CZP. If a 30% discontinuation rate is applied to all biologic DMARDs after year 1, and a further 10% after each subsequent year, the discounted cost savings with CZP over a three-year period are lower than originally reported ($136 to $22,465 versus $760 to $27,985 as originally reported by the manufacturer). Further, if a one-year time horizon is considered, at the approved doses, CZP is more costly than golimumab and adalimumab (see Results and Conclusions).
- **Limitations with the MTC:** The critical appraisal of the MTC within CDR Clinical Review (Appendix 7) identified several limitations, including the following:
  - *Comparative safety not assessed*: An analysis of the safety data was not reported using the MTC methods; therefore the comparability of CZP with that of other biologic DMARDs in terms of harms could not be assessed.
  - *Differences in study design*: At least four studies included in the MTC, including the study of CZP versus placebo (RAPID-PsA), allowed patients to "escape" before the week 24 end point. There were two other studies where the designs were unclear. The submitted MTC report failed to report how these patients were analyzed in each of the studies and how the missing data were managed in the MTC. This limitation suggests more uncertainty is associated with the 24-week analysis than with the analysis at the earlier time points (e.g., 12 weeks or 16 weeks).
  - *Clinical heterogeneity*: The patient characteristics in studies included in the network meta-analysis (NMA) were not well reported; thus, the comparability of the populations is unknown. This, along with differences in patient inclusion criteria, disease severity, and prior therapy, highlights potential issues of heterogeneity among the trials, which should have been explored by the manufacturer.
  - *Uncertain long-term comparative effectiveness*: CDR appraisal of the NMA indicates that although CZP demonstrated a similar efficacy relative to other comparators in terms of ACR response, Psoriasis Area and Severity Index (PASI), and PsARC, given the limitations with the longer term data, inferring longer-term comparative effectiveness between comparator treatments is uncertain — especially given the lower response rates at the initial time point (weeks 12 to 16) in comparison to the comparator treatments in outcomes such as ACR and PASI.

Issues for Consideration

- **Availability of biosimilar infliximab and list price of etanercept:** Although not currently listed by public drug plans, a subsequent-entry biologic (SEB) infliximab received a positive listing CDEC recommendation in November 2014, and has a lower price ($650 per 100 mg vial) than the branded infliximab.[7] The inclusion of SEB infliximab on public drug formularies may result in CZP being more costly compared with SEB infliximab. The results are explored in the following two bullet points. It should also be noted that the price of etanercept has increased on the Ontario Drug Benefit Expanded Access Program Formulary since August 2014. CDR used the January 2015 list price for the reanalyses.
- **Weight-based dosing:** Only infliximab (branded and SEB) requires weight-based dosing. In patients weighing 60 kg or less, CZP is more costly than SEB infliximab (+ $3,671 for year 1, + $4,602 for subsequent years).
- **Infliximab dosing:** One of the three plans that lists infliximab for PsA (British Columbia) indicates that lower doses of infliximab may be used (3 mg/kg). Assuming a patient requires three vials (i.e., weighs between 67 kg and 80 kg), CZP will be more costly than SEB infliximab dosed at 3 mg/kg every eight weeks (+ $3,671 for year 1, + $4,602 for subsequent years), but will still be cost-saving compared with branded infliximab (savings of $4,430 in year 1 and $1,980 in subsequent years).
- **Price reduction:** CDR calculated that based on year 1 costs, the price of CZP would need to be reduced by 5.6% (i.e., unit cost of $629) in order to be cost-neutral compared with the lowest-priced biologic DMARD (golimumab SC).

Results and Conclusions

CDR critical appraisal of the manufacturer's MTC indicated that the comparative effectiveness of CZP with other biologic DMARDs beyond 12 weeks to 16 weeks is uncertain given that patients were allowed early escape in some of the studies after this time.

At currently published prices, for a patient weighing between 61 kg and 80 kg, CZP is more costly than golimumab SC (+ $1,028) and adalimumab (+ $21), but less costly than etanercept (–$1,048), branded infliximab 5 mg/kg (–$12,331), and SEB infliximab 5 mg/kg (–$1,529) in the first year of treatment. CZP is also less costly than ustekinumab (–$3,695) at the publicly reimbursed price for other indications. In subsequent years, CZP may be less costly than comparative treatments (with savings ranging from $965 to $10,374), with the exception of SEB infliximab, where patients receive three vials or less per dose (incremental cost between $377 and $4,602).

