CDEC FINAL RECOMMENDATION

OMALIZUMAB
(Xolair — Novartis Pharmaceuticals Canada Inc.)
Indication: Chronic Idiopathic Urticaria

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that omalizumab be listed for the treatment of adults and adolescents with chronic idiopathic urticaria (CIU) who remain symptomatic despite H_1 antihistamine treatment, if the following clinical criterion and conditions are met:

Clinical criterion:
- Moderate to severe CIU who remain symptomatic (presence of hives and/or associated itching) despite optimum management with available oral therapies

Conditions:
- Substantial reduction in price
- Six-month initial course of treatment.

Reasons for the Recommendation:
1. Three randomized controlled trials (RCTs) (ASTERIA I, ASTERIA II, and GLACIAL) demonstrated that 12 weeks of omalizumab 150 mg or 300 mg administered every four weeks resulted in statistically significant improvements in the symptoms of CIU (as measured with the Urticaria Activity Score over seven days [UAS7]).
2. Controlled efficacy data from the included trials were limited to 24 weeks of treatment; therefore, the available evidence does not support initial treatment beyond 24 weeks.
3. At the submitted price of $612.00 per vial, the CADTH Common Drug Review (CDR) estimated that the incremental cost per quality-adjusted life-year (QALY) for omalizumab 300 mg plus standard of care (SOC) versus SOC alone exceeds $120,000 per QALY; therefore, omalizumab is not considered to be cost-effective at the submitted price.

Of Note:
CDEC noted that some patients with CIU may benefit from re-treatment with omalizumab after 24 weeks; however, there were no data available to evaluate the efficacy and safety of omalizumab in patients requiring re-treatment.

Background:
Omalizumab is a humanized, recombinant, immunoglobulin G (IgG) monoclonal antibody that binds to immunoglobulin E (IgE) and prevents it from binding to its high-affinity receptor on mast cells and basophils, thereby reducing IgE-induced mast cell and basophil degranulation and the release of histamine. Omalizumab is indicated for the treatment of CIU in adults and adolescents who remain symptomatic despite H_1 antihistamine treatment, and for the treatment of moderate to severe persistent asthma in adults and adolescents whose symptoms are inadequately controlled with inhaled corticosteroids.

Omalizumab is supplied as a lyophilized, sterile powder in a single-use vial designed to deliver 150 mg of omalizumab for subcutaneous (SC) injection upon reconstitution. For the treatment of CIU, omalizumab is administered by a health care provider every four weeks at a dose of 150 mg or 300 mg.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals with CIU.

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

- Patients reported that CIU attacks are unpredictable in both timing and severity, causing anxiety, affecting sleep, and impacting their diet and their ability to obtain employment. A majority of patients reported a decrease in self-confidence and feeling the need to hide the affected skin.
- Patients reported that CIU has a negative impact on family members and caregivers. Caregivers have to deal with the anxiety and depression of the patient and often need to help the patient with self-care, grooming, washing, and other self-care activities.
- Concerns with current treatment options include lack of effectiveness and intolerable side effects.

Clinical Trials
The CDR systematic review included three phase 3, double-blind, multi-centre, placebo-controlled RCTs: ASTERIA I (N = 319) was 24 weeks in duration; ASTERIA II (N = 323) was 12 weeks in duration, and GLACIAL (N = 336) was 24 weeks in duration. ASTERIA I and ASTERIA II randomized patients (1:1:1:1 ratio) to one of three doses of omalizumab (75 mg, 150 mg, or 300 mg) or placebo. These studies were conducted with adult and adolescent patients with refractory CIU receiving concomitant standard-dose H_1 antihistamine therapy. Patients were given the first dose of study medication at day one and were re-treated every four weeks. Only the 150 mg and the 300 mg doses of omalizumab are approved for treatment of CIU in Canada. Therefore, the data for the 75 mg omalizumab treatment group were not reported in the CDR review.

