CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

USTEKINUMAB
(Stelara — Janssen Inc.)
Indication: Crohn's disease

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ustekinumab be reimbursed for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, loss of response to, or were intolerant to either immunomodulators or one or more tumour necrosis factor-alpha antagonists, or have had an inadequate response to, intolerance to or demonstrated dependence on corticosteroids, if the following clinical criterion and conditions are met:

Clinical criteria:
Treatment with ustekinumab should be discontinued if patients do not achieve clinical response within eight weeks of induction therapy.

Conditions:
1. The cost of treatment with ustekinumab should not exceed the drug plan cost of the least costly alternative biologic treatment option.
2. Patients treated with ustekinumab should be under the care of a specialist physician with experience in the diagnosis and management of Crohn's disease.

Reasons for the Recommendation:
1. Three phase III, placebo-controlled, double-blind, randomized controlled trials (RCTs) investigated the effects of ustekinumab on treatment induction (UNITI-1 and UNITI-2) or maintenance (IM-UNITI) in patients with moderate-to-severe Crohn's disease. A higher proportion of patients receiving ustekinumab achieved clinical remission at eight weeks than those receiving placebo in both UNITI-1 and UNITI-2. Additionally, in IM-UNITI, the proportion of ustekinumab-treated patients compared with placebo who achieved clinical remission and corticosteroid-free clinical remission was greater at 44 weeks.
2. There is insufficient evidence to determine if there is a meaningful clinical difference between ustekinumab and other biologics for the induction and/or maintenance treatment of Crohn's disease. Although three indirect comparisons reviewed by the CADTH Common Drug Review (CDR) included comparisons of ustekinumab against other biologic treatments for Crohn's disease, limitations associated with these comparisons precluded any definitive

conclusions regarding the efficacy and safety of ustekinumab compared with the efficacy and safety of infliximab, adalimumab, and vedolizumab.

3. Based on CDR re-analyses to account for limitations in the manufacturer's economic model, the incremental cost-utility ratios (ICURs) for ustekinumab range from $115,431 to $189,403 per quality-adjusted life-year (QALY) when compared with conventional therapy, and from being dominant to $870,045 per QALY when compared with other biologic therapies. However, the uncertainty about the effectiveness of ustekinumab compared with that of other biologics (including biosimilar infliximab) limits the conclusions that can be drawn about the relative cost-effectiveness of these drugs.

Of Note:
In the included trials, the relevant components of a clinical response to treatment were:

- A reduction from baseline in the Crohn's Disease Activity Index (CDAI) score of ≥ 100 points, OR
- A CDAI score of < 150 points in patients with a baseline CDAI score of ≥ 220 to ≤ 248 points.

Patients who had a Crohn's disease-related surgery (with the exception of drainage of a cutaneous or perianal abscess or seton placement) before week eight of induction treatment were considered to be non-responders, regardless of CDAI score.

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 the first IL-12/IL23 inhibitor available in Canada. Ustekinumab is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, loss of response to, or were intolerant to either immunomodulators or one or more tumour necrosis factor-alpha antagonists, or have had an inadequate response to, intolerance of or demonstrated dependence on corticosteroids. Ustekinumab is also 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 as a solution for intravenous (IV) infusion (130 mg/26 mL [5 mg/mL]). The product monograph recommends patients with Crohn's disease receive a single IV tiered dose of ustekinumab based on body weight (approximating 6 mg/Kg) at initiation (i.e., week 0) for induction. Patients with Crohn's disease are administered a subcutaneous (SC) injection of 90 mg at week eight after the IV induction dose and every eight weeks thereafter as maintenance treatment. According to the product monograph, some patients may receive an alternative maintenance regimen of ustekinumab 90 mg SC every 12 weeks at the discretion of the treating physician. Patients who inadequately respond to 90 mg SC dosing every 12 weeks may be switched to the every eight week regimen.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs of ustekinumab in the treatment of Crohn's disease, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals living with Crohn's disease.

Patient Input Information
Two patient groups responded to the CDR call for patient input (the Gastrointestinal Society and Crohn's and Colitis Canada). Information was collected through discussions and interviews with patients and caregivers; surveys and questionnaires; and a review of published reports and information. CDEC heard the following:

- Crohn's disease can have profound effects on a patient's physical, emotional, and social well-being. Patients often experience debilitating symptoms, including bloody diarrhea, bloating, abdominal pain, fatigue, and a lack of control over bowel movements.
- Patients may experience fear, anxiety, and stress due to the uncertainty regarding where and when they may experience an urgent bowel movement or a disease flare. These symptoms can significantly limit their ability to participate in the activities of daily living, including work and school.
- Patient groups indicated that individuals with Crohn's disease found biologic drugs worked well when other treatments have failed; however, not everyone responds to the currently available treatments, so more options are needed.
- Patient groups expressed an understanding of the potential risks associated with biologic treatments and noted that those living with Crohn's disease are often willing to accept these risks rather than undergo surgery, which they consider to be a last resort.