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, and as such, may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR BIOLOGIC DMARD TREATMENTS FOR PATIENTS WITH PSORIATIC ARTHRITIS

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Annual Drug Cost ($)
Certolizumab pegol (Cimzia)	**200 mg**	**Pre-filled syringe**	**664.5100**	**Year 1: 400 mg at week 0, 2, & 4, then 200 mg every 2 weeks or 400 mg every 4 weeks**	**Year 1: 19,271 Thereafter: 17,277**
Biologic DMARDs					
Golimumab SC (Simponi)	50 mg	Pre-filled syringe or auto-injector	1520.2100	50 mg monthly	18,243
Adalimumab (Humira)	40 mg	Pre-filled syringe or pre-filled Pen	740.3600	40 mg every other week	19,249
Etanercept (Enbrel)	25 mg	Vial	195.3125	50 mg weekly (one 50 mg dose or 25 mg dose administered every 3 or 4 days)	20,313
	50 mg	Pre-filled syringe	390.7425		20,319
Infliximab[a] (Remicade)	100 mg/vial	Vial	987.5600	5 mg/kg[b] initial dose followed by additional 5 mg/kg[b] doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter	5 mg/kg at weeks 0, 2, and 6, then every 8 weeks[c] Year 1: 31,602 Thereafter: 25,677
Infliximab biosimilar[a] (Inflectra)	100 mg/vial	Vial	$650.00[e]	5 mg/kg[b] initial dose followed by additional 5 mg/kg[b] doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter	5 mg/kg at weeks 0, 2, and 6, then every 8 weeks[c] Year 1: 20,800 Thereafter: 16,900
Ustekinumab (Stelara)	45 mg/0.5 mL 90 mg/1.0 mL	Vial	4593.1400	45 or 90 mg at week 0 and week 4, then every 12 weeks thereafter	Year 1: 22,966 Thereafter: 19,903

DMARD = disease-modifying antirheumatic drug.
[a] Yearly drug costs were based on patients within the weight range 61 kg to 80 kg.
[b] Only British Columbia, Saskatchewan, and the Yukon list infliximab for PsA. While dose is not stated for Saskatchewan and Yukon, British Columbia indicates a dose of 3mg/kg should be used for infliximab in PsA patients.[8]
[c] Average of eight doses for the first year and 6.5 doses per year thereafter.
[d] Average of 10 doses for the first year and nine doses per year thereafter.
[e] Inflectra CDEC Recommendation report, November 2014.[7]
Source: Ontario Drug Benefit Formulary (ODBF) and ODBF Exceptional Access Program (accessed January 2015) unless otherwise indicated.

APPENDIX 1: PRICE REDUCTION ANALYSIS

CDR calculated the price reduction that would be required for CZP to be cost-neutral compared with the lowest-priced biologic DMARD in year 1 (golimumab SC). As shown in Table 2, the price of CZP would need to be reduced by 5.6% for the cost to be equivalent to golimumab SC in year 1, which would lead to a saving of approximately $13,359 against the most expensive biologic DMARD in year 1 (branded infliximab).

TABLE 2: COMMON DRUG REVIEW ANALYSIS FOR THREE DIFFERENT PRICE REDUCTION SCENARIOS FOR CZP

Scenario	Current Price	Year 1 Cost	Reduction Needed	Reduced Price	Savings[a] (Min. to Max.)
Price reduction needed to equal least expensive biologic DMARD	$664.51	$19,271	5.6%	$629.05	–$13,359 to $0

CZP = certolizumab pegol; DMARD = disease-modifying antirheumatic drug.
[a] Savings compared to all biologic DMARDs in Year 1.

APPENDIX 2: REVIEWER WORKSHEETS

TABLE 3: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	Certolizumab pegol (Cimzia) 200 mg/mL pre-filled syringe
Treatment	Certolizumab pegol 400 mg loading dose at weeks 0, 2, and 4; then 200 mg every two weeks or 400 mg every four weeks
Comparator(s)	**Primary analysis** • Adalimumab (Humira) 40 mg every other week • Etanercept (Enbrel) 50 mg every week • Golimumab (Simponi) 50 mg once a month (same date each month) • Infliximab (Remicade) 5 mg/kg given at weeks 0, 2, and 6; then 5 mg/kg at every 6 weeks to 8 weeks thereafter **Sensitivity analysis** • Ustekinumab (Stelara) 45 mg or 90 mg at week 0 and week 4, then 45 mg or 90 mg every 12 weeks thereafter
Study Question	From the Ministry of Health and societal perspectives, what is the cost of Cimzia relative to alternative TNF-α inhibitors in the treatment of adult patients with active PsA who have failed one or more DMARDs?
Type of Economic Evaluation	Cost-minimization analysis

