CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

USTEKINUMAB (STELARA/STELARA I.V. — JANSSEN INC.)
Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that ustekinumab be reimbursed for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic, or have medical contraindications to such therapies, only if the following conditions are met.

Conditions for Reimbursement

Renewal Criteria
The patient must have achieved clinical response to induction therapy within eight weeks for reimbursement of treatment with ustekinumab to continue to maintenance therapy.

Prescribing Conditions
The prescribing of ustekinumab for the treatment of ulcerative colitis should be restricted to gastroenterologists.

Pricing Conditions
The drug plan cost of treatment with ustekinumab should not exceed the drug plan cost of the least costly biologic currently reimbursed for the treatment of ulcerative colitis.

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USTEKINUMAB (STELARA/STELARA IV — JANSSEN INC.)

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ustekinumab be reimbursed for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic, or have medical contraindications to such therapies, only if the following conditions are met.

Conditions for Reimbursement

Renewal Criteria
The patient must have achieved clinical response to induction therapy within eight weeks for reimbursement of treatment with ustekinumab to continue to maintenance therapy.

Prescribing Conditions
The prescribing of ustekinumab for the treatment of UC should be restricted to gastroenterologists.

Pricing Conditions
The drug plan cost of treatment with ustekinumab should not exceed the drug plan cost of the least costly biologic currently reimbursed for the treatment of UC.

Reasons for the Recommendation

1. The results of a single, two-phase, randomized controlled trial (RCT), UNIFI, demonstrated that treatment with ustekinumab was more effective than placebo at inducing (at eight weeks) and maintaining (for another 44 weeks) clinical remission of UC, including corticosteroid-free remission and endoscopic healing.
2. No conclusions could be drawn regarding the comparative effectiveness and safety of ustekinumab to other treatment options for UC because of the lack of head-to-head comparisons and the limitations associated with the sponsor-provided network meta-analysis (NMA). Therefore, CDEC could not determine whether ustekinumab provides meaningful clinical value compared with the biologics and Janus kinase inhibitors that are currently reimbursed for UC.
3. Based on publicly available prices, the annual cost of the infliximab biosimilar (the least costly biologic for this indication) is $15,776 and $13,804 in the first and subsequent years, respectively. Given the uncertainty regarding the comparative clinical effectiveness of ustekinumab compared with other biologics and the limitations of the cost-utility analysis, there is insufficient evidence to justify a cost premium over the least expensive biologic reimbursed for the treatment of moderate-to-severe UC. As well, the cost-effectiveness of ustekinumab would be affected by the additional dose administration sometimes necessary (in approximately 58% of patients based on data from the UNIFI trial) to achieve induction response. Limitations with the comparative effectiveness data make it difficult to determine the exact impact of the additional induction dosing.

Discussion Points

- Ustekinumab provides another treatment option with a different mechanism of action from the other currently available therapies for UC. There is limited evidence from the UNIFI trial in patients who failed on a tumour necrosis factor–alpha inhibitor or vedolizumab that ustekinumab is effective versus placebo in inducing and maintaining clinical remission and response.
- CDEC discussed the best measure of clinical response at eight weeks and noted the impracticality of requiring endoscopy at this time point for all patients with UC taking ustekinumab given both the invasive nature of the procedure and the limitations associated with timely access and associated costs of health care resources in Canada. While the total Mayo score was used throughout the clinical trials, the requirement for an endoscopy for a total Mayo score makes this measure impractical to implement as a criterion for reimbursement. In the absence of the total Mayo score, there are two alternatives: use of the partial Mayo score (which does not require colonoscopy); or, leave the determination for discontinuation to the clinical judgment of prescribing gastroenterologists in consultation with the patient. The partial Mayo score was not prioritized in the statistical testing hierarchy in the UNIFI trial and as a result, CDEC cannot categorically recommend its use. Therefore, the committee concluded

that the determination of whether a patient has achieved a clinical response should be left to the clinical judgment of the prescribing gastroenterologist in consultation with the patient.

