CDEC FINAL RECOMMENDATION

CERTOLIZUMAB PEGOL
(Cimzia — UCB Canada Inc.)
Indication: Psoriatic Arthritis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that certolizumab pegol (CZP) be listed for use alone, or in combination with methotrexate, 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 (PsA) who have failed one or more disease-modifying antirheumatic drug (DMARD), if the following conditions are met:

Conditions:
- List in a manner similar to other biologic DMARDs for the treatment of PsA
- The annual drug plan cost for the treatment of PsA with CZP should not exceed the annual drug plan cost of treating PsA with the least costly biologic DMARD reimbursed.

Reasons for the Recommendation:
1. One double-blind randomized controlled trial (RCT) (RAPID-PsA; N = 409) conducted in patients with active PsA demonstrated that treatment with CZP at a dose of either 200 mg every two weeks or 400 mg every four weeks resulted in statistically significant and clinically meaningful improvements in American College of Rheumatology (ACR) 20 response rates after 12 weeks of treatment.
2. At the submitted price ($664.51 per 200 mg/mL pre-filled syringe), the annual cost of CZP for patients weighing 61 kg to 80 kg is $19,271 in the first year and $17,277 in subsequent years, which is more than golimumab (+$1,028) and adalimumab (+$21), but less than etanercept (−$1,048), branded infliximab (−$12,331), subsequent entry biologic (SEB) infliximab (−$1,529), and ustekinumab (−$3,695) in the first year of treatment, based on publicly available prices.

Background:
CZP subcutaneous (SC) injections are approved for the following indications: treatment of adults with moderately to severely active PsA who have failed one or more DMARDs; treatment of adults with active ankylosing spondylitis; and treatment of adults with moderately to severely active rheumatoid arthritis. This CADTH Common Drug Review (CDR) submission is for the treatment of active PsA for adult patients who have failed one or more DMARDs.

The recommended loading dose of CZP for adults with PsA is 400 mg (given as two SC injections of 200 mg each) at weeks 0, 2, and 4. The recommended maintenance dose is 200 mg every two weeks or 400 mg every four weeks.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of CZP for the treatment of PsA, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues that are important to individuals living with PsA.

Patient Input Information
The following is a summary of information provided by three patient groups that responded to the CDR call for patient input:

- Individuals living with PsA suffer from a multitude of symptoms that impact daily activities and significantly reduce quality of life. Persistent pain, swelling, and stiffness due to inflammation can be debilitating and leave patients unable to perform normal activities, and can lead to sleepless nights and persistent fatigue. The skin manifestations associated with PsA can be highly visible, causing heightened anxiety and depression.
- Existing therapies include non-steroidal anti-inflammatory drugs, analgesics, biologic and non-biologic DMARDS, and exercise. Patients are challenged by the heterogeneity of response to treatments and the waning effectiveness of therapies experienced by some individuals. Patients indicate that a large array of treatment options is needed to ensure that they have access to effective therapies.

Clinical Trials
The CDR systematic review included one phase 3, double-blind RCT (RAPID-PsA; N = 409). Patients with active adult-onset PsA who have failed one or more DMARD were eligible for enrolment in the trial. The proportion of patients enrolled who had failed previous therapy with one or more tumour necrosis factor inhibitors was capped at approximately 40%. The study compared the efficacy and safety of CZP 200 mg every two weeks or CZP 400 mg every four weeks versus placebo during a period of 24 weeks.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- ACR response criteria — provides a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and tender joint counts and at least three of five additional disease criteria including: patient/physician global assessment of disease activity (10 cm visual analogue scale [VAS]), health assessment questionnaire (HAQ), patient assessment of pain intensity, level of C-reactive protein (CRP), or erythrocyte sedimentation rate (ESR).
- Psoriatic Arthritis Response Criteria (PsARC) — measures signs and symptoms of PsA assessed by tender and/or swollen joint count, physician global assessment (0 to 5 Likert scale), and patient global assessment (0 to 5 Likert scale). PsARC responders were those with at least a 30% reduction in tender or swollen joint count, as well as a one-point reduction on the five-point patient and/or physician global assessment scales, and no worsening of any score.
- Disease Activity Score (DAS) 28 and CRP — DAS 28 (CRP) criteria consist of four components: swollen joints (28 count), tender joints (28 count), patient global assessment of

disease activity, and CRP. Scores range from 0 to 9.4, with higher scores indicating greater disease activity. The threshold values are 2.6, 3.2, and 5.1 for remission, low disease activity, and high disease activity, respectively.

