CADTH CANADIAN DRUG EXPERT REVIEW COMMITTEE FINAL RECOMMENDATION

ADALIMUMAB
(Humira — AbbVie)
Indication: Ulcerative Colitis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that adalimumab not be listed at the submitted price for the treatment of adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy including corticosteroids, azathioprine, and/or 6-mercaptopurine or who are intolerant to such therapies.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) (ULTRA 1 [N = 576] and ULTRA 2 [N = 518]) demonstrated that treatment with adalimumab was superior to placebo for inducing remission in patients with UC at eight weeks. For ULTRA 2, adalimumab remained superior to placebo for remission induction at 52 weeks. A third trial in a Japanese population (M10-447 [N = 274]) also demonstrated that treatment with adalimumab was superior to placebo for inducing clinical remission at 52 weeks.
2. The comparative clinical benefits and risks as well as the relative cost-effectiveness of adalimumab with alternative biologic treatment options for UC are uncertain.

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."
- CDEC noted that the proportions of patients achieving clinical remission with adalimumab were small and that the effect estimates may have been affected by the small sample size in ULTRA 1 and by the method used to impute data for patients who withdrew from ULTRA 2.
- CDEC also noted that the proportion of patients achieving clinical response with adalimumab was not statistically significantly different when compared with the proportion of responders for the placebo group at 8 weeks in ULTRA 1. The product monograph states that patients who have not responded by 8 weeks of therapy should not be continued on adalimumab.

Background:
Adalimumab is a recombinant human immunoglobulin monoclonal antibody indicated for use in the treatment of a variety of conditions, including rheumatoid arthritis, polyarticular juvenile

idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and pediatric Crohn disease, UC, hidradenitis suppurativa, and psoriasis. This CADTH Common Drug Review (CDR) submission is for the treatment of adult patients with moderately to severely active UC who have had an inadequate response or are intolerant to conventional therapy including corticosteroids, azathioprine, and/or 6-mercaptopurine. As stated in the product monograph, the efficacy of adalimumab has not been established in patients who have lost response to or were intolerant to tumor necrosis factor (TNF) inhibitors.

The recommended dosage regimen for the treatment of UC with adalimumab is subcutaneous (SC) administration of 160 mg in week 0, 80 mg in week 2, then 40 mg every other week thereafter as monotherapy or in combination with conventional therapies.

Summary of CDEC Considerations

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

Patient Input Information

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

- During flare-ups, patients with UC experience urgent and frequent bowel movements (usually between five and 20 per day and sometimes more), rectal bleeding and bloody diarrhea (which can lead to anemia in severe cases), cramping, abdominal pain, fatigue, and fluctuations in body weight. In addition, patients may experience extra-intestinal manifestations of UC, such as fever, arthritis, mouth or skin ulcers, tender and inflamed nodules on the shins, and other systemic disease symptoms.
- The symptoms of UC can profoundly affect a person's physical, emotional, and social well-being by causing anxiety and stress, limiting one's ability to work and participate in daily activities.
- The treatment of UC is multi-faceted and includes managing the symptoms and targeting the underlying inflammation. Patient groups noted that biologic treatments can provide an alternative to surgery (which is not a cure and which sometimes gives rise to serious complications) for patients who have failed conventional therapies. They also emphasized that biologic treatments, while frequently being the most effective, are often not accessible to patients due to their high cost.
- The patient groups said that a therapy such as adalimumab that can be administered by SC injection is particularly attractive to individuals living in rural and remote areas who have to travel long distances for therapies administered by infusion.
- Both patient groups noted that sometimes an effective biologic therapy loses some of its effectiveness over time; thus there is particular value in having another biologic available.

Clinical Trials

The CDR systematic review included three double-blind (DB) RCTs. Two of the studies, ULTRA 1 (N = 576) and ULTRA 2 (N = 518), were multinational and one study, M10-447 by Suzuki et al. (N = 274), was conducted exclusively in Japan. Evidence from a long-term, open-label (OL) extension study, ULTRA 3, was summarized in an appendix of the CDR systematic review.