Clinical Trials
The systematic review included four, multisite, multinational, double-blind, placebo-controlled RCTs: two phase III induction treatment studies, UNITI-1 (N = 769) and UNITI-2 (N = 640); one phase III maintenance treatment study, IM-UNITI (N = 397); and one Phase II induction and maintenance study, CERTIFI (N = 526). The results from the UNITI studies and IM-UNITI were the focus of the CDR review; results from the induction phase of CERTIFI were considered supportive only.

UNITI-1 and UNITI-2 were identically designed studies to evaluate the efficacy and safety of IV dosage regimens of ustekinumab (tiered weight-based dose approximating 6 mg/kg or 130 mg [not Health Canada approved]) versus placebo for inducing clinical response at six weeks in patients with moderately to severely active Crohn's disease. UNITI-1 included patients who had had an inadequate response or were intolerant to one or more tumour necrosis factor (TNF) antagonist therapies, whereas UNITI-2 included patients who had had an inadequate response or were intolerant to conventional therapy only (i.e., corticosteroids or immunomodulators such as 6-mercaptopurine, azathioprine, and methotrexate). Patients in UNITI-2 could have previously received TNF antagonists but were required to not have failed treatment.

The IM-UNITI study was designed to evaluate the efficacy and safety for two subcutaneous maintenance regimens of ustekinumab (90 mg every eight weeks [Q8W] or every 12 weeks [Q12W]) in patients with moderately to severely active Crohn's disease who had been induced into clinical response with ustekinumab in the induction studies, UNITI-1 and UNITI-2.

Evidence from an interim analysis of the IM-UNITI long-term extension study and three indirect comparisons (1 submitted by the manufacturer and two identified in a search of the literature conducted by CDR) summarized in the CDR systematic review were also discussed.

Outcomes

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

- clinical remission (CDAI score ≤ 150)
- clinical response (reduction from baseline in CDAI score of ≥ 100 points; or a CDAI score of < 150 points in patients with a baseline CDAI score of ≥ 220 to ≤ 248 points)
- corticosteroid-free clinical remission
- health-related quality of life as assessed by: the Short Form (36) Health Survey (SF-36) and the Inflammatory Bowel Disease Questionnaire (IBDQ)
- mucosal healing determined by histology or endoscopy
- need for surgery for Crohn's disease
- serious adverse events, total adverse events, and withdrawals due to adverse events.

Clinical response at six weeks was the primary outcome of the induction phases studies, UNITI-1 and UNITI-2. Clinical remission at 44 weeks was the primary end point of the maintenance phase study, IM-UNITI.

Efficacy

Clinical Remission

- A statistically significantly higher proportion of patients treated with ustekinumab (approximately 6 mg/kg) (20.9% and 40.2) than with placebo (7.3% to 19.6%) were induced into remission at week 8 in UNITI-1 and UNITI-2, respectively.
- Statistically significantly higher proportions of patients treated with ustekinumab Q12W (48.8% and 42.6%) and ustekinumab Q8W (53.1% and 46.9%) were in clinical remission and corticosteroid-free remission (respectively) at week 44 of IM-UNITI than with placebo (35.9% and 29.8%).
- The results for clinical remission were considered likely to be clinically significant.

Clinical Response

- The proportion of patients in clinical response at week 6 was statistically significantly higher with the ustekinumab groups (33.7% and 55.5%) as compared with the placebo groups (21.5% and 28.7%) in UNITI-1 and UNITI-2, respectively.
- Almost 60% of patients randomized to ustekinumab maintenance treatments in IM-UNITI were responders at week 44, whereas 44% of those assigned to placebo achieved clinical response. The comparison versus placebo was statistically significant for both ustekinumab regimens.

Health-Related Quality of Life, Functional and Disability Outcomes

- Ustekinumab-treated patients generally demonstrated statistically significant improvements in IBDQ total score in both the induction and maintenance studies, as compared with patients receiving placebo. Similar results were reported for changes in the SF-36 physical component scores (PCS) and mental component scores (MCS). However, the clinical significance of the health-related quality of life outcomes is uncertain as some of the

comparisons did not achieve the published minimally clinically important differences for each outcome measure.
- Likewise, in general, statistically significantly greater proportions of patients treated with ustekinumab induction and maintenance therapy (as compared with placebo) had a ≥ 16-point improvement from baseline in the IBDQ score, or at least a five-point improvement from baseline in the PCS and MCS scores of the SF-36. However, the clinical significance of these results versus placebo is unclear.