- European League Against Rheumatism (EULAR) — a response of "good" is defined as an improvement in DAS 28 (CRP) of > 1.2 and a score ≤ 3.2 (possible scores range from 0 to 28).
- Psoriasis Area and Severity Index (PASI) — an instrument used to assess and grade the severity of psoriatic lesions and the patient's response to treatment (scores range from 0 to 72).
- HAQ — a self-assessment questionnaire of eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities); patients' difficulty in performing these activities is scored from 0 (without any difficulty) to 3 (unable to do).
- Short Form-36 (SF-36) — a 36-item, general health status instrument consisting of eight health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, role limitations due to physical challenges, and role limitations due to emotional challenges. The physical component summaries (PCS) and the mental component summary (MCS) range from 0 to 100, with higher scores indicating better health status.
- Psoriatic Arthritis Quality of Life instrument (PsAQoL) — a PsA-specific quality of life instrument that consists of 20 items with a score ranging from 0 to 20. Higher scores indicate worse health-related quality of life.
- Modified Total Sharp Scores (mTSS) — measures the presence of erosions in the hands and feet and the presence of joint space narrowing in the hands, wrists, and feet. The scores for each feature for the individual joints are summed. For erosion scores, 16 locations in each hand and wrist and 12 locations in each foot were scored using a 6-point scale from 0 to 5. For joint space narrowing, 15 locations in each hand and wrist and 6 locations in each foot were scored using a 5-point scale from 0 to 4. The mTSS scores range from 0 to 528, with higher scores indicating greater disease severity.
- Work productivity — assessed using the Work Productivity Survey (WPS), a nine-question instrument used to assess the impact of arthritis on productivity inside and outside the home during the preceding four weeks.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The two primary efficacy end points in RAPID-PsA were ACR 20 response at week 12 (200 mg every two weeks and 400 mg every four weeks, evaluated separately) and change from baseline in mTSS at week 24 (both CZP combined).

Efficacy

- Both CZP regimens were statistically superior to placebo for the proportion of patients achieving ACR 20 response. The differences in proportions versus placebo were (CZP 200 mg every two weeks and CZP 400 mg every four weeks, respectively):
  - 12 weeks: 33.7% (95% confidence interval [CI], 22.8% to 44.6%) and 27.6% (95% CI, 16.5% to 38.7%)
  - 24 weeks: 40.2% (95% CI, 29.5% to 51.0%) and 32.8% (95% CI, 21.8% to 43.8%).
- The proportions of patients achieving ACR 50, ACR 70, DAS 28, EULAR response of good, and PsARC response for both CZP regimens were also statistically superior to placebo at

weeks 12 and 24. The CDR-calculated differences of proportions at 24 weeks versus placebo were (CZP 200 mg every two weeks and CZP 400 mg every four weeks, respectively):
  - ACR 50: 32% (95% CI, 22% to 42%) and 28% (95% CI, 18% to 37%)
  - ACR 70: 24% (95% CI, 16% to 32%) and 19% (95% CI, 11% to 27%)
  - [redacted]
  - [redacted].
- The proportion of patients with an improvement of ≥ 0.3 in HAQ was statistically significantly greater in the CZP groups compared with placebo. The mean absolute differences reported versus placebo were (CZP 200 mg every two weeks and CZP 400 mg every four weeks, respectively):
  - 12 weeks: 24.3% (95% CI, 13.5% to 35.1%) and 27.6% (95% CI, 16.7% to 38.5%)
  - 24 weeks: 33.8% (95% CI, 23.5% to 44.2%) and 32.7% (95% CI, 22.3% to 43.1%).
- The proportion of patients achieving a 75% or 90% reduction in PASI was statistically significantly greater in the CZP groups compared with placebo at weeks 12 and 24. The differences of proportions at 24 weeks versus placebo were (CZP 200 mg every two weeks and CZP 400 mg every four weeks, respectively):
  - PASI 75: 47.1% (95% CI, 34.6% to 59.7%) and 45.4% (95% CI, 32.1% to 58.8%)
  - PASI 90: 40.9% (95% CI, 29.4% to 52.3%) and 29.7% (95% CI, 17.9% to 41.6%).
- The mean changes from baseline to 12 weeks and 24 weeks in SF-36 PCS and SF-36 MCS were statistically significantly greater in both CZP groups compared with the placebo group. The least squares mean differences versus placebo at 24 weeks were (CZP 200 mg every two weeks and CZP 400 mg every four weeks, respectively):
  - [redacted]
  - [redacted].
- Both CZP treatment groups demonstrated statistically significantly greater improvement in PsAQoL compared with placebo at weeks 12 and 24.
- There was no statistically significant difference between the CZP groups and placebo in mTSS at week 24 when the pre-specified imputation methods to account for missing data were used. In a post-hoc analysis, using the median mTSS change from baseline in the whole study population to impute missing values, CZP was associated with a statistically significant reduction in radiographic progression compared with placebo (least squares mean mTSS change from baseline: combined CZP groups 0.06, placebo group 0.28, $P = 0.007$).
- Compared with placebo, there was a statistically significant difference at week 24, for all eight questions of the WPS with CZP 200 mg every two weeks and five of eight questions with CZP 400 mg every four weeks.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one serious adverse event was 5.8%, 9.6%, and 4.4% in the CZP 200 mg every two weeks, CZP 400 mg every four weeks, and placebo groups, respectively.
- The proportion of patients who withdrew from the trial as a result of adverse events was 2.9%, 4.4%, and 1.5% in the CZP 200 mg every two weeks, CZP 400 mg every four weeks, and placebo groups, respectively.
- The proportion of patients who experienced at least one treatment-emergent adverse event was 68.1%, 71.1%, and 67.6% in the CZP 200 mg every two weeks, CZP 400 mg every four weeks, and placebo groups, respectively. The most commonly reported adverse events for

