CDEC FINAL RECOMMENDATION

CERTOLIZUMAB PEGOL
(Cimzia — UCB Canada Inc.)
Indication: Ankylosing Spondylitis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that certolizumab pegol (CZP) be listed for reducing the signs and symptoms of active ankylosing spondylitis (AS) in adult patients who have had an inadequate response to conventional therapy, if the following conditions are met:

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

Reasons for the Recommendation:
1. One double-blind randomized controlled trial (RCT) (AS-001) demonstrated that treatment of AS with CZP 200 mg every two weeks or 400 mg every four weeks resulted in statistically significant and clinically meaningful improvements in clinical response, disease activity, and function at 12 weeks and 24 weeks when compared with placebo.
2. At the submitted price ($664.51 per 200 mg/mL pre-filled syringe), for patients weighing 61 kg to 80 kg, the annual cost of CZP is more than the cost of golimumab (+$1,028) and adalimumab (+$21) and is less than the annual cost of etanercept (−$1,048), branded infliximab (−$20,231 to −$12,331), and subsequent entry biologic (SEB) infliximab (−$6,729 to −$1,529) for the first year of treatment.

Background:
CZP subcutaneous injections are approved for the following indications: management of AS for adult patients who have had an inadequate response to conventional therapy, management of moderately to severely active rheumatoid arthritis, and management of moderately to severely active psoriatic arthritis. The current CADTH Common Drug Review (CDR) submission is for the management of active AS for adult patients who have had an inadequate response to conventional therapy.

The recommended loading dose of CZP for adult patients with AS is 400 mg (given as two subcutaneous injections of 200 mg each) at weeks 0, 2, and 4. After the loading dose, 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 AS, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues that are important to individuals with AS.

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

- Symptoms of AS include pain in the sacroiliac joints, the hips, the lower back spreading up to the neck, morning stiffness, fatigue, and depression. Those affected with AS reported that their quality of life is reduced given the symptoms, disability, and difficulty participating in daily activities.
- Existing therapies include non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, biologic and non-biologic DMARDS, and exercise. Patients noted the need for several treatment options as biologics are not effective for all patients, and treatment response may be different for each individual.
- Treatment with NSAIDs and exercise are effective at controlling milder disease conditions, but more severe cases and those non-responsive to therapy can be debilitating.
- Fewer therapies are approved for treating AS than other forms of arthritis.

Clinical Trials
One phase 3, double-blind RCT met the inclusion criteria for the CDR systematic review. AS-001 randomized (1:1:1) 325 adult patients with active axial spondyloarthritis including an AS subpopulation of 178 patients and a non-radiographic axial spondyloarthritis subpopulation (n = 147). Patients were randomized to either CZP 200 mg every two weeks, CZP 400 mg every four weeks, or placebo during a treatment period of 24 weeks. In accordance with the Health Canada-approved indication, only results for the AS subpopulation were considered by CDEC.

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

- Assessment of SpondyloArthritis International Society (ASAS) 20 — defined as an improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 numerical rating scale in at least three of four domains.
- ASAS 40 — defined as an improvement of at least 40% and absolute improvement of at least 1 unit in at least three of four ASAS domains.
- Disease activity — assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The BASDAI is a self-reported instrument used to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness as compared with the previous week. The minimal clinically important difference (MCID) used to interpret scores is considered to be 10 mm on a visual analogue scale or 22.5% of the baseline score.

- Functional and disability outcomes — assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath Ankylosing Spondylitis Metrology Index (BASMI)
  - BASFI is a 10-item, disease-specific instrument that measures physical function. The MCID is considered to be 7 mm on a visual analogue scale (VAS) or 17.5% of the baseline score.
  - BASMI characterizes spinal mobility based on five clinical measures: cervical rotation, tragus to wall distance, lumbar flexion, intermalleolar distance, and lateral spinal flexion. The MCID has not been defined for this end point.
- Health-related quality of life — assessed using the Ankylosing Spondylitis Quality of Life assessment (ASQoL) and EuroQol Health Status Questionnaire (EQ-5D).
- ASQoL — an 18-item disease-specific questionnaire for measuring health-related quality of life in patients with AS.
- 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 summary (PCS) and the mental component summary (MCS) range from 0 to 100, with higher scores indicating better health status.
- 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.

