CDEC FINAL RECOMMENDATION

USTEKINUMAB
(Stelara — Janssen Inc.)
Indication: Psoriatic Arthritis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that ustekinumab not be listed at the submitted price for the treatment of psoriatic arthritis.

Reasons for the Recommendation:
1. Two double-blind, placebo-controlled, randomized controlled trials (RCTs) (PSUMMIT-1 [N = 615] and PSUMMIT-2 [N = 312]) demonstrated that ustekinumab (45 mg and 90 mg) was associated with improved rates of American College of Rheumatology (ACR) 20 response at 24-weeks in patients with active psoriatic arthritis.
2. At the submitted price, ustekinumab was not shown to be cost-effective relative to conventional management for both anti-TNF alpha treatment-experienced and treatment-naive patients. In addition, the manufacturer's indirect treatment comparison suggested that other biological response modifiers may be more efficacious for the management of psoriatic arthritis and some are less costly.

Of Note:
Based on a review of the clinical evidence, CDEC noted that a reduced price would increase the likelihood of a recommendation to "list with clinical criteria and/or conditions."

Background:
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds to the shared p40 subunit of interleukin (IL)-12 and IL-23. Ustekinumab is indicated for the treatment of the following: adult patients with active psoriatic arthritis, taken alone or in combination with methotrexate (MTX); and, adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Ustekinumab is available as a single-use pre-filled syringe (45 mg/0.5 mL or 90 mg/1.0 mL) and is administered by subcutaneous injection of 45 mg or 90 mg at weeks 0, 4, and every 12 weeks thereafter.

Summary of CDEC Considerations
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of ustekinumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients and caregivers.

Patient Input Information

The following is a summary of information provided by five patient groups that responded to the CDR call for patient input.

- Individuals living with psoriatic arthritis suffer from a multitude of symptoms that impact daily activities. Joint 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. Many patients also have itchy, painful, disfiguring psoriatic plaques that cause some patients to feel significant embarrassment and self-consciousness.
- In addition to the prominent physical symptoms, those with psoriatic arthritis also suffer emotionally and experience helplessness, frustration, fear, anxiety, isolation, and depression as they are often unable to work, can lose their independence, and may require constant assistance to perform daily tasks.
- Existing treatments are often associated with significant adverse events; however, most patients are able to tolerate these provided the treatment is effective. Patients noted that treatments often eventually become ineffective and that a large array of treatment options is needed to ensure that patients have access to effective therapies.
- Patients expressed a preference for a medicine that is administered less frequently than other currently available treatments.

Clinical Trials

The CDR systematic review included two double-blind, placebo-controlled RCTs (PSUMMIT-1 [N = 615] and PSUMMIT-2 [N = 312]) that evaluated the efficacy and harms of ustekinumab 45 mg and 90 mg in patients with active psoriatic arthritis. Patients had active disease despite being treated with disease-modifying antirheumatic drugs (DMARDs) and/or non-steroidal anti-inflammatory drugs (NSAIDs), or who were intolerant to DMARDs and/or NSAIDs. With the exception of MTX, no concomitant DMARDs were allowed during the studies. Patients who previously used anti-TNF alpha therapy were not eligible for PSUMMIT-1, but 60% of patients in PSUMMIT-2 had previously used anti-TNF alpha therapy. The patients were blinded for 108 weeks (PSUMMIT-1) and 60 weeks (PSUMMIT-2), but only the first 24 weeks of both studies were placebo controlled. Both study protocols permitted early escape at week 16, and all patients taking placebo were reassigned to ustekinumab at week 24.

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 psoriatic arthritis 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 1-point reduction on the 5-point patient and/or physician global assessment scales, and no worsening of any score.

- Disease Activity Score (DAS) 28 and CRP — DAS 28 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.
- Psoriasis Area and Severity Index (PASI) — 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-assessed 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 8 health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional challenges. The physical component summaries (PCS) and the mental component summary (MCS) range from zero to 100 with higher scores indicating better health status.

The primary outcome in both included studies was the proportion of patients achieving ACR 20 response at 24 weeks.

Efficacy

- In both PSUMMIT-1 and PSUMMIT-2, the proportion of patients achieving ACR 20 at week 24 was larger in the ustekinumab 45 mg (42% and 44%) and 90 mg (44% and 50%) groups, relative to placebo (20% and 23%); $P < 0.001$ for all comparisons versus placebo.
- At week 24, statistically significant results were observed for all ustekinumab doses versus placebo for the proportion of patients achieving ACR 50 response. However, the proportion of ustekinumab patients achieving ACR 70 response versus placebo only achieved statistical significance in PSUMMIT-1.
- For each of the individual components of the ACR response criteria, ustekinumab 45 mg and 90 mg were both statistically significantly better compared with placebo.
- After week 24, all patients were scheduled to receive ustekinumab in both trials. At study end, the ACR response rate in the group that originally received placebo was similar to the response rate of those who were originally randomized to ustekinumab.
- HAQ-DI (disability index) scores for patients treated with ustekinumab 45 mg and 90 mg were statistically significantly improved relative to placebo in both trials. The proportion of patients with an improvement of ≥ 0.3 was greater in the ustekinumab 45 mg and 90 mg groups relative to placebo (statistically significant for all comparisons).
- There were statistically significantly greater proportions of PsARC responders in the ustekinumab 45 mg and 90 mg groups compared with placebo at week 24 in both PSUMMIT-1 and PSUMMIT-2 ($P < 0.001$).
- There was no statistically significant difference between the ustekinumab and placebo groups for the proportion of patients achieving DAS 28 remission in PSUMMIT-2; however, there was a statistically significant difference observed in PSUMMIT-1. At week 24, the proportion of patients in the ustekinumab 45 mg and 90 mg groups achieving a DAS response was higher than placebo ($P < 0.001$) in both trials.