all three groups were nasopharyngitis ([redacted], [redacted], and 7.4%) and upper respiratory tract infection ([redacted], [redacted], and 5.1%) in the CZP 200 mg every two weeks, CZP 400 mg every four weeks, and placebo groups, respectively.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing CZP with the four biologic DMARDs (adalimumab, etanercept, golimumab, and infliximab) 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 during a three-year time frame. Ustekinumab was not included in the base-case analysis as it was not listed on a provincial formulary for this indication at the time of the submission. The assumption of clinical similarity was based on a mixed treatment comparison (MTC) that assessed ACR 20, ACR 50, PsARC, PASI 75, HAQ-DI, SF-36, and pain and fatigue at 24 weeks (safety was not assessed). The manufacturer's base-case analysis considered only drug acquisition costs, with an assumed patient weight of 80 kg, 100% compliance with treatment regimens, and no dropouts.

CDR identified the following key limitations with the manufacturer's economic submission:

- The manufacturer's three-year time horizon in the base-case analysis is arbitrary. If a one-year time horizon is considered, CZP is more costly than golimumab and adalimumab. CDR also applied a 30% discontinuation rate to all biologic DMARDs after the first year and a further 10% after each subsequent year, resulting in lower discounted cost savings with CZP during a three-year period than originally reported ($136 to $22,465 versus $760 to $27,985).
- CDR identified several limitations with the MTC, including the lack of comparative safety data, heterogeneity across the included studies, and uncertainty in the long-term effectiveness of treatments.

CDR also considered the potential availability of SEB infliximab at a lower price than branded infliximab.

At the submitted price of $664.51 per 200 mg/mL pre-filled syringe ($19,271 in the first year and $17,277 in subsequent years), for a patient weight ranging from 61 kg to 80 kg, CZP is more costly than golimumab (+$1,028), and adalimumab (+$21), but less costly than etanercept (−$1,048), branded infliximab (−$12,331) and SEB infliximab (−$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 current comparative treatments (savings ranging from $965 to $10,374), with the exception of SEB infliximab (where patients receive three vials or less per dose, the incremental cost is between $377 and $4,602).

Other Discussion Points:

CDEC noted the following:

- RAPID-PsA required patients to have an erythrocyte sedimentation rate (ESR) of at least 28 mm/hour or a CRP above the upper limit of normal to be eligible for enrolment in the trial. The clinical expert consulted by CDR noted that in routine clinical practice a substantial proportion of the patients who would be treated with a biologic DMARD would not have inflammatory markers elevated to this degree. The study results may not be generalizable to PsA patients with lower ESRs.

- The manufacturer's MTC did not evaluate end points related to safety; therefore, the comparative safety of CZP with other biological DMARDs could not be assessed.
- The MTC suggested that CZP had similar efficacy compared with etanercept, adalimumab, golimumab, infliximab, and ustekinumab. Heterogeneity across the included studies was not fully evaluated in the MTC, limiting the ability to draw conclusions from these analyses.
- There was no statistically significant difference between the CZP and placebo groups in change from baseline in mTSS at 24 weeks (a co-primary end point of the trial) when the pre-specified imputation methods to account for missing data were used.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:
- There are no direct comparisons evaluating the efficacy and safety of CZP versus other biologic DMARDs for the treatment of PsA.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

March 18, 2015 Meeting

Regrets:
One CDEC member was unable to attend the meeting.

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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