GLACIAL compared omalizumab 300 mg with placebo (3:1). The study was conducted with adult and adolescent patients with refractory CIU receiving concomitant therapy including H_1 antihistamines at up to four times the approved dose, and H_2 antagonists or leukotriene receptor

antagonists, or both. Patients were dosed and monitored in the same manner as in ASTERIA I and ASTERIA II. All three studies had a 16-week treatment-free follow-up period.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol.

- UAS7 — The Urticaria Activity Score (UAS) end points were collected via the electronic Urticaria Patient Daily Diary. The daily UAS is the sum of the daily Itch Severity Score and the daily Number of Hives Score. The UAS7 is the sum of the daily UAS scores over one week, with higher scores indicating more severe symptoms. The minimal clinically important difference (MCID) for UAS7 has been reported to be 9.5 to 10.5. UAS7 was assessed using the following end points:
  - Change from baseline to weeks 12 and 24
  - Proportion of patients with UAS7 ≤ 6 at weeks 12, 24, 28, and 40
  - Proportion of patients with complete response (UAS7 = 0) at weeks 12 and 24
  - Time to UAS7 MCID response
  - Proportion of responders who maintained their response (UAS7 ≤ 6) to week 28 or week 40
  - Time to relapse in week 12 or week 24 responders.
- Weekly Itch Severity Score (WISS) — the sum of the daily Itch Severity Score tabulated over seven consecutive days. The MCID for WISS has been reported to be 4.5 to 5.0.
- Weekly Number of Hives Score (WNHS) — the sum of the daily Number of Hives Score tabulated over seven consecutive days. The MCID for WNHS has been reported to be 5.0 to 5.5.
- Dermatology Life Quality Index (DLQI) — a 10-item questionnaire that assesses six different aspects that may affect quality of life: symptoms and feelings; daily activities; leisure activities; work or school; personal relationships; and treatment. Higher scores indicate a greater impairment in quality of life. The MCID for DLQI in CIU patients has been reported to be in the range of 2.24 to 3.10.
- Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) — a validated CIU-specific quality of life measure that includes a 23-item, self-administered questionnaire that assesses six quality of life dimensions: pruritus; swelling; impact on life activities; sleep problems; limits; and looks. Overall CU-Q2oL scores are converted to a 0 to 100 scale, with higher scores indicating greater quality of life impairment. The MCID for the CU-Q2oL is unknown.
- EuroQol 5-Dimensions Questionnaire (EQ-5D) — a generic quality of life instrument consisting of five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analogue scale for rating health today. Weighted scoring produces an EQ-5D index score, with a higher score indicating better general health.
- Total adverse events, serious adverse events, withdrawals due to adverse events, and notable harms.

The primary objective of ASTERIA I and ASTERIA II was to evaluate whether omalizumab was superior to placebo for improving WISS after 12 weeks. The primary objective of GLACIAL was to evaluate the safety of omalizumab compared with placebo.

Efficacy

- Both the 150 mg and 300 mg doses of omalizumab were statistically superior to placebo for improvement in UAS7, WISS, and WNHS in all three included studies. The least squares mean differences (LSMD) versus placebo were (150 mg and 300 mg, respectively):