- Statistically significant improvements in the SF-36 PCS were reported for ustekinumab 45 mg and 90 mg versus placebo at week 24. The only statistically significant improvements observed for the SF-36 MCS was for the ustekinumab 90 mg dose versus placebo in PSUMMIT-1.

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event was reported as follows:
  - PSUMMIT-1: ustekinumab 45 mg (2%), ustekinumab 90 mg (2%), and placebo (2%).
  - PSUMMIT-2: ustekinumab 45 mg (1%), ustekinumab 90 mg (0%), and placebo (5%).
- The proportion of patients with at least one adverse event was reported as follows:
  - PSUMMIT-1: ustekinumab 45 mg (41%), ustekinumab 90 mg, (44%) and placebo (44%).
  - PSUMMIT-2: ustekinumab 45 mg (63%), ustekinumab 90 mg (61%), and placebo (55%).
- The proportion of patients who withdrew as a result of adverse events was:
  - PSUMMIT-1: ustekinumab 45 mg (0.5%), ustekinumab 90 mg (1%), and placebo (2%).
  - PSUMMIT-2: ustekinumab 45 mg (2%), ustekinumab 90 mg (2%), and placebo (8%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis over a lifetime (52 year) time horizon comparing ustekinumab with placebo in patients with psoriatic arthritis. For patients with no previous exposure to anti-TNF alpha medications (anti-TNF alpha naive patients), ustekinumab was compared with golimumab, infliximab, adalimumab, etanercept, and placebo; while for patients previously exposed to anti-TNF alpha, ustekinumab was compared with placebo. Treatment effects were based on PsARC, and PASI 50, 75 and 90 response rates. In the analysis of anti-TNF alpha naive patients, comparative clinical efficacy was obtained from a mixed treatment comparison (MTC) conducted by the manufacturer. For the analysis of anti-TNF alpha experienced patients, clinical efficacy was based on a subgroup analysis of the PSUMMIT-2 study. The manufacturer reported that ustekinumab is associated with an incremental cost per quality-adjusted life-year of $40,958 compared with placebo in anti-TNF alpha naive patients and $46,962 when compared with placebo anti-TNF alpha experienced patients. Based on the manufacturer's MTC, ustekinumab is less effective than other biologic therapies. Thus, the economic evaluation found that ustekinumab was dominated (less effective and more costly) when compared with golimumab; and less effective and less costly than infliximab, adalimumab, and etanercept.

CDR noted the following key limitation with the manufacturer's economic evaluation: it was assumed that patient's quality of life would rebound to the baseline value after treatment discontinuation, and the model used efficacy estimates that differed from the ones reported in the MTC. CDR explored this assumption using corrected efficacy estimates, and it was noted that where quality of life rebounds to a value reflective of the natural disease progression, the cost per quality-adjusted life-year estimate for ustekinumab increases to $73,082 compared with placebo in anti-TNF alpha naive patients and $82,611 compared with placebo in anti-TNF alpha experienced patients.

Ustekinumab (45 mg or 90 mg at week 0 and week 4, then every 12 weeks thereafter; $19,903 to $22,966) is more expensive than adalimumab (40 mg every other week; $19,249), golimumab (50 mg monthly; $18,243), certolizumab pegol (400 mg at week 0, 2 and 4 then 200 mg every 2 weeks; $17,325 to $19,318); similar to etanercept (50 mg weekly or 25 mg twice weekly; approximately $20,200); and less expensive than infliximab (5 mg/kg at weeks 0, 2 and 6, then every 8 weeks thereafter; $25,376 to $31,232 based on 70 kg patient weight).

Other Discussion Points:
CDEC noted the following:

- The MTC submitted by the manufacturer demonstrated consistently lower response rates with ustekinumab compared with anti-TNF alpha medications.

Research Gaps:
CDEC noted that there is limited or an absence of evidence regarding the following:

- There is an absence of long-term efficacy and safety data for the use of ustekinumab in patients with psoriatic arthritis.
- There were no trials identified comparing ustekinumab with anti-TNF alpha medications for the treatment of psoriatic arthritis.
- The design of PSUMMIT-1 and PSUMMIT-2 were insufficient to characterize the comparative efficacy of ustekinumab in preventing or slowing the progression of structural damage associated with psoriatic arthritis.

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.

September 17, 2014 Meeting
Regrets:
None

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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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