Efficacy

- Both CZP regimens were statistically superior to placebo for the proportion of patients achieving ASAS 20 response. The differences of proportions versus placebo were (CZP 200 mg every two weeks and CZP 400 mg every four weeks, respectively):
  - 12 weeks: 20.1% (95% confidence interval [CI], 2.7% to 37.5%) and 27.4% (95% CI, 9.7% to 45.2%)
  - 24 weeks: 34.4% (95% CI, 17.7% to 51.1%) and 36.3% (95% CI, 19.1% to 53.5%).
- For ASAS 40 response, both CZP regimens were statistically superior to placebo. The differences of proportions versus placebo were (CZP 200 mg every two weeks and CZP 400 mg every four weeks, respectively):
  - 12 weeks: 20.7% (95% CI, 5.0% to 36.4%) and 30.7% (95% CI, 14.1% to 47.3%)
  - 24 weeks: 31.9% (95% CI, 16.5% to 47.3%) and 43.1% (95% CI, 27.2% to 59.1%).
- Both CZP regimens were statistically superior to placebo for improvement in BASDAI and BASFI scores. The mean differences versus placebo were (CZP 200 mg every two weeks and CZP 400 mg every four weeks, respectively):
  - BASDAI (12 weeks): −1.49 (95% CI, −2.20 to −0.78) and −1.40 (95% CI, −2.15 to −0.66)
  - BASDAI (24 weeks): −1.87 (95% CI, −2.57 to −1.16) and −1.85 (95% CI, −2.59 to −1.11)
  - BASFI (12 weeks): −1.15 (95% CI, −1.88 to −0.42) and −1.13 (95% CI, −1.89 to −0.36)
  - BASFI (24 weeks): −1.62 (95% CI, −2.38 to −0.86) and −1.55 (95% CI, −2.34 to −0.75).
- There was no statistically significant difference between either of the CZP groups and placebo for BASMI linear score.
- For health-related quality of life, both CZP treatment groups demonstrated a numerically greater improvement in ASQol and SF-36 at week 12. Patients receiving CZP reported improvements in mobility, self-care, and usual activities (EQ-5D dimensions) at week 12.

- There was a statistically significant difference for one of eight questions of the WPS among the CZP 200 mg every two weeks group, and five of eight WPS questions for the CZP 400 mg every four weeks group when compared with placebo at week 12. There was a statistically significant difference for three of eight questions among the CZP 200 mg every two weeks group, and four of eight questions for the CZP 400 mg every four weeks group when compared with placebo at week 24.

Harms (Safety and Tolerability)

- [redacted]
- [redacted]
- [redacted]

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 in adults with active AS who have had an inadequate response to conventional therapy during a three-year time horizon. The assumption of clinical similarity was based on a manufacturer-funded mixed treatment comparison (MTC) that assessed the main efficacy parameters (ASAS 20, ASAS 40, BASDAI, BASFI, and SF-36), but did not assess safety. The manufacturer's base-case analysis considered only drug acquisition costs, with an assumed patient weight of 80 kg, 100% compliance with treatment, 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 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 over three years than originally reported (from $136 to $30,937 compared with $760 to $39,065).
- 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) or adalimumab (+$21), but less costly than etanercept (−$1,048), branded infliximab (−$20,231 to −$12,331) and SEB infliximab (−$6,729 to −$1,529) in the first year of treatment. In subsequent years, CZP may be less costly than currently available comparative treatments (savings ranging from $965 to $10,374), with the exception of

SEB infliximab (where patients receive three vials or less per dose every eight weeks, incremental cost between $377 and $4,602).

Other Discussion Points:
CDEC noted the following:

- Given the small sample size, meaningful conclusions could be made from the subgroup analyses for prior tumour necrosis factor (TNF) inhibitor exposure and baseline C-reactive protein (CRP).
- The MTC suggested that CZP had similar efficacy compared with etanercept, adalimumab, and golimumab, but had lower efficacy than infliximab at 12 weeks in terms of ASAS 20, BASDAI, and BASFI. Heterogeneity across the included studies was not fully evaluated in the MTC, limiting the ability to draw conclusions from these analyses.
- 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.

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 AS.
- Patients who have had a primary failure to any TNF inhibitor were excluded from AS-001.

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.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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