Target Population	Patients representative of the following baseline characteristics:
	• Age ≥ 18 years
	• Adult-onset PsA of ≥ 6 month's duration as defined by the CASPAR criteria
	• Active psoriatic skin lesions or documented history of psoriasis
	• Active arthritis, defined as having:
	  ○ ≥ 3 tender joints
	  ○ ≥ 3 swollen joints
	  ○ ESR ≥ 28 mm/h or CRP > upper limit of normal (7.9 mg/L)
	• Previously failed ≥ 1 DMARDs

Perspective	• Public payer perspective • Societal perspective
Outcome(s) Considered	• ACR20 • ACR50 • PsARC • PASI 75 • HAQ-DI • SF-36 (PCS and MCS) • Pain • Fatigue
Key Data Sources	
Cost	Ontario Drug Benefit Expanded Access Program (April 2014)
Clinical Efficacy	Manufacturer-supplied mixed-treatment comparison
Harms	Results from RAPID-PsA reported. Comparative safety data not reported
Time Horizon	Three years

Results for Base Case	From the public payer perspective, over a three-year time horizon, the Total Cost of Cimzia is expected to be $51,277, which is less than the cost of alternatives: • Range in Total Costs of alternatives: $52,037 to $79,262 • Range in Incremental Savings: $760 to $27,985

ACR = American College of Rheumatology; CASPAR = Classification Criteria for Psoriatic Arthritis; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire – Disability Index; MCS = mental component summary; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor.

Manufacturer's Results

The manufacturer reported that using CZP at the current market and proposed drug benefit price, relative to alternative anti-TNFs, would result in cost savings to CDR participating drug plans. The unit cost of CZP was $664.51, which may differ from other anti-TNF treatments, given the differential dosing regimens. The cost and number of doses per year are reported in Table 4.

TABLE 4: DRUG UNIT COSTS AND DOSES PER YEAR FOR EACH PRODUCT IN THE BASE CASE

Drug Product	Unit	Unit Price	Average Number of Doses (Year 1)	Average Number of Doses (Year 2)	Average Number of Doses (Year 3)
CZP	200 mg	$664.5100	29	26	26
Adalimumab	40 mg	$740.3600	26	26	26
Etanercept	50 mg	$388.6050	52	52	52
Infliximab[a]	100 mg	$987.5600	32	28	24
Golimumab	50 mg	$1,520.2100	12	12	12
Ustekinumab	45 mg	$4,593.1400	5	5	4

CZP = certolizumab pegol.
Source: Manufacturer's Pharmacoeconomic Submission, Table 3, page 22.[2]
[a] Assumed an average weight of 80 kg and a maintenance dose every seven weeks.

The manufacturer indicated that from the public payer perspective, CZP at the current market and proposed drug benefit price would result in cost savings relative to alternative anti-TNFs for CDR participating drug plans (Table 5).

The manufacturer calculated the three-year cost to treat one patient with CZP to be $51,277. The three-year cost for treating one patient with the other anti-TNFs ranged from $52,037 to $79,262.

TABLE 5: MANUFACTURER'S COST-MINIMIZATION ANALYSIS

Drug Product	Three-Year Drug Cost	Incremental Cost (Versus CZP)
CZP	$51,276.91	NA
Adalimumab	$54,908.80	$3,631.89
Etanercept	$57,641.78	$6,364.87
Infliximab[a] (brand)	$79,261.57	$27,984.65
Golimumab	$52,036.79	$759.87

CZP = certolizumab pegol.
Source: Summary of Manufacturer's Pharmacoeconomic Submission, Table 4, page 23.[2]
[a] Assumed an average weight of 80 kg and a maintenance dose every seven weeks.

The manufacturer also reported the results of four one-way sensitivity analyses. These are summarized in Table 6 below.

TABLE 6: MANUFACTURER'S SENSITIVITY ANALYSIS

Parameter	Original	Revised	Incremental Range in Savings (CZP Versus Comparators)
Base Case			$760 to $27,985
Compliance	100%	80%	$608 to $22,388
Dropout Rates	0% all years	0% year 1, 20% year 2, 50% year 3	$141 to $23,115
Discount Rate	5%	0%	$902 to $29,130
Markup	Not included	8%	$821 to $30,223
Cost of Ustekinumab	Not included	$4,953.1400 per syringe	$760 to $27,985

CZP = certolizumab pegol.
Source: Summary of Manufacturer's Pharmacoeconomic Submission, Table 5, pages 23–24.[2]

CDR Results

The three-year time horizon submitted by the manufacturer appears to be arbitrary; given the lack of appropriate long-term comparative effectiveness data, a shorter time horizon (one year) may have been more appropriate. Although CDR did not undertake any reanalyses based on the manufacturer's submission, the reviewers refer the reader to the cost comparisons in Table 1, and suggest these to be appropriate in determining the incremental costs and cost savings associated with CZP in year 1 compared with the other indicated and listed biologic DMARDS.