- ULTRA 1 consisted of an eight-week DB treatment period and an OL extension phase of up to 52 weeks. Participants were randomized (1:1:1) to receive adalimumab 160 mg/80 mg/40 mg (i.e., 160 mg at week 0, 80 mg at week 2, and 40 mg every other week starting at week 4), adalimumab 80 mg/40 mg (i.e., 80 mg at week 0, 40 mg at week 2, and 40 mg every other week starting at week 4), or placebo.
- ULTRA 2 consisted of a 52-week, DB phase (eight weeks induction and 44 weeks maintenance). Participants were randomized (1:1) to receive adalimumab 160 mg/80 mg/40 mg or placebo.
- M10-447 consisted of a 52-week, DB phase (eight weeks induction and 44 weeks maintenance). Participants were randomized (1:1:1) to receive adalimumab 160 mg/80 mg/40 mg, adalimumab 80 mg/40 mg, or placebo.

All three studies permitted dose escalation from every other week to weekly dosing for patients with an inadequate response after the end of the eight-week induction period.

Outcomes

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

- Clinical remission — defined as Mayo score ≤ 2 with no subscore > 1. The Mayo scoring system consists of stool frequency subscore (from 0 [normal number of stools] to 3 [≥ 5 stools above normal]); rectal bleeding subscore (RBS) (from 0 [no blood seen] to 3 [blood alone passed]); endoscopy subscore (from 0 [normal] to 3 [severe]); and Physician's Global Assessment subscore (from 0 [normal] to 3 [severe]).
- Clinical response — defined as a decrease of Mayo score ≥ 3 points and a decrease ≥ 30%, and RBS of 0 or 1, or a decrease of RBS ≥ 1.
- Short Form (36) Health Survey (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, and role limitations due to physical and 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.
- Inflammatory Bowel Disease Questionnaire (IBDQ) — a 32-item questionnaire that assesses symptoms, general health, mood, and social/work problems resulting from UC. An increase in IBDQ score indicates alleviation of the disease, and a decrease in score indicates aggravation. An IBDQ responder was defined by an increase of at least 16 points from baseline.
- Serious adverse events (SAEs), total adverse events (AEs), and withdrawals due to AEs.

The primary outcome of ULTRA 1 was the proportion of patients achieving clinical remission at eight weeks, and the co-primary end points of ULTRA 2 and M10-447 were the proportions of patients achieving clinical remission at eight weeks and 52 weeks.

Efficacy

- Compared with placebo, the proportion of patients achieving clinical remission at eight weeks was statistically significantly greater with adalimumab in ULTRA 1 (19% versus 9%) and ULTRA 2 (17% versus 9%); however, there was no statistically significant difference in M10-447. Both ULTRA 2 and M10-447 demonstrated a statistically significantly greater proportion of adalimumab-treated patients achieving clinical remission at 52 weeks (17% versus 9% in ULTRA 2 and 23% versus 7% in M10-447). The differences in proportions in the ULTRA studies were reported as:

  - ULTRA 1: 9.2 (95% confidence interval [CI], [redacted]) at week 8 ($P = 0.031$)
  - ULTRA 2: 7.1 (95% CI, 1.2 to 12.9) at week 8 ($P = 0.019$) and 8.8 (95% CI, 2.8 to 14.5) at week 52 ($P = 0.004$)
  - Differences in proportions and 95% CIs were not reported in Study M10-447.
- There was no statistically significant difference between adalimumab and placebo for the proportion of patients demonstrating clinical responses at week 8 in ULTRA 1 (55% with adalimumab and 45% with placebo). In contrast, a statistically significantly greater proportion of adalimumab-treated patients achieved a clinical response compared with placebo-treated patients at week 8 and week 52 in both ULTRA 2 and M10-447. The differences in proportions in the ULTRA studies were reported as:
  - ULTRA 1: 10.0 (95% CI, [redacted]) at week 8
  - ULTRA 2: 15.6 (95% CI, [redacted]) at week 8 and 11.7 (95% CI, [redacted]) at week 52
  - Differences in proportions and 95% CIs were not reported in Study M10-447.
- In ULTRA 1, there was no statistically significant difference between adalimumab (61%) and placebo (58%) for the proportion of IBDQ responders at eight weeks. In ULTRA 2, the proportion of IBDQ responders at week 8 was greater with adalimumab (58%) than with placebo (46%), a difference in proportions of 12.2 (95% CI, [redacted]). The proportion of IBDQ responders was also higher with adalimumab (26%) than with placebo (16%) at week 52 (a difference in proportions of 9.7 [95% CI, [redacted]]). Although this outcome was included in the hierarchical statistical analysis plan, testing should not have been performed for this outcome because a previous outcome in the hierarchy failed to reach statistical significance. Therefore, these results should be considered exploratory for IBDQ responders. In M10-447, the proportion of IBDQ responders was not reported as statistically significantly different between adalimumab and placebo (42% versus 40%) at eight weeks; however, there was a statistically significantly greater proportion of clinical responders with adalimumab compared with placebo at 52 weeks (25% versus 13%, $P \leq 0.01$).
- In ULTRA 1, [redacted] in SF-36 PCS score with adalimumab compared with placebo [redacted] between groups on the SF-36 MCS. In ULTRA 2, [redacted] between groups [redacted]. SF-36 was not an outcome measure in M10-447. The differences in proportions in the ULTRA studies were reported as:
  - ULTRA 1 (SF-36 PCS): [redacted] (95% CI, [redacted]) at [redacted]
  - ULTRA 2 (SF-36 PCS): [redacted] (95% CI, [redacted]) at [redacted] and [redacted] (95% CI, [redacted]) at [redacted]
  - ULTRA 1 (SF-36 MCS): [redacted] (95% CI, [redacted]) at [redacted]
  - ULTRA 2 (SF-36 MCS): [redacted] (95% CI, [redacted]) at [redacted] and 1.2 (95% CI, [redacted]) at [redacted].
- In ULTRA 1, there was no statistically significant difference in the proportion of patients with mucosal healing between adalimumab and placebo. In ULTRA 2, a statistically significantly greater proportion of adalimumab-treated patients experienced mucosal healing compared with placebo-treated patients at eight weeks (41% versus 32%, $P = 0.032$) and 52 weeks (25% versus 15%, $P = 0.009$). In M10-447, the proportion of patients with mucosal healing was also greater with adalimumab compared with placebo at eight weeks (44% versus 30%, $P = 0.045$) and 52 weeks (29% versus 16%, $P = 0.015$).

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one AE was:
  - ULTRA 1: 50% in the adalimumab group and 48% in the placebo group
  - ULTRA 2: 83% in the adalimumab group and 84% in the placebo group
  - M10-447: 44% in the adalimumab group and 47% in the placebo group.
- The proportion of patients who experienced at least one SAE was:
  - ULTRA 1: 4% in the adalimumab group and 8% in the placebo group
  - ULTRA 2: 12% in both the adalimumab and placebo groups
  - M10-447: 4% in the adalimumab group and 7% in the placebo group.
- The proportion of patients who discontinued the study as a result of AEs was:
  - ULTRA 1: 5% in both the adalimumab and placebo groups
  - ULTRA 2: 9% in the adalimumab group and 13% in the placebo group
  - M10-447: 7% in the adalimumab group and 4% in the placebo group.

The most common AE and AE leading to withdrawal in all three studies was UC.

Injection site reactions and infectious AEs were the most common notable harms. Injection site reactions occurred in more adalimumab than placebo patients across the studies. Infectious AEs occurred in 14% of adalimumab patients versus 16% of placebo in ULTRA 1 (8 weeks), 45% versus 40% in ULTRA 2 (52 weeks), and 19% versus 16% of patients in M10-447 (52 weeks). Malignancies, hypersensitivity reactions, opportunistic infections, and death (due to tuberculosis, n = 1) occurred very infrequently in the trials.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis (CUA) comparing adalimumab + standard of care (SOC) with SOC alone in patients with moderately to severely active UC, with efficacy data primarily obtained from the ULTRA 2 and ULTRA 3 trials. In addition, a cost-minimization analysis (CMA) comparing adalimumab + SOC with infliximab + SOC and golimumab + SOC individually, assuming equivalent efficacy and safety of the drugs based on a network meta-analysis was also provided. Both analyses were undertaken from the perspective of the Canada public payer, over a 10-year time horizon. The manufacturer reported that the incremental cost-utility ratio (ICUR) for adalimumab + SOC compared with SOC alone was $76,817 per quality-adjusted life-year (QALY). The CMA concluded that adalimumab + SOC was cost-saving compared with infliximab + SOC or golimumab + SOC.