  - Change from baseline in UAS7:
    - ASTERIA I: −6.54 (95% confidence interval [CI], −10.33 to −2.75) and −12.80 (95% CI, −16.44 to −9.16)
    - ASTERIA II: −7.69 (95% CI, −11.49 to −3.88) and −12.40 (95% CI, −16.13 to −8.66)
    - GLACIAL: −10.02 (95% CI, −13.17 to −6.86) with 300 mg.
  - Change from baseline in WISS:
    - ASTERIA I: −2.95 (95% CI, −4.72 to −1.18) and −5.80 (95% CI, −7.49 to −4.10)
    - ASTERIA II: −3.04 (95% CI, −4.85 to −1.24) and −4.81 (95% CI, −6.49 to −3.13)
    - GLACIAL: −4.52 (95% CI, −5.97 to −3.08) with 300 mg.
  - Change from baseline in WNHS:
    - ASTERIA I: [redacted] (95% CI, [redacted] to [redacted]) and [redacted] (95% CI, –9.10 to [redacted])
    - ASTERIA II: −4.51 (95% CI, −6.65 to −2.36) and −7.09 (95% CI, −9.26 to −4.93)
    - GLACIAL: −5.90 (95% CI, −7.72 to −4.07) with 300 mg.
- A statistically significantly greater proportion of omalizumab-treated patients achieved the UAS7 MCID response compared with placebo. The hazard ratios for time to achieving a UAS7 MCID response for omalizumab versus placebo were (150 mg and 300 mg, respectively):
  - ASTERIA I: [redacted] (95% CI, [redacted] to [redacted]) and [redacted] (95% CI, [redacted] to [redacted])
  - ASTERIA II: [redacted](95% CI, [redacted] to [redacted]) and [redacted] (95% CI, [redacted] to [redacted])
  - GLACIAL: [redacted] (95% CI, [redacted] to [redacted]) with 300 mg.
- With the exception of the omalizumab 150 mg group in the ASTERIA I trial, changes in DLQI and CU-Q2oL were statistically significant and favoured the omalizumab treatment groups over placebo. The LSMD versus placebo were (150 mg and 300 mg, respectively):
  - Change from baseline in DLQI:
    - ASTERIA I: −1.31 (95% CI, −3.46 to 0.84) and −4.08 (95% CI, −5.96 to −2.20)
    - ASTERIA II: −2.51 (95% CI, −4.64 to −0.38) and −3.79 (95% CI, −5.85 to −1.73)
    - GLACIAL: −4.67 (95% CI, −6.28 to −3.06) with 300 mg.
  - Change from baseline in CU-Q2oL:
    - ASTERIA I: −3.9 (95% CI, −11.2 to 3.4) and −10.6 (95% CI, −17.2 to −4.0)
    - ASTERIA II: −8.2 (95% CI, −14.3 to −2.1) and −14.0 (95% CI, −19.8 to −8.2)
    - GLACIAL: −13.4 (95% CI, −18.2 to −8.6) with 300 mg.
- With the exception of the omalizumab 300 mg group in the ASTERIA I trial (P = 0.0062), differences in change from baseline in EQ-5D index scores between the omalizumab groups and placebo were not statistically significant.
- The majority of efficacy outcomes assessed after the 16-week treatment-free follow-up period did not maintain statistical significance compared with placebo.

Harms (Safety and Tolerability)

- The proportions of patients who experienced at least one serious adverse event were:
  - ASTERIA I: 3.4% with omalizumab 150 mg, 0% with omalizumab 300 mg, and 5.0% with placebo
  - ASTERIA II: 0% with omalizumab 150 mg, 2.5% with omalizumab 300 mg, and 2.5% with placebo
  - GLACIAL: 2.8% with omalizumab 300 mg and 3.6% with placebo.
- The proportions of patients who experienced at least one adverse event were:
  - ASTERIA I: 69.0% with omalizumab 150 mg, 56.8% with omalizumab 300 mg, and 51.3% with placebo

  - ASTERIA II: 47.7% with omalizumab 150 mg, 44.3% with omalizumab 300 mg, and 40.5% with placebo
  - GLACIAL: 65.1% with omalizumab 300 mg and 63.9% with placebo.
- The most commonly reported adverse events were nasopharyngitis and headache. Across all three studies, the proportion of patients who reported headache was consistently greater in the omalizumab groups compared with the placebo groups.
- The proportions of patients who withdrew as a result of adverse events were:
  - ASTERIA I: 2.3% with omalizumab 150 mg, 1.2% with omalizumab 300 mg, and 2.5% with placebo
  - ASTERIA II: 1.1% with omalizumab 150 mg, 0% with omalizumab 300 mg, and 1.3% with placebo
  - GLACIAL: 1.2% with omalizumab 300 mg and 1.2% with placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing omalizumab plus SOC with SOC alone, over a 20-year time horizon, under the perspective of a publicly funded health care system, with adults and adolescents 12 years of age and over with moderate to severe symptomatic CIU (UAS7 ≥ 16) despite SOC. The manufacturer considered three different scenarios in its analysis, where the dosage of omalizumab varied (150 mg or 300 mg) and where different definitions of SOC were used:

- Scenario 1 compared omalizumab 300 mg as a third- or fourth-line drug added on to SOC, defined as up to four times the standard H_1 antihistamine dose, combined with H_2 antagonists, leukotriene receptor antagonists, or both, with SOC alone.
- Scenario 2 compared omalizumab 150 mg as a second-line drug added on to SOC, defined as standard H_1 antihistamine dose with SOC alone.
- Scenario 3 compared omalizumab 300 mg as a second-line drug added on to SOC, defined as standard H_1 antihistamine dose with SOC alone.