If a longer time horizon is preferred, assuming a discontinuation rate of 30% after year 1 (thus applied to the year 2 cost), and a further 10% every year thereafter (applied to year 3) for all treatments, the resulting cost savings are reduced from the manufacturer's base-case analysis (Table 7). Discontinuation rates were applied for subsequent years.

TABLE 7: CDR SENSITIVITY ANALYSIS BASED ON REVISED DISCONTINUATION RATES

Drug Product	Year 1 Cost	Year 2 Cost	Year 3 Cost	Total Cost	Incremental Savings (Versus CZP)
CZP	$19,271	$11,489	$9,356	$40,116	
Adalimumab	$19,249	$12,801	$10,424	$42,474	$2,358
Etanercept[a]	$20,313	$13,512	$11,003	$44,833	$4,717
Golimumab	$18,243	$12,131	$9,878	$40,252	$136
Ustekinumab					
Infliximab (branded)[b]	$31,602	$17,075	$13,904	$62,581	$22,465
Infliximab (SEB)[b]	$20,800	$11,239	$9,151	$41,190	$1,074

CZP = certolizumab pegol; SEB= subsequent entry biologic.
[a] The 50 mg dose has been used to compare versus CZP.
[b] Assumed an average weight of 80 kg.

Only three provinces currently reimburse infliximab for PsA (British Columbia, Saskatchewan, and Yukon). Of these, only British Columbia specifies a dose that should be used, and indicates that physicians should administer infliximab at a dose of 3 mg/kg.[8] Given that infliximab may be used at a lower dose where listed, and that dosing is weight-based, a sensitivity analysis assessing the comparative cost of CZP and infliximab 3 mg/kg was undertaken (Table 8). Note: this does not take into account any differences in clinical effectiveness that result from a lower dose of infliximab. The results indicate that CZP is still cost-saving compared with branded infliximab, but the amount of cost saving is reduced (range: $1,980 to $10,356). When comparing CZP to SEB infliximab, CZP is more costly then SEB infliximab when the infliximab maintenance dose is every eight weeks ($3,671 to $4,602), and slightly cost-saving when the infliximab maintenance dose is every six weeks ($229 to $273).

TABLE 8: CDR SENSITIVITY ANALYSIS BASED ON REVISED INFLIXIMAB DOSE

Comparators	Strength	Dose Form	Price ($)	Average Dose	Yearly Drug Cost ($)	Incremental Cost (Versus CZP)
Certolizumab pegol (Cimzia)	**200 mg**	**Single-use pre-filled syringe**	**664.5100**	**Year 1: 400 mg at weeks 0, 2, and 4, then 200 mg every 2 weeks or 400 mg every 4 weeks**	**Year 1: 19,271 Thereafter: 17,277**	**N/A**
Infliximab[a] (Remicade)	100 mg/vial	Vial	987.5600	3 mg/kg dose at weeks 0, 2, and 6, then every 8 weeks thereafter	3 mg/kg at weeks 0, 2, and 6, then every 8 weeks[b] Year 1: 23,701 Thereafter: 19,257	$4,430 $1,980
Infliximab[a] (Inflectra)	100 mg/vial	Vial	650.00[c]	3 mg/kg dose at weeks 0, 2, and 6, then every 8 weeks thereafter	3 mg/kg at weeks 0, 2, and 6, then every 8 weeks[b] Year 1: 15,600 Thereafter: 12,675	–$3,671 –$4,602

CZP = certolizumab pegol; N/A = not applicable.
Source: Ontario Drug Benefit Formulary (ODBF) and ODBF Exceptional Access Program (accessed December 2014) unless otherwise indicated.
[a] Yearly drug costs were based on patients requiring three vials (i.e., within the weight range 67 kg to 80 kg).
[b] Average of eight doses for the first year and 6.5 doses per year thereafter.
[c] Inflectra CDEC Recommendation report, November 2014.[7]