CDR identified several limitations with the manufacturer's CUA that were tested through reanalyses. These included:

- The utility values applied to the model health states were obtained from a number of published sources. Different published sources report different utility scores for each health state. These values vary significantly. Uncertainty in health state utility values was assessed by CDR, considering the range of possible values.
- The rate of surgery used by the manufacturer was based on pooled data from three publications reporting rates in Europe, which are higher than estimates reported in a published Canadian study.
- The rate of dose escalation observed in the ULTRA trials is likely to differ from Canadian clinical practice, based on feedback from the clinical expert consulted by CDR and an observational cohort study of adalimumab in UC patients. The CUA results are not sensitive to varying this parameter.

- The cost of SOC was based on information from an infliximab trial. Data from ULTRA 2 suggests that the cost of SOC may be double than what was included in the analysis.
- The manufacturer assumed discontinuation of biologics between week 8 and week 104. Discontinuation rates observed in ULTRA 1 and ULTRA 2 suggested this is not appropriate.

Addressing the above limitations, CDR found that the ICUR for adalimumab + SOC compared with SOC alone ranged from $67,000 to $130,000 per QALY.

CDR noted that the manufacturer did not include the effects of treatment waning in its analysis, which favours adalimumab. CDR was not able to assess this limitation given the model structure. The population assessed in the CUA included patients experienced and naive to anti-TNF alpha drugs (40% of patients in ULTRA 2 had received treatment with an anti-TNF alpha in the five years leading up to the trial). Published data suggest a lower rate of response for anti-TNF alpha–experienced patients, which would increase the ICUR. The comparative cost-effectiveness of adalimumab compared with vedolizumab in patients with moderately to severely active UC is not known and could not be assessed by CDR.

The analysis of adalimumab + SOC compared with infliximab + SOC or golimumab + SOC is dependent on the assumption of equal safety and efficacy. The CDR clinical review identified substantial uncertainty regarding the comparative effectiveness of treatments, and as such, validity of the CMA is uncertain.

At the submitted marketed price of $740.36 per 40 mg/0.8 mL syringe or auto-injector, adalimumab ($22,211 in year 1, $19,249 thereafter) is priced similarly to golimumab ($22,803 in year 1, $19,763 thereafter), and less expensive than infliximab ($31,602 in year 1, $25,677 thereafter) and vedolizumab ($26,320 in year 1, $21,385 thereafter).

Other Discussion Points:

CDEC noted the following:

- In the pivotal trials, several important parameters (such as clinical response and quality of life) did not consistently demonstrate statistically significant improvement with adalimumab compared with placebo, resulting in uncertainty in assessing the clinical benefits associated with adalimumab.
- There is limited evidence available regarding the potential effects of adalimumab on reducing the incidence of, namely, colectomy, improving quality of life, and reducing the number of missed school or work days, which were identified as important outcomes for patients based on the patient input received.
- Five indirect comparisons were summarized in the CDR systematic review; however, given the numerous limitations and inconsistent findings, it is not clear whether a difference exists among the biologics with respect to inducing and maintaining remission, response, and mucosal healing in patients with moderately to severely active UC.
- The SC mode of administration for adalimumab may offer increased convenience for some patients.

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

- There are no studies directly comparing adalimumab with other biologics approved for use in the treatment of UC.
- The included studies were of insufficient duration to assess the risk of harms such as malignancy and opportunistic infections.

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

March 16, 2016 Meeting
Regrets:

Two CDEC members were 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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