- Definitive conclusions could not be drawn regarding the longer-term effects of ustekinumab on health-related quality of life (HRQoL), productivity, and prevention of colectomy. HRQoL and productivity, outcomes important to patients, were not included in the hierarchical statistical analysis plan for the UNIFI trial and were therefore not adjusted for inflated type I error. There were too few colectomy events (three patients treated with placebo and two patients in the combined ustekinumab group) to draw any conclusions related to this outcome.
- CDEC noted that 101 patients who did not respond to ustekinumab 6 mg/kg IV at week eight in the induction treatment phase of the UNIFI trial received a second dose of ustekinumab (90 mg subcutaneously [SC]) and 59 (58.4%) of these patients responded at week 16. The committee recognized that requiring the patient to reach clinical remission or response at eight weeks of treatment with ustekinumab is not consistent with clinical practice, where clinicians may administer a second dose of ustekinumab to induce response. It is unclear how ustekinumab compares with other biologics and Janus kinase inhibitors in this regard because of the absence of comparative data in the subgroup of delayed responders.
- Limitations of the reviewed NMA include uncertainty about the effect estimates due to heterogeneity, intransitivity, and uncertainty due to the use of multiple assumptions of the imputation method (for mimicking a treat-through design needed for obtaining pooled estimates of effect), and overestimated precision for reported comparisons, particularly for the one-year outcomes. No adverse event comparisons were obtained for the NMA. The heterogeneity was due to differences in designs of the maintenance phase studies included in the network. No formal statistical assessment of overall heterogeneity nor the inconsistency of the network were presented. Variations in placebo effect estimates across studies (likely due to the subjectivity of Mayo scoring) as well as possible violations of the assumptions of transitivity for the NMA also support heterogeneity concerns. Different routes of drug administration and dose or regimens could also provide different placebo effect estimates. Individual studies had a moderate risk of bias (some had unclear randomization process, unclear blinding, and unbalanced dropout rates with no intention-to-treat analysis). These limitations precluded drawing concrete conclusions on the comparative effectiveness and safety of ustekinumab for the maintenance treatment of UC.

Background

Ustekinumab is a human monoclonal antibody that affects the interleukin pathways in the pathogenesis of inflammatory bowel disease (IBD) and other immunomodulated conditions. It is approved by Health Canada for the treatment of adults with chronic moderate-to-severe plaque psoriasis, active psoriatic arthritis, and Crohn disease. The current indication under review is for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic, or have medical contraindications to such therapies. The recommended dosage for ustekinumab in the treatment of UC is as a single weight-based IV infusion (approximating 6 mg/kg) followed by a 90 mg SC dose eight weeks later, then 90 mg SC every eight weeks thereafter. The product monograph also provides the following guidance:

- In some patients, such as those with low inflammatory burden, a single dose of ustekinumab IV followed by a 90 mg SC dose eight weeks later, then every 12 weeks thereafter may be considered at the discretion of the treating physician. The dose frequency should be adjusted to every eight weeks if inadequate response occurs.
- Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose.
- Immunomodulators and/or corticosteroids may be continued during treatment with ustekinumab. Corticosteroids may be reduced or discontinued in accordance with standard of care in patients who have responded to treatment with ustekinumab.

Submission History

Ustekinumab has been previously reviewed for the treatment of:

- adults with chronic moderate-to-severe plaque psoriasis who are candidates for systematic therapy or phototherapy, for which the CADTH Canadian Expert Drug Advisory Committee recommended ustekinumab be reimbursed for the treatment of adult patients with active plaque psoriasis, alone or in combination with methotrexate (May 20, 2009)
- psoriatic arthritis, where CDEC recommended that ustekinumab not be reimbursed at the submitted price (September 17, 2014)

- adult patients with moderately to severely active Crohn 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; CADTH CDEC recommended ustekinumab be reimbursed (February 15, 2017).