[redacted]

Mucosal Healing

- Mucosal healing was assessed for a subgroup of patients from the UNITI and IM-UNITI studies (N = 252). The proportion of patients with mucosal healing at week eight of induction was 9.0% and 4.1% for the pooled ustekinumab and placebo groups, respectively (*P* = 0.141).
- The mean change from baseline in Simplified Endoscopic Activity Score for Crohn's disease at week eight of induction (endoscopy substudy primary outcome) was statistically significantly improved (decreased) in the ustekinumab group (–2.8 [5.7] points; *P* = 0.012) than in the placebo group (–0.7 [5.0]).
- The efficacy of ustekinumab maintenance for endoscopic outcomes could not be determined, primarily because of the very small sample size (N = 70).

Need for Surgery for Crohn's Disease

[redacted]

Harms (Safety and Tolerability)

The proportions of patients who experienced at least one adverse event or serious adverse event were similar between the ustekinumab and placebo groups across all of the included studies. Nasopharyngitis and upper respiratory tract infections appeared to be more frequent with ustekinumab treatment as compared with placebo. As expected, patients treated with ustekinumab tended to report more administration-related reactions than those on placebo; however, there were no reports of anaphylaxis in any of the studies. Higher proportions of patients receiving placebo as compared with ustekinumab discontinued due to an adverse event, primarily because of gastrointestinal-related events including worsening Crohn's disease.

[redacted]

Cost and Cost-Effectiveness

Ustekinumab is available as a pre-filled syringe of 90 mg/1 mL for SC injection at $4,593 per syringe and as a single-use vial of 130 mg/26 mL solution for IV infusion at $2,080 per vial. At the recommended weight-based dose of approximately 6 mg/kg IV injection at induction

followed by 90 mg SC injection at week 8, and every 8 weeks or every 12 weeks thereafter, the annual costs with ustekinumab are expected between $24,612 and $33,798 (based on a patient weight of 69.8 kg) in the first year, and between $19,904 and $29,855 in subsequent years. The manufacturer submitted a cost-utility analysis comparing ustekinumab (90 mg every 12 weeks or every 8 weeks, as well as a regimen representing a blend of the two) with infliximab (brand and biosimilar), adalimumab, vedolizumab, and conventional therapy (including corticosteroids or immunomodulators) for the treatment of moderately to severely active Crohn's disease. The analysis was conducted from a Canadian public payer perspective over a 25-year time horizon. Two target populations were considered (patients with moderately to severely active Crohn's disease who failed conventional therapy only (FCTO) and patients who failed TNF antagonist therapy) and a mixed population of the two. The model structure consisted of a decision tree to model the induction treatment phase and a Markov structure to model maintenance treatment for the remainder of the time horizon. Model transition probabilities for the induction and the maintenance phases were based on manufacturer-provided indirect comparisons and the IM-UNITI trial assessing ustekinumab.

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

- Model transition probabilities were based on indirect comparisons and the IM-UNITI trial. Based on identified limitations with the indirect comparisons, no definitive conclusion regarding the comparative efficacy of ustekinumab against infliximab, adalimumab and vedolizumab for induction could be made.
- The approach used by the manufacturer to adjust the maintenance phase transition probabilities is uncertain and might have favored ustekinumab.
- The extrapolation of treatment effect over a 25-year time horizon does not account for the expected waning of treatment effects; this biases the results in favour of ustekinumab.

Based on CDR re-analyses that varied health state utility values, and assessed the impact of excluding the effect of real-world evidence on the transition probabilities after one year in the maintenance phase of the model, the ICUR for ustekinumab when compared with conventional therapy was $115,474 per QALY gained in the FCTO population; $131,297 per QALY gained in the TNF antagonist failure population; and, $119,058 per QALY in a mixed population. Among biologic therapies, ustekinumab every 12 weeks was the most cost-effective with an ICUR of $115,474 per QALY compared with conventional therapy in the FCTO population; other biologics were either dominated or subjected to extended dominance. In the TNF antagonist failure patients, the most cost-effective treatment was biosimilar infliximab with an ICUR of $90,277 per QALY compared with conventional therapy, followed by ustekinumab every 12 weeks with an ICUR of $228,571 per QALY compared with biosimilar infliximab, remaining biologic therapies were dominated or subjected to extended dominance. These results should be interpreted with caution considering the uncertainty of the comparative efficacy of ustekinumab versus other biologics.

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, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

February 15, 2017 Meeting

Regrets:

One CDEC member did not attend.

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*.

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