TABLE 9: KEY LIMITATIONS

Identified Limitation	Description	Implication
Inclusion of all comparators	Ustekinumab was included in a sensitivity analysis as it had yet to receive a positive recommendation from CDEC or be listed on a provincial formulary for this indication; however, SEB infliximab was not included. This is likely due to the lack of CDEC recommendation or listing on a provincial formulary for this indication at the time of submission, as well as the lack of a publically available price.	CZP is likely cost-saving compared with ustekinumab at the published prices, but more costly than SEB infliximab.
Time Horizon		
Early discontinuation	The analysis does not look at the time at which discontinuation may occur.	Given the higher cost for CZP in Year 1 than some of the other biologic DMARDs, use of CZP may result in a greater cost to plans compared with certain other available biologic DMARDs.
Long-term comparative effectiveness	As noted in the next section on the limitations of the MTC, the longer-term comparative effectiveness is uncertain.	It is more informative to disaggregate costs for year 1 versus subsequent years.
Potential treatment waning	Although CDR clinical reviewers indicate similar results between analyses at 24 weeks and 96 weeks (~2 years), given the lack of longer-term data for CZP in this indication, it is uncertain whether there would be any waning of treatment effect and whether this would differ from other treatments.	May underestimate or overestimate the potential savings or costs.
Based on Mixed-Treatment Comparisons[5,6]		
Mixed-treatment comparison: Harms	Safety comparisons were not made using the MTC methods; therefore, the comparative safety of CZP has yet to be fully evaluated.	Uncertainty regarding comparative harms.
Mixed-treatment comparison: Study designs	At least four studies (including the study of CZP versus placebo; RAPID-PsA) allowed patients to "escape" before the week 24 end point (two studies — PSUMMIT 1 and 2 — did not report whether early escape was allowed). The document failed to report how these patients were analyzed in each of the studies and how the missing data were managed in the MTC.	This limitation suggests more uncertainty is associated with the 24-week analysis than with the analysis at the earlier time point. Uncertainty regarding comparative efficacy.
Mixed-treatment comparison: Long-term effectiveness	Four studies included early-escape designs or crossover designs prior to the 24-week time point; thus, the 24-week results may be less valid than the 12-week results.	Uncertainty regarding long-term comparative efficacy.

Identified Limitation	Description	Implication
Mixed-treatment comparison: Study heterogeneity	Details of patient demographic and disease characteristics in the individual studies were not reported; thus, heterogeneity between the trials could not be assessed.	Uncertainty regarding comparability of studies included in MTC.
Mixed-treatment comparison: Conduct	It would have been expected that further analyses would have been undertaken, such as excluding specific randomized controlled trials due to lower quality, small samples, or early escape plan before the end point or lack of intention-to-treat analysis to test whether those specific studies were affecting the observed results.	Uncertainty regarding comparative efficacy.

REFERENCES

1. Cimzia® (certolizumab pegol): solution for injection in a single-use pre-filled glass syringe, 200mg/mL [product monograph]. Oakville (ON): UCB Canada, Inc.; 2014 Jan 15.
2. Pharmacoeconomic evaluation. In: CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Oakville (ON): UCB Canada, Inc.; 2014 Aug 29.
3. CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Oakville (ON): UCB Canada Inc.; 2014 Aug 29.
4. CEDAC final recommendation: Certolizumab Pegol (Cimzia - UCB Canada). Indication: Rheumatoid arthritis [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2010 May 27. [cited 2015 Jan 26]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Cimzia_May-28-2010.pdf
5. Becker B, Strand L, Tater K, Xu Y, Ashaye AO. A systematic review of Cimzia© and biologic DMARDs in the treatment of psoriatic arthritis. Version 3.0. In: CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Bethesda (MD): Evidera; 2013 Oct 4.
6. Fahrbach K, Xu Y, Ashaye AO. Cimzia© and biologic DMARDs in the treatment of psoriatic arthritis: an adjusted mixed treatment comparison analysis. Version 2.2. In: CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Lexington (MA): Evidera; 2014 Jul 31.
7. Canadian Agency for Drugs and Technologies in Health. Final CDEC recommendation: infliximab (Inflectra - Hospira Healthcare Corporation). Indication: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis [Internet]. Ottawa: CADTH; 2014 Dec 19. 7 p. [cited 2015 Jan 6]. (CDEC Meeting - November 19, 2014). Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_SE0384_Inflectra_Dec-23-14.pdf
8. BC PharmaCare. Special authority request: adalimumab/etanercept/golimumab/infliximab for psoriatic arthritis [Internet]. Victoria: British Columbia Ministry of Health; 2015. [cited 2015 Jan 13]. Available from: https://www.health.gov.bc.ca/exforms/pharmacare/5360fil.pdf