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of RCTs of ustekinumab, a summary and critique of a sponsor-provided indirect comparison, and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with UC, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups answered CADTH's call for patient input for this submission: Crohn's and Colitis Canada and the Gastrointestinal Society. Patient perspectives were obtained from different sources of information, such as surveys and interviews. The following is a summary of key input from the perspective of the patient group(s):

- Both groups described how UC represents a disabling, lifelong gastrointestinal condition that primarily affects working-age individuals in their day-to-day lives. Patients sometimes experience isolation; anxiety; and debilitating, frequent, and urgent bowel movements.
- Patients often seek treatment options that can reduce or eliminate their symptoms and are regularly longing for treatments that could protect their ability to work, attend school and social events, and perform basic day-to-day activities.
- The patient groups reported that many current treatments can have undesirable effects due to the need for long-term use (e.g., glucocorticoids), and that they require new and effective options to achieve mucosal healing and decrease debilitating symptoms.
- Patients preferred drugs that are convenient and easy to use.
- Given that all individuals respond differently to therapies, it was considered imperative that patients have a variety of options for treatment.

Clinical Trials

The CADTH systematic review included one double-blind RCT, the UNIFI study, composed of an eight-week induction phase and a 44-week maintenance phase. The induction phase included 961 patients randomized to one of three groups: placebo IV (N = 319), ustekinumab IV (weight-based dosing approximating 6 mg/kg; N = 322), or ustekinumab IV 130 mg (N = 320); only the weight-based dosage is approved by Health Canada and germane to this review. All patients received a single administration of the treatment to which they were randomized. Patients were evaluated at week eight post-randomization for clinical remission, defined using the total Mayo score. Two definitions of clinical remission were used in all patients regardless of geographical location to accommodate US and global regulatory preferences (US versus outside the US). Patients who were not in clinical remission at this stage received an additional single dose of ustekinumab, either 90 mg SC if they initially received ustekinumab (any dose), or 6 mg/kg IV if they were initially allocated to placebo. Those in the induction ustekinumab groups (either dose) who responded to induction at week eight were eligible to continue to the maintenance phase; those in the induction placebo group who did not respond at week eight but responded at week 16 to ustekinumab 6 mg/kg IV (administered at week eight) were also eligible to continue to the maintenance phase. These groups of patients formed the randomized population of the maintenance phase. Patients in the induction ustekinumab groups who did not respond at week eight but responded at week 16 (delayed responders) were allowed to move into the maintenance phase and continued to receive ustekinumab 90 mg SC every eight weeks. At the same time, patients in the placebo group who were in clinical remission continued to receive placebo during the rest of the maintenance phase (44 weeks). These patients were grouped into the non-randomized population of the maintenance phase. Finally, all patients who did not respond to ustekinumab at week eight and at week 16 were excluded from the maintenance phase and were followed up for safety through week 44.

Overall, the risk of bias in the UNIFI study is low, with no limitations in the randomization process, blinding, differences in baseline characteristics, and assessment of outcomes or attrition rates throughout both phases of the study. In terms of the study's external

validity, one concern was the number of patients (59 out of 101; 58.4%) who initially did not respond in the induction study to ustekinumab 6 mg/kg IV at week 8 and received a second dose of ustekinumab (90 mg SC) and responded at week 16.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed the following:

- Clinical remission: The US definition was an absolute stool number of three or less, a rectal bleeding subscore of zero, and a total Mayo endoscopy subscore of zero or one; and the global definition was a total Mayo score two or greater, with no individual subscore greater than one
- Corticosteroid-free clinical remission
- Clinical response: A decrease from baseline in the total Mayo score by 30% or more and by three or more points, with either a decrease from baseline in the rectal bleeding subscore of one or more points or a rectal bleeding subscore of zero or one
- HRQoL
  - Inflammatory Bowel Disease Questionnaire (IBDQ) total score: The IBDQ assesses HRQoL in patients with IBD (e.g., UC and Crohn disease). An absolute score change of 30 points or more, or 15 points or more above the placebo score, was associated with clinical benefits in patients with IBD.
  - Short Form 36 Health Survey (SF-36): The SF-36 is a generic self-reported health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. The SF-36 also provides two component summaries, the physical component summary and the mental component summary. For both the physical component summary and the mental component summary, as well as the individual subscale scores in SF-36, an absolute score increase of three to five points was shown to capture minimal clinically important differences (MCIDs) in various conditions, including colitis.
  - EuroQol 5-Dimensions Visual Analogue Scale: The EuroQol 5-Dimensions 3-Levels is a generic preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments, including IBD. No MCID data were found for patients with UC; however, in patients with IBD, an MCID of 0.05 for the utility index score and 10.9 for the Visual Analogue Scale was determined.
- Mucosal healing: A combination of endoscopic healing (an improvement in the endoscopic appearance of the mucosa, defined as a total Mayo endoscopy subscore of zero or one) and histologic healing (based on features of the Geboes Score, defined as neutrophil infiltration in 5% or less of crypts; no crypt destruction; and no erosions, ulcerations, or granulation tissue)
- Productivity
- Adverse events

Efficacy

From the induction phase, the group who received IV ustekinumab 6 mg/kg had a higher proportion of patients who achieved clinical remission (15.5%) than those patients who received placebo (5.3%) ($P < 0.001$) at week eight based on the global definition of clinical remission (Mayo score of two points or less, with no individual subscore of greater than one). Similar results were reported based on the US definition of clinical remission (an absolute stool number of three or lower, a Mayo rectal bleeding subscore of zero, and a Mayo endoscopy subscore of zero or one). Sensitivity analyses supported the robustness of the primary analysis. Pre-specified subgroup analyses were consistent with the primary analysis. Other efficacy outcomes of interest for this review, such as clinical response at week eight, endoscopic healing, changes in the IBDQ, and mucosal healing, were statistically significantly improved in the ustekinumab groups compared with the placebo group.

Of the 961 patients randomly allocated to ustekinumab or placebo in the induction phase, 783 were eligible to enter the maintenance phase, of which 523 patients were assigned to the randomized population (due to their response to ustekinumab IV), while 260 were allocated to the non-randomized population because they were late responders or responded to placebo only. Those in the randomized population were assigned to again receive SC maintenance injections of 90 mg of ustekinumab (either every 12 weeks [n = 172 patients] or every eight weeks [n = 176]) or placebo (n = 175). In the randomized population of the maintenance phase, the percentage of patients who had clinical remission (global and US definitions) at week 44 was statistically significantly higher among patients assigned to 90 mg of SC ustekinumab every 12 weeks (approximately 39%) or every eight weeks (approximately 43%) than

among those assigned to placebo (approximately 24.0%) (P = 0.002 and P < 0.001, respectively). Sensitivity analyses supported the primary analysis. Subgroup analyses were also generally consistent with the primary analysis for the full population. Statistically significantly higher proportions of patients in the ustekinumab groups at week 44 maintained clinical response, corticosteroid-free remission, and endoscopic healing compared with the placebo group. There were too few events (three patients treated with placebo and two patients in the combined ustekinumab group) related to colectomies to draw conclusions.

Harms (Safety)

There were fewer serious adverse events in the induction and maintenance phases of the UNIFI study with ustekinumab (3.4% and 7.3% in the combined groups, respectively) than with placebo (6.6% and 9.7%, respectively). The higher frequency in the placebo group was seemingly driven by a larger percentage of patients reporting UC as an adverse event, likely reflecting a lack of efficacy from placebo. A larger percentage of patients in the placebo group (11.6%) withdrew from the maintenance phase due to an adverse event compared with those in the ustekinumab groups (5.1%); no patients withdrew from the induction phase due to an adverse event. Through 52 weeks of exposure, there were two deaths (one each from acute respiratory distress syndrome and hemorrhage from esophageal varices) and seven cases of cancer diagnosed (one each of prostate, colon, renal papillary, and rectal cancer, and three nonmelanoma skin cancers) among 825 patients who received ustekinumab, and no deaths and one case of cancer diagnosed (testicular cancer) among 319 patients who received placebo.