The model included five key health states based on the UAS7: severe urticaria (UAS7 score of 28 to 42), moderate urticaria (UAS7 score of 16 to 27), mild urticaria (UAS7 score of 7 to 15), well-controlled urticaria (UAS7 score of 1 to 6), and urticaria-free (UAS7 score of 0). Patients began in either the moderate or severe urticaria health states and cycled through the model every four weeks for 24 weeks. Patients who responded to treatment at 24 weeks (defined as UAS7 ≤ 6) were eligible for re-treatment upon relapse (defined as UAS7 ≥ 16). Progression through the model was also driven by whether patients experienced a spontaneous remission of symptoms or dropped out. Efficacy and safety data were sourced from ASTERIA I, ASTERIA II, and GLACIAL, while utility values were obtained from pooling the data from these trials. The manufacturer reported that omalizumab 300 mg plus SOC versus SOC alone is associated with an incremental cost-utility ratio (ICUR) of $52,213, $57,193, and $81,210 per QALY, for scenarios 1, 2, and 3, respectively.

CDR identified a number of limitations with the submitted economic evaluation:

- The manufacturer did not include a treatment waning effect.
- There is uncertainty in the natural remission rates (higher rates than those assumed by the manufacturer's base case are reported in literature).
- The manufacturer assumed that patients in the mild CIU health state following initial treatment would not be re-treated upon relapse, which is uncertain.

CDR reanalysis focused on the 300 mg dose of omalizumab, as the 150 mg dose did not provide a clinically significant response in terms of change in UAS7 score at weeks 12 and 24. At a dose of 300 mg SC every four weeks, when omalizumab is used as either a second-line, or third- or fourth-line drug added on to SOC in patients refractory to H_1 antihistamines, CDR found that the ICURs for omalizumab plus SOC compared with SOC alone were above $120,000 per QALY. At a price reduction of 60%, the ICUR for omalizumab 300 mg plus SOC compared with SOC alone would be $50,764 if omalizumab is used as a second-line drug, and $43,606 if it is used as a third- or fourth-line drug.

At the submitted price of $612 per 150 mg single-use vial and at the recommended dose of 150 mg or 300 mg every four weeks, the annual cost of omalizumab is $7,956 (150 mg dose) and $15,912 (300 mg dose).

Other Discussion Points:

CDEC noted the following:

- In accordance with clinical practice guidelines jointly issued by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization, clinicians in Canada typically use maximally tolerated doses of second-generation H_1 antihistamines up to four times the indicated dose before adding additional medications for patients with inadequately controlled symptoms.
- Although statistically significant, the 150 mg dose of omalizumab in ASTERIA I and ASTERIA II failed to provide a clinically significant response on UAS7, WISS, or WNHS compared with placebo, based on published MCID values for these outcomes.
- The Canadian product monograph for omalizumab states that a five-year observational study demonstrated that there was a disproportionate increase of overall cardiovascular and cerebrovascular disorders observed in the omalizumab-treated cohort compared with the non-omalizumab cohort.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- The included clinical trials were limited to 24 weeks of treatment; therefore, the longer-term efficacy of omalizumab in the treatment of CIU requires further evaluation.
- There are no data to evaluate how or when treatment should be stopped or reinitiated after discontinuation.
- There are no studies directly comparing omalizumab against less costly oral drugs (e.g., montelukast or cyclosporin A) for the treatment of CIU.

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

April 8, 2015 Meeting

Regrets:
None

Conflicts of Interest:
One CDEC member did not participate in the deliberation or vote due to a conflict of interest.

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 CDR reviews and used in 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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