Indirect Treatment Comparisons

One sponsor-submitted systematic review and NMA was reviewed. This synthesis assessed the efficacy of ustekinumab indirectly compared with other interventions, namely infliximab, adalimumab, vedolizumab, ustekinumab, golimumab, tofacitinib, and placebo. It evaluated treatment effects on clinical remission, clinical response, and mucosal healing in patients who experienced biologic and non-biologic failures, and also in the induction and maintenance phases of drug administration. Based on the NMA of the induction phase, ustekinumab had higher odds of clinical response, clinical remission, and mucosal healing compared with placebo and adalimumab (in patients who experienced biologic and non-biologic failure for clinical response, but only in patients who experienced biologic failure for clinical remission and mucosal healing). For the rest of the comparisons, ustekinumab did not increase or decreased the odds of any of these outcomes when compared with infliximab, vedolizumab, golimumab, and tofacitinib. For the maintenance phase analyses, ustekinumab had higher odds of clinical response in patients who experienced non-biologic failure compared with adalimumab, golimumab, tofacitinib, and placebo, but not against vedolizumab; while in patients who experienced biologic failure, it was only better than placebo. For clinical remission, ustekinumab provided higher odds against golimumab, adalimumab, and placebo in the non-biologic failure group (but not against vedolizumab, infliximab, or tofacitinib); in the biologic failure group, ustekinumab was only better than placebo. Finally, ustekinumab had higher odds of mucosal healing in patients who experienced non-biologic failure than adalimumab, golimumab, and placebo, but it was no better than infliximab, tofacitinib, and vedolizumab. Limitations of the NMA include uncertainty about the effect estimates (mostly due to concerns of unaccounted for heterogeneity), intransitivity, uncertainty due to the use of multiple assumptions of the imputation process, and overestimated precision for reported comparisons. The NMA did not include assessments of comparative safety.

Cost and Cost-Effectiveness

Ustekinumab is available as a 130 mg/26 mL solution vial for IV-tiered infusion and as a pre-filled syringe of 90 mg/1 mL for SC injection. The recommended dose of ustekinumab during the induction phase is a single IV-tiered infusion based on body weight (6 mg/kg) and SC injections of 90 mg every eight weeks during the maintenance phase. At the sponsor-submitted price of $2,080 per 130 mg/26 mL solution vial for IV infusion and $4,593 for a pre-filled syringe of 90 mg/1 mL for SC injection, the annual cost of treatment per patient with ustekinumab is estimated to be $33,798 in the first year and $32,152 annually thereafter.

The sponsor submitted a cost-utility analysis comparing ustekinumab with other biologic therapies or continuing conventional therapy (a mix of 5-aminosalicylates, corticosteroids, and immunomodulators) for Canadian adults with moderately to severely active UC who have inadequate, intolerant, or failed response to conventional therapy or biological agents. Two patient populations were modelled separately: the “non-biological failure” (biologic-naive) and the “biologic failure” (biologic-experienced) subgroups. Comparators included in the analysis differed by subgroup. All biologic therapies (infliximab, infliximab biosimilars, adalimumab, golimumab, vedolizumab, and tofacitinib) and conventional therapies were considered as comparators in the biologic-naive population, while in

the biologic-experienced population, infliximab, infliximab biosimilars, and golimumab were omitted as comparators. The analysis was conducted from the perspective of the Canadian publicly funded health care system over a 10-year time horizon. The sponsor submitted a hybrid model that consisted of a decision tree and a Markov state transition model that captured patients' disease progression through the treatment induction and maintenance phases, respectively. Patients first entered the decision tree with active UC and started induction with ustekinumab or biologic therapies, or continued conventional therapy. At the end of the induction phase, patients could achieve clinical remission (a Mayo score of two or less with no individual subscore of greater than one), respond without clinical remission (a decrease from baseline in total Mayo score of three or more points and at least 30%), fail to respond to induction therapy (i.e., remain in active UC), or die. Thereafter, patients entered their corresponding health state within the Markov model, which captured the long-term clinical progression, including the clinical effects of the maintenance phase of treatment and the potential impact from surgical intervention. Patients who demonstrated clinical remission or response without remission would remain in these respective states whereas patients who lost response to treatment or who failed to respond to induction therapy would transition to the active UC health state and switch over (i.e., discontinue their biologic) or continue receiving conventional therapy. Comparative efficacy for ustekinumab and all included comparators were derived from a sponsor-commissioned NMA based on a fixed-effects model. Health state utility values for patients and the utility decrement for adverse events were obtained from the literature. Based on a sequential analysis of the sponsor's base case, the incremental cost-utility ratio for ustekinumab was $68,133 per quality-adjusted life-year (QALY) gained compared with an infliximab biosimilar in patients who are biologic naive and $79,040 per QALY gained compared with tofacitinib in patients who are biologic experienced.

CADTH identified several key limitations with the submitted analysis:

- Relative treatment effects for both subgroups were based on a sponsor-commissioned NMA that had considerable methodological issues. Uncertainty regarding the comparative efficacy for ustekinumab exists given the risk of bias associated with individual studies and observed violations of transitivity. In particular, there is considerable uncertainty associated with data from the maintenance phase due to methodological differences in trials design.
- Relevant comparators (i.e., infliximab, infliximab biosimilars, and golimumab) were not considered in the biologic-experienced analysis.
- A 10-year time horizon was chosen for the economic analysis rather than a lifetime time horizon despite UC being a lifelong chronic condition.
- The proportions of patients receiving low- and high-maintenance doses in the economic model were varied across biologic treatments but did not always reflect the doses studied in the trials informing the NMA. This resulted in treatment costs that were misaligned with the doses studied in the trials and that informed relative treatment efficacy within the sponsor's model.
- The use of arbitrary definitions of uncertainty for most parameters in the model introduced instability to the model.

CADTH attempted to address the identified limitations by selecting the random-effects model of the NMA to inform the treatment effects in the induction phase; incorporating a lifetime time horizon (50 years); and changing the proportion of patients receiving low- and high-dose biologics in the economic model to reflect the values studied in the respective trials. CADTH reanalyses of the biologic-naive population determined that conventional therapy would be the optimal therapy if the willingness-to-pay threshold is up to $53,546 per QALY; thereafter, ustekinumab would be the optimal therapy. Importantly, the CADTH base-case results for the biologic-experienced population could not be reported probabilistically due to model instability. In this subgroup, the deterministic results suggest that conventional therapy would be the optimal therapy up to a willingness-to-pay threshold of $63,058 per QALY; thereafter, ustekinumab would be the optimal therapy. Of note, the sponsor's submitted NMA did not report superiority between ustekinumab over other biologics with the same indication and considerable uncertainty remains regarding the comparative treatment efficacy of ustekinumab with available treatments in both the biologic-naive and biologic-experienced subgroups.

Several methodological concerns with the sponsor-commissioned NMA could not be addressed and as such the results of this economic evaluation should be viewed with caution. The cost-effectiveness of ustekinumab compared with infliximab (branded or biosimilar) and golimumab in the biologic-experienced population is further unknown.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 15, 2020 Meeting (Initial)

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None

June 17, 2020 Meeting (Reconsideration)

Regrets

None

Conflicts of Interest

None